INSTITUTIONAL REVIEW BOARD & ETHICS

COMMITTEE GUIDELINES

Shifa International Hospital Ltd. (SIH)

Shifa Tameer-e-Millat University (STMU)

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FUNCTIONS:

The Medical Staff Affairs Committee of Shifa International Hospital (SIH) constituted an Ad Hoc committee entitled the **Institutional Review Board (IRB) & Ethics Committee (EC) with** the following Mandate:

1.1 Mandate:

The committee is mandated to initiate and maintain an ethical ambiance in the hospital and to oversee that ethical standards of medical and administrative research practices are adhered to. The mission of Institutional Review Board and Ethics Committee (IRB & EC) at Shifa Tameer-e-Millat University and Shifa International Hospital and all its associated Teaching and Non-Teaching entities is to promote the growth of scientific research, to ensure a safe and ethical research environment, and to protect the rights and welfare of the human subjects involved in research activities conducted under its authority according to the international ethical principles and guidelines.
One of the major functions of the committees is to review all research being conducted at these institutions from a Scientific and Ethical point of view. A description of the IRB & EC functions and obligations and major prerequisites are as per international guidelines from various international and national guidelines and sources as listed below:

1. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research.* http://www.hhs.gov/ohrp/policy/belmont.html
2. International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guideline. Available at https://ichgcp.net/ and INTEGRATED ADDENDUM TO ICH E6(R1) at https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
3. *World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.* http://www.wma.net/en/10home/index.html
4. *The Nuremberg Code: Directives for Human Experimentation* http://www.hhs.gov/ohrp/archive/nurcode.html
5. U.S. Food and Drug Administration (FDA) http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/.htm
6. DRAP: Drug Regulatory Authority of Pakistan. CONDUCT OF CLINICAL TRIALS GUIDELINES. Document No: PHSR/GL/CT-007 Available at https://www.dra.gov.pk/wp-content/uploads/2021/12/PS-guide.pdf
7. Government of Pakistan National Institutes of Health, Health Research Institute National Bioethics Committee (NBC) Pakistan. RESEARCH ETHICS -GUIDANCE DOCUMENT. Available at http://nbcpakistan.org.pk/assets/nbc-erc-guidance-sheet-(2022).pdf

Brief description of above is in Annexure 1.

1.2 Entities

The following are some of the current entities to which IRB&EC rules apply:

SHIFA INTERNATIONAL HOSPITAL LTD (SIH)

FACULTY OF HEALTH SCIENCES

- Shifa School of Health Professions Education (SHPE)
- Shifa College of Medicine (SCM)
- Shifa College of Dentistry (SCD)
- Department of Podiatric Medicine (DPM)
- Shifa School of Universal Health Coverage (SUHC)

FACULTY OF NURSING AND MIDWIFERY

- Shifa College of Nursing (SCN)

FACULTY OF PHARMACEUTICAL AND ALLIED HEALTH SCIENCES

- Shifa College of Pharmaceutical Sciences (SCPS)
- Department of Rehabilitation Sciences (DRS)
- Department of Biosciences (DBS)
- Shifa College of Medical Technology (SCMT)
- Department of Management Sciences (DMS)

FACULTY OF SOCIAL SCIENCES AND HUMANITIES

- Department of Clinical Psychology (DCP)
- Department of Social Sciences and Humanities

FACULTY OF COMPUTING

- Department of Computing

IRB & EC is registered at The Office for Human Research Protections (OHRP) https://www.hhs.gov/ohrp/index.html Registration Number IORG0010635.

1.3 STMU/SIH POLICY TO OVERSEE AND REVIEW HUMAN SUBJECTS RESEARCH

POLICY SIH-SCRC-017

1.3.1. Purpose

The Institutional Review Board & Ethics Committee (IRB & EC), Data & Safety Monitoring Board (DSMB) in collaboration with Shifa Clinical Research Center (SCRC) at Shifa International Hospital (SIH) have established a process for initial and ongoing review of all human subjects' research.

1.3.2. Scope

The review process shall apply to all the research projects being conducted at SIH, Shifa Tameer-i-Millat University and its allied institutions.

1.3.3. Policy

SIH has two bodies for oversight all research in the hospital involving human subjects carried out in the hospital, i.e.

- Institutional Review Board & Ethics Committee (IRB& EC)
- Data and Safety Monitoring Board (DSMB)

1.3.4. Procedure and Responsibilities

a. Institutional Review Board & Ethics Committee

All research projects involving human subjects, whether as individuals or communities, including the use of foetal material, embryos and tissues from the recently dead, supported and undertaken by SIH faculty, staff or students, wherever conducted, shall be reviewed by the IRB & EC and SCRC before the study begins.

Some research that involves human subjects may be exempted from the regulations requiring IRB & EC approval. Examples include educational research, testing and survey procedures where no identifying information will be recorded that can link subjects to the data, and disclosure of the data could not reasonably place the subjects at risk of civil or criminal liability or be damaging to the subjects financial standing, employability, or reputation. Such exemption would be conditional to:

- The informed consent is taken from the research subject.
- The information gathered being relevant/beneficial to the research subject and his/her community.
- Weigh relative risks and benefits to subjects.
- Provision of confidentiality and security of research information
- Proposal includes planning for sharing study findings with the research subject/s and the relevant communities planned, as well as mechanisms for informing the research subject.
- Also exempted are the uses of existing data, documents or specimens, where no identifying information will be recorded that can link subjects to the data. Examples:
    - Literature review; and theoretical analysis. In such cases the only ethical Concern would be acknowledgement of sources.
    - Analysis of data, documents, specimen, not linked to individual subjects.
- Evaluation studies of intervention programmes/projects, especially by those who were partners in planning the intervention.
- All researchers must give the subject participants the option of sharing the results and specify how this will be done.
- Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others.

- The human subjects in your project must participate willingly, having been informed about the research. Please provide all information that is likely to affect the person irrespective of age, sex, or literacy level of the subjects. If the human subjects in your project are part of a vulnerable population, such as prisoners, children or mentally handicapped then the researcher should clearly state why is it necessary to have such groups as their research subjects and how do they plan to administer the informed consent.
- The researcher should submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, potential conflicts of interest and incentives for subjects.
- Specify the cost of management directly related to the study and indicate what portion of the cost would be incurred by the study participants.
- The researcher should also declare any personal and institutional benefits (monitory or otherwise including travel) accrued through study participation.
- Please also specify benefits of the study to the funding agency or sponsors if any.
- The research protocol should indicate that there is compliance with the ICH -GCP guidelines. In case of conflict kindly specify the particular clause, which is being contravened.
- Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person.
- Non-medical research should be conducted by suitably qualified persons.
- The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy and confidentiality of the patient's information. Minimize the impact of the study on the subject's physical, mental and social integrity.
- In the conduct of research, the investigator must at all times respect the personality, rights, wishes, beliefs, consent and freedom of the individual subject.
- Volunteers and patients should be reimbursed for travel and any out of pocket expenses e.g. any wage loss if applicable.
- The deadline for submission of the application is 2 weeks prior to the meeting.

b. IRB & EC Guidelines:

The IRB & EC shall be concerned with research on human subjects and animal subjects both. The terms of reference have taken into consideration recommendations of a sub-committee of the Bio-ethics Group of FHS and particularly the report of the Royal College of Physicians of London (1996) titled "Guidelines on the Practice of Ethics Committees in Medical Research Involving Human Subjects". The terms have been derived mainly from principles and generalized for application to both bio-medical and social science research. A deliberate attempt has been made to avoid detail, with the expectation that experience will determine the need for revision and elaboration.

All research projects involving human subjects, whether as individuals or communities, including the use of foetal material, embryos and tissues from the recently dead, supported and undertaken by SIH faculty, staff or students, wherever conducted, shall be reviewed by the IRB & EC before a study can begin. Similarly, all research projects involving Animal subjects shall be reviewed by IRB & EC before the conduct of the study and only lawfully acquired animals shall be used for research purposes.

The duration of approval for a study shall be limited. Any change in conditions that could affect the rights of subjects during a study must be approved for the study to continue.
The Committee shall provide written guidelines on ethical considerations for research involving humans and review them at least once in two years. The guidelines shall be based on but not restricted to the following principles:
Respect for an individual's capacity to make reasoned decisions, and protection of those whose capacity is impaired or who are in some way dependent or vulnerable.

- The risks of the proposed research in respect of expected benefits, the research design and competence of the investigators having been assessed. Applications will be acknowledged and researchers shall be informed of the review date. The researchers shall also be communicated regarding the incompleteness of an application. This will obviously delay the review process.
- The outcome of review shall be communicated to the researchers within 2 weeks after the IRB & EC meeting.
- In cases where the IRB & EC requests supplementary information or changes to documents from the applicant, such information should be provided at least a week before the next meeting.
- In cases where clarification is sought and researchers fail to respond within 3 months, IRB & EC will send a reminder and allow a further 3months period for response. Beyond these 6 months, the file will be closed.
- Researcher may be asked to present the case in the meeting if required.
    - Follow-up (of the researcher).
    - At the end-report

A proposal must state the purpose of the research; the reasons for using humans as the subjects; the nature and degree of all known risks to the subjects; and the means for ensuring that the subjects' consent will be adequately informed and voluntary.
The subjects of research should be clearly aware of the nature of the research and their position in respect of it.
Consent must be valid. The participants must be sufficiently informed and have adequate time to decide without pressure. Consent must be obtained from the subjects, preferably written.
Subjects must be able to easily withdraw from a research protocol without giving reasons and without incurring any penalty or alteration in their relationship with providers of services.
Further guidance should be obtained from publications, such as the World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects (1989), consultation with experts and other sources, according to need.
Specify procedures, including periodic appraisal of the progress of approved projects, for ensuring that subjects of research are protected from harm, their confidentiality is maintained, and their rights are respected.
The Committee shall report annually or more frequently, as necessary, to the Hospital Leadership.

c. Method of Working:

The Committee will need substantial administrative and secretarial assistance from the Research Office. Authors of research proposals may be invited to attend meetings of the IRB & EC when their study is being reviewed.

Some business may be conducted by mail, but reasonably frequent meetings are essential to allow a committee ethos to develop.

A quorum should include a lay person, a research oriented member who is broadly familiar with the proposed field of study, and a member of each gender.

d. Documents Accompanying the Application:

- The IRB & EC application form should be submitted. Information in the form should be typed.
- Research protocol (clearly identified and dated), together with supporting documents and annexes. This should always include description of the ethical considerations involved in the research.
- Questionnaire (if applicable) intended for research participants should be included.
- When the research involves a study product (such as a pharmaceutical or device under investigation), an adequate summary of all safety, pharmacological, pharmaceutical, and toxicological data available on the study product, together with a summary of clinical experience with the study product to date (e.g. recent investigator's brochure, published data, a summary of the product's characteristics).
- A description of the process to be used to obtain and document consent.
- Informed consent form (clearly identified and dated) in the language(s) understood by the potential research participants and, when required in other languages.
- A statement describing any compensation for study participation (including expenses and access to medical care) to be given to research participants.

e. Approval Conditions:

- Approval is given for a specified period. If the project takes longer than the specified period to complete, a request for an extension of the ethics clearance should be sought.
- Approval is given on condition that any alterations proposed to the approved protocol are submitted to the Committee for approval prior to the alterations being affected.
- Approval is given on condition that a copy of the research project final report is lodged with the Ethics Committee for its information.
- Approval is given subject to researchers notifying the Ethics Committee if and when a project is curtailed, terminated or completed.
- Approval is given for therapeutic trials subject to the principal investigator notifying the Ethics Committee within seven (7) days of any adverse event or occurrence that takes place during that trial.
- Research could be audited by IRB & EC during the research period to ensure compliance with guidelines.

f. Procedure for Issue of Exemption Letter by IRB & EC for Selected Studies:

The studies in which human subjects are not involved directly, or no intervention is done are often exempted from full IRB & EC review. Since majority of journals ask for approval by an Institutional Review Board or by IRB & EC before accepting a manuscript for publication, it is necessary that the researchers get an approval or an exemption letter from IRB & EC before starting the study as it is unprincipled for IRB & EC to review studies retrospectively. It is the responsibility of researchers to obtain such a letter before any study is started.

This point is again restated for emphasis: even if studies fall in the exemption category, they still need to be submitted to IRB & EC for obtaining a letter of exemption prior to the commencement of the study as IRB & EC does not allow retrospective review of studies, even for the purpose of publication.

A system should be put in place in Unit / departments whereby studies are signed-off by the Unit Head / Departmental Chair prior to their commencement. This precautionary safeguard has been advised by the Research Department to ensure that no controversial or sensitive studies are conducted even though they may have obtained clearance from relevant SIH subcommittees.

Studies which may qualify for exemption from ethical review:

- Retrospective review of clinical data without any identifiable information about patients. The data may be obtained from patient's charts. (Details of data which can be extracted is given elsewhere).
- Prospective data collection from patient's charts without any identifiable information about patients.
- Analysis of laboratory data without any identifiable information about patients. (Details of data which can be extracted is given elsewhere).
- Clinical audits.
- Evaluation of practice guidelines without identifying information about the users of those guidelines.
- Case reports without identifying the study subjects or photographs unless written consent has been obtained from study subject or his/her legal guardian.
- Studies in which human have not participated as study subjects.
- Other studies in which humans are not involved, such as, research on policy documents. However, if the policies are termed as 'classified', consent from the appropriate authorities should be obtained for their use in research or resulting publications.
- Autobiographical studies in which the sample is the researcher himself/ herself.
- Quality assurance performance review studies. In such studies organizations may evaluate their programs to improve their services, such as reports internal to the organization. Findings from these studies may be relevant to other stakeholders.
- Review of studies involving public data, for instance, published biographies, newspaper accounts of individuals' activities and published minutes of meetings, educational tests and survey procedures. Care should be taken to handle the information in such a way so as not to pre-empt any disclosure.
- Auto ethnographical studies where researcher uses his/ her own experiences in order to gain deeper understanding of a group's culture and/ or theorize modes of human behavior within a

group and across different groups. Research in such studies would involve documentary evidences available publicly.

Examples of auto ethnography can be found in the 'Journal of the Society for the Study of Symbolic Interactionism', 'Journal of Contemporary Ethnography' and the Journal of Humanistic Ethnography. Care should be taken to not disclose personal information about others with whom the writer has had a close relationship. For example, a teacher in his/ her autobiography cannot publish details or personal views, photographs and confidential statements of his/ her students without permission.

Reflective practice/ professional development studies where practitioners can develop a greater level of self-awareness about the nature and impact of their performance for professional growth and development. Examples of such studies can be found in journals of reflective practice.

g. Collaborative studies with other institutions:

 Due credit will be given to the Shifa faculty, Shifa Tameer-e-Millat University (STMU) and its affiliated institutions as per authorship agreement (authorship agreement in IRB & EC Research application form). Shifa co-investigator who has given permission/approval to collect data from the department shall be given authorship (First/second/third author). Authorship will be based on International Committee of Medical Journal Editors (ICMJE) guidelines/ recommendations.

 Memorandum of Understanding (MOU) must be in place between STMU/concerned department/institution and outside institution.

Note: *All the research proposals submitted to IRB & EC for seeking their approval get reviewed by IRB & EC reviewers as per the standard Review Proforma*

h. Data and Safety Monitoring Board

i. Role of DSMB:

The DSMB will oversee all Institutional researches and Internationally Sponsored Clinical trials that involve human subjects at Shifa International Hospitals Ltd., and Shifa Tameer-e-Millat University. DSMB will focus on the compliance of ethical and scientific standards necessary for carrying out medical research.

DSMB Monitoring activity shall include the following:

ii. DATA AND SAFETY MONITORING PLAN (DSMP):

DSMP is the interim progress that Principal Investigator (PI) of the respective Study will share with the DSMB after every one-fourth completion of the Study.

iii. DSMP for Institutional Studies:

Items are as below:

- Informed Consent of all the enrolled participants (accurately obtained; informed consent should be obtained as per GCP for Randomized Controlled Trials
- Description of how Adverse Events (AEs) are graded, if any, and management of AE or other Study risks on AE reporting form (available on intranet under Pharmacy section)

- Updated or valid GCP certificates of all the investigators
- Work plan is being followed as mentioned on IRB Application form
- Ensure the confidentiality of participants
- Report Protocol deviations and protocol violations, if any
- Hygiene practices in the laboratory and area where research work is being conducted
- High Standard of personnel hygiene

- No person known to be suffering from communicable disease or to be a carrier of such a disease and no person with open lesions or skin infection shall be engaged in research activities
- Records of the data collected (Raw data and Consent forms will be retained (5 years) and submitted upon request if required)

iv. DSMP for Internationally Sponsored Clinical Trials:

Items are as below:

- Informed Consent of all the enrolled participants (accurately obtained; as per GCP and trial protocols)
- AE report forms (reported on Sponsors shared AE report form)
- Updated or valid GCP of trial team
- Factors that might affect the study outcome or compromise the confidentiality of the trial data, such as, protocol violations, unmasking etc.
- Documentation & Record keeping (as per GCP and trial protocols)
- Pharmacy role as per GCP and trial protocols (for drug intervention trials)
- Hygiene practices in the laboratory and area where research work is being conducted
- High Standard of personnel hygiene
- No person known to be suffering from communicable disease or to be a carrier of such a disease and no person with open lesions or skin infection shall be engaged in research activities

v. Parameters of DSMB Monitoring

DSMB team is responsible for monitoring and reporting
Parameters are as below:
Institutional Review Board & Ethics Committee (IRB & EC) Approval: This is to ensure IRB & EC approval was obtained before the conduct of the study.
In case of Residents' Synopsis, IRB & EC approval is mandatory before proceeding with College of Physicians and Surgeons Pakistan (CPSP) submission

- Informed consent monitoring
- Updated or valid GCP certificate (for randomized controlled trials)

- Accurately and timely reporting of AEs: For Institutional research, follow Adverse event reporting form available on intranet under Pharmacy section; and for International Clinical trials, follow Sponsors shared AE report form
- Factors that might affect the study outcome or compromise the confidentiality of the trial data, such as, protocol violations, unmasking etc.
- Documentation & Record keeping
- Pharmacy monitoring in case of Drug intervention trials

- Hygiene practices in the laboratory and area where research work is being conducted, high Standard of personnel hygiene; and no person known to be suffering from communicable disease or to be a carrier of such a disease and no person with open lesions or skin infection shall be engaged in research activities
- Professional performance of staff participating in research
- An interim progress report
- **Note:** PI of the Study shall be responsible for all the elements/Parameters of monitoring
- ***vi. DSMB Monitoring report to PI:***

- DSMB team will prepare a monitoring report that will be shared with the PI of the Study
- Study shall be altered or stopped based on review of study-related events occurring during the conduct of the study, specific study endpoints, and the decisions prompted. Studies may be stopped when there is greater than expected morbidity or mortality rate.

- Stopping rules shall not be implemented for International clinical trials. If International clinical trials are not being conducted according to GCP or trial protocols, then PI and the research members involved in the trial from Shifa Clinical Research Center shall be questioned.

- Study extension or follow-up (as per study specific reason)

- Protocol modification based on data trend

- Timelines for feedback report (2 weeks after submission of report by DSMB)

- In case of failure to submit and comply with DSMB protocols, study shall be stopped within one week of deadline date, and PI needs to give proper explanation of violation of DSMP.

- **Note:**
- DSMB shall meet the requirements of National Bioethics Committee (NBC) of Pakistan, Joint Commission International Accreditation (JCIA) and Good Clinical Practices (GCP)

- For International Clinical Trials, the DSMB monitoring report shall be also shared with the Sponsors of the trial.

- DSMB shall share the review process and monitoring report with IRB & EC annually.

vii. Definitions of Specific Events:

- **AE**: (An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment).

- **SAE:** (A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient

- hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.)

- **ADR:** (An adverse drug reaction is an unintended reaction to a drug taken at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the

- Modification of physiological function. In clinical trials, an ADR would include any injuries by overdosing, abuse/dependence, and unintended interactions with other medicinal products).

- **SUSAR :**(A Suspected Unexpected Serious Adverse Reaction is known as a SUSAR. Sometimes during a clinical trial for a certain drug, there may be serious adverse reactions in subjects given the drug, that may or may not be dose-related, but are unexpected, as they are not consistent with current information).
- Time frame for reporting unanticipated problems/adverse events:
  - AE: 7 days
  - SAE: 24 hours

Annexure 1.

1.4 ETHICAL PRINCIPLES: Key Features

1.4.1. THE BELMONT REPORT:

NIH Ethical Principles and Guidelines for the Protection of Human Subjects of Research
The National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research issued "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." The report sets forth three principles underlying the ethical conduct of research: Respect for persons, Beneficence, and Justice.

1.4.2. THE NUREMBURG CODE:

Trials of War Criminals Before the Nuremberg Military Tribunals under Control Council. Law No. 10, Vol 2, pp. 181-182. Washington, D.C.: U.S. Government Printing Office, 1949.
Developed in response to the Nuremberg Trials of Nazi doctors who performed unethical experimentation during World War II, the Code was the first major international document to provide guidelines on research ethics. It made voluntary consent a requirement in clinical research studies, emphasizing that consent can be voluntary only if participants are able to consent; they are free from coercion (i.e., outside pressure); and they comprehend the risks and benefits involved.

1.4.3. WORLD MEDICAL ASSOCIATION "DECLARATION OF HELSINKI"

At the 18th World Medical Assembly in Helsinki, Finland, the World Medical Association adopted **12 principles** to guide physicians on ethical considerations related to biomedical research. It emphasizes **the distinction between medical care that directly benefits the patient and research that may or may not provide direct benefit**. These guidelines were revised at subsequent meetings in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset West, Republic of South Africa) and 2000 (Edinburgh, Scotland).

1.4.4. INTERNATIONAL CONFERENCE ON HARMONIZATION / GOOD CLINICAL PRACTICES (ICH/GCP) GUIDELINES FOR CLINICAL CONDUCTION OF RESEARCH

- Clinical Research should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
- Before research is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual study subject and society.
- Research should be initiated and continued only if the anticipated benefits justify the risks.

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

- The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical research (drug studies).

- Clinical research project should be scientifically sound, and described in a clear, detailed protocol.

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

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

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

- Freely given informed consent should be obtained from every subject prior to clinical research participation.

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

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

- Any Investigational product/s should be used in accordance with the approved protocol only.
- ADDENDUM This principle applies to all records referenced in this guideline, irrespective of the type of media used. 2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). 2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice 10 2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

- ADDENDUM Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.

Annexure 2 Specific Policies

1.5 POLICY FOR INFORMED CONSENT IN RESEARCH

1.5.1. Purpose

The main aim of this policy is to define and implement an informed consent process that enables patients to make informed and voluntary decisions about participating in clinical research.

1.5.2. Scope

The policy shall apply to all the research studies being conducted at Shifa International Hospital, Shifa Tameer-i-Millat University (STMU) and its allied institutions.

1.5.3. Policy

When patients and families decide to participate in clinical research, clinical investigations, or clinical trials, informed consent is granted. The individual(s) providing the information and obtaining the consent is noted in the patient record and verified by signature.

For International Clinical trials, site shall use study specific informed consent form (including Patient Information Sheet and informed consent certificate) provided by the sponsors. Informed consent form shall include all the necessary information for patients or their representatives as per International Conference on Harmonization - Good Clinical Practices (ICH-GCP) guidelines and Joint Commission International Standards on Informed Consent. Informed consent form shall be discussed and reviewed in full quorum IRB & EC meeting for final approval.

For in-house research, IRB & EC and SCRC have developed their standard informed consent template including patient information sheet and informed consent certificate both. Informed consent form shall include all the necessary information for patients or their representatives as per ICH-GCP guidelines and Joint Commission International Standards on Informed Consent.

1.5.4. Procedure and Responsibilities

Basic elements Basic elements of informed consent in seeking informed consent the following information shall be provided to each subject, irrespective of the sponsor:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, the patient’s role in the research and identification of any procedures which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- Information about the procedure to be followed.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained

- For research involving more than minimal risk, an explanation as to whether any compensation and any explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:
- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or foetus, if the subject is or may become pregnant) which are currently unforeseeable.

- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

- Any additional costs to the subject that may result from participation in the research.

- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

- A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject

- The approximate number of subjects involved in the study

Note: All Informed Consent Forms must be in English and Urdu language or any other language that the subject understands. The identity of the person providing the above information is noted as part of the consent process and the provision of information is ensured by signature of that individual and the entry is dated.
For investigators who cannot speak any language other than Urdu and English, services of translators in the hospital shall be availed. Translator shall act as a witness.

a. Protecting Vulnerable Patients:
For the purpose of definition, vulnerability is operationally defined as 'the potential risks associated with the physical and mental status of an individual which might reasonably be anticipated irrespective of the context in which care is provided'.
Increasingly, vulnerability is being described in terms of potential for exposure to deliberate maltreatment (active) and unintentional or thoughtless acts (passive). There are many risks involved, which mean that the potential for a breach of care is always present and is not restricted to specific care contexts.

Safeguards are put into place through the hospital's research review function to protect vulnerable patients who may be at risk for coercion or undue influence to participate in research projects.
Shifa International Hospital has defined its population of vulnerable patients. Vulnerable patients include children, prisoners, pregnant women, persons with mental disabilities, persons who are economically or educationally disadvantaged, and others who have diminished or no capacity to make informed or voluntary decisions to participate in research. Another group that can be considered a vulnerable population is staff of the hospital. Staff may feel under pressure to participate; for example, when the Principal Investigator is their supervisor.

b. Information about Research to Patients and Families:

Patients and families are informed about how to gain access to clinical research, clinical investigation, or clinical trials when relevant to the patients' treatment needs. This is done through either SCRC website or informing practitioners in the hospital about current and future trials in the hospital. When patients are asked to participate, they need information on which to base their decisions. That information includes expected benefits;

- Potential discomforts and risks;
- Alternatives that might also help them; and
- Procedures that must be followed.

The following information is provided to any patient or his family when informing them about a research:

- Patients and families asked to participate are informed about expected benefits.
- Patients and families asked to participate are informed about potential discomforts and risks.
- Patients and families asked to participate are informed about alternatives that might also help them.
- Patients and families asked to participate are informed about the procedures that must be followed.
- Patients and families are assured that their refusal to participate or withdraw from participation will not compromise their access to the hospital's services.
- Patients and families are informed about their rights to confidentiality and security of information SCRC has developed brochures containing information for patients and their families about researches being conducted in Shifa International Hospitals Ltd.

1.6 POLICY FOR LAWS, REGULATIONS AND HOSPITAL LEADERSHIP IN HUMAN SUBJECTS RESEARCH

1.6.1. Purpose

The aim of this policy is to focus on the laws, regulations and hospital's leadership necessary to undertake human subject's research of scientific metric. The protection of rights, welfare and well-being of human subjects involved in research shall not be separated from the commitment to patient care.

1.6.2. Scope

This policy shall follow for every human subject's research undertaken at Shifa International Hospital, Shifa Tameer-i-Millat University and its allied institutions.

1.6.3. Policy

The institute shall comply with the most conservative requirements of human subject's research including ethical laws and regulatory requirements.

1.6.4. Procedure and Responsibilities

a. Officials responsible for policies and procedure: Any investigator who wishes to conduct human subject's research shall channel it through Shifa Clinical Research center (SCRC) and Institutional Review Board & Ethics Committee (IRB & EC). SCRC shall take a lead in running the clinical trials. IRB & EC shall give the initial approval of the research study after thorough review. Data and Safety Monitoring Board (DSMB) shall oversee the ongoing research studies involving human subjects as per the established policies and procedures.

b. Patient protection irrespective of the sponsors of research, including indemnity coverage: Hospital shall provide indemnity coverage to the projects that are approved by IRB & EC. Hospital shall ensure that an indemnity fund is available to adequately compensate patients/subjects participating in clinical research who experience an adverse event. For this purpose, adequate funds shall be earmarked by the leadership.

c. Compliance with regulatory requirements: SCRC shall ensure that the research complies with the following regulations:

- Policies and procedures of Shifa International Hospital
- Any relevant laws and regulations (Drug Regulatory Authority of Pakistan, National Bioethics Committee of Pakistan)
- Ethical framework of Shifa International Hospital

d. Professional requirements related to research:

Only a clinician with valid medical license can serve as a Principal Investigator and Co-investigator of human subject's research. SCRC shall be the designated authority to guide all the principal investigators to ensure professional requirements related to research. Every member of the research team must be Good Clinical Practices (GCP) certified and duties shall be delegated after a valid GCP certification.

Transfer criteria for patient admission to specialized ward due to research: A patient enrolled in a research may require admission or transfer to a specialized ward due to research to meet the needs. The patient may be transferred to a higher or lower level of care depending on not just the research protocol, but also on patient's medical condition. The patient may be admitted to Intensive care unit (ICU), Cardiac care unit (CCU), surgical care unit, surgery or medical floor or any other floor or unit due to research.

The admission process shall be the same as hospital's standard or protocol for any medical condition. The decision to admit or transfer the patient shall be taken by Primary Consultant after thorough discussion with the Principal Investigator of the study. The complete information regarding admission, transferring and receiving department, reason for transfer or admission, mode of transfer, name and designation of transferring and receiving clinician, status of vital signs before the transfer, clinical events during the transfer, treatment given and timelines shall be recorded in patient's medical record file. Any additional test for research purpose shall be ordered by the clinician and entered in patient's medical record file. The cost associated with patient's admission, extra care for any medical condition for research purpose shall not be borne by the patient.

1.7 DATA AND SAFETY MONITORING BOARD POLICY

1.7.1. Purpose

Data and Safety Monitoring Board (DSMB) is a committee of clinical research experts, such as physicians statistician, and patient advocates who monitor the progress of a research study involving human subjects, review safety and effectiveness data and compliance of ethical and scientific quality standards while the research study is ongoing at Shifa International Hospitals Ltd. (SIHL), Shifa Tameer-e-Millat University (STMU) and its allied institutions.

1.7.2. Scope

Data Safety Monitoring Board shall accumulate research data, in order to monitor the progress of a research study and to make recommendations on whether to continue, modify or stop the study for safety or ethical reasons.

a. Data And Safety Monitoring Board (DSMB) Members

- Chairman DSMB
- Vice chairman DSMB
- Research Pharmacist
- Statisticians
- Research Nurse
- Director Shifa Clinical Research Center (SCRC)
- STMU member
- SCN member
- SCM member

1.7.3. Policy

a. Mandate:

The DSMB shall oversee all Institutional researches and Internationally Sponsored Clinical trials that involve human subjects at SIHL, STMU and its affiliated institutions. DSMB shall focus on the compliance of ethical and scientific standards necessary for carrying out medical research.

b. Conflict of Interest:

No member of the DSMB should have direct involvement in the conduct of the study. Furthermore, no member should have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the DSMB. Chairman Institutional Review Board (IRB)/Principal Investigator (PI) of an ongoing trial cannot be Chairman of DSMB. Furthermore, if any member of the DSMB is part of a clinical trial in any capacity, he/she must be excused from the DSMB deliberations of that particular trial.

Meeting Schedule:

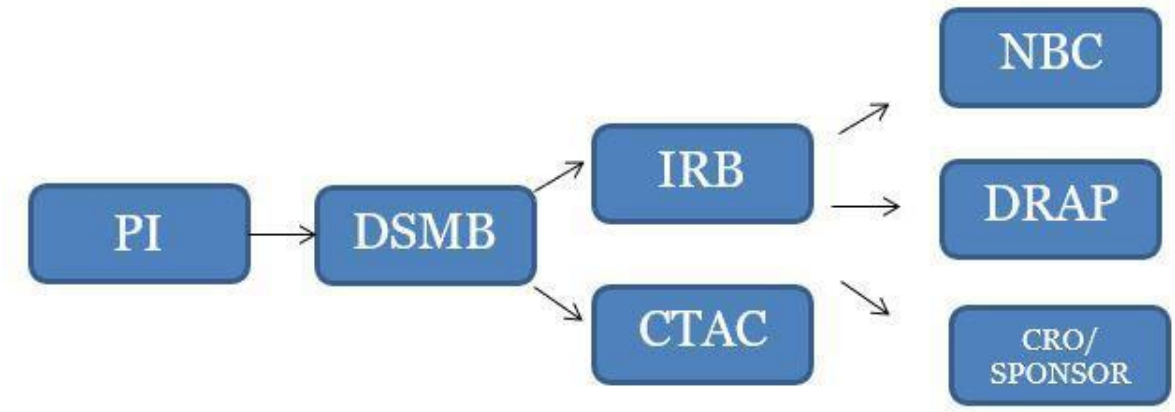
The Board will meet on quarterly basis. The meetings may be assembled as an in-person meeting or mail correspondence more often if needed.

d. Reporting Responsibilities:

SCRC trial dashboard will monitor every trial on a monthly basis. A red code will be assigned if the trial has safety or ethical concerns. A green code will be assigned if the trial conduct is complaint to ethical standards.

The PI of the Research studies must inform the DSMB about on-going research especially related interim/cumulative data for evidence of study-related adverse events, data quality and other factors mentioned at specific times from initial approval there from IRB.

The Chair of DSMB must review in a meeting with other members such submitted data.



The Chair of DSMB will issue a written report describing all recommendations including additional safety steps.

This report will be disseminating from the DSMB to the PI through the Chairperson IRB & Ethics Committee (EC) in writing.

In order to assure and maintain scientific integrity of the DSMB, the issues of avoidance of conflict of interest, confidentiality and independence are primary.

1.7.4. Procedure and Responsibilities

It comprises of 2 parts, i.e., Data and Safety Monitoring Plan (DSMP) and DSMB Monitoring parameters.

a. DSMP:

DSMP is the interim progress that Principal Investigator (PI) of the respective Study will share with the DSMB after every one-fourth completion of the Study.

DSMP for Institutional Studies:

Items are as below:

- Informed Consent of all the enrolled participants (accurately obtained; informed consent should be obtained as per Good Clinical Practices (GCP) for Randomized Controlled Trials).

- Description of how Adverse Events (AEs) are graded, if any, and management of AE or other Study risks on AE reporting form (available on intranet under Pharmacy section).
- Updated or valid GCP certificates of all the investigators.
- Work plan is being followed as mentioned on IRB Application form.
- Ensure the confidentiality of participants.
- Protocol deviations and protocol violations, if any.
- Records of the data collected.

c. DSMP for Internationally Sponsored Clinical Trials:

- Items are as below:
- Informed Consent of all the enrolled participants (accurately obtained; as per GCP and trial protocols).
- AE report forms (reported on Sponsors shared AE report form).
- Updated or valid GCP of trial team.
- Factors that might affect the study outcome or compromise the confidentiality of the trial data, such as, protocol violations, unmasking etc.
- Documentation & Record keeping (as per GCP and trial protocols).
- Pharmacy role as per GCP and trial protocols (for drug intervention trials).

d. Parameters of DSMB Monitoring

- DSMB team is responsible for monitoring and reporting.
- Parameters are as below:
- Institutional Review Board & Ethics Committee Approval: This is to ensure IRB & EC approval was obtained before the conduct of the study.
- In case of Residents' Synopsis, IRB & EC approval is mandatory before proceeding with College of Physicians and Surgeons Pakistan (CPSP) submission.
- Informed consent monitoring.
- Updated or valid GCP certificate (for randomized controlled trials).
- Accurately and timely reporting of AEs: For Institutional research, follow Adverse event reporting form available on intranet under Pharmacy section; and for International Clinical trials, follow Sponsors shared AE report form.

- All adverse events must be reported to Quality department in a timely manner by filling out an incident reporting form (FM-8.5-008).
- Factors that might affect the study outcome or compromise the confidentiality of the trial data, such as, protocol violations, unmasking etc.
- Documentation & Record keeping.

- Pharmacy monitoring in case of Drug intervention trials.
- Professional performance of staff participating in research.
- An interim progress reports.

Note: PI of the Study shall be responsible for all the elements/Parameters of monitoring.

e. DSMB Monitoring report to PI:

DSMB team will prepare a monitoring report that will be shared with the PI of the Study

- Study shall be altered or stopped based on review of study-related events occurring during the conduct of the study, specific study endpoints, and the decisions prompted. Studies may be stopped when there is greater than expected morbidity or mortality rate.
- Stopping rules shall be implemented for International clinical trials. If International clinical trials are not being conducted according to GCP or trial protocols, then PI and the research members involved in the trial from Shifa Clinical Research Center shall be questioned.
- Study extension or follow-up (as per study specific reason).
- Protocol modification based on data trend.
- Timelines for feedback report (2 weeks after submission of report by DSMB).
- In case of failure to submit and comply with DSMB protocols, study shall be stopped within one week of deadline date, and PI needs to give proper explanation of violation of DSMP.

Note:

- DSMB shall meet the requirements of National Bioethics Committee (NBC) of Pakistan, Joint Commission International Accreditation (JCIA) and Good Clinical Practices (GCP).
- For International Clinical Trials, the DSMB monitoring report shall be also shared with the Sponsors of the trial.
- DSMB shall share the review process and monitoring report with IRB & EC annually.

f. Definitions of Specific Events:

- **AE**: (An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment).

- **SAE:** (A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect).
- **ADR:** (An adverse drug reaction is an unintended reaction to a drug taken at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. In clinical trials, an ADR would include any injuries by overdosing, abuse/dependence, and unintended interactions with other medicinal products).

- **SUSAR :**(A Suspected Unexpected Serious Adverse Reaction is known as a SUSAR. Sometimes during a clinical trial for a certain drug, there may be serious adverse reactions in subjects given the drug, that may or may not be dose-related, but are unexpected, as they are not consistent with current information).

1.8 POLICY FOR INFORMATION TO PATIENTS ABOUT THEIR PROTECTION AS RESEARCH SUBJECT

1.8.1. Purpose

The aim of this policy is to provide information to patients and their families about how patients who choose to participate in clinical research, clinical investigation or clinical trials are protected.

1.8.2. Scope

This policy applies to all the individuals/investigators involved in human subject's research undertaken at Shifa International Hospital (SIH).

1.8.3. Policy

The safety and well-being of a patient shall be the integral part of clinical research. Patient's well-being will not be compromised for research purposes. Proper information shall be provided to the patients chosen to enroll in research regarding the protection of their well-being, safety and privacy of clinical information.

1.8.4. Procedure and Responsibilities

To assist with decisions regarding participation in clinical research, clinical investigation. Or clinical trials, the investigators shall provide the following information to patients regarding their protection:

- A description of any reasonably foreseeable risks or discomfort to the subject. List all reasonably foreseeable risks, if any, of each of the procedures to be used in the study, and any measures that will be used to minimize the risk. In case of any adverse event, proper management will be provided. The whole cost will be borne by the hospital or sponsors of the research. There will be no financial burden on the patient/subject
- A description of any benefits to the subject or to others which may reasonably be expected from the research. Benefits may be divided into benefit to the individual, benefit to the community in which the individual resides, and benefit to the society as a whole as a result of finding an answer to the research question. If there is no direct benefit to the participant, clearly inform this to the patient.
- The research is entirely voluntary. Patients have right to refuse and if they agree to participate, they may withdraw themselves from the study at any time, without giving a reason, by informing the investigators of their decision. Leaving the study or choosing not to be taking part will not result in any penalty or loss of benefits to which they are entitled, and their refusal to participate and withdraw from the participation will not compromise their access to the hospital's services
- Information about the hospital's process of obtaining consent. The written informed consent will be obtained from the patient (subject) or family member (legal representative), verified by signature of investigator. For investigators who cannot speak any language other than Urdu and English, services of translator in the hospital shall be availed. Translator will act as a witness. A copy of signed informed consent form will be placed in patient's medical record file
- Confidentiality and privacy: The patient/subject's personal information will not be shared to anyone outside of research team and the information will be kept private. The investigators may retain and store the personal data for an additional period of time as necessary for research.
- The study is reviewed and approved by suitably constituted Institutional review board & ethics committee (IRB & EC) of SIH, which is a committee whose take is to make sure that research subjects are protected from harm.

1.9 POLICY FOR TERMINATION OF PREGNANCY

TERMINATION OF PREGNANCY AFTER 120 DAYS

1. Termination of pregnancy after 120 days is to be considered only in case of significant risk to the life of the mother.
2. A special committee has been made which will decide about all cases of termination of pregnancy after 120 days. This policy encompasses SIH, Shifa Foundation and all Official Clinics.
3. The rules apply both to the ambulatory and inpatient facilities.

1.10 POLICY FOR EXEMPTION

1. All research activities involving human subjects must be reviewed and approved by an IRB & EC unless it can prospectively be determined that the research falls into an exemption category. Remember that even then all exempted research will still need to be submitted to the office of the IRB & EC for determining exemption and for record keeping.

2. These exemptions DO NOT APPLY when deception of human subjects maybe an element of the research; when the activity might expose the human subjects to discomfort or harassment beyond levels encountered in the daily life; or where study subjects are involuntarily confined or detained in penal institutions or any other institution of confinement.

CATEGORY ACTIVITIES	
CATEGORY #1	Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as: a. Research on regular and special education instructional strategies b. Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods
CATEGORY #2	Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behaviour, unless: a. Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; AND b. Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation

	NOTE: The exemption under Category 2 DOES NOT APPLY to research involving survey or interview procedures or observation of public behaviour when individuals are under the age of 18, or are subjects of the activity except for research involving observations of public behaviours when the investigator(s) do not participate in the activities being observed.
CATEGORY #3	Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behaviour that is not exempt under Category 2, **IF**: a. The human subjects are elected or appointed public officials or candidates for public office, **OR** b. The confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
CATEGORY #4	a. Research, involving the collection or study of previously existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that the subjects cannot be identified directly or through identifiers linked to the subjects. b. Most of research at SIH has so far been from old records (Refrospec) but formal application and exemption from full review must be sought first.
CATEGORY #5	Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: a. Public benefit or service programs; b. Procedures for obtaining benefits or services under those programs; c. Possible changes in or alternatives to those programs or procedures; OR d. Possible changes in methods or levels of payment for benefits of services under those programs

CATEGORY #6	Taste and food quality evaluation and consumer acceptance studies, a. If wholesome foods without additives are consumed; OR b. If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminants at or below the level found to be safe, by the Food and Drug Administration or an Environmental Agency

1.11 POLICY FOR RESEARCH INVOLVING PREGNANT WOMEN

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.

b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

c) Any risk is the least possible for achieving the objectives of the research.

d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

g) For children who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;

h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy; a. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

i) Individuals engaged in the research will have no part in determining the viability of a neonate.

B. RESEARCH INVOLVING, AFTER DELIVERY, THE PLACENTA, THE DEAD FETUS OR FETAL MATERIAL:

a. Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.

b. If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of this part are applicable

1.12 IRB &EC CONFLICTS OF INTEREST POLICY

DEFINITION:

Conflicts of interest comprise those which may not be fully apparent and which may influence the judgment of author, reviewers, and editors. They have been described as those which, when revealed later, would make a reasonable reader feel misled or deceived. They may be personal, commercial, political, academic or financial. "Financial" interests may include employment, research funding, stock or share ownership, and payment for lectures or travel, consultancies and company support for staff.

ACTION:

(1) Such interests, where relevant, must be declared to editors by researchers, authors, and reviewers.

(2) Editors should also disclose relevant conflicts of interest to their readers. If in doubt, disclose. Sometimes editors may need to withdraw from the review and selection process for the relevant submission.

1.13 POLICY FOR RESEARCH INVOLVING NEONATES

Neonates may be involved in research of all of the following conditions are met:

a) Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

- Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
- Each individual providing consent under paragraph (b) (2) or (c) (5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
- Individuals engaged in the research will have no part in determining the viability of a neonate.
- The requirements of paragraph (b) or (c) of this section have been met as applicable.

b) Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met:

(1) The IRB determines that:

(i) The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or

(ii) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

(2) The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest

c) Nonviable neonates. After delivery nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met:

1. Vital functions of the neonate will not be artificially maintained;
2. The research will not terminate the heartbeat or respiration of the neonate;
3. There will be no added risk to the neonate resulting from the research;
4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
5. The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of §46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph (c) (5).

d) Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

1.14 BRAIN DEATH POLICY

Brain death is not synonymous with brain stem death and does not mean death. Brain death **including** brain stem death means death. The brain stem contains cardiac and respiratory centers. This Brain Death Criteria is to help in decision of those patients who have significant brain injury or pathology. Muslim medical experts have defined death in the following way:

An individual is considered dead in one of the following two situations: A) Complete irreversible cessation of respiratory and cardiovascular systems. B) Complete irreversible cessation of the functions of the brain including the brain stem. This should be confirmed by the accepted medical standards.

In case of brain death it is required to have the presence of a reliable medical specialist well experienced in the clinical diagnosis of brain and brain stem death and the various implications of such diagnosis. This Brain Death Criteria has been sub divided for

I- Non Transplant Patients
II- Transplant Patients.

I- DEFINITION OF BRAIN DEATH FOR NON-TRANSPLANT PATIENTS

A person is pronounced legally dead and consequently, all dispositions of the Islamic Law in case of death apply if one of the two following conditions has been established:

1. There is total cessation of cardiac and respiratory functions, and doctors have ruled that such cessation is irreversible.
2. There is total cessation of all cerebral functions and experienced specialized doctors have ruled that such cessation is irreversible.

In this case it is permissible to take the person off the resuscitation apparatus, even if the function of some organs e.g. lungs are still artificially maintained.

Reference:
"The Resolution of the Pan-Islamic Council Jurisprudence and Resuscitation Apparatus (1986) adopted a definition that is similar to the Uniform determination of Death Act (1981) in the United States. Based on this resolution the legal definition of death in Islam was changed to the above definition"

DIAGNOSTIC CRITERIA FOR CLINICAL DIAGNOSIS OF BRAIN DEATH (AAN-AMERICAN ACADEMY OF NEUROLOGY)

A. Prerequisites. Brain death is the absence of clinical brain function when the proximate cause is known and demonstrably irreversible.

1. Clinical or neuroimaging evidence of an acute Central Neuron System catastrophe that is compatible with the clinical diagnosis of brain death

2. Exclusion of complicating medical conditions that may confound clinical assessment (no severe electrolyte, acid-base, or endocrine disturbances)

3. No drug intoxication or poisoning

4. Core temperature ≥ 36° C (≥ 97°F), for Children Core temperature >35º C (> 95º F)

B. The three cardinal findings in brain death are coma or unresponsiveness, absence of brainstem reflexes, and apnea.
   1. Coma or unresponsiveness--no cerebral motor response and no eye opening to pain in all extremities (nail-bed pressure and supraorbital pressure)

   2. Absence of brainstem reflexes
      a) Pupils
         (a) No response to bright light in both eyes
         (b) Size: midposition (4 mm) to dilated (9 mm)
      b) Ocular movement
         (a) No oculocephalic reflex (testing only when no fracture or instability of the cervical spine is apparent and tympanic membrane is intact)
         (b) No deviation of the eyes to irrigation in each ear with 50 ml of cold water (allow 1 minute after injection and at least 5 minutes between testing on each side)
      c) Facial sensation and facial motor response
         (a) No corneal reflex to touch with a piece of tissue, cotton swab
         (b) No grimacing to deep pressure on nail bed, supraorbital ridge, or temporomandibular joint
      d) Pharyngeal and tracheal reflexes
         (a) No response after stimulation of the posterior pharynx with tongue blade
         (b) No cough response to bronchial suctioning

   3. Apnea--testing performed as follows:
      a) Prerequisites
         (a). Core temperature ≥ 36.5°C or 97°F

         (b). Systolic blood pressure ≥ 100 mm Hg (Systolic blood pressure not ≤ 2 SD for children and infants)

(c). Euvolemia. *Option:* positive fluid balance in the previous 6 hours

(d). (Normal $PaCO_2$) *Option:* arterial $PaCO_2$ 35 - 45 mm Hg

(e). Absence of hypoxia (Normal PaO_2) *Option:* preoxygenation to obtain arterial $PaO_2 \geq 200$ mm Hg

b) Connect a pulse oximeter.

c) Deliver 100% O_2 for at least 10 minutes, 6 L/min, arterial $PaO_2 \geq 200$ mm Hg into the trachea. *Option:* place a cannula at the level of the carina.

d) Reduce ventilation frequency to 10 BPM, to eucapnia.

e) Reduce PEEP to 5 cm H_2O.

f) Disconnect patient from ventilator.

g) Look closely for respiratory movements (abdominal or chest excursions that produce adequate tidal volumes).

h) Measure arterial PaO_2, $PaCO_2$, and pH after approximately 8 minutes and reconnect the ventilator.

i) If respiratory movements are absent and arterial $PaCO_2$ is ≥ 60 mm Hg (*option:* 20 mm Hg increase in $PaCO_2$ over a baseline normal $PaCO_2$), the apnea test result is positive (i.e., it supports the diagnosis of brain death).

j) If respiratory movements are observed, the apnea test result is negative (ie, it does not support the clinical diagnosis of brain death), and the test should be repeated.

k) Connect the ventilator if, during testing, the systolic blood pressure becomes ≤ 90 mm Hg or the pulse oximeter indicates significant oxygen desaturation and cardiac arrhythmias are present; immediately draw an arterial blood sample and analyze arterial blood gas. If $PaCO_2$ is ≥ 60 mm Hg or $PaCO_2$ increase is ≥ 20 mm Hg over baseline normal $PaCO_2$, the apnea test result is positive (it supports the clinical diagnosis of brain death); if $PaCO_2$is < 60 mm Hg or $PaCO_2$ increase is < 20 mm Hg over baseline normal $PaCO_2$, the result is indeterminate, and an additional ancillary test can be considered. These include, but not limited to, EEG and Cerebral Angiography.

TIMING OF DECLARATION:

Patients who are dead on arrival in the Emergency Room may be declared dead after being

examined by a qualified and experienced doctor.
However, for the patients who are in Coma and on the respirator in the Intensive Care Unit, the following recommendations are to be followed:

a) Once the physician declares patient's death after initial evaluation per criteria, AAN recommended the single confirmation of Brain Death but in Islam, physician must wait at least 6 hours for a 2nd evaluation of the patient. In Islam, timing of the 2nd evaluation depends on the age of the patient. A 2nd confirmation is a must.

b) Per AAN guidelines only one qualified physician may declare death in a patient. However, in Islam, life is considered as very sacred and must be dealt with that way. So at least 2 qualified physicians must declare Brain Death. This should be documented in the chart. The family must be duly counselled in this regard as well.

c) Observation Period (Interval between examinations)
After completion of the first examination, a second examination should be conducted after the stipulated time interval. The findings are to be recorded in the death by brain death criteria documentation form (See Appendix III – Death Documentation Form by Brain Function Criteria) and signed by the consultants conducting the examination. The recommended time intervals between the first and second examinations are given in Table 1.

d) For Paediatrics
Assessment of neurologic function may be unreliable immediately following cardiopulmonary resuscitation or other acute sever brain injury, and evaluation for brain death should be deferred for 24 to 48 hours or longer if there are concerns or inconsistencies in the examination.

Table 1. Recommended time interval between first and second examination in various age groups **

Age	Inter Examination Interval
1. ≤ 30 days	24 hours
2. ≥ 30 days – 18 years	12 hours
3. Adults (≥ 18 years)	6 hours

*Please note that Apnea Test is confirmatory test
** Evaluation may be deferred for 24- 48 hours or longer if there are inconsistencies in the examination

II- DEATH CRITERIA FOR TRANPLANT PATIENTS:

A transparent ethical policy is needed for potential donors who are declared dead. Actual brain death is Brain Stem Death.

- At least 3 qualified physicians (at least one should be a neurologist, neurosurgeon or

an intensivist from ICU) should be involved in *"IRB Sub Committee for Transplant Patients*".

- For all potential organ donors, a 2nd confirmation is a must, and it should be done after 6 hours of observation period.
- The transplant coordinator will counsel the patient's family in a very sensitive way but only after unequivocal 2nd confirmatory exam of brain death is carried and communicated to the family.
- Sometimes a first evaluation may be enough to declare death (trauma) and if family agrees. A 2nd confirmation may be done after 6 hours of initial evaluation.
- No member of the team (IRB Transplant Ethical sub Committee) should be
    i. A member of the organ transplantation team
    ii. A family member of the deceased person
    iii. Have any special interest in the declaration of death
    iv. Blemished by any accusation by the family of the deceased that he had committed any professional misconduct
    v. Proposed 'Form' for issuing a Brain Death Certificate must be properly signed by every member of the medical team and against each item

Note:

1. **First examination at initial diagnosis of brain death.**

2. **Second examination six hours after initial diagnosis.**

DEATH DOCUMENTATION FORM BY BRAIN DEATH CRITERIA

Name:_____MR #:_____
Age:_____ Sex:_____ Nationality: _____ Blood Group:____
Hospital: _____ Date of Admission: _____

FIRST EXAM	Consultant A	Consultant	Consultant C Only for transplant donor
1. PRECONDITIONS: i. It is absolutely certain that irremediable brain damage has occurred due to			
ii. More than six hours have passed since the initial insult iii. For Pediatric Patient see below			
iii. Coma with no spontaneous respiration.			
2. EXCLUSIONS: i. Hypothermia (core temperature < 36°C)			
ii. Sedation (blood test or hospital record should indicate absence of significant levels of sedative drugs or muscle relaxants)			
iii. Systolic BP ≤ 100 mm Hg iv. Systolic blood pressure not ≤ 2 SD for age in children and infants			
v. Significant metabolic or endocrine causes of coma			
3. CLINICAL ASSESSMENT: i. Lack of response to pain stimulation (Spinal reflexes excepted)			
ii. Absence of brain stem reflexes:			
a) Pupillary response to light			
b) Corneal reflex			
c) Oculocephalic reflex			
d) Oculovestibular reflex (50 ml. of ice-cold water at 0°C in adults, 20 ml. in children)			
e) Gag reflex			
f) Cough reflex			
CONFIRMATORY TEST: **APNEA TEST**	**$PaCO_2$ Baseline:** **$PaCO_2$ After test:**	**Date:**	**Signature:**
ANCILLARY TESTS: **1. EEG** **2. Absence of Brain circulation evidenced by either:** • **Cerebral angiogram [ ]** • **Radionuclide angiography [ ]** • **Transcranial doppler [ ]**	**Result:**	**Date:**	**Signature:**

FIRST EXAM	**Time**	**Date**	**Signature**
Consultant A(name)			
Consultant B(name)			
Consultant C(name)			

Note: Recommended time interval between first and second examinations in various age groups

Age:	Inter Examination Interval
≤ 30 days	24 hours
≥ 30 days – 18 years	12 hours
Adults (≥ 18 years)	6 hours

Please note that Apnea Test is confirmatory test
** Evaluation may be deferred for 24- 48 hours or longer if there are inconsistencies in the examination

DEATH DOCUMENTATION FORM BY BRAIN DEATH CRITERIA

Name:_____ MR #:_____
Age:_____ Sex:_____ Nationality: _____ Blood Group:_____
Hospital: _____ Date of Admission: _____

SECOND EXAM	Consultant A	Consultant B	Consultant C Only for transplant donor
1. PRECONDITIONS: i. It is absolutely certain that irremediable brain damage has occurred due to			
ii. Appropriate time has passed between the first and second examination.			
iv. Coma with no spontaneous respiration.			
2. EXCLUSIONS: vi. Hypothermia (core temperature < 36°C)			
vii. Sedation (blood test or hospital record should indicate absence of significant levels of sedative drugs or muscle relaxants).			
viii. Systolic BP ≤ 100 mm Hg ix. Systolic blood pressure not ≤ 2 SD for children and infants			
x. Significant metabolic or endocrine causes of coma.			
3. CLINICAL ASSESSMENT: A. Lack of response to pain stimulation (Spinal reflexes excepted).			
B. Absence of brain stem reflexes:			
i. Pupillary response to light			
ii. Corneal reflex			
iii. Oculocephalic reflex			
iv. Oculovestibular reflex (50 ml. of ice-cold water at 0°C in adults, 20 ml. in children)			
v. Gag reflex			
vi. Cough reflex			
CONFIRMATORY TEST: **APNEA TEST**	**$PaCO_2$ Baseline:** **$PaCO_2$ After test:**	**Date:**	**Signature:**
ANCILLARY TESTS: **1. EEG** **2. Absence of Brain circulation evidenced by either:** • **Cerebral angiogram [ ]** • **Radionuclide angiography [ ]** • **Transcranial doppler [ ]**	**Result:**	**Date:**	**Signature:**
Name:	**Time:**	**Date:**	**Signature:**
Consultant A			
Consultant B			
Consultant C			
Medical Director			
Stamp of the Hospital:			

Note: Recommended time interval between first and second examinations in various age groups

Age:	Inter Examination Interval
≤ 30 days	24 hours
≥ 30 days – 18 years	12 hours
Adults (≥ 18 years)	6 hours

Annexure 3 IRB FORM

IRB Ref #		
Date:	_____	**Revision #**
Received:	_____	_____

Shifa International Hospital / Shifa Tameer-e-Millat University/Shifa Clinical Research Center

IRB & EC RESEARCH APPLICATION FORM

Institutional Review Board & Ethics Committee (IRB & EC) Office: 051-846-3075
Sector H-8/4 Islamabad Pakistan Fax: 051-486-3109
Email: irbshifa@shifa.com.pk

Submission Category: (Please check all that apply)

- ☐ New Protocol: (Study never performed. Include all documents listed in checklist)
- ☐ Renewal or Modifications (Please complete Form "B")
  (Study has previously been approved by IRB. Include the IRB Approval letter.

Application for

- ☐ Full Review
- ☐ Expedite Review
- ☐ Exempt Review

Checklist

- ☐ Research Proposal Application Form with Checklist
- ☐ Protocol (single copy)
- ☐ Data Collection Forms (surveys, questionnaires, Performa's, data collection etc.)
- ☐ Patient Information Sheet and Informed Consent Form (English with Urdu Translation)
- ☐ ONLY one page of resume and Google Scholar of Principal Investigator(s) and Co-Investigator(s)
- ☐ **Full Financial and Conflict of Interest Disclosure**
- ☐ Valid GCP training certificate (mandatory for any human and all Randomized control trial)[1]
- ☐ SCRC has reviewed the protocol
- ☐ Approval from the Departmental Head
- ☐ The study team members are identified and authorship agreed as per ICMJE guidelines[2]
- ☐ Surveillance for clinical trial will routinely be provided to IRB/ DSMB (as per definitions of Specific events described in DSMB Protocol)
- ☐ An interim progress and final report will be provided to IRB/ DSMB

[1] https://gcp.nidatraining.org/
[2] https://www.icmje.org/

- Signed "Undertaking on Plagiarism" by all the investigators
- Raw data and Consent forms will be retained (5 years) and submitted upon request if required
- Signed MOU between collaborative institutions
- Meet Indemnity Insurance
- Any additional document that requires approval

Declaration for collaborative studies

I _____ certify that I am the Principal Investigator (Corresponding author) of the research protocol submitted titled: _____

_____and, I will abide by all the rules and regulations of IRB & EC as mentioned above including

For collaborative studies with other institutions

- ☐ Shifa co-investigator identified who will have the primary responsibility of keeping integrity of all data from SIH/STMU and its affiliated institutions and departments
  - Shifa co-investigator:_____
- ☐ PI will present the protocol in IRB meeting as per agenda
- ☐ Supervisor will attend the IRB meeting for Investigators' synopsis/dissertation/thesis
  - Supervisor:_____
- ☐ Due credit will be given to the Shifa faculty, STMU and institution as per authorship agreement. Shifa Co-investigator who has given permission/approval to collect data from the department must be given authorship (First/Second/Third author).
- ☐ Authorship will be based on ICMJE guidelines/recommendations
- ☐ Memorandum of Understanding (MOU): Mandatory between STMU/concerned department and outside institutions at time of submission.
- ☐ ***I confirm that for any violations from original protocol including methods, study title, sample size, study design, financial disclosure, and consent and authorship agreement I will be liable for disciplinary action as per IRB &EC rules.***

Undertaking for Plagiarism

- I certify that this is my own work, based on my personal study and/or research and that I have acknowledged all material and sources used in its preparation, whether they be books, articles, reports, lecture notes, and any other kind of document, electronic or personal communication.
- I also certify that this study/protocol has not previously been submitted, and that I have not copied in part or whole or otherwise plagiarised the work of other researchers.

Signature of PI:_____
Contact number:_____
Shifa co-investigator Signature:_____

A. COVER PAGE

TITLE OF PROPOSAL

_____

_____

TYPE OF PROJECT

☐	Human	☐	Chart Review
☐	Diagnostic	☐	Therapeutic
☐	Laboratory	☐	Animal Study
☐	Device/Innovation	☐	Others

Entity:

☐	SIH	☐	SCM	☐	SCN
☐	SCPS	☐	DRS	☐	SCMT

PRINCIPLE INVESTIGATOR OTHER STUDY TEAM MEMBERS

Principal Investigator: (Person noted as Principal Investigator in the IRB approval notice.)

Name of PI + Qualification	**Title / Position**	**Department**	**Signature**
Contact No.		**Email**	

Other Study Team Members:

Before signing the authorship agreement please read the ICJME guidelines

- Authorship will be based on ICMJE recommendations and guidelines
- All conflicts of interest, real and perceived, and funding sources have been reported at the time of proposal submission to IRB & EC
- All the authors agreed to be accountable for all aspects of the work

Name	**Title/Position**	**Department**	**Authorship/Contribution Agreement***	**Signature**

*I confirm that I am an author on the above mentioned study, which is currently being submitted for the approval of IRB & EC. By signing this authorship agreement and contribution, I confirm that I agree to all the recommendations/guidelines and terms of aforementioned for the authorship contribution by ICMJE.

B. STUDY DETAILS AS PER ATTACHED GUIDELINE (Annexure-I), Follow below items 1-15 ; For CPSP Synopsis (Use CPSP format as per Annexure-I)

1- WHAT IS THE PURPOSE OF THE STUDY? (Please give a brief background of the study)
Required component:

- Adequate literature review and identification of "gaps" (i.e. what is not known)
- Hypothesis well defined

2- WHAT ARE THE OBJECTIVES OF THE STUDY?
Required component:

- Clear Primary research question
- Clear secondary question (if any)

3- STUDY DESIGN:
Required component:

- Appropriate research strategy
- Appropriate variables selected & defined
- State study design
    - Systematic Review, RCT, Retrospective , Survey etc
    - Observational study, Design Cohort, Case control, Cross Sectional Survey,
    - Qualitative study & survey / Forum groups

4- DESCRIPTION OF METHODS USED IN PROTOCOL
Required component:

- Appropriate sampling method
- Valid and reliable data collection method
- Inclusion & Exclusion Criteria
- Sample Size determination
- Appropriate choice of controls (if applicable)
- State of subjects randomization or not

5- STATISTICAL METHODS:
Required component:

- Appropriate method
- Do the statistical test answer the research question
- Valid and reliable data collection method

6- DURATION OF THE STUDY
Required component:

- Mention the duration of the study after approved from IRB

7- ADVERSE/SERIOUS ADVERSE EFFECTS / POTENTIAL HAZARDS
Required component:

- Explain how these events would be managed? Who will bear the cost?

8- POTENTIAL RISK TO THE PARTICIPANTS

9- POTENTIAL BENEFIT TO THE PARTICIPANTS

10- EFFORTS AT MINIMIZING SELECTION BIAS, AWARENESS BIAS, DETECTION BIAS:

11- EFFORTS TO LIMIT LOST TO FOLLOW-UP & ATTRITION

12- EFFORTS TO INTEGRATE AND CONTROL FOR CONFOUNDING FACTORS:

13- WORK PLAN / TIMELINE:

Required Elements:

- Appropriate well declared work plan
- Appropriate and adequate follow-up time

14- EXPLAIN WHAT MEASURES WILL BE TAKEN TO SAFEGUARD PATIENT'S/SUBJECT'S CONFIDENTIALITY & DATA SECURITY

15- REFERENCES

Required component:

- Mention at least 6 latest and relevant references from literature

C. SOURCE OF FUNDING

☐ Funds Required ☐ Sponsored ☐ No funding required

Please specify the name of the funding source: _____

D. SERVICES

Will services at SIH & SCM be utilized which are not considered part of routine medical care?

☐ Yes ☐ No

Payment of Arrangements: If "Yes" is checked in the above section, an explanation of payment arrangements is required and must be included with this submission packet. (Use Form C' Budget Form)

E. SETTINGS/FACILITIES TO BE USED FOR THE STUDY (In case of multi-centered studies, kindly list the name of participating centers/countries) (Please check all that apply)

☐ Inpatient ☐ Outpatient
☐ Shifa Department (Please specify) _____

F. FULL FINANCIAL DISCLOSURE:

G. SECTION APPROVAL:

1. **Title of Proposal:**

   _____

   _____

2. **Principal Investigator:**

   _____

3. **Location(s) where the study will be performed:**

   _____

4. **Approval:**

   I have reviewed this proposal and agree that it is scientifically and medically sound. I feel that beds and other facilities (if applicable) are adequate. I approve the participation of the concerned personnel of my department in this study.

   _____
   Chief of Department / Section Head

For any violations from original protocol including methods, study title, sample size, study design, financial disclosure, and consent and authorship agreement is liable for disciplinary action as per IRB &EC rules.

H. OTHER STUDY RELATED INFORMATION

- Add any other information that you deem necessary

***** The Ethics Committee must approve Informed Consent Form.***
***** Add pages if necessary.***