

National Ethical Guidelines For
Health Research in Nepal
And
Standard Operating Procedures



Nepal Health Research Council (NHRC)
Ramshah Path, Kathmandu, Nepal

January 2011

Publisher
Nepal Health Research council (NHRC)
Ramshah Path, Kathmandu, Nepal

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Revised Edition: January, 2011

Printed Copies: 1000

Print & Design in Nepal by
S.S. Printing Press
Phone No.: +977-1-4700864

Acknowledgement

National Ethical Guidelines for Health Research in Nepal plays an important role in maintaining the high ethical and scientific standards for conducting health research. Therefore, the **National Ethical Guidelines for Health Research in Nepal and Standard Operating Procedures** are important documents to fulfill the objectives of NHRC.

I wish to express my sincere thanks and gratitude to the members of the **Taskforce Committee**: Coordinator Prof. Ramesh Kant Adhikari, Dr. Aarati Shah, Dr. Ramesh Prasad Acharya, Dr. Arjun Karki, Mr. Harihar Dahal and Prof. Shiba Kumar Rai and Member-Secretary Dr. Shanker Pratap Singh for their impressive contributions and dedication to this most important task. I would also like to give special thanks to the former Member-Secretaries Dr. Sharad Raj Onta, Dr. Sarita Upadhyaya and Dr. Shri Krishna Giri who provided valuable contribution. I also sincerely thank Fr. Joseph L. Thaler, M.M. and Mr. Meghnath Dhimal, Chief Research Officer of Nepal Health Research Council for their contribution in editing the revised guidelines. I would like to acknowledge all others who made valuable contributions and who have partnered with NHRC to make the updating of the ethical guidelines possible.

I would also like to express my heartfelt gratitude to Maryknoll Fathers and Brothers Project for the support. I am also most grateful to the NHRC staffs for their support especially to Ms. Shailee Singh Rathour and Mr. Gopal Krishna Prajapati for their multifaceted assistance in finalizing this document.

Prof. (Dr.) Chop Lal Bhusal
Executive Chairman
Nepal Health Research Council

Preface

Nepal Health Research Council (NHRC) has been entrusted with the responsibility of promoting quality health research because of its mandate that situates it as the apical body for all health research in the country. As per **Nepal Health Research Council (NHRC) Act 1991** and its by-laws, NHRC is permitted to publish and disseminate guidelines in order to make health research more scientific and ethically sound. NHRC has taken unique steps with the contributions and input from various experts as well as from different disciplines during several workshops and meetings in order to publish these ethical guidelines.

To date NHRC has published a variety of Guidelines that include the following: **National Ethical Guidelines for Health Research in Nepal, 2001, National Health Care Waste Management Guidelines, 2002, Ethical Guidelines for the Care and Use of Animals in Health Research in Nepal, 2005, National Guidelines on Clinical Trials with the Use of Pharmaceutical Products, 2005, and Guidelines for Institutional Review Committees for Health Research in Nepal, 2005.**

During the Workshop on *Ethics in Health Research* which was organized by NHRC on March 13-14, 2008 the suggestion surfaced that it was now important to revise the **National Ethical Guidelines for Health Research in Nepal**. Therefore, seven members were delegated as a Taskforce Committee to accomplish this task and over the period of revision a series of workshops were held to garner further suggestions for revisions. The revised Guideline was disseminated in the Workshop on the *Finalization of the Revised National Ethical Guidelines for Health Research in Nepal on April 26, 2010*. With the accumulated valuable suggestions from this workshop definitive steps were taken to finalize the ethical guidelines. The document is divided into three sections. **Section A: Guiding Principles for Health Research Involving Human Participants. Section B: Basic Principles of Health Research**

Involving Human Participants and Section C: Standard Operating Procedure For The Ethical Review Board of Nepal Health Research Council. In the revised Guidelines the section on the **Standard Operating Procedure** (SOP) has been added and is being implemented by the Ethical Review Board of NHRC.

This document is an updated edition of **National Ethical Guidelines for Health Research in Nepal and Standard Operating Procedure** which will assist the Ethical Review Board of NHRC in the achievement of its commitment to promote, protect the dignity, rights, safety and well being of all in health research involving the culture and environment of Nepal.

Acronyms

CIOMS:	Council of International Organization of Medical Sciences
EB:	Executive Board
ERB:	Ethical Review Board
NHRC:	Nepal Health Research Council
IRC:	Institutional Review Committee
SOP:	Standard Operating Procedure
WHO:	World Health Organization
WMA:	World Medical Association

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Section A

GUIDING PRINCIPLES FOR HEALTH RESEARCH INVOLVING HUMAN PARTICIPANTS

1. Introduction

The word *ethics* is derived from the Greek word ‘ethos’, which means ‘character’, ‘disposition’ or ‘a fundamental outlook influencing behaviour related to customs and moral values of the people’. Aristotle described ethics as moderation in the choice between extremes or as the decision of a prudent person.

Ethics is the branch of philosophy which deals with the process of determining correctness of an activity. It draws guidance from the moral principles prevalent in the society. Ethics is guided by the concept of human rights, social and professional responsibility.

In health research, ethics is concerned with the process of determining whether an activity proposed under research is ethical or not. It concerns primarily with safeguarding the interests of research participants and aims to promote their dignity and rights.

2. Historical Background

Codes of medical ethics are to be found as far back as Babylon with Hammurabi’s “Code of Law” (Babylon 1790 BC), Agnivesa’s “Charaka Samhita” (Indian subcontinent 800 BC to 400 AD) and the Hippocratic Oath (Greece 600 BC). Recorded writings on medical ethics are to be found even earlier in the ancient writings of Egyptian, Arabic and Greek scientists and philosophers. More recently, in the west the concept of just moral propriety in medicine was propounded by Thomas Hobbes in 1651 and that of medical humanism by John Gregory in the 18th century. Thomas Percival came up with the concept of bio-ethics and legislative aspects of ethics related behavior.

In 1946 the International Health Conference meeting in New York adopted the constitutional structure of the World Health Organization (WHO), which formally came into existence in 1948. This constitution reiterated the responsibilities of government and health professionals for promoting and protecting the health of individuals and populations.

As the key organization responsible for health within the structure of United Nations, the WHO promotes the *Universal Bill of Human Rights* which includes *Universal Declaration of Human Rights* composed in 1948, the *International Covenant of Economic, Social and Cultural Rights* (1966, ratified in 1976) and the *International Covenant of Civil and Political Rights* (1966). These three instruments define and describe basic human rights and fundamental freedoms. They form the nucleus of an interlocking set of international conventions, resolutions and declarations intent on promoting the rights and freedoms of persons through law. *The Universal Declaration on Human Rights* is supported and promoted by Nepal Health Research Council in all its activities.

Ethics related to health and biomedical research is a more recent phenomenon. The first international document on this subject is the Nuremberg Code in 1947. This was followed by a series of international declarations, conventions and covenants related to ethics in health, health care and research. The most prominent of these documents are the World Medical Association (WMA) *Declaration of Helsinki*, the Council of International Organization of Medical Sciences (CIOMS) *International Ethical Guidelines for Biomedical Research Involving Human Subjects* and the WHO and ICH *Guidelines for Good Clinical Practice*.

The Nepalese national ethical guidelines for health research is cognizant of these declarations, code and guidelines and has followed the spirit in which they are written.

3. Definitions

Research: The term research refers to a set of activities designed to develop or to contribute to generalizable knowledge consisting of theories, principles, relationships or the accumulation of information which they are based, that can be corroborated by accepted scientific methods of

observation and inference. **Health research** includes medical and behavioural studies related to human health. “**Biomedical**” research refers to research related, directly or indirectly, to the advancement of medicine. “**Clinical**” research refers to any study of which one or more components is diagnostic, prophylactic or therapeutic in nature and is applied to human participants.

Research involving human participants may involve physical, chemical, psychological or social interventions, or it may be strictly observational or historical in its methodology. The study of existing records or generated records containing biomedical or other information, or of tissue samples or biological material, about individual that may or may not be identifiable, is also to be understood as research involving human participants.

Research involving human participants includes the following:

- 3.1. Studies of physiological, biochemical or pathological processes.
- 3.2. Studies of responses to physical, chemical, genetic, psychological or social interventions.
- 3.3. Controlled trials of diagnostic, preventive or therapeutic methods or measures in persons designed to demonstrate a specific generalized response to these measures against a background of individual biological variation.
- 3.4. Studies designed to determine the consequences for Individuals and communities of specific preventive or therapeutic measures.
- 3.5. Studies concerning human health related behaviour in a variety of circumstances and environments.
- 3.6. Studies in which environmental factors are manipulated in a way that could affect incidentally exposed individuals; for example, exposure to toxic chemicals, radiation, or pathogenic organisms or agents (or the absence of these); also psychosocial challenges or deprivations, and the implementation of health policy or management options influencing environment of the participants should be considered as research involving human participants.

- 3.7. Epidemiological or observational studies aimed at exploring the distribution and determinants or risk factors or health related events or problems in a specified population and geographic area in order to prevent, control, and or manage health problems and or promote healthy or environment friendly behavior.

4. Ethical Principles

The ethical principles which guide the health research and care are the principles of respect for autonomy of an individual, beneficence, non malfesance and the principle of justice. While conducting research at a community level involving humans in groups, all these principles are considered in a composite way. The principle of respect for the environment proposes to ensure respect for the culture of communities, their environment, benefit to the members of the community and not harming them ensuring that the justice is done to them.

4.1. Principle I: Respect for the Autonomy of the Participant

The obligation to respect the dignity of participating individuals in all activities of health and biomedical research is the cornerstone of research ethics. This principle is based on the premise that an individual when informed of all aspects of an activity can decide for her/himself a correct course of action. This requires specific attention to the following:

- 4.1 (a) An individual's right to decide what is best for her/him can not be overruled by any consideration of person
- 4.1 (b) Researchers must actively safeguard the interests of the persons with impaired or diminished autonomy and ensure that the vulnerable people are afforded security against harm, abuse or exploitation
- 4.1 (c) No researches should take precedence over respect for human rights, fundamental freedom and human dignity, and practices contrary to human dignity should be prohibited.

The provisions of respect for autonomy of the human \participants in health research are implemented primarily through the instrument of “informed consent”

4.2. Principle II: Beneficence and Non-Maleficence

The principle of beneficence requires that the research activity should benefit the participants directly or indirectly, in the present or in future, individually or through collective benefits. If none of these benefits are obvious, the researcher should ensure that the participation in research does not lead to any harm. All attempts to maximize the benefits and minimize the risks should have been taken by the researcher.

This requires that all health and biomedical research activities be preceded by a careful assessment of the potential risks and burdens in comparison to the potential benefits to the prospective research participant and their communities. This does not preclude the participation of healthy volunteers in research. However, in all cases the research should promote the health of the population represented.

Beneficence and non maleficence also requires that the researchers are qualified to carry out proposed research that they are committed to promoting, protecting the health of the participants and their communities. The principle of non maleficence proscribes those researches which are likely to cause deliberate harm to the participants.

4.3. Principle III: Justice

Justice requires that persons in similar circumstances be treated alike and that differences between persons due to circumstances be acknowledged and addressed. In the context of health research, justice requires that persons having similar health complaints or threats be treated equally.

Justice also requires the equitable distribution of the burdens and benefits of research. Differences in such distribution are justifiable only if they are based on morally relevant distinctions between persons, for example, in cases where it is necessary to ensure the protection of the rights and welfare of vulnerable persons.

The protection of persons in vulnerable situations is of special importance. Persons in vulnerable situations are those who are unable to express or protect fully their own interests owing to such impediments as lack of capacity to consent fully, an inability to obtain alternative means of medical care and or other health necessities, or because they are junior

or subordinate member of a hierarchical group. Accordingly, special provisions must be made for the protection of the rights and welfare of all the persons in vulnerable situation.

4.4. Principle IV: Respect for the Environment

This principle requires that health research is undertaken within a context of respect for the social, cultural and natural heritage of a society. This fundamental ethical principle is re-enforced by WMA Declaration of Helsinki, which stresses the special precautions that must be exercised for the protection of the environment in the conduct of research. In view of the increasing world movement for the protection of the environment, every researcher is responsible for a moral engagement to protect the social, cultural and natural heritage of communities and societies. This responsibility includes commitment to the following:

- 4.4 (a) To ensure the proper and safe disposal of biologically hazardous waste from laboratory, clinical and field research
- 4.4 (b) To safeguard the cultural, linguistic and religious heritage of communities and individuals
- 4.4 (c) To treat the biologic and genetic heritage of the people with respect and caution. This requires respecting the principles of informed consent and confidentiality of genetic data

5. Application of Ethical Principles in Health Research

5.1 Informed Consent

For all health research involving human participants, the investigators must obtain the informed consent of the prospective participants or in the case of an individual who is not capable of giving informed consent, the proxy consent of a properly authorized representative.

The informed consent process can be analyzed as having the following components:

5.1.1 Information

The research participants should be given sufficient Information of the proposed research including information on the research procedures, their purpose, risks and discomforts and anticipated

benefit, alternative procedures and a statement offering the participant the opportunity to ask questions and to withdraw any time from the research without any fear of negative consequences.

A special problem of consent arises when informing participants of some pertinent aspect of research that is likely to impair the validity of the research. Such circumstances should be discussed with the ERB who will then decide on the matter.

5.1.2 Comprehension

It is the investigator's responsibility to ascertain that the research participant is competent and has comprehended the information. If the research participant is not capable of comprehending the information or is incompetent, the proxy consent of a properly authorized representative is necessary.

It is necessary to adapt the presentation of the information to the participants' capacities in a language the participant can understand. necessary attention and sensitivity should be given to cultural particularities.

5.1.3 Voluntariness

Informed consent is valid only if it is given voluntarily. Therefore there should be no coercion in the form of any threat or undue influence in the form of excessive, unwarranted, inappropriate or improper award.

When the research design involves no more than minimal risk, that is, risk that is no more likely and not greater than attached to routine medical or psychological examination, and it is not practical to obtain informed consent from each participant, the Ethical Review Board may waive some or all of the elements of informed consent.

Even though the legal guardian of a child or a person with a mental disorder gives the actual consent for participation in research, whenever possible, the assent of the child or the person with a mental disorder, to the extent possible, has to be obtained.

5.1.4 Process and Information Contained in an Informed Consent Form

5.1.4 (a) Obtaining consent from the participants

It is important to know who will explain the research questions, and who will receive the informed consent from the participant. Consider how much time is essential for this important matter.

5.1.4 (b) Is there any coercion or deception?

The consent form must clearly indicate that the participants volunteer of their own free will for the research. There should be no coercion or deception during the process of obtaining consent.

5.1.4 (c) The consent form should be prepared in English as well as the relevant local language and should include the following information:

1. The nature of the study-whether investigational, in terms of the use of drugs or procedure, or whether information seeking, or if questionnaires or interviews are to be used
2. The number of participants
3. The purpose/objective of the study
4. The expected duration of the research study and the frequency of the participant's involvement
5. The participant's responsibility
6. A statement that the participation is voluntary
7. A statement that the participant can withdraw from the study at any time without giving any reason and without fear
8. A statement guaranteeing confidentiality
9. A statement of any re-imbursalment/compensation for the research participant
10. A statement on exactly what is expected of the research participant
11. In the case of a **clinical trial**, the following information should be included

- a. The Trial treatment and the probability for random assignment to different treatments
- b. A detailed explanation of the trial procedures including all invasive procedures
- c. The potential or direct benefits (if any) from participation
- d. The alternative procedure(s) or treatment(s) that may be available
- e. The risks,discomforts, and inconveniences associated with the study
- f. The provisions for management of adverse reaction
- g. The provision of insurance coverage for any permanent disability death caused directly by the investigational treatment or procedure
- h. That a study participant will be given information that may be relevant to his/her willingness to continue participation
- i. The name and address, including telephone numbers, of the person to be contacted in case of adverse events or for any information related to the trial
- j. Sentence indicating that the participant has understood all the information in the consent form and is willing to volunteer/participate in the research
- k. Signature space for the research participant, a witness and the date

5.2 Assessment of Risks and Benefits

The principle of beneficence requires that the research be justified on the basis of a favorable risk/benefit assessment. The term ‘risk’ refers to a possibility that harm may occur. The term ‘benefit’ in research refers to something of a positive value related to health or welfare. The most likely types of harm to research participants are physical pain or injury or psychological effects. However, other kinds of harm must not be overlooked which include legal, social, and economic. Benefits may also be of the corresponding types.

Making precise judgments about the risk/benefits ratio is difficult in most instances as only rarely can quantitative techniques be available to judge research proposals. Therefore systematic, non-arbitrary analysis of risks

and benefits should be adopted as far as possible. For this purpose, through accumulation and assessment of information about all aspects of the research should be done, and alternatives should be considered systematically.

In assessing the justifiability of research, consideration of the following is the minimum:

- 5.2.1 It should be judged whether the use of human participants is in fact necessary at all
- 5.2.2 Brutal or inhumane treatment of human participants is never justified
- 5.2.3 Risks should be reduced to those necessary to achieve the research objectives
- 5.2.4 When research involves significant risk, extra ordinary insistence on the justification of the risk is necessary
- 5.2.5 When vulnerable populations are involved in research, the necessity of involving them should be clearly demonstrated
- 5.2.6 Relevant risks and benefits should be clearly and thoroughly spelled out in the documents used in the informed consent process

5.3. Selection of the Research Participants

- 5.3.1. The system of justice requires that there be fair procedures and outcome in the selection of research participants. Individual justice in the selection of participants requires that researchers exhibit fairness. Thus they should not offer potentially beneficial research only to some who are in their favor or select only ‘undesirable’ participants for risky research. Social justice requires that distinction be drawn between classes of participants that ought and ought not to participate in any particular kind of research. Thus, it is a matter of social justice that there is an order of preference in the selection of classes of participants (e.g. institutionalized, mentally infirmed or prisoners may be involved as research participants, if at all, only on certain conditions). Special attention should be taken in research involving medical students and soldiers because of their potentially vulnerable situation.

- 5.3.2. In accordance with this principle, a new drug or appliance developed elsewhere can only be tested in the Nepal after a Phase 1 trial has been conducted elsewhere.
- 5.3.3. Prisoners must not be made subjects of intervention research that involves more than minimal risk, as the consent given by them may not be given voluntarily or may have been unduly influenced by expectations of reward. Other types of research involving prisoners will be reviewed fully by the ERB.
- 5.3.4. Pregnant and nursing women should not be participants in a clinical trial except those that are designed to protect or advance the health of pregnant or nursing women or fetuses or nursing infants and for which they are the only suitable participants.
- 5.3.5. Children cannot be considered ‘mini adults’, and therefore any new drug intended for use in children has to be studied in children for its rational and scientific use. However, before undertaking research in children, it has to be ensured that:
 - 5.3.5 (a) Children will not be involved in research that might be carried out equally well in adults
 - 5.3.5(b) The purpose of the research is to obtain knowledge relevant to the health needs of the children
- 5.3.6. Before undertaking research in mentally disadvantaged persons the following has to be ensured:
 - 5.3.6 (a) Such research cannot be carried out satisfactorily in person in full possession of their mental faculties (i.e. persons capable of consent)
 - 5.3.6 (b) The purpose of the research is to obtain knowledge relevant to the health needs of persons with mental disorders

5.4. Best Research Practices

- 5.4.1. Research involving human participants should be carried out by qualified, competent, and responsible investigators according to a research proposal (protocol) that clearly identifies the purpose, questions, and methodology of the study. The proposal should be scientifically and ethically appraised by one or more suitably and legally constituted review body, independent of the investigators. The

implementation of the research should follow best research practices including internationally accepted Good Clinical Practice Guidelines, Good Laboratory Practice Guidelines, and Good Manufacturing Practice Guidelines.

- 5.4.2. Data should be handled, processed, and analyzed by competent and qualified persons led by qualified health professionals. Ethical responsibility of managers/handlers of data for safety, confidentiality, and prevention of misuse should be strictly upheld.

5.5. Externally Sponsored Research

The following conditions must be considered before externally sponsored research can take place in Nepal:

- 5.5.1. The research is preferably responsive to the health needs and priorities of Nepal as well as being sensitive to the existing environmental factors including culture, religious and social values
- 5.5.2. The research cannot be carried out reasonably well in the sponsors' country
- 5.5.3. The research protocol has the approval of the Ethical Review Board/Institutional Review Board of the country of the sponsor
- 5.5.4. The sponsor should consider means in which the research capability of Nepal can be strengthened and other means of compensating the community
- 5.5.5. The research process should be transparent
- 5.5.6. External sponsors should apply insurance to research participants in health research that involves more than minimal risks
- 5.5.7. In case it is necessary to transfer biological samples abroad, a memorandum of understanding has to be signed by the sponsor and NHRC defining clearly the purpose for the transfer, the material that is being transferred, ownership of intellectual property rights, and provisions for privacy protection
- 5.5.8. The proposal has to be approved by NHRC

5.6. Scientific Merit of a Health Research Proposal

A technical team will review the proposals before submitting it for ethical review. The scientific merit of a submitted research proposal will be evaluated on the following criteria:

- 5.6.1. Relevance of the study to the national health priorities
- 5.6.2. Clearly stated objectives, hypothesis and conceptual framework
- 5.6.3. Methodology suggested is valid for the objectives to be achieved
- 5.6.4. Sampling frame and size are adequate to reach the valid conclusion
- 5.6.5. Plans for data collection and analysis are adequate and appropriate
- 5.6.6. Researcher(s)/the research institution(s) have the capability of conducting the research. This includes submitting CVs of the researcher(s) as well as the necessary documentation from the institution(s)
- 5.6.7. Plans for supervising and monitoring the data collection and analysis are appropriate
- 5.6.8. Mechanism for the dissemination of the findings has been articulated
- 5.6.9. Mechanism for the utilization of the study findings by other researchers or by the health system has been specified
- 5.6.10. The scientific merit of the proposal could include provisions for research involving qualitative methodologies

Section B

BASIC PRINCIPLES OF HEALTH RESEARCH INVOLVING HUMAN PARTICIPANTS

All health research conducted in Nepal must have the approval of the Ethical Review Board (ERB) of the Nepal Health Research Council (NHRC) or a similar body authorized by NHRC.

The approval for research is granted after a meticulous review. The review process is guided mainly by the principle of protection of the research participants, creation of generalizable and scientifically valid knowledge and equitable utilization of such knowledge.

In order to achieve these aims the following ethical guiding principles are to be followed:

1. Essential Research

Research involving human participants should have been considered essential for the understanding of a problem or disease process, or to identify a better diagnostic, therapeutic or preventive approach to a disease.

2. Voluntary Participation

The human participation in research must have been ensured voluntarily. The voluntary participation should be secured through a process of providing information to the participants, comprehension by participants of the aims, objectives of research; risks and benefits involved and an understanding that the participation is with their consent, voluntary and with a provision that the participant can withdraw any time without any negative consequences.

3. Children in Health Research

No research which could be done in adults should be carried out in children. Only those researches which are of relevance to children should be carried out on children. Research involving children should be carried out only after taking informed consent from the parents or legal guardian of the child.

4. Pregnant Women in Health Research

Research involving pregnant women and lactating mothers should not be carried out unless the study is related to pregnancy and lactation.

5. Other Vulnerable People in Health Research

Special attention should be given while recruiting participants from vulnerable groups of people such as prisoners, students or military personnel or adults who are mentally challenged or in an unconscious state.

6. Potential Benefit

The participation in a research activity should be of potential benefit to the participant or to his or her community or the population in general.

7. Harm and Risks

The participation in a research activity should not in any way harm the research participant. If there are risks involved in participating in the research, it should be of minimal nature. The risks/benefit ratio must be in favor of benefits and the researcher must demonstrate that all efforts have been made to minimize the risks and maximize the benefits.

8. Compensation

The researcher should have made provisions for compensating the research participants or if relevant to the community for the harms incurred in the research process. In addition, the researcher should have made provisions to compensate the efforts and time of the participants for the purpose of research. The information related to the provision for compensation should have been communicated to the research participant.

9. Qualifications and Competence for the Research

Principal investigator of any research must have relevant qualifications and competence to conduct research.

10. Equal Distribution

The selection of research participants should be such that there is equal distribution of the burden and benefits of participation among population groups of different geographical regions or ethnicity or socioeconomic status as far as possible.

11. Dissemination of Research Findings

The research findings and their application or any further research emanating from such research should be brought into the public domain through scientific and other publications. The research findings should be shared with the local stakeholders preferably through publication in local scientific journals. In case the researcher plans to publish the scientific paper in an internationally acclaimed indexed journal, a summary from such a publication must be published in the local scientific publication. Publications resulting from the research should be subject to such rights as are available to the researcher and her/his associates as determined by the law(s) in force at that time.

12. Institutional Research Arrangements

The research activity should be carried out only after making necessary institutional arrangements required to conduct the research. Such institutional arrangements should include involvement of competent researchers and support staff, organizational set up conducive to research, ensuring safety and confidentiality of data and disseminating the research findings. Institutional arrangements for preservation and archiving of research materials, data and reports also must be in place. The research conducted in any institution should have received approval from the institutional chief and other related authorities.

13. Confidentiality and Disclosure

The research activity is carried out in such a way that the identity and data related to human participants are kept confidential as far as possible. However, under compelling scientific and legal situations, such disclosures could be made without informed consent of the participant. Recommendations of Data Safety Monitoring Board or a similar body will constitute the scientific reason and order from a court of law will be considered as compelling legal reason.

14. Professional, Legal and Moral Responsibility

Researchers and his/ her team, institution where the research is conducted, sponsors and agencies funding the research should take professional, legal and moral responsibility to abide by the principles, guidelines and directives of the Ethical Review Board or Institutional Review Committee.

15. Transparency and Conflict of Interest

The researchers and their associates will conduct the research with fairness, honesty, impartiality and transparency. All involved in the research activity will fully disclose their interest in different aspects of study and their conflicts of interest, if any. Failure to disclose relevant information can lead to suspension of the approval of research activity or penalty determined by law. In case of suspension of the research, researcher should have ample occasion to lodge a complaint against such a decision to a body constituted by the Ethical Review Board of Nepal Health Research Council.

16. Research and the Environment

Researchers will respect the environment while conducting any health research. Respect for the environment is demonstrated through research being undertaken within a context of social, cultural and natural heritage of a society. Health research proposals will have to ensure proper and safe disposal of all kinds of hazardous waste from a laboratory, clinical or field research and also safeguard the cultural, linguistic and religious heritage of individuals and communities.

17. International and/or Externally Sponsored Research

Research conducted in collaboration with international or external sponsorship can be conducted only if it is of relevance to the Nepalese people and/ or which can't be conducted in the sponsoring country alone. Externally sponsored research should demonstrate provisions for capacity building and strengthening that field of research. It is mandatory that such research have one co-investigator from Nepal.

18. Transfer of Biological Samples Outside of Nepal

If the health research involves the transfer of biological samples to other countries, the researcher(s) will provide convincing reasons for the same. Such transfers will be permitted only for the reasons originally stated in the research proposal. Such research must be sensitive to the need and existing culture and social norms of the communities where it will be carried out.

19. Approval Required for all Health Research in Nepal

All health research conducted in Nepal will have to receive approval from Ethical Review Board of Nepal Health Research Council or of the Institutional Review Committees approved by NHRC. Researchers conducting health research without such approval are liable to penalty determined by law.

Section C

STANDARD OPERATING PROCEDURE FOR THE ETHICAL REVIEW BOARD OF NEPAL HEALTH RESEARCH COUNCIL

Introduction

Nepal Health Research Council (NHRC) was established in 1991 by the Government of Nepal through an Act of Parliament with the objective of promoting scientific study and quality research in Nepal. One of the activities entrusted by this Act is to review all health research proposals to be conducted in Nepal for the scientific quality and ethical propriety and to take the necessary steps to approve or disapprove such research proposals. In order to carry out this task, NHRC developed the National Ethical Guidelines for Health Research in Nepal and constituted an Ethical Review Board (ERB) in accordance with the provisions made in the Guidelines.

In order to facilitate the work of ERB, a Standard Operating Procedure (SOP) has been developed. This SOP will guide the ERB to carry out its responsibilities in a consistent and smooth manner.

The purpose of this SOP is to safeguard the dignity, rights, safety and well being of research participants and promote scientific and ethical health research in Nepal.

1. Functions and Duties of the ERB

- 1.1. To review research proposals according to the National Ethical Guidelines for Health Research in Nepal with a view to approve, amend or reject the proposal
- 1.2. To supervise or monitor the implementation of health research projects approved by ERB

- 1.3. To conduct training programmes for members and reviewers of ERB and Institutional Review Committees (IRCs) on the ethical review process
- 1.4. To resolve ethical issues arising out of reviewing, approving , supervising and disseminating the research findings
- 1.5. To promote research in the process of review, implementation , supervision of research and dissemination of research findings
- 1.6. To accredit IRC's and oversee their functions and guide them periodically

2. Membership of ERB

- 2.1 Executive Board of NHRC will appoint the members and chairman of the ERB and the member secretary of NHRC will act as the secretary of the ERB.
- 2.2. Member Secretary of NHRC will prepare a list of potential candidates for the ERB membership and submit these names to the Chairman of NHRC who in consultation with EB of NHRC will make the appointments. Members will be drawn from multiple disciplines and members unaffiliated with NHRC will be included in the ERB. Potential candidates should be drawn from among the senior health professional possessing at least postgraduate qualification in a related scientific discipline, having received training in ethics and the ethical review process and served in an IRC or ERB as a member for at least a term of three years.
- 2.3. Member Secretary of NHRC, while preparing the list of potential candidate will give due consideration to the possible conflicts of interest of the different candidates. Each potential candidate will be asked to indicate possible conflicts of interests that might arise in the course of their ERB work. The Member Secretary records this data and informs the Chairman.
- 2.4. While making the appointment, at least 33% to 50% of the members of the existing ERB will be retained in order to ensure continuity of experience.

Term of appointment to the ERB

- 2.5. The ERB member will be appointed for the duration of a three year term.
- 2.6. **Policy for renewal:** in order to maintain continuity of experience at least 33 to 50% of the members will be retained in a new ERB.
- 2.7. **Disqualification procedure:** A member who was found upon an investigation conducted by ERB acting contrary to the interests of NHRC, breaching the conditions of appointment will be disqualified from continuing in the ERB. This qualification would be made by the EB of NHRC. Legal prosecution will also lead to disqualification.
- 2.8. **Resignation:** a member who does not want to continue in on the ERB can submit his or her resignation to ERB of NHRC. On acceptance of the resignation by the ERB membership on the ERB will cease.
- 2.9. **Replacement procedure:** the process followed for appointment of members will be followed to replace the ERB members.

Conditions of appointment to the ERB

- 2.10 Member accepting to serve on the ERB should agree that his or her name, professional qualification, experience and affiliations would be publicized through the reports of NHRC, ERB.
- 2.11 Member accepting to serve in the ERB should agree that the remunerations paid to him or her in course of ERB work will be recorded and will be made available to the public on request.
- 2.12 Member accepting to serve in the ERB will have to sign a confidentiality agreement regarding meeting deliberations, applications, information on research participants and related matters.
- 2.13 All administrative staff working for ERB will also have to sign a confidentiality agreement regarding meeting deliberations, applications information on research participants and related matters.

Office of the ERB

- 2.14 NHRC will assign space within the premises of NHRC for the exclusive use by Chairman or coordinator of the ERB and administrative staff.
- 2.15 ERB of NHRC will have its own phone, fax, photocopy cupboard and administrative staff.

Meetings

- 2.16 Member Secretary of the ERB will prepare the agenda for the meeting in consultation with the Chairman of the ERB. The Member Secretary will also keep minutes of the meeting and notify decisions to the researcher. The Member Secretary will be assisted in his or her tasks by an administrative secretary.
- 2.17 ERB will prepare a regular annual report which will be published after its approval by EB of NHRC.

Quorum requirements for ERB

- 2.18 ERB will have 11 members.
- 2.19 At least 6 members must be present to compose a quorum. Presence of members of only one gender will not constitute a quorum.
- 2.20 At least one member present should have expertise in areas other than the subject under discussion. Preferably a member from outside of the health science background must be present.

3. *Independent Consultant(s) to the ERB*

- 3.1 ERB will prepare a list of independent consultants who can be called upon by ERB to provide expert opinion on proposed research proposals. These consultants will be subject specialists, methodologists, Environmentalists, legal specialists, ethicists, sociologists, psychologists, anthropologists or representative of specific communities, patient groups and special interest groups.
- 3.2 Independent consultants who agree to help the ERB will have to sign a confidentiality agreement regarding their assignment, meeting deliberations, applications, information on research participants and related matters.

- 3.3 Independent consultants will be paid remuneration as per NHRC regulations.

4. On-Going Education of the ERB Members

- 4.1 All new ERB members will be provided with orientation training.
- 4.2 ERB will conduct regular training programmes for ERB members and Institutional Review Committee members at least two times in a year. Such training programmes will provide opportunities for hands on experience of reviewing the research proposals as well as problems faced while reviewing, implementing or disseminating of research.
- 4.3 ERB will forward requests from ERB members for participation in national, regional or international training programmes' on ethics in health research. EB of NHRC will try to accommodate such requests as far as possible.

5. Submitting the Application

Individuals or institutions desirous of conducting health research in Nepal are required to submit their health research proposal to ERB of NHRC.

5.1 Application Submission

- 5.1.1 The Principal Investigator (PI) and/or the one responsible for the health research will submit the health research proposal for review

5.2 Application Requirements Include

- 5.2.1 Application: Application should be addressing to the Member Secretary of ERB
- 5.2.2 Format for Application: Application should be submitted in the format provided by NHRC. The prescribed format can be accessed from the website (www.nhrc.org.np) of NHRC or a hard copy can be obtained from NHRC office
- 5.2.3 Language of Applications: All Applications should be submitted in English

- 5.2.4 Application should include one hard copy and an electronic copy of the proposal.
- 5.2.5 Only those applications fulfilling the requirements will be accepted for review. Deficits in the application shall be informed to the applicants within two weeks of submission. Incomplete applications will have to be resubmitted
- 5.2.6 A receipt of the accepted application will be provided to the researcher
- 5.2.7 Application Fee: Applications should be submitted along with processing fee as per NHRC rule/ decision made by the Executive Board of NHRC
- 5.2.8 Additional documents or changes: ERB can request the applicant for supplementary documents/or changes to the proposal during the review which will be communicated to the applicant and the application will be considered in the subsequent meeting after those changes are made by the researcher.
- 5.2.9 Amendments: If any amendments are made in the proposal already submitted and approved, the researcher must submit in writing the changes made with reasoning. The proposal will be reviewed again in the ERB, taking the amendments into consideration during the re-approval process.
- 5.2.10 Informed consent: Application should include the Informed Consent Form as a separate copy which is to be used while undertaking the research. In addition, this can include a translation copy, in a local language if that is applicable.

5.3 Documentation Requirements for the Application

All the documents that are required by the ERB for a process of review and approval should be submitted along with the application. If any additional documents are required during the review process, the researcher will be notified by ERB.

- 5.3.1 The application form should be submitted with the signature and date of submission using the NHRC format
- 5.3.2 Application must include the most current version of the curriculum vitae of the Principal Investigator and co-investigators with special mention of academic qualification and research experiences
- 5.3.3 Application must include the protocol of the proposed research project in the provided format together with the supporting documents. (A copy of research tools, questionnaires etc)
- 5.3.4 A copy of informed consent form should be included in the application. This should include a detail description of the process of giving the information to the research participant and its content, process of obtaining the consent, the person responsible for obtaining the informed consent and documentation of the signature of the researcher/research participant and /witness if applicable
- 5.3.5 Any compensation to be given to the research participant should be clearly mentioned. (E.g. any transportation costs, food, free health care or insurance coverage etc that is to be borne by the researcher)
- 5.3.6 In case of clinical trials, description about the study design, the trial phase, and a detail description of the safety of the product or procedures must be mentioned. It should include the pharmacological, pharmaceutical, and toxicological data available and also include the investigators brochure
- 5.3.7 A signed statement by the researcher stating that he or she will abide by the ethical principles of research
- 5.3.8 Information about any previous submission of this

- application to ERB or any other Institutional Review Committee and the result of such submission in the past will have to be provided along with the application
- 5.3.9 A declaration of the conflict of interest, if applicable, should be mentioned in the application

6. Ethical Review Process

The ERB will review all the submitted health research proposals in a timely manner and in accordance with the set review process.

6.1 Meeting of the ERB

The meetings of the ERB will be held on a regularly scheduled dates that will be announced in advance. The Member Secretary of ERB with the permission of the Chairman of the ERB will call the meeting. The followings are considered as applicable for an ERB meeting:

- 6.1.1 The meeting of ERB will be planned in accordance with the workloads and number of proposals received for review. Normally, ERB will meet once a month
- 6.1.2 ERB members will be informed about the meeting at least 72 hours prior to the scheduled date
- 6.1.3 If felt necessary by the ERB, the applicant researcher or sponsor of the research can be invited to present the proposal or elaborate on specific issues of the proposal. Similarly, if necessary, experts can also be invited to the meeting for expert opinion about the research
- 6.1.4 Minutes will be kept of all decisions and procedures of the meeting
- 6.1.5 All the members and invitees present in the meeting should sign the minutes to indicate their presence

6.2 Elements of the Review Process

Technical Review by the Reviewers: Once the application is submitted and screened for completeness of documents, technical review of the proposal is done by the internal reviewers for the

scientific and technical contents. The application received after internal review is then subjected for review by the external reviewers.

Ethical Review: Those applications which qualify are then submitted to the Member-Secretary of the Ethical Review Board and then discussed in full board ERB meeting for ethical review.

6.2.1 Scientific Design of Research Proposal and Conduct of Research

- 6.2.1.a The appropriateness of the study design in relation to the objectives of the study
- 6.2.1.b **Statistical methods:** sampling method, sample size and analysis of data
- 6.2.1.c Justification of predictable risks and inconveniences against the anticipated benefits for the research participants and community by the proposed study
- 6.2.1.d Justification of the use of control arm (if relevant for the study)
- 6.2.1.e Criteria for prematurely withdrawing research participants
- 6.2.1.f Criteria for suspending or terminating the research
- 6.2.1.g Provisions for data safety monitoring board(DSMB)
- 6.2.1.h Plan for dissemination or publication of research results
- 6.2.1.i Infrastructure and other facilities in the institutions conducting the research
- 6.2.1.j Suitability of researcher's qualification and experiences for The proposed research
- 6.2.1.k Description of the population from which the research participants will be drawn
 - 6.2.1.l Inclusion criteria for the research participants
 - 6.2.1.m Exclusion criteria for the research participants
 - 6.2.1.n Protection of research participants
 - 6.2.1.o Measures to ensure the confidentiality of the research participants
 - 6.2.1.p Description about who has access to data and biological samples
 - 6.2.1.q The compensation provided to the participants in case of adverse drug reaction and or adverse events

6.2.1.r Description of the process of reporting any adverse drug reaction and/or adverse event

6.2.1.s Description about the provision of availability of the research product for the participants after completion of the research project

6.2.2 Informed consent process

6.2.2.a A full description of the process for obtaining informed consent including the description about who is responsible for obtaining the informed consent

6.2.2.b Process of communication with the research Participants about the objectives, methods, risks and benefit of the research

6.2.2.c Description about obtaining consent from the vulnerable research participant (e.g. children, elderly, disabled, prison population, people in uniform services, etc.)

6.2.2.d Description about the provision for the participants to queries and complaints during the course of research

Community considerations

6.2.2.e The relevance of the research for the community from where research participants are drawn

6.2.2.f The process taken for the consultation and communication with the community

6.2.2.g Description about how the research results will be Available for the community

6.3 Expedited Review

In the following situations the ERB will allow the Member Secretary to expedite the review of the proposal.

6.3.1 If the research is non interventional, based on secondary data, leading to thesis or has received approval from the Institutional Review Committee

6.3.2 If the research is carried out under the circumstances of outbreak, disaster and other emergency conditions

- 6.3.3 If the proposal is found technically and scientifically sound after reviewing by internal reviewer of NHRC
- 6.3.4 The Member Secretary should inform to NHRC Chairman and in the ERB meeting about the proposals expedited.

7. Decision Making

The ERB will consider the following while making decision about the research proposal

- 7.1 The ERB will make the decision only if the meeting has met required quorum as noted in 2.18-20
- 7.2 Normally the decision will be taken by consensus, (if consensus is not possible then a vote will be taken)
- 7.3 The ERB member should withdraw from the decision process when conflict of interests arises; the member should declare the conflict of interest
- 7.4 The ERB may approve the proposal conditionally with specific suggestions to the researcher
- 7.5 The negative decision on a proposal should be supported by clearly stated reasons

8. Communicating a Decision

On behalf of the Ethical Review Board, the Member Secretary will communicate its decision to the applicant in writing within two weeks after the meeting. The communication of the decision will include, but is not limited to the following information:

- 8.1 The exact title of the research proposal reviewed
- 8.2 The clear identification of the protocol of the proposed Research or amendment, date and version number (if applicable) on which the decision is based;
- 8.3 The names and (where possible) specific identification numbers (version numbers/dates) of the documents reviewed, including the potential research participant information sheet/material and informed consent form;
- 8.4 The name and title of the applicant
- 8.5 The name of the research site(s)

- 8.6 The date and place of the decision
- 8.7 A clear statement of the decision reached
- 8.8 Any advice by the ERB
- 8.9 In the case of a conditional decision, any requirements by the ERB, including suggestions for revision and the procedure for having the application re-reviewed
- 8.10 In the case of a positive decision the following is required:
 - 8.10.1 A statement of the responsibilities of the applicant
 - 8.10.2 Confirmation of the acceptance of any requirements imposed by the ERB
 - 8.10.3 Deadlines for the submission of progress report(s)
 - 8.10.4 The need to notify the ERB in cases of protocol amendments (other than amendments involving only logistical or administrative aspects of the study)
 - 8.10.5 The need to notify the ERB in the case of amendments to the recruitment material, the potential research participant information, or the informed consent form
 - 8.10.6 The need to report serious and unexpected adverse events related to the conduct of the study
 - 8.10.7 The need to report unforeseen circumstances, the termination of the study, or significant decisions by other Ethical Committees
 - 8.10.8 The information the ERB expects to receive in order to perform ongoing review and deadlines for the submission of final report
 - 8.11 The schedule/plan of ongoing monitoring by the ERB
 - 8.12 In the case of a negative decision, clearly stated reason(s) for the negative decision
 - 8.13 Signature (dated) of the Member Secretary (or other Authorized person) of the ERB

9. Follow up of the ERB

ERB will establish a follow-up procedure for following the progress of all studies for which a positive decision has been reached, from the time the decision was taken until the termination of the research.

- 9.1 The follow-up review intervals will be determined by the nature and the events of research projects, though each protocol should undergo a follow-up review at least once a year
- 9.2 The following instances or events require the follow-up review of a study
 - 9.2.1 Any protocol amendment
 - 9.2.2 Serious and unexpected adverse events related to the conduct of the study or study product, and the response taken by investigators, sponsors, and regulatory agencies
 - 9.2.3 Any event or new information that may affect the benefit/ risk ratio of the study
- 9.3 A decision of a follow-up review will be issued and communicated to the applicant, indicating a modification, suspension, or termination of the ERB's original decision or confirmation that the decision is still valid
- 9.4 In the case of the premature suspension/termination of a study, the applicant should notify the ERB of the reasons for suspension/termination; a summary of results obtained in a study prematurely suspended/terminated should be submitted to the ERB
- 9.5 The applicant will inform the ERB at the time of the completion of a study
- 9.6 The applicant will submit to the ERB a copy of the final summary or final report of a study
- 9.7 The ERB can issue an approval letter for publication as per need

10. Documentation and Archiving

All documentation and communication of ERB will be dated, filed, and archived according to written procedures. A statement is required defining the access and retrieval procedure (including authorized persons) for the various documents, files, and archives. The documents will be archived for a minimum period of 5 years following the completion of a study.

Documents that should be filed and archived include

- 10.1 The Constitution, written standard operating procedures of the ERB, and regular (annual) reports

- 10.2 The curriculum vitae of all ERB members
- 10.3 A record of all income and expenses of the ERB, including allowances and reimbursements made to the secretariat and ERB members
- 10.4 The published guidelines for submission established by the ERB
- 10.5 The agenda of the ERB meetings
- 10.6 The minutes of the ERB meetings
- 10.7 All materials submitted by an applicant
- 10.8 The correspondence by ERB members with applicants or concerned parties regarding application, decision, and follow-up
- 10.9 A copy of the decision and any advice or requirements sent to an applicant
- 10.10 All written documentation received during the follow-up
- 10.11 The notification of the completion, premature suspension, or premature termination of a study
- 10.12 The final summary or final report of the study

APPENDICES

Appendix I

Checklist for the Ethical Review of Proposals

Review of the research proposal for ethical clearance:

Title of the research proposal:

Date of review:

Reviewer:

Issue under Consideration	Questions related to the main Issues	Yes	No.	Remarks
Consent	Provision for informed consent			
	Clarity of the topics to the subjects.			
	Voluntariness of the consent			
	Inducements to participate, monetary or others			
	Unconditional withdrawal allowed?			
	Mechanism for taking consent from minors and disabled			
	Possibility of tricking participants to participants			
Benefits to the Participants	Possibility of intervention (Vaccine, drug or supplementation) being available to the participant population if found effective.			
Application of Ethical Principals	Is the study essential to accomplish the goal?			
	Is there no other way to obtain the information?			
	Do the benefits outweigh the risks?			
	Are the risks reasonable and not excessive?			

	Do the researchers have adequate qualifications and competencies?			
Obligations of the sponsors	Assurance of medical services related to research for study participants.			
	Assurance of access to beneficial results to study participants			
	Reasonable mechanisms for care and compensation in case of injury, resulting from research.			
	Provision of mechanism for capacity building of the national research institutions in the host country			

Appendix II

Ethical Questions

ETHICALLY DRIVING QUESTIONS FOR CONSIDERATION BY THE ETHICAL REVIEW BOARD

1. What questions does this research answer?
2. Are those questions relevant to the needs of the country?
3. Has/ve such research (es) been already conducted in Nepal?
Elsewhere?
4. Has another ERB reviewed this proposed research? If yes, what was their decision?
5. Is it necessary to involve human subjects for the research?
6. Whom does the research put at risk?
7. What are risks? Identify them.
8. Whom does the research benefit?
9. Do the participants benefit at all from the study?
10. Do the participants have any risk from participating in the study ? If so, what are those risks?
11. Do the benefits outweigh any risks?
12. How is informed consent obtained from the participants, and is the type of informed consent appropriate?
13. How can the participants opt out of the research once it is started?

14. Is the research" externally sponsored? If yes, what are the responsibilities of the external sponsor?
15. Is there 'any transfer of technology involved during the research process?
16. How are the' sponsors going to strengthen the research capability of the host institution?
17. Is there going to be transfer, of biological materials?
18. Is there provision of Data Safety Monitoring Board (DSMB) for clinical trial study?
19. Is the clinical trial registered elsewhere?

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