

# **National Ethical Guidelines for Health Research in Nepal, 2019**



**Nepal Health Research Council (NHRC)**  
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## **Foreword**

### **Message from the Chairman Nepal Health Research Council**

It is indeed a great pleasure and privilege for NHRC to revised a document entitled "National Ethical Guidelines for Health Research Involving Human Participants and use of Animals. NHRC is currently exploring the new idea to overcome the challenge of health research. I hope, this guideline builds on these initiatives. NHRC has always been on the forefront to set the standards for ethics in health research. The council brought out a policy document in 2001 and further revised in 2011.

These guidelines are a result of expert in-depth discussions and debates, involving the diverse stake-holders, secretrait of NHRC, ERB board members and also the ex-chairman and advisor opinion. I believes NHRC ethical guidelines will respected and used as a reference nto only in Nepal but a number of other countries and researchers.

This version of guidelines has addressed the newer emerging ethical issues keeping in view the social, economic, cultural, legal and religious aspects of our country. The guideline will be successful to sensitize the government authority, health care institutions, policy makers, planners, research institutions and social scientists of Nepal.

I expect that the researchers will be able to get more clarity on NHRC ERB requirements, understanding on the standard

templates, checklists for submission, and monitoring compliance need. It is believed that with the concerted efforts and collaboration of Government, NHRC, private, public and other relevant organizations, our goal of preparing national guidelines will ultimately lead to the development of sound ethical in Nepal. I am confident that the government, health care institutions, and last but not the least individual will contribute to make it a success. My thanks go to WHO, NHRC staff, ERB secretaries and consultants involved in the preparation of these guidelines. I wish that the researcher and research institutions will be enormously benefitted by these revised guidelines.

**Professor Dr. Anjani Kumar Jha**

Executive Chairperson, Nepal Health Research Council

July 2019

## **Preface**

Nepal Health Research Council (NHRC) has been entrusted and mandated with the responsibility of promoting quality health research in the country. Nepal Health Research Council (NHRC) Act 1991 and its by-laws have mandated NHRC to publish, disseminate and implement guidelines to make health research scientifically and ethically sound. NHRC has taken steps with the contributions from experts to develop and update the ethical guidelines at different times.

NHRC has developed and published a variety of Guidelines including, National Ethical Guidelines for Health Research in Nepal-2001 (first edition) and 2011 (second edition), National Health Care Waste Management Guidelines-2002, Ethical Guidelines for the Care and Use of Animals in Health Research-2005, National Guidelines on Clinical Trials with the Use of Pharmaceutical Products-2005, and Guidelines for Institutional Review Committees-2005.

Realizing the need for timely revision, addressing to incorporate newer developments in medicine, science and technology, NHRC executive committee formed a team of Ethical Review Board (ERB) members and secretariat staffs to update the existing version of the Ethical Review Guideline in 2018. The current version of the guideline has tried to address newer concepts in ethics, developments in medicine, science and technology. The guideline has specific separate sections on basic and general ethical principle, responsible conduct of research, ethical review procedure, informed consent process, vulnerability, clinical trials, public health research, social and behavioral science research, human genetic testing, bio-banking, research involving animal experimentation, and insect vectors. This guideline is based on basic principles of Nuremberg Code in 1947, 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.

This version has envisioned separate SOPs for each components including operation/functioning of the ERB, review process and reviewer's roles and responsibilities, Material Transfer agreement for transferring biological materials addressing intellectual property rights of the research organizations/researchers within the country. This document has tried to bring in concept of mitigation of conflict of interest for the reviewers/ERB members while performing their assigned duties, separate sections on requirements for externally funded research, monitoring of ethical conduct of research, bio-repository, animal handling and research using genetic materials/embryos, research during emergencies.

ERB expects all the researchers and institutions involved in research adhere to the principles and guidelines as laid down in this document. At the end but not least ERB acknowledges the contribution of experts, earlier ERB members and all who have directly and indirectly contributed to bring this guideline to this stage. Any constructive feedback for improvement in subsequent revision are highly appreciable.

Prof. Dr. Prakash Ghimire  
Chair ERB/NHRC on behalf of ethical review board  
July 2019

## **Acknowledgement**

## **Abbreviations**

AE	Adverse Events
AMR	Antimicrobial Resistance
CIOMS	Council of International Organizations of Medical Sciences
CoI	Conflict of Interest
CRO	Contract Research Organization
CTR	Clinical Trail Registration
CV	Curriculum Vitae
DDA	Department of Drug Administration
DSMB	Data Safety & Monitoring Board
DTA	Data Transfer Agreement
E-consent	Electronic Informed Consent
ERB	Ethical Review Board
GCP	Good Clinical Practice
GIS	Geographical Information System
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GoN	Government of Nepal
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors

IMP	Investigational Medicine Product
IPR	Intellectual Property Rights
IRC	Institutional Review Committees
LAR	Legally Authorized Representative
LGBT	Lesbian, Gay, Bisexual, Transgender
MoU	Memorandum of Understanding
MTA	Material Transfer Agreement
NHRC	Nepal Health Research Council
NPR	Nepalese Rupees
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCR	Responsible Conduct of Research
SAE	Serious Adverse Events
SOP	Standard Operating Procedure
US\$	United States Dollar
TB	Tuberculosis
ToR	Terms of Reference
UN	United Nations
WHO	World Health Organization
WMA	World Medical Association

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## Section 1. Introduction

Research involving human beings needs to be scientifically valid and robust and should be conducted according to accepted ethical standards. Research ethics provides guidelines for responsible conduct of research on human beings. It primarily protects research participants and also educates and monitors researchers conducting health research to ensure a high quality of ethical standard. In health research, ethics concerns itself primarily with the promotion and safeguarding of the dignity, rights and well-being of research participants.

### 1.1 Historical Background

The fundamental concept of the word **ethics** is derived from the Greek word “*ethos*”, which means character, disposition or a fundamental outlook that influences behavior 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.

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 Samhit*” (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 18<sup>th</sup> century. Thomas Percival came up with the concept of bio-ethics and legislative aspects of ethics related behavior.

In 1946, the International Health Conference 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 (UN), the WHO promotes the "*Universal Bill of Human Rights*" which includes "*Universal Declaration of Human Rights*" promulgated in 1948, the "*International Convention of Economic, Social and Cultural Rights*" (1966, ratified in 1976) and the "*International Convention on Civil and Political Rights*" (1966). These three instruments define 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 (NHRC) in all its activities.

Ethics related to health and biomedical research is relatively recent phenomenon. The first international document to 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 important series of documents is *Declaration of Helsinki*, adopted by the World Medical Association (WMA) in 1964. It has since been revised and updated several times (1975, 1983, 1989, 1996, 2000, 2002, 2004, 2008, and 2013). It added three major influential points to what was previously outlined in the "*Nuremberg Code*". The first included point was a theoretical difference between clinical, therapeutic, or diagnostic research and non-therapeutic biomedical scientific research. The "*Declaration of Helsinki*" did not adequately consider the final right of the independent review. However, it recommended the written records of informed consent, extra protection for vulnerable people, and responsibilities of the medical researcher who enrolls his/her own patients for research purposes. Even after the formulation of "*Nuremberg Code*" in

1947 and “*Declaration of Helsinki*” in 1964, ethical violations among human beings were continued. One of such example was the Tuskegee Syphilis study (1932-1972).

In 1979, the “Belmont report” identified three basic principles of research ethics, namely (i) respect for person, (ii) beneficence, and (iii) justice. These three principles were considered as the fundamental requirements for meeting the legitimate research where humans are included as study participants. In 1982, the Council of International Organizations of Medical Sciences (CIOMS) issued the “*International Ethical Guidelines for Biomedical Research Involving Human Subjects*”. This ensured the effective application of ethical principles set forth in the “*Declaration of Helsinki*”, particularly in developing countries. The guidelines were revised in 1993 and 2002. In 1996, the “*International Conference on Harmonization (ICH)*” finalized the “*Guidelines for Good Clinical Practice (GCP)*”. This standardized the scientific and ethical requirements for clinical research leading to the approval of new drugs. In 2006, the WHO published the *Handbook for Good Clinical Research Practice* to support researchers in the implementation of GCP standards in all types of human research. In 2002, the Nuffield Council on Bioethics (UK), the “*Ethics of Research related to Health Care in Developing Countries*” emphasized the requirement to examine the ethical issues raised when research related to health care is conducted in developing countries and funded by sponsors from developed countries. The major recommendation of council focused on the inclusion and development of local partners in the health research.

National Ethical Guideline for Health Research in Nepal, is cognizant of these declarations, code and guidelines. This has followed the spirit in which they are written. In 1995, the NHRC

published the first document on research ethics titled *NHRC's Ethical Guidelines*. In 2001, the NHRC published the "*National Ethical Guidelines for Health Research in Nepal*". Following these publications, NHRC has organized several workshops and consultative meetings on research ethics in Nepal. In 2005, the NHRC published "*Ethical Guidelines for the Care and Use of Animals in Health Research in Nepal*" and "*National Guidelines on Clinical Trials with the Use of Pharmaceutical Products*". The workshop, organized by the NHRC on March 13 to 14, 2008, focused on ethics in health research, recommended that it was important to revise the National Ethical Guidelines published in the year 2001. Subsequently, the guideline was revised in the year 2010, published in 2011 and named as "*National Ethical Guidelines for Health Research in Nepal and Standard Operating Procedure (SOP)*".

The socio-cultural ethos in the federal context of Nepal and its different levels of standards of healthcare pose distinctive challenges to the application of universal ethical principles to health research. In the last seven years several ethical issues have evolved demanding further revision of the existing guideline published in the year 2011 and preparation of the current "*National Ethical Guidelines for Health Research in Nepal, 2019*". The updated guideline presents its contents in section-wise format, wherein various aspects of research ethics have been described in a chronological order, and also covered some newer areas, which were not included in the previous guideline.

## **1.2 Scope of the Guideline**

The current guideline is applicable to all types of health research to be conducted in Nepal involving human beings, their biological specimens and data. As there may be some risk and harm or inconvenience to the research participants during the study process, protection of such participants should be incorporated

into the research design phase. Every health research should ethically be justified by its social value.

The purpose of health research should be:

- (i) Focused towards increasing knowledge on the human condition while retaining sensitivity to the federal, provincial and local Nepali culture and its various social dimensions including due consideration to natural environment;
- (ii) Conducted under circumstances such that human beings who are participating in any health research are dealt within an approach that is beneficial to and respect their dignity and well-being, under situations of professional unbiased treatment and transparency; and
- (iii) Subjected to a regime of assessment during the research process including reporting of the outcomes thereof.

## Section 2. Ethical Principles

The ethical principles should be considered as an important human value. The ethical principles of the health research take into account the principles of respect for autonomy of an individual, beneficence, non-maleficence, justice and environment. While conducting research at a community level involving humans in groups, all these principles are applied in a composite way. The principle of respect for the environment aims to ensure cultural respect and benefit of community members, their environment, and do not harming them, and ensuring the justice to them.

### 2.1 Basic Ethical Principles

The following four basic ethical principles: (a) respect for the autonomy of an individual, (b) beneficence and non-maleficence, (c) justice and (d) respect for the environment, form the basis for the ethical evaluation of health research proposals in Nepal.

#### **a) Respect for the Autonomy of an individual (participant)**

The obligation to respect the dignity of participating individuals in all activities of the research is the cornerstone of the ethics. This principle is based on the foundation that an individual when informed of all aspects of the research activities, can individually decide a correct course of action for participation or rejection, and withdrawal at any time. This requires specific attention to the following:

- An individual's right to decide what is best for her/him cannot be over ruled by researchers.
- Researchers must safeguard the interests of individuals

with impaired or diminished autonomy and ensure that the vulnerable people are secured against any harm, abuse or exploitation.

- No research should take precedence over respect for human right, 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” process.

### **b) Beneficence and Non-maleficence**

Beneficence is the obligation to maximize possible benefits and to minimize the harms of individuals. This requires that all health research projects be preceded by careful assessment of the potential risks and burdens, in comparison to the potential benefits to the prospective research participants and their communities. This does not prevent the participation of healthy volunteers in research. However, in all cases the research should promote the health of the population represented. Non-maleficence means do no harm, and requires not to cause deliberate harm to the study participants.

### **c) Justice**

Justice requires individuals in similar circumstances be treated alike, and the differences between persons due to circumstances be acknowledged and addressed. For example, individuals with similar health complaints should be treated equally. Further, Justice requires an equitable distribution of

the burdens and benefits in research. Differences should be in such distribution are justifiable only if they are based on morally relevant distinctions between individuals. For example, in cases where it is essential to ensure the protection of the rights and welfare of vulnerable persons.

The protection of person's in vulnerable situations is important. People in such situations include those who are unable to express or protect their interest fully or partially. Such impediments lack of capacity to consent adequately, an inability to obtain alternative means of medical care and or other health care necessities. These individuals could also be juniors or subordinate members of a hierarchical group and legally incompetent. Thus, special provision is mandatory for the protection of the rights and welfare of all the people in vulnerable situation.

#### **d) Respect for the Environment**

This principle requires that the health research should be undertaken with respect for the social, cultural, and natural environment and historical heritage of a society. This principle is re-enforced by WMA declaration of Helsinki, which focus on special precautions for the protection of the environment in the conduct of research. Every researcher is accountable for moral engagement of protection of social, cultural and natural environment and historical heritage of communities and societies, as well as biodiversity. This responsibility includes commitments: to ensure proper and safe disposal of any hazardous waste from laboratory/clinical/field research; to safeguard the cultural, linguistic and religious heritage of communities, individuals and biodiversity; to treat the biologic and genetic heritage of the people with respect and these take outmost caution.

These four basic ethical principles have been extended into 12 general principles.

## 2.2 General Ethical Principles

- (i) **Principle of essentiality:** With due consideration of all the options within the existing knowledge, the use of human participants is considered to be essential for the proposed research. An ERB should assess the proposed research.
- (ii) **Principle of voluntariness:** The right of the human participants should be respected in terms of their agreement to participate or not to participate in health research at any time. Informed consent guarantees that the rights of participants are protected.
- (iii) **Principle of non-exploitation:** The human participants should not be exploited and discriminated. During equitable selection process in health research, benefits and risks should be distributed fairly. Appropriate precautions required to safeguard vulnerable populations to guarantee this aspect and utmost.
- (iv) **Principle of social responsibility:** Health research needs to be planned and conducted in such a way that it should not disturb social harmony in community relationships, and should avoid creation or deepening of social and historic divisions. The research outcome must benefit the society as a whole.
- (v) **Principle of ensuring privacy and confidentiality:** Researchers are required to maintain privacy of the participants. Identity and records of the participants should be kept confidential and access of such information should be limited to authorized individuals. However, privacy of certain information such as suicidal ideation, homicidal tendency, positive status of infectious diseases (HIV, TB, Leprosy, Bird Flu, Swine Flu, etc.) can

be breached in consultation with the ERB and judicial bodies (if necessary) for valid scientific or legal explanations as the right to life of other individual overtakes the right to privacy of the research participants.

- (vi) **Principle of risk minimization:** All the stakeholders (researchers, ERB members, regulators and sponsors) should take precaution during research process to ensure that the risks are minimized and suitable care and compensation is given if any harm happens.
- (vii) **Principle of benefit maximization:** Researchers must be careful during research process in such a way that the benefits (direct or indirect) are maximized to the research participants and society.
- (viii) **Principle of professional competence:** Individuals who are capable, experience and have the suitable qualification and training, should plan, conduct, evaluate and monitor the health research process.
- (ix) **Principle of institutional arrangements:** Institutions where the health research is being planned and conducted must have policies for suitable research governance and take the responsibility to expedite research by creating enabling environment through delivering essential infrastructure, human resources, funds and opportunities for training.
- (x) **Principle of transparency and accountability:** Transparency and accountability are two important elements of good governance, wherein the research plan and results arising from the research are brought into the domain of public through data base, reports and publications while protecting the privacy of the participant's right. Stakeholders (researchers, ERB members, regulators and sponsors) involved in the particular research should disclose any existing Conflict of Interest (CoI) and manage it properly. Health research should be conducted in an unbiased, honest, justifiable and transparent way to assure accountability. Research

related data including records and notes should be preserved for the specified period of time for any possible external inspection/audit and other reasons.

- (xi) Principle of totality of responsibility:** All the stakeholders involved in health research are accountable for their engagements and bound directly or indirectly with the national ethical guidelines and related protocols, SOP and directive standards for their professional, social and moral responsibilities.
- (xii) Principle of environmental protection:** Researchers are accountable for ensuring environment protection and resources during research process and bound with existing guidelines and related protocols, SOP and directive standards

All the investigating team members should take accountability and responsibility to abide and maintaining the above outlined principles while conducting the research in health or research for health involving human participants.

### **Section 3. Responsible conduct of Health Research**

Researchers have a significant role and responsibility to prevent scientific fraud and research misconduct. Researchers are guided by the standard ethical norm, value and relevant law. Research teams are expected to maintain high ethical standards and fundamental values of research. The Responsible Conduct of Research (RCR) has following major components: research values, norms and standard; policies and priorities that influence health research; issues during research planning and conduction including standardization of tools and calibration of instruments to be used in research; professional, legal and moral responsibilities of researchers, sponsors and institutions; research monitoring, reviewing and reporting; authorships in research publications; handling research misconduct, clinical trials registration, and collaboration & networking in research.

Research and academic institutions must establish a research office within their institution to facilitate and manage research, grants and all aspects of RCR. Health researches to be conducted by such institution must take prior ethical approval either from ERB of NHRC or from IRC existing in their own institutions. Such institution must follow guidelines developed by NHRC and prevailing law of the country. Such institutions should develop SOPs to address all aspect of RCR.

#### **3.1 Research Values, Norms and Standard**

Research is guided by research values, norms and highest ethical standard which include objectivity, accountability, accuracy, social justice, efficiency, transparency, personal integrity, best research practices, and relevant policies related to RCR. For maintaining RCR, following points must be taken into consideration by the investigators:

- Accountability for people/society/community
- Mentoring of health researchers
- Contemporary ethical issues for conduction of health research must be tackled
- Sensitivity to Nepali socio-cultural/religion/caste/ethnicity and their values and norms of health research

### **3.2 Policies and Priorities that influences Health Research**

Health research must be guided by relevant health and related policies and priorities adopted by the country. Researcher must protect its study participants and research institution should develop SOP based on national guidelines<sup>1</sup> published by NHRC and relevant policies for the protection of human participants. For animal research, researchers must follow all the existing policies and guidelines for the care and use of animals in health research.

### **3.3 Specific Issues during Research Planning and Conduction**

Conflict of Interest may occur while designing the study, selection of participants, interpretation of data, ethical review of research and research publication. Hence, there is a need to develop and follow policies and procedures to identify, mitigate and manage such CoI from different levels such as researchers, reviewers, institutions and ethics committees.

## **Identifying, mitigating and managing CoI**

1. ***At the level of Researchers:*** Researchers must declare CoI (financial and non-financial) during research process and also ensure investigators' commitment, time and devotion.
2. ***At the level of reviewers:*** Reviewers should declare CoI during review process if any of his/her close friends, family members and/or students has submitted the research proposals for obtaining research grants and approval. Reviewers should declare CoI if they are directly or indirectly involved in the research study.
3. ***At the level of research institutions:*** Institution must declare CoI during research process and develop SOP to mitigate CoI issues if any. Such issues should be communicated in a transparent way.
4. ***At the level of ERB:*** ERB members must declare their CoI (if any) and take appropriate actions to recuse themselves from the review and decision-making process on the protocol(s) related to their CoI; and make suitable advices for its execution. ERB must evaluate the study in light of any disclosed CoI and ensure that an appropriate action has been taken to mitigate this.

## **Data acquisition, management, sharing and ownership**

Researchers should be sensitive to research participants and their related environment and use best practices during data collection process. Investigators should be responsible for knowing when and from where the permission is needed to collect the data. Data collectors must have suitable qualification and training for collecting reliable and valid data.

- Collected data should be entered and analyzed in appropriate data management software and findings should be shared to right people at right places. Data should be archived in proper place.
- Data ownership matters, publication rights, and accountability should cautiously be worked out well before data collection and investigators should ensure such clarity. Memorandum of Understanding (MoU) (if needed) should be made between investigators and institutions or sponsors in advance.
- Proper attention should be given while developing the protocol, its tools and SOP. All the research results should accurately be recorded, interpreted and reported. Research must be conducted by using suitable method to provide reliable data. Implementation of poorly designed research study should be avoided as far as possible.
- For biological samples, researchers should maintain the ownership of such sample and it should be mentioned in the informed consent document.
- Institutes executing the research must protect the data, and biological samples (if any).

Data protection and archiving is an important and it may be required at a later stage to confirm research findings, establish priority, or be validated by other researchers. Liable data handling starts with proper storage and protection from damage, loss or theft. Appropriate care should be made to reduce the risk of damage, loss or theft, fire, flood and other disastrous events. Data files should properly be archived and these must be saved and outmost in a secure place including back-up system. Data governance mechanism should be in place.

Data for the following study types cannot be collected without having prior permission from the relevant authorities:

- Human participants in health research
- Animals use in health research
- Biological specimen collection
- Use of data sets from the bio-samples stored in the Bio-bank for future research
- Data from hospital/medical/police records, some institutions/library, databases and archives,
- Photographs, recorded messages and notes, and
- Other copyrighted or patented processes or materials

Data sharing plan (when, and with whom) should be mentioned in research proposal. After completing of the study, it is expected that the final data sets might have freely been available for other researchers for cross-check and future research. Data can be placed in a public domain must be in an anonymized form unless prior permission.

### **3.4 Professional, Legal and Moral Responsibilities of Researchers, Sponsors and Institutions**

- Study team that conduct the research, sponsor that funds the research and institution where the research is conducted, should take respective professional, legal and moral responsibility to follow all the principles, guidelines and directives of the ERB.
- Researchers from collaborating sites should adequately be represented throughout the study period including from proposal developing stage. Same study protocol and SOP should be followed in each site unless prior permission.

- Sponsor should be responsible for unbiased contract negotiation during collaborative research partnership for benefit sharing and avoid unauthorized use of bio-samples, data and human resources.
- Sponsor/lead institution should offer some opportunities for building capacity in health research.

### **Obligations/Duties of Researcher**

- Identify the vulnerability of the human participants and ensure their protection
- Select the participants based on inclusion and exclusion criteria of the study as specified in the protocol
- Mechanism of early identification and prevent misconduct of research
- Conflict of Interest issues must be declared
- Follow the SOPs
- Ensure a balanced risk-benefit ratio
- Ensure competency of the prospective research participants to provide informed consent/assent
- When a prospective participant lacks the capacity to consent, take proxy informed consent from Legally Authorized Representative (LAR)
- Respect disagreement from the study participant
- Seek permission from relevant authorities (admitted patients in the hospital, students in the school, orphans in the orphanage, geriatric population in old age home, tribal communities, etc.) if required
- Follow existing relevant guidelines/regulations during research process
- Obtain approval if any changes are required in the original approved protocol
- Inform to ERB if any miss-happening/adverse events (if relevant) occur during research implementation process

## **Obligations/Duties of Sponsor**

- Justify the inclusion of vulnerable groups in the proposal and make provisions for safeguarding them
- Justification for excluding some specific participants (if any) who meet the inclusion criteria
- Facilitate monitoring and guarantee that procedures are in place for Quality Assurance (QA) and Quality Control (QC)
- Ensure that research participants and study team are well protected especially when the study is on sensitive topics
- Select investigator(s), ensure availability of study site(s), assure relevant qualification of study team to conduct the study
- Develop, maintain, modify and ensure the availability of research support systems and tools.
- No undue influence on research design, data collection, data analysis and publication of research findings

## **Responsibility of Researchers**

- Submit the proposal in the prescribed format of ERB
- Use ERB approved version of the questionnaires and consent form including its Nepali translation
- Communicate essential information adequately for informed consent in an understandable language by prospective research participants
- Use appropriate method in case of differently abled prospective research participants to enhance the participant's understanding (braille for visually impaired participant)
- Provide an opportunity to ask questions related to the study and also provide enough time to come for a decision after participants' discussion with their family members and friends.
- Should not influence or threaten or pressurize and must not provide unjustifiable assurances to a prospective participant

- Ensure that the participant has understood all aspects of the research and that the consent is given voluntarily. If prospective participant and/or the LAR are illiterate, a witness who is not connected to the study (impartial witness) should be present throughout the consent process.
- Apply a test of understanding tool whenever possible for sensitive studies. The test may be repeated until the prospective research participant has actually understood the contents of the research.
- When a prospective participant is ready to participate but not willing to sign or give a thumb impression or cannot do so, then verbal/oral consent may be taken in the presence of an impartial witness who should sign and date the consent document, but this has to receive prior approval from ERB. This whole process can be documented through video recording process, wherein the participant, the investigator, and the impartial witness should have to be seen and voice should clearly be heard in the recorded frame.

***Note:** Verbal/oral consent should only be taken in exceptional conditions and for precise, reasonable explanations, only with ERB approval.*

- Take fresh informed consent or re-consent of each participant under circumstances described in the section 5.7.
- Assure prospective participants that their decision whether or not to participate in the study will not affect their rights, or any other benefits to which they are entitled.
- Reimburse participant's travel and incidental expenses occurred while participating in the study, but this has to receive prior approval from ERB.
- Ensure free treatment for research related injury and if required, provide payment of compensation as per recommendation of the relevant authority.
- Ensure that the participants can continue to access regular treatment and care even after their withdrawal from the study.

### **3.5 Research Reporting**

- Completed research report should be submitted to NHRC and can be published.
- All reviewers and editors evaluating the report/paper of research should perform their task honestly. The research report should be transparent and trustful and the researchers' integrity is beyond doubt.
- Researchers should acknowledge all the contributors of the research study in the report.
- Investigators may provide research based data in the public domain after necessary approval from the NHRC or relevant authority

### **3.6 Authorships in Research Publications**

- Research institution should follow the authorship policies and guidelines of International Committee of Medical Journal Editors (ICMJE)
- The authorship should be reflected at the time of beginning of the study and should not be accepted the gifted and 'ghost' authors.
- The principal author should do the most of the research work related to the manuscript submitted for the publication. For academic thesis research, the student should be candidate as the principal author. For fulfillment criteria of authorship, all efforts should be made to provide the candidate an opportunity for authorship based on guideline of ICMJE.

## **Criteria for Authorship in research publication according to ICMJE**

1. Substantial contributions to the idea or the work design, or the acquisition, analysis, or interpretation of finding for the work;
2. Drafting the work or modifying it for key intellectual content;
3. Final approval of the version to be published;
4. Agreement to be responsible for each phases of the work and confirming that questions related to the correctness are properly examined and undertaken.

### **3.7 Handling Research Misconduct**

Research misconduct may occur due to fabrication, distortion and plagiarism of data.

- ERB must examine all claims of misconduct as present or future participants' lives may be threatened if evidences are not presented precisely. Such investigation must be done timely and fairly manner and its findings should be made public after completing the investigation.
- NHRC addresses research misconduct in line with the prevailing law of the country.

### **3.8 Clinical Trials Registration**

All research involving human participants including any interventions/trial such as vaccines, drugs, herbal products, complementary medicine, device, surgical procedures, alternative medicine procedure, and public health intervention using clinical procedures should be registered in the accredited clinical trial registry. Researcher should provide its registration number to the ERB of NHRC during submission of the clinical trial proposal for ethical approval.

### **3.9 Collaboration and Networking in Research**

Collaboration and networking could be done with colleagues / experts / sponsor / institution to conduct individual research. This could be inter/intra departmental/ institutional or provincial/national/international, and also multi-center involving public and or private research institution and agencies.

The main issues related to collaborations concern sharing tools & techniques, representation of sample, follow same SOP, ownership of materials and data, Intellectual Property Rights (IPR), joint publication, handling research data, managing CoI, commercializing study results, etc. Relevant agreements related to these issues should be mentioned in the MoU, and ERB needs to review and approve the MoU.

Investigators must be aware of all above mentioned aspects including provincial, national and international requirements for research collaboration and its necessary approval and agreement processes.

Researcher should be cautious enough to judge whether such collaboration create the impression of exploitation by developed country experimenting on Nepalese population or not. Researcher needs to play a smart role in such aspect including IPR and equitable sharing of research benefits.

Collaboration with international agencies (public or private) may include either execution of various components of the research or even a single component like laboratory testing. Before the sponsor agency/province/country initiates collaboration, relevant regulatory requirements including ethical guidelines should be followed.

## **Externally Sponsored Research**

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

- The research should be based on needs and priorities of the Nation as well as being sensitive to the exiting socio-environmental contexts including socio-cultural, religious and social norms and value.
- The research cannot be carried out reasonably well in the sponsor's country.
- The research protocol should be approved from the sponsor country.
- The sponsor should consider means in which the research capacity of Nepal can be strengthened and other means of appropriately compensating the community.
- The research process should be transparent and be of the highest ethical standard.
- External sponsors should provide insurance/compensation to research participants as well as study team members in health research that involves more than minimal risks
- If it is necessary to transfer biological specimens abroad, a MoU has to be signed by the sponsor/collaborating institute and researcher/research implementing institute defining clearly the purpose for the bio-sample transfer (refer section 4.8), its justification, Material Transfer Agreement (MTA), ownership of IPR, and provisions for privacy protection. The ERB may provide permission for transferring the biological samples based on existing guideline and regulatory directives.
- The research proposal has to be approved by ERB.

## **Institutional Research Arrangements**

The collaborative research activity should be carried out only after making required institutional arrangements to conduct the research. Such institutional arrangements should include involvement of competent researchers and support staff, organizational set up conducive to research, SOP, ensuring safety to the research participants and confidentiality of data and disseminating the research findings. Institutional arrangements for preservation and archiving of research materials, data and reports must be kept in secured place. Sponsor/Institution/researchers should ensure whether such arrangements for the research study are in place or not. The collaborative institutions should follow the same standard of the protocol and procedures. The research conducted in any institution should obtain no objection letter from the institution.

## **Special Considerations in Collaborative Research**

- There should be good communication among collaborative partners. In case of any conflict or unfavorable events or any change made between the partners, these should be notified to the ERB, and decision will be made as per existing policies/guidelines/relevant laws/SOP.
- The context, magnitude and probability of all possible harm resulting from involving in the study should be mentioned in the collaborative research proposal.
- The possible harms and benefits should equally be distributed amongst the research participants to be recruited by all collaborative centers.
- All collaborative research involving human participants should have access to the best standard care and treatments available in Nepal.

- For International collaborative research, there should be one Nepalese lead Principal Investigator and site Co-Principal investigators relevant to the research project, and Nepalese lead PI should take all legal, technical and ethical responsibilities of the project in Nepal.
- International collaborative partners should strengthen Nepalese capacity in terms of developing knowledge, testing of specimens, providing appropriate technical support and capacity building trainings.

## **Section 4. Ethical Issues during Research Process**

Health researchers face several ethical challenges during research process. These challenges turn out to be ethical issues in dealing with vulnerable population, during assessment of risks and benefits, while maintaining privacy and confidentiality, providing equal distribution, compensation and payment, maintaining transparency, potential CoI, sample (biological/non-biological) collection, its storage and transfer and research benefit sharing. Not along with these, sometime researchers may be in dilemma as to what sort of qualification and competence that he or she might require to conduct health research in Nepal. Although there are several ethical issues, all health researches should be conducted in accordance with the ethical principles as outlined in section 2.

### **4.1 Research among Vulnerable Populations**

Vulnerable populations are those populations that are unable to protect their own safeties against the potential risks of participating in health research. Such populations may have a reduced capacity to provide informed consent, or they may require special legal protections as per country's law. Such populations need greater protection than normal against the potential risks of participating in research. Moreover, researcher may consider the selected individual as vulnerable if he or she has following characteristics.

- Autonomy is compromised or incompetent of making a voluntary informed decision for him/herself, for example individual who is unconscious, or differently abled;
- Able to provide informed consent, but his/her understanding is compromised because of his/her conditional events, or unjustifiably influenced either by

the fear of revenge in case of refusal to provide consent or anticipation of benefits;

- Susceptible for exploitation due to of his/her disadvantaged situation generated from social, economic and political settings.

Following is the list of populations that ERB commonly consider as vulnerable populations. However, such populations may be considered as vulnerable at some or all times.

- Children (minors or individuals under the legal age of consent, i.e. less than 18 years)
- Elderly people (e.g., more than 60 years)
- Pregnant or lactating women
- Differently abled person
- Refugees, immigrants, migrant workers
- Slum dwellers
- Sex workers
- Under trial population
- Victims of traumatic events [e.g., abuse (drug, sex, etc.), natural disasters (earthquake, flood, landslide, etc.), conflict/war/riot, etc.]
- Individuals with mental illness or cognitive impairment
- Individuals with a life-threatening illness or condition (e.g., cancer, HIV/AIDS, etc.) or terminally ill persons
- Disadvantaged, marginalized, tribal and indigenous communities including ethnic and sexual minorities [for examples, orphans, persons below the poverty line, untouchables, backward classes, socially isolated people, Lesbian, Gay, Bisexual, Transgender (LGBT)]
- Individuals who are highly dependent to follow the command of their superior, especially under a hierarchical system [for examples, prisoners, para-public forces (armies, armed forces, police forces), students, employees, etc.]

- Individuals who has poor decision-making powers/poor access to healthcare

If vulnerable populations are to be included in research, the ERB will often require to have specific procedure in place to protect such research participants. So investigating team must ensure that extra efforts are in place to protect the rights, dignity, safety and wellbeing of such participants. Vulnerable populations should be empowered, possibly to the highest level, to enable them to decide by themselves whether or not to give informed consent / assent for participation in the health research. If vulnerable people lack the ability to consent, a LAR must be involved in decision making procedure. Privacy and confidentiality of such people should be maintained properly to safeguard such populations.

**Additional safeguards/protection mechanisms:** Vulnerable populations are at high risk of being manipulated or easily affected by the view or desire of their caregiver or parents/guardians. They may be willing to please their caregivers or may be incapable of disagreeing with them. Similarly, if the caregiver is likely to be benefited by the dependent's participation in the study, they may be under pressure from the caregiver to consent for the study. Therefore, when recruiting the vulnerable individuals as research participants, additional precaution should be taken to avoid exploitation/revenge/reward/recognition, etc. or any other conditions that are likely to undermine the voluntariness of their consent to participate in the study. Following points must be addressed wherever relevant to ensure the additional protection mechanisms:

- Inclusion of the vulnerable population in the study must be justified and this justification provided by the researcher

should satisfy the ERB which should be noted in the meeting proceeding.

- ERB should review additional safety measures.
- Benefits and risks of vulnerable population including their risk minimization strategies should carefully be examined by the ERB.
- There should be no coercion, force, undue influence, threat or incentives for participation during the investigating period.
- Information about the research, benefits, risks and alternatives (if any) may repeatedly (if needed) be provided to vulnerable people into their own language or the language they understand.
- Investigators should be careful if there are any possibility of conflicting interests between the vulnerable participant and LAR.
- Care should be taken specifically when the vulnerable participant is recruited from the general population or enrolled as a normal control in certain types of health research, as the participants may be prone to discrimination or stigmatization. Therefore, researchers must demonstrate the effort to address these issues.
- There should be a support system to deal with associated medical and social problems if persisted during the initial phase of research study particularly while dealing with vulnerable populations suffered with natural disasters (earthquake, flood, landslide, etc.) and conflict/war/riot. Supplementary care (setting up of a health facility, school for unattended children participant, counseling center), wherever possible may be delivered while setting up such support system.

**Researches involving children:** Health research which can be done in adults should not be done in children. Only those researches which are of relevance to children should be carried out in children. Research involving children should be carried out

only after taking informed consent from their parents or LAR. Health research in children can be carried out if the situation, condition, disorder or diseases fulfils one of the following conditions:

- It is only seen in childhood.
- The information likely to be generated cannot be obtained by any other alternative means.
- If it is seen in adults as well, the issues are significantly different for adults and children.
- If there is only minor increase in the risk of test intervention, and the importance of the knowledge expected to be gained is high.
- Safety of drugs/vaccines need to be checked among adult population before administering these among children. However, the adverse effects of these drugs/vaccines may be different in adult population as compared to children due to differences in their physiology of development stage.
- Drug delivery formulations (e.g. syrups) are required for precise, safe, and edible administration of drugs to age specific children population.
- In case of children without immediate guardians such as street children, due approval should be taken from competent administrative authorities.

**Research among reproductive aged, pregnant and lactating women:** Research involving women in special situations such as pregnant women and lactating mothers should not be carried out unless the study is related to pregnancy and lactation, and the required information cannot be generated from other means.

Similarly, for some groups of women, informed consent can be challenging because of socio-cultural reasons. In these cases, with due respect to the woman's autonomy, the researcher must also

follow the requirements of local cultural practices so as not to disturb the harmony in the household/family/community.

Researchers should stipulate its proper justification for inclusion of pregnant and lactating women in the clinical trials e.g. trials designed to test the safety and efficacy of a drug for reducing perinatal transmission of HIV infection from mother to child, trial of a device for detecting fetal abnormalities etc.

Reproductive aged women should be informed of the probable risk to the fetus if they become pregnant during the period of their recruitment in the clinical trials. In such circumstances, researchers need to advise these women to use an effective contraceptive method, and tell about the options available in case of failure of contraception. In case, if women become pregnant, they should not automatically be removed from the clinical trial study unless and until there is an evidence not showing potential harm to the fetus. However, women must be offered the option to withdraw or continue. If women agree to continue in the clinical trial, researchers and sponsors should monitor such women more precisely and offer the required support to the women for a necessary period of time.

**Research involving sexual minorities and sex workers:** To include sexual minorities and sex workers in the study, there are unique challenges related to privacy, confidentiality, possibility of stigma, discrimination and exploitation that lead to increased vulnerability of these participants. So, the safety of their dignity and provision of quality healthcare under these conditions should well be addressed in the study proposal. For example, for the studies involving sexual minority, a representative of the sexual minority group, LGBT community can be invited to participate in the ERB meeting and necessary advices can be taken to identify

the measures to protect the prospective vulnerable populations and this representative can act as an interface between the researcher(s) and the community.

**Research among tribal and indigenous population:** Research can only be conducted among tribal and indigenous population if it is of a precise diagnostic, therapeutic and protecting nature with suitable benefits to such population. Prior to entering the tribal areas, due approval from the relevant administrative authorities should be taken. In case of absence of competent local level authority, permission from tribal leaders or other culturally appropriate authority or socially acceptable person should be taken. Informed consent needs to be taken in consultation with the persons who know the local language/dialect of the tribal/indigenous population and there should be an appropriate witness during individual consent taking process. For any research that utilizes tribal/indigenous knowledge that have potential for commercialization, the details should be shared with the tribal groups and clearly mentioned in the proposal.

Research involving individuals with mental illness or cognitive impairment: Mental illness should be considered as a substantial disorder of thinking, mood, and perception, memory that clearly impairs judgment for a decision, behavior, and capability to recognize reality or ability to meet the normal demands of life. Persons suffering with mental disorder should not be understood that they are not in a capacity of understanding or inability to provide informed consent. Similarly, the population in whom conscious mental activities such as thinking, understanding, learning, and remembering (called as cognition) are not fully functional are regarded as cognitively impaired or affected. Such persons may be intellectually or mentally disabled, unconscious

and suffering from dementia (a neuropsychological disorder). These people may not fully understand (either temporarily or permanently) the information provided during the informed consent process. So, the study that includes such population should carefully be reviewed by the ERB.

Sometimes, because of the participant's vulnerability and risk of harming their life e.g. in person with suicidal ideation, those who have substance abuse disorder etc., there may be conditions, where breach of confidentiality may happen. In such situations, it should be revealed to the participant that his/her privacy may be breached for reporting to family members, police, or other authorities or they may have to be admitted in the health care facility upon expression of such thoughts of harm to self or others. While some interventions, like admitting in the health care facility and treatment for suicidal/homicidal thoughts, may primarily be for the participants' own benefit, they themselves may not recognize these as such and may want to reject to join in a study if any such interventions are needed. So, such type of interventional study must be of short period, as least restrictive as possible and conducted as and when necessary, in accordance with relevant laws.

Research among Individuals who are highly dependent to follow the command of their superior: Researcher enrolling Individuals like students, employees, prisoners, persons under trials, armies, armed/police forces personnel, etc. should ensure that this group of participant are specifically relevant to the research questions and is not merely a matter of convenience. Such individuals should not be in a position to disagree to participate for fear of authority and so additional efforts are needed to respect their autonomy. Researcher should describe to the senior authority

about the mechanism to avoid coercion of such individuals due to being part of the hierarchical system. So, the ERB should carefully review the study that includes such individuals, if required should invite the senior authority to the ERB meeting.

Research among terminally ill persons: Persons who are in search of new interventions having exhausted all available therapies may be ready to provide consent for any new intervention that is not yet validated. In such circumstances, there should be appropriate consent procedures and the ERB should carefully review the recruitment procedures of such persons during the research process. There should be a process of additional monitoring to detect any adverse events at an early stage. If the new intervention is beneficial to the persons, the ERB should carefully review post-trial access to the medication.

Other vulnerable groups: Special attention should be given and additional precaution should be taken while recruiting participants from other vulnerable groups such as disadvantaged, marginalized, ethnic minorities, persons below the poverty line, untouchables, socially isolated people, orphans, refugees, immigrants, migrant workers, slum dwellers, victims of traumatic events (natural disasters, riot, etc.), differently abled person and Individuals who have poor decision-making powers. Such precautions might be necessary to avoid exploitation/retaliation/reward/recognitions and other inducements. Since the autonomy of such individuals is already compromised, researchers have to justify their inclusion in the study, and such justification should satisfy the ERB. This should be recorded in the ERB meeting minute.

## 4.2 Assessment of Risks and Benefits

The risk is the probability of causing harm or discomfort expected as legal, economic, social, physical pain or injury or psychological effects. Such probable risks should be justified by the social and scientific value of health research. Risks should be minimum in nature. Risk can be categorized as (i) less than minimum risk, (ii) minimum risk, (iii) minor increase over minimum risk (low risk) and (iv) more than minimum risk (high risk). Their descriptions have been given in box 1.

### BOX 1. RISK CATEGORIZATION AND ITS DESCRIPTIONS

<b>Types of Risk</b>	<b>Descriptions</b>
<b>Less than minimal risk</b>	Probability of harm or discomfort anticipated in the research is nil or not expected. For example, research on anonymous or non-identified data/samples, data available in the public domain, meta-analysis, etc.
<b>Minimal risk</b>	Probability of harm or discomfort anticipated in the research is not greater than that ordinarily encountered in routine daily life activities of an average healthy individual or general population or during the performance of routine tests where occurrence of serious harm or an adverse event (AE) is unlikely. Examples include research involving routine questioning or history taking, observing, physical examination, chest X-ray, obtaining body fluids without invasive intervention, such as hair, saliva, urine, etc.
<b>Minor increase over minimal risk or Low risk</b>	Increment in probability of harm or discomfort is only a little more than the minimal risk threshold. This may present in situations such as routine research on children and adolescents; research on persons incapable of giving consent; delaying or withholding a proven intervention or standard of care in a control or placebo group during randomized trials; use of minimally invasive procedures that might cause no more than brief pain or tenderness, small bruises or scars, or very slight, temporary distress, such as drawing a small sample of blood for testing; trying a new diagnostic technique

	in pregnant and breastfeeding women, etc. Such research should have a social value. Use of personal identifiable data in research also imposes indirect risks. Social risks ( <i>stigma, work place discrimination, loss of respect, disclosure to family, isolation etc.</i> ), economic risk (loss of employment), psychological harm ( <i>if research is sensitive in nature and someone might become stigmatized if it is known that they are on the study, e.g. an HIV study</i> ) and discomfort may also fall in this category.
<b>More than minimal risk or High risk</b>	Probability of harm or discomfort anticipated in the research is invasive and greater than minimal risk. Examples include research involving any interventional study using a drug, device or invasive procedure such as lumbar puncture, lung or liver biopsy, endoscopic procedure, intravenous sedation for diagnostic procedures, etc.

**Source:** ICMR, 2017, National Ethical Guidelines for Biomedical and Health Research involving Human Participants, Page 6

Benefits to the participants refer to any sort of favorable outcome (direct or indirect) of the research. The participation in a research process should be of potential benefit to the participant or to his or her community or the population in general. Sometimes, benefits are commonly presented as available only during the study, which means the benefits end when the research is completed. The duration of any benefit associated or derived from the research participation must be clear to the potential participants beforehand. Benefits include the potential for better treatment, either immediately or in the future, and financial benefits in terms of compensation for being on the study and free or reduced price of the medical price. Special care is needed in determining how benefits are presented in individuals with limited access to health care services. Offering free health care to individuals who would otherwise not have access to it is a powerful incentive to participate in a research study and is potentially coercive. Researchers are responsible for ensuring

that potential participants' decisions are not clouded by the promise of health care or a potentially better (but unproven) new treatment. ERB should carefully review this.

The risk/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. However, making precise judgments about the risk/benefit 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, thorough accumulation and assessment of information about all aspects of the research should be done, and alternatives should be considered systematically.

Relevant risks and benefits should clearly be spelled out in the documents used in the informed consent process. When research involves significant risk, there should be an extra justification of such risk, and ERB should review this and record in the ERB meeting report. In most of the cases, ERB should ensure a favorable balance of benefits and risks, and assess the plans for decreasing the risks before approving the proposal. If there are any altered risks in the study, the ERB should also assess such risks during continuing review process.

### **4.3 Privacy and Confidentiality**

Researcher should protect the confidentiality of the research based information provided by the participants and the community. Although every effort will be made to keep the identity and data related to participants confidential as far as possible, sometime it may not be possible to do so under certain situations. Under compelling scientific and legal situations, such disclosures could be made with the permission of the ERB.

Recommendations of Data Safety & Monitoring Board (DSMB) or a similar body will constitute the scientific reason [threat to a person's or community's life, Serious Adverse Events (SAEs) that are required to be communicated to an appropriate regulatory authority etc.] and specific order from a court of law will be considered as compelling legal reason.

Researcher should not publish any information or photographs that may disclose the participant's identity unless and until obtaining his/her consent. Sensitive information like participant's HIV or leprosy status, mental or social status, preferable sex, etc. should be protected to avoid stigmatization and/or discrimination. Anonymity of individual's information is important while conducting research with stored biological samples or medical records/data, and access to these should be restricted.

**Data Privacy and Security:** Now-a-days several agencies are maintaining and storing variety of health databases on their server, which may not be research initially, but they may offer a huge possibility for subsequent research as well as commercialization in future. If such databases are used for research purpose like drawing information for particular disease group, it should be reviewed by an ERB. When the research based data is outsourced or sold (commercial gain), data privacy, data security, and possibility of legal liability should be safeguarded. There should be a mechanism (like auditing) to detect misuse of research based datasets. Research based data sets which are maintained in electronic formats, connected with internet or other networks, using cloud computing technologies may pose additional risks to privacy and confidentiality of the stored data sets. Therefore, appropriate measure should be adopted to

respect and protect privacy and confidentiality of participants' data sets as given in box 2.

### **BOX 2 MEASURES FOR RESPECTING AND PROTECTING PARTICIPANT'S PRIVACY AND CONFIDENTIALITY**

1. Ensure physical safety and security of the involved devices and computer servers (Firewalls, etc.)
2. Take data security measures such as password protection, etc.
3. Provide differential and role-based controlled access to data elements for members of the research team
4. Ensure use of data encryption when data is transferred from one location/device to another

**Source:** ICMR, 2017, National Ethical Guidelines for Biomedical and Health Research involving Human Participants, Page 136

### **4.4 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 provinces, geographical regions or ethnicity or socioeconomic status as far as possible. If there is a possibility for commercialization, there should be a plan for direct or indirect benefit sharing with participants. Such thing must be decided before beginning the study. If benefits are solely for those who are better-off themselves, vulnerable people should not be included in the study. There should be specific criteria for participant's selection and efforts must be taken to guarantee that participants are not exploited or over-sampled during the research process.

## 4.5 Compensation and Payment

The researcher should have made provisions to compensate the participants in the research for any harms they suffered during the research process. Furthermore, the researcher should have made provision for compensating the participants' efforts and time for research purposes. The information related to the provision for compensation should have been communicated to the research participant.

### **Payment for participation**

- If feasible based on resource availability, research participants may be reimbursed for expenses incurred in connection with their participation in research, such as expenses related to travel. Research participants may also be compensated for time spent, difficulty encountered, and other accompanying expenditures, e.g. loss of food supplies and earnings.
- The research participants should not be required to pay for any expenses incurred beyond routine clinical care that are research - related investigations, patient work-ups, interventions or related therapy. If participants will be offered free medical care for non-research-related conditions during the study period, such ancillary care may not become an undue inducement, but it has to be reviewed by the ERB.
- Sometime, research participants may also receive extra medical facilities at no cost.
- When consent is given on behalf of a participant by the LAR, payment should not become an undue inducement and this needs to be reviewed carefully by the ERB.

### **Compensation for research related harm**

Participants in research who suffer direct psychological, physical, social, legal or economic harm as a result of their participation are entitled to financial or other assistance after due evaluation to compensate them equitably for any temporary or permanent damage. Dependents of the participants are entitled to financial compensation in the event of death. The research proposal should have a built - in provision to mitigate harm associated with research.

- The researcher is responsible for reporting all SAEs to the ERB within 48 hours. Serious Adverse Events can be reported by on-line ERB platform or e-mail or fax communication (including on non-working days). Trial should be halted until further notice in case of series of SAEs. It is also necessary to submit a report on how the SAE was related to the research within two weeks of its onset.
- After receiving the SAE report, the ERB is accountable for reviewing the SAE's associated with the research and suggesting the kind of support to be provided to the participants if required.
  - It is the responsibility of the sponsor (whether a pharmaceutical company, government or NGO, national or international donor agency) to incorporate insurance coverage or provision for possible compensation for research related injury or harm.

***Note:** In investigator initiated research, the investigator/institution where the research is conducted becomes the sponsor.*
  - The researcher should maintain a budgetary provision for insurance coverage and/or compensation depending upon the type of study, expected risks and proposed number of participants in applications for research grants to funding agencies.
- All Adverse Events (AE) should be documented and reported to the ERB on a schedule based on the level of risk.

## 4.6 Qualification and Competence for the Research

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

- Principal investigator should have basic knowledge of research methodology and research ethics. He/she should have a professional competency in order to plan and execute the research project. He/she should be able to utilize his/her time properly in a balanced manner and be motivated enough to carry out the research project.
- A researcher should not have any pre-conceived notion, rather he/she should maintain objectivity while collecting the data. He/she should be able to develop or select appropriate tools and capable enough to collect reliable and valid data from the targeted populations.
- A researcher must have at least basic idea of data analysis, but also must be able to interpret the outputs of the analyzed data sets, and write the research report.
- A researcher or research team member should have proper communication skill and ability to establish rapport with the targeted populations, relevant authorities and collaborating institutions (if any) for facilitating the research process.

## 4.7 Transparency and Conflict of Interest

Transparency of research is central to the practice of ethical research. It has the following four major key elements: (1) research registration, (2) making the research outcome available for public, (3) letting study participants know about the research results, and (4) making research based data available for further/future research. The researchers and their associates

should conduct the research with fairness, honesty, impartiality and transparency. All involved in the research activity should disclose their interest in different aspects of study and their CoI, if any. Failure to disclose relevant information may lead to suspension of the approval of research activity. In case of suspension of the study, researcher may place a complaint against such a decision to the ERB.

Conflict of interest may occur in the conditions where professional judgment about a primary interest in research participants' benefit inclines to be unduly influenced by a secondary interest, financial or non-financial (personal, academic or political). This can be at the level of investigators, ERB members, Institutions or sponsors. So, it is essential to declare CoI (in any) at the beginning and ascertain suitable mechanism to manage it. Investigators should guarantee that the documents submitted to the ERB contain a disclosure of CoI (financial or non-financial) that may affect the research, and ERB should evaluate such study in order to ensure that proper means of mitigation are taken. Members within ERB should also declare their own CoI (if any) and manage accordingly as per adopted SOPs if CoI is detected at the institutional or researchers level.

#### **4.8 Data/Bio-sample Collection, Storage, Security, Transfer and Bio-banking**

Whenever investigator is about to initiate the research study, he/she needs to consider how the primary/secondary data including bio-samples will properly be collected and stored. The researcher also needs to think who will have access to the records of the data/bio-samples and how such data/bio-samples will appropriately be secured and transferred from one place to

another place within Nepal and even outside the country (if needed).

### **Data collection, storage, security and transfer**

It is always important to define primary and secondary data collection sources. Primary data collection sources comprise observations, questionnaire, pro-forma, personal interview, experiments, survey, etc.; whereas secondary data collection sources include journal articles, internal records, government/non-government publications, books, websites, etc. Once data is collected, researchers have to explain how such data will be stored and in which storage medium (paper or electronic based). Even after processing/analyzing the data, researcher needs to mention for how many years such data will be kept for use in the future.

Investigators need to mention the details of measures to be taken to secure research based data in the field, work and home settings including physical security of equipment (if any), digital security mechanisms, such as system, program and file passwording, file cabinet security process like lock & key that can only be accessed by agreed members of the research team, data storage and back-up plan. Failure to address security issues may be considered as breaching the ethics rules.

While accessing the sensitive data from the medical records of the people living/suffered with TB/leprosy/HIV/AIDS/Cancer, etc., and also police records of people involved in accidents, alcoholism, prostitution, criminal proceedings for any offense, drug abuse, etc., researcher needs to be obtained a regulatory permission from the responsible authority of the relevant section,

and apply ethical principles while retrieving such data from medical or police records.

If researcher would like to transfer any form of data from Nepal to abroad, he/she must have to mention the reason for such transfer along with signature of the Data Transfer Agreement (DTA) between host and collaborating institution(s) and it should clearly be mentioned in the proposal as otherwise it may be viewed as breaching the protection for the rights and freedoms of participants' data. One copy of such data should be stored in the host institution in Nepal.

***Note:** GoN's Individual Privacy Act, 2018 is applicable for governing the protection of individual private information during data storing and transfer process.*

#### **4.9 Biological specimen collection, storage, security and bio-banking**

Biological specimens could be whole blood, cord blood, dried blood spots, serum, sperm, semen, tumor cells, embryos, urine, hair, tissues, organs, cerebrospinal fluids, DNA, etc. Researcher needs to quantify the number of biological samples and its volume to be collected from the targeted research participants. Investigator should provide the justification of the required volume of bio-samples.

The investigator should have to explain how such biological specimens will be stored/processed once collected and at which temperature these specimens will be kept for short term and long term storage. Such biological specimens may be stored in researcher's/Institute's/NGO's/pharmaceutical company's refrigerator/freezer or in bio-banks. Researcher must have to

explain the power back up aspects of refrigerator/freezer, and write sample coding (bar/manual coding) strategy. After storing the bio-samples, researchers must apply appropriate security system like lock and key (or digital door with password) in the refrigerator/freezer/bio-bank room and surveillance camera within the premises of bio-sample storing areas. Researchers must also ensure that they use appropriate facilities, equipment, policies and procedures to store bio-specimens safely, and in accordance with applicable standards including SOP. Security system should prevent non-authorized persons from accessing bio-samples and also the data generated from these. All the data sets should be in coded or double coded form and should only be accessible to authorized persons. Failure to address security issues may be considered as breaching the ethics rules.

For collaborative study, researcher should store duplicate biological specimens either in Nepal or abroad (preferably in his/her affiliated institution). This is essential for future research or some laboratory data audit process and researcher must commit to make available such bio-samples in Nepal at free of cost (if stored in abroad) whenever demanded by the government authority for verification process.

Description of bio-bank and types of biological specimens described in box 3.

### **BOX 3. DESCRIPTION OF BIO-BANK AND TYPES OF BIOLOGICAL SPECIMENS**

<p><b>Bio-bank:</b> Bio-banks can store biological specimens such as whole blood, cord blood, dried blood spots, serum, sperm, semen, tumor cells, embryos, urine, hair, tissues, organs, cerebrospinal fluids, DNA, etc. Bio-samples stored in the bio-bank may be obtained in small to large numbers from researcher's/Institute's/NGO's/pharmaceutical</p>
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company's refrigerator/freezer or other bio-banks. All the ethical issues concerning for bio-banking should have to be adopted with greater responsibility pertaining their ownership, access and benefit sharing to the community or individual. If researchers would like to conduct any further study in the stored bio-samples, he/she must obtain prior ethical approval from the ERB and may need to undergone for taking individual informed consent.

Biological specimens to be stored in the bio-bank may be of following types.

Anonymous or unidentified	No identifiers are present from the start or if collected, are not maintained. Such samples are received by bio-banks without any identifiers and supplied to researchers.	
Anonymized	This involves systematic de-identification, reversible or irreversible: link of samples/data to personal identity is reversibly or irreversibly cut.	
	<p><b>Coded or reversibly anonymized:</b></p> <p>There is an indirect link of sample/ data to the participant's identity with restricted access. This link could be re-linked if required; therefore, it may also be termed reversible anonymization.</p>	<p><b>Irreversibly anonymized:</b></p> <p>Link to the participant's identity is removed and cannot be re-linked.</p>
Identifiable	A direct link of sample/data to the participant's identity exists.	

**Source:** ICMR, 2017, National Ethical Guidelines for Biomedical and Health Research involving Human Participants, Page 129

Key aspects for maintaining confidentiality and privacy of donors related to biological specimens stipulated in box 4.

**BOX 4. KEY ASPECTS FOR MAINTAINING CONFIDENTIALITY AND PRIVACY OF DONORS RELATED TO BIOLOGICAL SPECIMENS AND/OR DATA**

1. The procedure of anonymization minimizes the connection between the identifiers and the stored sample by delinking the person from her/his biological material.
2. Maintaining confidentiality of data and respecting ethnic identity is of prime importance, especially in population based genetic studies.
3. More precautions should be sought when the research pertains to stigmatizing diseases.
4. When data pertains to public health research, it may be dealt with in the manner described in section 7.5.

**Source:** ICMR, 2017, National Ethical Guidelines for Biomedical and Health Research involving Human Participants, Page 129

**Biological specimen transfer**

If the study involves the transfer of biological samples to other countries, researcher must have to provide strong justification for such transfer in the research proposal. Such justification may be taken into consideration if the proposed methods/tests are not applied by any registered laboratories in National Public Health Laboratory (NPHL) in Nepal. Investigators may be allowed to transfer only processed/extracted amplified bio-samples, for example, serum/plasma sample not the whole blood, DNA/RNA not the whole genome, etc. However, ERB needs to verify such justifications for appropriate decision.

Despite of availability of such tests in Nepal, if researcher (Nepali student) has an opportunity to test the bio-samples at free of cost in abroad, he/she may ask permission to ERB for transferring such bio-samples. In this case, researcher needs to provide its supporting document and ERB needs to verify this.

Researchers need to fill up the table (Annex - I) and ERB will make the decision accordingly.

**Note:** *Export of biological specimens from Nepal to other countries needs to fulfill specific requirements of the existing laws/rules/regulations including protection of biodiversity and genetic materials (2) of the country.*

Any research involving exchange of biological materials/specimens with collaborating institution(s) within the country or abroad must sign the MTA with possibility of MoU justifying the purpose and quantity of the bio-samples being collected and addressing issues related to confidentiality, sharing of data, joint publication policy, IPR and benefit sharing, post analysis, handling of the left-over bio-samples after laboratory investigations, safety norms, etc. Researcher should explain that laboratory test of bio-samples will safely be done as per accepted universal or relevant regulatory standards of the country.

#### **4.10 Research Benefit Sharing**

The study team should make plans wherever appropriate for post-research access and sharing of intervention benefits with both types (intervention as well as control groups) of the research participants. Researcher can describe post-research access arrangements or other care into the study protocol, and the research team should communicate the study findings to the research participants wherever relevant.

The benefits accumulating from the study should be made available to individuals, communities and populations whenever pertinent. Sometimes community people may be given more benefit in an indirect way by establishing health facilities or schools, and providing education on good health practices than direct benefit to the individual person.

Participant will not be able to receive any feedback on individual data if the findings are in an aggregate form. So such data must be discussed with the community, especially when the study involves vulnerable populations like indigenous/tribal/ethnic populations and people living with certain diseases.

In the condition where participants are not prepared to face the research outcome, researcher needs to prepare an enabling environment or develop an appropriate mechanism (wherever possible) to communicate their findings. Sometime participants would like to have an aggregate report of all the results of the study which could become a shared benefit for the community. In this condition, study team may put all the results in publicly accessible web-site. However, there are some participants which may choose not to be contacted about their results.

Investigators and sponsors should attempt to continue to offer beneficial interventions, which were part of the research initiative even after the completion of research and till the local administrative and social support system is restored to provide regular services (if possible).

If researcher thinks that the data and/or biological materials have possible commercial value, this must clearly be highlighted in the informed consent form with clarity about benefit sharing. This form must explain whether donors, their families, or communities would receive any benefits (financial or non-

financial) by having access to the tests, products, or discoveries resulting from the study.

## Section 5. Informed Consent Process in Health Research

Informed consent is a process in which prospective participants are informed about all the aspects of the research study that are important for the participant, ensuring that the information is easily comprehended by the participants to make a voluntary decision about his/her participation in the study.

### 5.1 Requisites

It is mandatory to obtain informed consent before beginning any procedure of the study involving human participants. It is also necessary to maintain the privacy and confidentiality of the participants at all stages of the study. Before taking an informed consent, following requisites should be fulfilled:

- The participant must be informed about all the aspects of the study that are important for him/her to make a decision, have the capacity to easily comprehend the proposed research, be able to make an informed decision on his/her willingness to participate and convey her/his decision to the researcher to give the consent.
- The consent should be given voluntarily, without any pressure or coercion of any sort or by offering any undue inducements.
- Written informed consent must be obtained for participants aged 18 years and above.
- Written assent must be obtained for children aged above 12 to below 18 years. In case of children aged 7 to below 12 years, written assent may not be required. However, verbal assent must be obtained in the presence of the parents or LAR and whole process should be recorded.
- Written proxy consent should be obtained from parent or LAR in case of children below 7 years.

- The prospective participant must be given adequate time both to read and decide about his/her participation in the study; if necessary, clarify the doubts should be clarified with the research team and/or discuss with family and friends.
- In case of individuals who are not capable of providing voluntary informed consent, the consent of LAR must be obtained.

## **5.2 Information**

Research participants should be given sufficient information about the proposed research including information on the research procedures, their purpose, risks/ discomforts, anticipated benefits, alternative procedures and a statement offering the participant the opportunity to ask questions and the right to withdraw at any time from the research without any fear of negative consequences. The information provided to the participants should be made in a language that he/she can easily understand. Also necessary attention should be given to the social and cultural context of the participant.

## **5.3 Comprehension**

It is the investigator's responsibility to ascertain that the research participant has comprehended the information. If the research participant is not capable of comprehending the information, the proxy consent of a LAR should be taken. One of the ways to ensure that the participant has comprehended the information is by giving the information in a language that he/she can easily understand.

## 5.4 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 gift.

## 5.5 Process of obtaining an Informed Consent

To obtain an informed consent, following aspects must be considered with care:

- (a) Obtaining consent from the participants:** It is important to know individual who will explain the research objectives, and receive the informed consent from the participant. It is worth estimating the time for receiving consent from the participants.
- (b) Is there any coercion or deception?** The consent form must clearly indicate that the participants agree on their own will to participate in the study. There should be no coercion or deception during the process of obtaining consent.
- (c) Is the consent form prepared in English, Nepali and other relevant languages (if applicable)** Researcher should include the following information in the consent form.
  1. A statement mentioning that it is a research and also the nature of the study - whether investigational, use of drugs/vaccine/devices/investigational products or procedures, whether information seeking, or if questionnaires or interviews are to be used
  2. Objectives and methods of the study
  3. Estimated number of participants to be enrolled
  4. Expected duration of the 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 or penalty and without fear or loss of benefits
8. A statement on exactly what is expected from the research participant
9. Direct or indirect benefits to the participant and community.
10. The risks, discomforts, and inconveniences associated with the study including possibility of any stigmatizing condition resulting from participation in the study
11. A statement to what extent confidentiality of records will be maintained and the anticipated consequences of breach of confidentiality
12. A statement clarifying any re-imburement/compensation/provision of management of AE or SAE/free treatment/incidental expenses/insurance coverage for the research participants depending on the type of study
13. A statement on the post research benefit sharing if research on biological specimens and/or data leads to commercialization
14. A detailed explanation about the study aspects that may be relevant to his/her willingness to continue participation
15. Period of storage of biological specimens/data
16. Possible use of stored biological specimens/data in future or to be used for secondary purposes including sharing with others (if any)
17. Sentence indicating that the participant has understood all the information in the consent form and is willing to participate in the study

18. Contact details (name and address including telephone numbers and e-mails) of responsible persons of the research team for any queries related to the study
19. Signature space for the research participant, a witness (if required) and the date and place

**Note:** The research participant who is being asked for the informed consent should not be in dependent relationship with the researcher. In case of a physician, conducting research among patients, must assign the responsibilities of taking consent to a person who is outside from the treating team.

## 5.6 E-consent

Electronic informed consent (E-consent) uses electronic formats, which can be used to provide the information related to the study and document it electronically using digital signatures. E-consent must contain all the elements of informed consent and the information provided through this format should be in a language easily understandable by the participant. Similarly, the electronic format should be simple to navigate and use. In case of any indication of discomfort in using the electronic media, it should not be used.

E-consent process is usually applied in the studies where investigators plan to collect the data on highly sensitive topics (such as domestic violence, genetic disorders, rape, unsafe sex, abortion and use of emergency contraceptive pills among unmarried females in Nepal etc.) and interview various stakeholders residing in different countries. E-consent process can also be used in the condition where researchers may have limited resources to conduct the study and the condition where it

may not be feasible to contact each and every research participant physically.

E-consent may be taken through e-mail or on-line web-site. On-line consent must be accompanied with web-site address, where E-consent format will appear at first and only after participant's electronic signature in this format, data collection form(s) will appear one by one or altogether.

All the contents of the E-consent, the process of providing information, the documentation of the E-consent including electronic signatures, the methods of maintaining privacy/confidentiality & security of information and the data use policies must be reviewed and approved by the ERB before starting the study. After starting the study, this process must be supervised by the PI or the appropriate designee.

## 5.7 Re-consent

Re-consent is required in the following situations:

- New information related to the study becomes available that may affect the participants or has implications for participants or which changes the risk benefit ratio.
- A participant enrolled using the consent of LAR, regains the ability to consent for himself/herself (e.g. who is unconscious regains consciousness or who had suffered loss of insight regains mental competence, a child becomes an adult during the study period, etc.).
- Study requires extension or a long-term follow-up.
- There is a modification in data collection methods, duration of participation, treatment modality, study sites, which may

impact the participant's decision on whether or not to continue in the study; and there is probability of revelation of identity (e.g. use of adequately camouflaged photographs) through publications or data presentation.

- In some of the above cases, additional re-consent of partner/spouse may also be required.

Examples of re-consent scenarios described in box 5.

#### **BOX 5. EXAMPLES OF SCENARIOS WHERE RE-CONSENT IS TAKEN**

**Secondary or extended uses of stored samples/dataset:** In such an instance, one of the preliminary considerations for ERB must be to identify the circumstances under which the research requires re-use of collected identifiable biological material to generate the data or utilize the pre-existing identifiable dataset. This must also include review of the informed consent obtained originally to see if re-consent is warranted. There may be situations where consent would be impossible or impracticable to obtain for such research, in which case the research may be done only after independent evaluation by ERB. (Declaration of Helsinki, October 2013).

**Pediatric donors:** In longitudinal studies once the child donor attains the legal age of consent a re-consent should be sought for the storage and use of her/his tissue or sample. In pediatric bio-banks or bio-banks with pediatric samples it is important to address the issue of children reaching legal age of consent. Sometimes re-contact may lead to withdrawal, resulting in limited data analysis. This may lead to bias or it could evoke emotional distress about past research. On the other hand, re-consent may give the participant the power to agree. A bio-bank should decide the policy it would like to adopt for re-contact.

**Source:** ICMR, 2017, National Ethical Guidelines for Biomedical and Health Research involving Human Participants, Page 131-132

## 5.8 Waiver of Consent

For certain conditions as mentioned in the box below, the ERB may consider granting the waiver of the consent if the researcher applies for a waiver. The waiver request may be made if the research involves less than minimal risk to participants and the waiver will not adversely affect the rights and welfare of the participants. However, researcher must justify this request by providing an explanation of why obtaining signed consent would add additional risk to the research participants and alternative provisions for informing them about the study.

Conditions for granting waiver of consent described in box 6.

### **BOX 6. CONDITIONS FOR GRANTING WAIVER OF CONSENT**

- Research cannot practically be carried out without the waiver and the waiver is scientifically justified;
- Retrospective studies, where the participants are de-identified or cannot be contacted;
- Research on anonymized biological samples/data;
- Certain types of public health studies: surveillance programs/program evaluation studies;
- Research on data available in the public domain; or
- Though attempts should be made to obtain the participant's consent at the earliest, there may be conditions such as humanitarian emergencies and disasters where the participant may not be able to give the consent

**Source:** ICMR, 2017, National Ethical Guidelines for Biomedical and Health Research involving Human Participants, Page 54

Conditions that are applied for waiver of informed consent in adults may also apply for waiver of assent in children. Waiver of assent may be allowed when the available intervention is anticipated to benefit the child but would be available only if the child participates in the study. However, this condition may be

accepted only in exceptional cases where all forms of assent have failed. In such circumstances, ERB approval should be obtained.

### 5.10 Consent taking in Special Situations

In certain conditions, investigators need to take consent from group leader, community, LAR etc. as described below:

- (a) **Consent from gatekeepers:** Sometimes, on behalf of a group, permission of the gatekeepers who are usually the head or leader of the political/social/cultural/professional group may be obtained in writing or audio/video recorded and should be witnessed.
- (b) **Community consent:** In certain populations, some participants may not participate in the research unless the community's consent is available. In such situations, community consent is required. When permission is obtained from an organization that represents the community, the quorum required for such a committee must be met i.e. the number of members required to be present while giving the consent. However, even after taking the community consent, individual consent is required.
- (c) **Consent from vulnerable groups:** Vulnerable persons are those individuals who are relatively or absolutely incapable of protecting their own interests because of personal disability, environmental burdens, social injustice, lack of power, understanding or ability to communicate or are in a situation that prevents them from doing so. The details on the common characteristics of the vulnerable groups and the example of vulnerable populations are provided in chapter 4.1. If vulnerable populations are to be included in research, all stakeholders must ensure that additional protections are in place to safeguard the dignity, rights, safety and wellbeing of these individuals. Because of their inability to consent, LAR may need to be involved in decision making. Also

because of their increased vulnerability, special care must be taken to ensure their privacy and confidentiality.

If the participant cannot sign, a thumb impression must be obtained. The researcher who administers the consent must also sign and date the consent form. In the case of institutionalized individuals, in addition to individual/LAR consent, permission for conducting the research should be obtained from the head of the institution.

In some types of research, the partner/spouse may be required to give additional consent where as in genetic research; other member of a family may become involved as secondary participants if their details are recorded as a part of the family history. If information about the secondary participants is identifiable, their informed consent will also be required.

In case of illiterate participant or LAR, the consent process should be witnessed by an impartial witness without any CoI (who is not a relative of the participant and is in no way connected to the conduct of research) such as other patients in the ward who are not in the study, staff from the social service department and counselors. The witness should be a literate person who can read the participant information sheet and consent form and understand the language of the participant.

### **5.11 Consent for studies using deception**

Some types of research studies require deception due to nature of research design. For example, a true informed consent may lead to modification and may defeat the purpose of research. Although deception is not permissible, approval should be taken from the ERB in circumstances where some information requires to be

withheld for validation until the completion of the study. A two-step procedure may be required comprising an initial consent and a debriefing after participation. In such instances, an attempt should be made to debrief the participants/communities after completion of the research.

These types of research may be carefully reviewed by the ERB before implementation and the possibility of unjustified deception, undue influence and intimidation should be avoided at all costs.

### **5.12 Procedures after the consent process**

After obtaining the consent, participant should be provided with a copy of Participant Information Sheet (PIS) and signed Informed Consent Form (ICF). If they are not willing to take the copies, the reason for their reluctance should be noted. The original PIS and ICF should be archived as per the guideline.

### **5.13 Documentation of the Consent**

Documentation of the informed consent process is an important task. The signed informed consent form or consent from the LAR (in case the participant is medically or legally incompetent) must be documented and safely archived. In all cases, the investigators must ensure that privacy of the participant and confidentiality of related data is maintained.

## Section 6. Ethical Review Process

Nepal Health Research Council entrusted by the Act of Parliament (Number 29, Section 6) of the year 1991, its functions, duties and rights are to review all health research proposals to be conducted in Nepal for the scientific quality and ethical appropriateness and to take the necessary steps to approve or disapprove such research proposals. The health research proposals involving human participants need to be reviewed and approved by ERB. Ethical Review Board is responsible for scientific review of research proposals through initial and continuous reviews including monitoring of the study to ensure ethical standards.

### 6.1 Formation and Terms of Reference of ERB

NHRC being the autonomous government body has right to establish independent ERB in order to review scientific quality and ethical standard of the research proposals involving human participants. The ToR of the ERB needs to be developed and approved by the NHRC executive board.

#### **Formation of the ERB:**

- Agenda for the formation of ERB should be placed in the executive board meeting of NHRC and approve it for further action. NHRC forms ERB under the section 10 of NHRC Act.
- Modality of the selection of the ERB members and its compositions should be discussed during the executive board meeting of NHRC and endorsed it.
- Executive committee members of the NHRC should prepare a roaster of experts representing from different fields and discuss in the meeting for selection.
- NHRC executive committee should select minimum 7 to maximum 15 members for ERB including ERB chair,

member-secretary and members. Selection of ERB members should be done with an attention to gender, age and disciplines balance.

- Member-Secretary of NHRC will be the Member-Secretary of the ERB but will not have voting rights.
- The tenure of the ERB will be three years.
- Standard Operating Procedure should be prepared for the selection of ERB members.

*Appointment of the ERB Chair/Members:* With the approval from the NHRC executive board, executive chief of NHRC will provide an appointment letter to the ERB chair, member-secretary and members. Appointment should be made for tenure of three years.

***Conditions of Appointment:* ERB members shall be appointed under the following conditions:**

- Non-affiliated to NHRC executive board except member-secretary of ERB
- Agree to make his/her profile public, as the member of ERB,
- Carefully read, understand and accept CoI for ERB members and declare CoI, if any,
- Sign a confidentiality agreement regarding ERB meetings, discussions and research proposals applied for ethical approval and its related matters,
- Should agree that the remunerations paid to him or her in course of ERB work will be recorded and made available to the public on request,

- Provide recent Curriculum Vitae (CV) and relevant training certificate(s) related to health research ethics, GCP etc., if applicable
- Aware and abide of NHRC relevant norms, values, culture, ethical issues, guidelines and regulations.

***Qualification of the ERB Chair/Members:***

***For ERB Chair:*** A well-respected person with post graduate qualification in health related sciences with more than 15 original research publication in Index Journal along with prior experience of having served/serving in any IRC or ERB. A very good understanding of research ethics is mandatory.

***For ERB Member-Secretary:*** A person with post graduate qualification in health related sciences with having basic knowledge and experience in health research and ethics. He/she should be motivated enough to carry out the task of ERB and have good communication skills and able to make harmony and coordination between ERB and NHRC.

***For ERB Member:*** A person with post graduate qualification in health related sciences [basic bio-medical sciences (biochemistry/pharmacy/microbiology etc.), medical/clinical sciences (obstetrics/gynecology/pediatrics/cardiology/opthalmology/d ermatology etc.), public health, epidemiology, nutrition, bio-statistics/statistics, etc.] with having basic knowledge and experience in health research and ethics. Apart from these, a person with graduate qualification in law with sufficient working experiences in health sector's rules and regulations including medico legal aspects. A person with post graduate qualification in sociology/anthropology with sufficient working experiences in social/cultural/ religious /ethnic settings including moral values. He/she should be motivated enough to carry out the task of ERB.

*Note: Sometime, there may be a need to include lay person as an ERB member. Lay person should be a literate person to be selected from the public or community, who has not pursued a health science related career in the last five years but involved in social and community welfare activities. Such member may be a representative of the community from where the research participants will be taken. Such person must be aware of the local language, culture and moral values of the community.*

### **Disqualification, Resignation, Cancellation, and Renewal of the ERB Chair/Members:**

- If an ERB member acts contrary to, or breaching the conditions of appointment, he/she may be disqualified by the NHRC executive board. Legal prosecution shall also lead to disqualification. If any members including ERB chair does not attend three consecutive ERB meetings without prior notice, he/she shall be disqualified to be act as a member of ERB.
- ERB chair/member may resign from their position by submitting a letter of resignation to the NHRC executive chief. Executive chief of NHRC should forward his/her resignation to the executive board of the NHRC. On acceptance of his/her resignation by the board, he/she will no longer be a chair/member of ERB.
- NHRC executive board has the right to replace the ERB chair/members in the case of their resignation/disqualification and sudden death. While replacing ERB chair/member for the remaining tenure, NHRC executive board should follow the same procedure mentioned in the conditions of appointment of new ERB chair/member. Such appointment should have to be done as early as possible but not more than three months.
- If any ERB chair/member will be nominated as an executive board member of the NHRC, his/her existing position in the ERB will automatically be cancelled.
- At least 33 to 50 percent of the existing ERB should be retained in a new ERB to maintain continuity of experience

and institutional memory. Appointments of ERB chair/member may be renewed by the NHRC executive board for up to two consecutive terms.

***ToR of ERB:*** The ERB is responsible to

- Review and ensure the rights, dignity, safety and well-being of human research participants and comply with national and international guidelines and provide constructive feedback with a view to approve, or disapprove the submitted research proposal. It should maintain its independence, without any CoI and influence from any person/organization.
- Maintain confidentiality of the documents and deliberations of ERB meetings and ensuring the privacy of the ERB decisions.
- Monitor the research activities for ensuring that the research is conducted according to the proposal approved by the ERB and investigate if there is any breach/violation/deviation in approved proposal.
- Accountable of any sort of research misconduct of the approved proposals.
- Provide assistance and facilitate the researchers for conducting research adhering to the ethical guidelines, rules and regulations of the nation and respect the local culture and traditions of the community in which the study is planned to be conducted.
- Provide approval for accreditation of IRCs, guide them periodically and oversee their functions and duties.
- Conduct meeting/workshop/training programs for members of IRCs and proposal reviewers on the ethical review process.
- Oversee the health researches involving human participants and analyze complaint(s) (if any) related to unethical conduct of research in the country and take appropriate decisions for actions, and

- Facilitate and provide protection to the researchers if necessary.
- Recommend to select the independent subject experts during the ERB discussion (whenever necessary).

***Special Conditions:*** To maintain ethics, decision making on time and regulating the health research under the jurisdictions of NHRC, ERB needs to function regularly, even in absence of NHRC executive board. In such a condition, ERB chair and members are mandated to function as per assigned ToR in the appointed tenure.

## 6.2 Office of the ERB Secretariat and its ToR

### ***Office of ERB Secretariat:***

- NHRC should set up a separate ERB secretariat office with necessary administrative support such as phone, internet, photocopy machine, scanner, printer, computers, file cabinets, desks, chairs, projector, meeting tables, etc.
- NHRC should assign an officer as a chief of the ERB secretariat. He/she should be supported with sufficient, well-educated and trained human resources. Chief of ERB secretariat should function to coordinate within ERB and between ERB and NHRC.
- The list of the names of ERB chair, member-secretary and members should be displayed in front of the ERB office. Their duties and responsibilities should clearly be stated and documented in the ERB office.
- NHRC should allocate adequate financial support for effective functions of ERB and its secretariat.

***ToR of ERB Secretariat:*** The ERB secretariat should work in consultation with ERB chair, ERB member-secretary and executive chief of NHRC, and is responsible to

- Prepare the pool of reviewers and independent subject experts who can be called upon by ERB to provide expert opinion on proposed research proposals.
- Obtain the CVs, signed confidentiality agreement and CoI form of each ERB chair, member-secretary, members and subject experts/reviewers, and document these and archive.
- Facilitate the financial transaction related to ethical review process.
- Maintain the electronic data base of health research proposals that are submitted for ethical review process and archiving it for effective and efficient tracking procedures.
- Screen and verify the submitted research proposals as per the checklist.
- Prepare, maintain and distribute research proposals to internal and external reviewers, and communicate their comments with the researchers and then with the reviewers as and when needed.
- Prepare the meeting agenda in consultation with ERB member-secretary and ERB chair.
- Prepare the summary of the research proposals for discussion in the ERB meeting.
- Facilitate in organizing ERB meetings regularly and communicate with the ERB chair/members.
- Prepare the meeting minutes, verify and sign it by ERB chair/member-secretary.
- Prepare the decision letter according to the approved minute, obtain signature from chairman/member-secretary/any designated officer of NHRC and communicate the decisions to the researcher. If NHRC authority is the applicant for obtaining ethical approval from ERB, decision letter may be issued by ERB secretariat.
- Organize ERB documentation, communication and archiving.

- Plan and organize monitoring of health researches being conducted in the country.
- Provide and update on relevant and contemporary ethical issues related to health research and its associated literatures to the ERB.
- Organize meeting/workshop/training related to research ethics.
- Plan and monitoring of the approved and proposal.
- Follow the additional responsibilities given by ERB chair/member-secretary and executive chief of NHRC.

### ***Capacity building of ERB and its Secretariat:***

- NHRC should conduct regular training programs related to research ethics for ERB members, ERB secretariat and IRC members at least once in a year. Such training programs will provide opportunities for hands on experience of reviewing the research proposals as well as problems faced while reviewing and implementing.
- Newly appointed ERB members and ERB secretariat staff should be oriented with the ethics related guidelines and SoPs.

### **6.3 Submission and Review Procedures**

The ERB is responsible to review all the submitted research proposals in a timely manner with standard review procedure. Investigators keen for conducting health researches in Nepal should submit their research proposals to ERB for ethical review.

***Application Submission:*** Principal Investigator and/or responsible study team member of the study can submit research proposal online accessing through the site <http://erb.nhrc.gov.np> to the ERB secretariat for ethical

review in the prescribed format along with required documents as per the following requirements.

- Application should be submitted in the format provided by NHRC. The prescribed format can be accessed from the NHRC website ([www.nhrc.gov.np](http://www.nhrc.gov.np)) by login as a researcher.
- Principal Investigator and Co-investigator should sign the cover letter with date.
- An auto generated acknowledgment email will be sent to the researcher.
- If any additional documents are required during the review process, the researcher will be notified by ERB secretariat.
- If any amendments are made in the proposal already submitted and approved study, the researcher must submit in writing the changes made with justification. Such changes along with its justification should be reviewed by the ERB, taking the requests into consideration for amendment process if agreed upon.
- Application should include the ICF (Nepali and English) as a separate copy (if required). In addition, this can include a translation copy, in a local language if relevant.
- Any compensation to be given to the research participant should clearly be mentioned. (e.g. any transportation costs, food, free health care or insurance coverage etc.).
- A signed statement by the researcher stating that he or she will abide by the ethical principles of research.
- A declaration of the CoI, if applicable, should be mentioned in the application.
- Only those applications fulfilling the requirements will be accepted for review. Incomplete submission will be informed to the applicants within two weeks of submission. Any required documents (if demanded) should have to be uploaded.
- Process and list of documents required for applying online proposal submission has been given in Annex – II.

***Elements of the Review Process:*** Once the research proposal is submitted and screened for completeness of documents by the ERB secretariat, technical review of the proposal is done by the internal and external reviewers. Once comments/suggestions received after technical review, responsible officer of the ERB secretariat communicates with researcher. Upon receiving the response from the researcher, it is subjected to same reviewer for its further process, and then finally forwarded to the ERB chair and members prior to ERB meeting.

*Review process specifies the following standards on health research study.*

- Relevant qualification and experiences of the PI for the proposed health research
- Infrastructure and other facilities in the institutions (if any) conducting the health research
- Description of the population from which the research participants will be drawn
- Justification of predictable risks and inconveniences against the anticipated benefits for the research participants and community
- Description about who has access to data and biological samples
- Justification of the use of control arm (if relevant for the study)
- Provisions for DSMB (if relevant for the study)
- The compensation provided to the participants in case of adverse drug reaction and or adverse events (if relevant for the study)
- Description of the process of reporting any adverse drug reaction and/or adverse event (if relevant for the study)

- Plan for dissemination or publication of research results
- Description about the provision of availability of the research product for the participants after completion of the research project

***Expedited Review:*** Under special conditions, the ERB may authorize the chair or member-secretary of the ERB to expedite the scientifically sound and completeness of the proposal after reviewing by internal reviewer (while there is minimal or nominal risk).

- Prepare the list of study proposals to be expedited.
- Organize the meeting with ERB chair or member-secretary.
- Prepare the meeting minute and sign it by ERB chair/member-secretary.
- Prepare the decision letter according to the approved minute, obtain signature from chairman/member-secretary/any designated officer of NHRC and communicate the decisions to the researcher. If NHRC authority is the applicant for obtaining ethical approval through expedited review process, decision letter may be issued by ERB secretariat.
- Inform the ERB meeting about expedited proposals.

**Expedited review can be done in the following conditions:**

- Research with no-intervention, based on secondary data, leading to thesis or has received approval from the other Ethics Committee.
- Research involving secondary review of the documents data and records.
- Research during outbreak, emergencies and disasters.
- The ERB member-secretary or secretariat should inform about the expedited proposals to the ERB.

## 6.4 Meeting of the ERB

The meeting of the ERB needs to be held on a regularly scheduled date that must be announced in advance. The member-secretary of ERB or ERB secretariat with the permission of ERB chair can call the meeting. The followings points are considered for ERB meeting:

- The ERB meeting is based on the number of proposals received for review and workload of the secretariat. Usually, ERB is being held once in a week.
- All the ERB members must be informed about the meeting at least 48 hours prior to the scheduled date.
- If felt necessary by the ERB, the PI or Co-investigator or study team members as mentioned in the research proposal can be requested to present the proposal or elaborate on specific issues of the proposal. Similarly, if necessary, related subject/area experts can also be invited to the meeting for expert opinion about the proposal.
- The decisions and procedures of the meeting should be kept in the meeting minute.
- All the attendees present during ERB meeting should indicate their presence in the attendance sheet/register. ERB minutes should be verified by ERB chair/member-secretary.
- Declaration of CoI before each agenda discussion. Withdrawal of member from meeting if they have CoI.

### ***Quorum requirements for ERB:***

- At least 51 percent ERB members must be present to compose a quorum in order to maintain valid advice and/or decision.
- The quorum should include both medical, non-medical and technical or/and non-technical members.

- Presence of members of only one gender is not constitute a quorum.
- At least one-member or subject expert who is presented during the meeting should have expertise in an area of the subject under discussion.
- Preferably a member from outside of the health science background (layperson/social scientist) must be present.
- No decision is valid without fulfillment of the quorum.
- Invited expert should not be counted in meeting quorum requirement.

## 6.5 Decision Making

The ERB must consider the following while making a decision about the research proposal.

- ERB meeting has met required quorum.
- Normally the decision can be taken by consensus; if a consensus is not possible, the voting process can be initiated.
- All ERB members present during the meeting have the right to express their opinion or vote to make a decision.
- The decision must be taken either by a consensus or majority vote and should be recorded. Any undesirable opinion (if any) should also be recorded with reasons.
- The ERB member should withdraw from the decision process when a CoI arises; for which the member should declare the CoI in advance.
- The ERB can approve the proposal conditionally with specific suggestions to the researcher.
- The negative decision on a proposal should be supported by clearly stated reason.

## 6.6 Communicating a Decision

On behalf of the ERB, ERB secretariat can communicate its decision to the applicant in writing within two weeks after the ERB meeting.

The communication of the decision includes, but is not limited to the following information:

- The exact title of the research proposal reviewed.
- The clear identification of the protocol of the proposed research or amendment, date and version number (if applicable) on which the decision is based.
- 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;
- The name and title of the applicant
- The date and place of the decision
- A clear statement of the decision reached
- Any advice by the ERB

## 6.7 Continuing Review

ERB can establish a follow-up procedure (continue review) for following the progress of all research studies for which an approved decision has been reached — from the time the decision was taken until the termination of the research. The follow-up review intervals shall be determined by the nature and the events of research projects.

The following instances or events require the follow-up review of a study.

- Any protocol amendment
- 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

- Any event or new information that may affect the benefit/risk ratio of the study

A decision of a follow-up review can 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.

- In 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.
- The applicant should inform the ERB after completion of a study.
- The applicant can submit to the ERB, a copy of the final report of a study.

*The procedure for continue review takes the following into consideration:*

- Progress reports, safety reports (if any), technical audit reports (if any), final reports, etc. documents to be reviewed.
- Experiences of the research participants (e.g. independent observation of the discussion being held during informed consent taking process, independent surveys of participants experiences)
- Notification from the applicant with regard to suspension/premature termination or completion of the study

## **6.7 Research Site Monitoring**

- ERB members/health research monitoring committee/officers of ERB secretariat/subject experts identified by ERB may visit study site/organization during the review process and should periodically monitor the approved research study.

- Monitoring should strictly be done for a research study that involves vulnerable or high-risk research participants or in the following situations.
  - Complaints received from research participants
  - An adverse information from media or another source
  - Non-compliance with ERB decision and direction
  - Any other aspects felt so by ERB

## **6.8 Documentation and Archiving**

All documents [ERB minutes, all materials submitted by an applicant, monitoring report, documents received during follow-up, reports (progress and final) submitted by the researchers, safety reports, complain reports, technical audit reports, signed CoI form, etc.] and communication of ERB must be dated, filed, and archived according to written procedures. The records must be kept in an appropriate storage container (cloud/Google drive/one drive/external drive) or NHRC library hard drive with an appropriate information retrieval back up plan. Apart from these, CVs of all ERB members, any published guidelines as recommended by ERB, and a record of all income and expenses of ERB (including allowances to the ERB members, monitoring team and secretariat during meeting, field visit and capacity development phases) should be documented. An authorized officer of ERB secretariat should sufficiently be trained to understand their responsibilities related to record keeping, retrieval, and maintain confidentiality.

ERB secretariat should inform the researcher/research organization that the research based data (filled questionnaire/pro-forma/electronically filled data set etc.), filled informed consent forms, collected bio-samples (back-up) and other related documents should be archived for at least five years (or more for some particular case) period after

completion of the study so that the records are accessible for technical auditors as and when needed.

## **Section 7. Specific aspects while conducting different types of research**

There are some specific requirements that investigators need to fulfill while conducting different types of studies; for example, research related clinical trials, synthetic biology, radioactive materials, X-rays, bioavailability, bioequivalence, public health, social and behavioral science, human genetics, humanitarian emergency, disaster, stem cell research for health and use of animals in health research. These requirements are discussed as follows:

### **7.1 Clinical Trials (Drugs, Vaccines, Devices and other Investigational Products including Traditional & Complimentary Medicines)**

All clinical trials are experimental and usually well designed studies. Manipulating things to be used in such trial would be drugs, vaccines, devices, herbal product, surgical techniques including traditional and alternate systems of medicine, etc. Such trials are usually targeted to healthy human participants and also patients for verifying the effects of the intervention on their health outcomes and/or identifying any adverse reactions/events to investigational products and/or to study the absorption, distribution, metabolism and excretion of the products with the objective of establishing their safety and efficacy.

This allows comparison of the research participants treated with an investigational product/any intervention to a control population (receiving placebo or an active comparator), so that the effect of the Investigational product can be determined and distinguished from other influencing effects like a placebo effect, concomitant treatment, spontaneous change, etc. Research participants must be made to understand that they may be

randomized to a placebo group and may receive an inert drug. Those participants who have been in the placebo group may be offered post-trial access to the Investigational product if found effective in other patients. Safety follow-up of human participants in the clinic trials must not be restricted to the period of the diagnostic process but may be prolonged for a longer period as per the pharmacokinetic and pharmaco-dynamic properties of the drug/vaccine. Long-term safety (when appropriate) must be considered.

Clinical trials are classified into Phases I to IV. NHRC is generally allowing to conduct Phase III trial in Nepal if new drug/vaccine has been developed in other country. Only in special condition, NHRC may allow Phase II trial to be conducted in Nepal, but never Phase I trial. NHRC can allow Phase I trial only in the condition when new drug/vaccine including traditional and complementary medicines are to be produced in Nepal. In this condition, newly produced product must go through pharmacological testing procedure such as its toxicity (LD 50 test), microbiological test, contamination of heavy metals, etc., and it should be under notification of Department of Drug Administration (DDA).

The ERB should review the pharmacology, toxicology, pharmacokinetics and safety data of the drug/vaccine to be used in the human participants. Signed final copy of the previously conducted clinical trial documents should be submitted to ERB. If researcher would like to conduct Phase III clinical trial in Nepal, he/she has to submit the signed copy of the previously conducted Phase I and II clinical trial documents including its publications to ERB.

In terms of any new **drugs/vaccines trials**, either person or institution should obtain license from the DDA for its

procurement and must follow NHRC clinical trial guideline. All clinical trials must be registered in the clinical trial registry and the registration details submitted to ERB during proposal submission phase.

Clinical trial must be commenced only with due explanation and with all possible participant protections in place if it is being planned among vulnerable populations.

- Women of childbearing age must be counselled to use effective contraceptive methods if clinical trials are conducted among these.
- If the study objective is to find new knowledge directly relevant to the fetus, the pregnancy or lactation (like gestational diabetes, pregnancy induced hypertension and HIV), pregnant women and fetuses can be included in the clinical trial.
- If lactating women participate in the clinical trial, they should not be encouraged to discontinue nursing for the sake of participation in the study except in the condition where breast-feeding is harmful to the infant. If lactating woman decides to stop breastfeeding, harm of cessation to the nursing infant should properly be evaluated. Milk formula as supplementary food may be considered in such cases.
- Terminally ill patients may be recruited in the clinical trial if their clinician thinks that this treatment (the investigational product) may be the last hope for cure, or a way to get free treatment for their disease which may otherwise be beyond their reach. So, the clinician should not recommend such treatment (the investigational drug) unless he/she thinks it might be helpful.
- Clinical trial is permissible in people living with HIV or HIV infected person or AIDS patients if the drug under the study cannot be tested in healthy participants due to predictable toxicity of the Investigational product. When a preventive HIV vaccine trial is conducted, it can result positive in

serological test and may create problems for travel and employment. However, this does not indicate any HIV infection. In such cases, the PI should issue a document stating that he/she was a research participant in a HIV vaccine trial and provide explanation on the serological test result.

*Note: As HIV is a sexually transmitted disease and is potentially life-threatening, the right to life of the sexual partner should be respected over the right to confidentiality of HIV the infected person.*

Clinical trial that incorporates devices, which may be an instrument, implant, material, whether used alone or in combination to be used internally or externally specially for human beings or animals for one or more of the specific purposes of treatment, detection, diagnosis, prevention of disease or disorder, monitoring, etc., such **device trial** should be conducted as per ethical principles applicable for drugs or vaccines trials and should be considered in the same way as for a new drug/vaccine licensing procedure adopted by the DDA. Sometimes, it may not be possible to remove the internal device if the research participant would like to withdraw from a trial. This should be explained to the participant prior their enrollment. When device is implanted within the human body, their follow up period would be long enough to find late onset of adverse reactions/events.

Based on the type of medical devices, the level of risk ranges from low to high. For example, use of thermometers/bandage/tongue depressors may put participant at lower risk, and hypodermic needles/suction equipment may give low-moderate risk. However, use of lung ventilator/bone fixation plate may put research participant at moderate-high risk, and similarly, heart valves/implant defibrillator may provide high risk.

Drugs/vaccine/device trial must provide the document that indicates “CoI”, wherein statement of declaration of the trial product to be used only for research purpose without any financial benefit. Apart from this, there is a need of “Investigator Voucher”, wherein detail of investigational product should be provided. There should be a statement regarding benefits and probable risks while using the trial product, and the insurance of research participants. Data Safety and Monitoring Board should have to be formed before initiating the trial. Within the DSMB, PI should have made a provision for one membership from ERB and one from DDA. Principal Investigator should write a formal request letter to ERB secretariat and DDA for such nomination. Ethical Review Board and DDA should nominate relevant person after approval of the proposal. There may be a provision of recruiting Contract Research Organization (CRO) which is responsible for evaluating clinical trial especially vaccine trial.

If the investigator would like to conduct **surgical intervention (trial)**, he/she should provide references for the process and define the most probable difficulties (if any) in the proposal for the ERB to review and perform risk-benefit assessment. In such a trial, it is preferable that a comparative study be conducted where the conventional method is compared to the “test” surgical intervention. Such **surgical intervention** must be guided as per ethical principles applicable for drug trial. Mock surgery must not be incorporated in the design of surgical intervention (trial), except in the situation where researcher provided his/her strong scientific reasons for it.

Community trials are trials carried out at the community level and the intervention is targeted to communities rather than at individuals. The randomization procedure can also be adopted at

the community level and the method of such trial is useful for studying disease prevention or public health intervention models. Ethical review of the community trial proposal may be treated differently than clinical trial proposal. ERB should review whether specific measures are established to protect the welfare of related community members who have not participated in the trial or not.

If researcher would like to conduct clinical trials on **traditional and complementary medicines**, such products must go through various testing procedures (heavy metal contamination, toxicity, microbiological testing, etc.) from the recognized laboratory and submit its result to ERB along with the scientific proposal. Investigators must follow “NHRC traditional and complementary medicine research guideline”.

## 7.2 Research in an area of Synthetic Biology

If an investigator would like to modify genetic material of living organisms or produce artificial life forms like biofuels, bioweapons, vaccines, diagnostics, etc., with an aim to manufacture it for commercial scale, he/she has to follow its ethical and legal aspects pertaining to the impact of this science on biosafety, biosecurity, IPRs, society, and socioeconomics in Nepal.

**Safety** measures must be followed as per the Environmental Protection Act, Biomedical Waste Management Rules, and other relevant laws applicable in Nepal. Appropriate safety training (like safe handling of the product) must be provided to researchers and staff working in an area of synthetic biology. Their periodic health check-ups should be done as they might have been exposed to occupational health hazards.

Some biological product may have dual use: one beneficial use for a particular purpose and the other for harmful use, for example, use as a biological weapon. In order to maintain security, the code of conduct for researchers involved in life sciences must be followed along with formation of a system for reporting and keeping observation to avoid misuse. There must be effective partnership between policy makers and researchers to generate a secure system.

Biomaterials and biocompatibility tests must be done as per relevant regulatory standards adopted by the GoN. The testing of such standards shall be done in a certified laboratory.

### **7.3 Research in an area of Radioactive Materials and X-rays**

If the radioactive substance is to be tested as a drug, it should be considered in the same way as for a new drug/vaccine licensing procedure adopted by the DDA. Such radioactive materials comprise a radioactive isotope and may be used for diagnostic or therapeutic purposes. When such materials and X-rays are being used in research, their permissible radiation limits must comply with regulatory authority guidelines, and this exposure must be within acceptable limits. Research site must have a license from the DDA to store, handle and dispense such materials. Researchers and staff must have received an appropriate safety training in safe handling of the radioactive materials and X-rays. Radiation workers or any person who has received more than the permissible amount of radiation in the past one year and vulnerable populations (particularly women of childbearing age and children) should be excluded from the study involving radioactive materials or X-rays. The proposal must make sufficient provisions for identifying pregnancies to prevent risks

of exposure to the embryo. Information about possible genetic damage to the offspring must be included in the ICF.

#### **7.4 Research for Bioavailability and Bioequivalence study**

All bioavailability and bioequivalence studies should be conducted scientifically in compliance with ethical code of conduct prior to Phase I study. Such studies are normally conducted in healthy human participants staying in indoor setting (like hospital). As such studies may pose risks because of the adverse reactions of the drug, all safeguards to protect research participants should be in place. Such study demands an evaluation of the risk-benefit profile of investigational and the reference (comparator) product.

The volume of blood drawn must be within physiological limits irrespective of study design and the ERB should take precise note on the volume of blood drawn depending on whether the research participant is a healthy adult or a child. The ERB should carefully review the enrollment methods, fee/compensation for participation and informed consent taking process.

#### **7.5 Public Health Research**

Benefits and risks of public health research are not restricted to a person, and it may influence populations, communities, and the environment. It is essential to understand that public health interventions have the possibility to exploit the vulnerabilities of the specific population and communities. Public health research must be designed through a process of ethical reflection, together with formation of suitable protections, oversight methods and governance mechanisms.

**Public health practice** includes data collection through vital statistics, disease reporting, cancer registries, medical records and Antimicrobial Resistance (AMR) surveillance; investigation of disease outbreaks, immunization coverage, Vitamin A distribution, disease specific supplementation program, health promotion; treatment compliances, monitoring and evaluation of specific ongoing health program. These data may be used by researchers for generating generalizable knowledge/evidence to improve public health program performance through public health research. ERB should have to differentiate between public health practice and research in order to determine its role with more clarity.

In **public health research**, a large volume of population based data available from the health management information system, national surveys, medical records, registries and other health and related data repositories. While such data permits longitudinal analysis over multiple years, there are possibilities of misinterpretation of the data, violations of terms and conditions for which data was allowed access, unauthorized and inappropriate data use, and unethical publication. Therefore, ERB should ensure that the study using population based data from secondary sources does not violate any ethical principles of public health research.

**Implementation research** facilitates informed decisions about health policies, programs and clinical practices. It is co-designed and co-implemented with implementers and end users to understand and encourage uptake of a completed research. Analysis of this is done with the intention to reach for equitable health impact on population. It is intended to explain how best to scale an intervention, or how to introduce/expand public health innovation, how and why a policy works. It is adaptive in nature and builds on operational research and implementation science

framework. Its proposal is different than other types of research that demand accurate pre-definition of interventions, delivery mode, outcome measurement and the role of research participants. Therefore, there is a need to understand this requirement of flexibility during ERB review process. ERB needs to assess stakeholder engagement – identifying and defining stakeholders’ roles and also responsibility of the investigator to scale-up, advocate, promote uptake, or sustain the public health intervention. ERB should review whether investigating team members involved in implementation of the research are protected from any harm related to the study interventions or not. ERB must guarantee that all research participants in their study receive the best available standard care as well as any benefits of health resulting from the study. It is also important to disseminate the research result at local level, making it observable and reliable for local authorities in designing upcoming interventions.

## **7.6 Social and Behavioral Science Research**

Social and behavioral science research is often different from public health, bio-medical and clinical research. Social science research efforts provide a deeper understanding of explanatory factors and informs policy-making activities about several aspects that can be considered to guarantee that social equity and inter-sectionality of populations. This kind of study generally focus on understanding human behavior, the details of symbolic communication of cultures (which includes a group’s skills, knowledge, attitudes, values and motives) and geographical contexts before implementation of intervention. ERB should be aware of the challenges around moral diversity among different cultures and societies. In Nepalese context, this is obvious due to multi-religious, caste, social-class, gender and geo-ethnic

variations which are important characteristics of society that need to be considered in socio-behavioral research proposals. In terms of rights and responsibilities of different stakeholders including research participants, investigators, reviewers, publishers, etc., the principles of social and behavioral science research ethics are similar to those for public health and biomedical research.

Although researchers may observe some technically unacceptable practices and behavior of the study participants during the study period, they are not required to interrupt such practices and behaviors and must document these into their research findings. ERB needs to review this and also investigator's obligation to data sharing and post-research benefits to the research participants on a case-by-case basis. If investigators find some patterns of behaviors such as suicidal tendency or infanticide among research participants, he/she must disclose this information to the relevant persons/authorities to save life or prevent damage intended by the participants. If researcher thinks that they might come up with sensitive incidental findings during research process, he/she needs to mention the method to handle these at individual, family and community levels in the proposal. When the study is on sensitive topics such as mental health, gender based violence, social exclusion and discrimination, researchers should be prepared enough to be in contact with support systems such as access to counselling centers, rehabilitation centers, police protection, etc. In such circumstances, Individuals with necessary domain knowledge and experience need to be invited during ERB meetings. ERB members and investigators must have a basic understanding of legal provisions in the related area.

The safety of the study team needs to be taken into consideration especially when the research is being conducted on sensitive topics or in sensitive areas as there would be a possibility of the research team being subjected to disturbing instances while conducting the study. Institution, sponsors and local authorities should be responsible for such safety concern. Besides this, a provision of insurance coverage should be in place to meet such challenges.

If researcher would like to conduct a study within communities, he/she should not hire a local person from the same village as an interpreter. In this case, an interpreter must be hired from some other nearby village so that his/her vulnerability and perceived threat from research participants can be mitigated. Research agency must develop SOPs for handling deteriorating/unforeseen situations (trauma, humiliation and threats of violence) which might happen either to participants and study team members.

For audio/visual recording of research participant's interviews, Investigators must take prior permission from the ERB with justifiable reasons. ERB must review psychological, emotional, social and informational harm (if any), which might have been resulted from participating in a study.

If research participants feel that they are not autonomous in decision making, individual informed consent has to be taken after obtaining the permission of spouse/family head/community head/leader/culturally appropriate local authority/health care provider or institution. So, consent taking process should respect local cultural customs. However, such permission does not substitute for individual consent unless a waiver has been approved by ERB. Considering the power differences between investigators and research participants, it would be difficult for the participants to explicitly refuse to

participate. Investigators must be aware to cultural signs of refusal, such as silence, body language, uncommunicative replies, etc., and should not continue the interview in these cases. ERB may take into account these contexts during review process. Sometimes, ERB may waive the requirement for individual informed consent if it is convinced that the study would not be carried out without a waiver, for example, study on harmful practices.

### 7.7 Research on Human Genetics

Investigators need to consider following general issues while conducting research on human genetics.

- **Genetic test** results may put research participants into psychological stress which may be in the form of anxiety, depression, and sometimes their family relationships might be disrupted. There may be a possibility of social stigmatization, discrimination in schooling, employment, health and general insurance. So, it is very important to maintain the confidentiality in genetic testing and follow appropriate communication skills during genetic counselling.
- Investigators and relevant ERB members must keep abreast of emerging genetic/ **genomic technologies** including genetic manipulations for known and unknown consequences for the future, so that any emergence of newer ethical concerns and issues might have been tackled in due course.
- Study team should be comprised of clinicians, geneticists, genetic counsellors and laboratory personnel.
- **Genetic testing** research if conducted among those participants who are unable to protect their rights and safety, like children, individuals with mental illness, people with rare diseases, cognitively impaired individuals, etc., ERB must review such kind of proposals with an expert to

understand the ethical implications and provide protections for research participants.

- **Genetic counselling** should be done by one of the research team members who is qualified and experienced enough in communicating the meaning of genetic information. Sometimes, participants may require termination of pregnancy because of having genetically abnormal fetus. Suitable choices must be provided to the family to enable them to come to a decision while disclosing such results during the study period. While communicating such information, there must be the presence of both spouses, and essential precaution should be taken so as not to break families. Such type of counselling should be done with extreme caution and patience, so that participant's psychosocial harm is minimized.
- **Genetic research** demands collection of family members' details. So, such members will be regarded as secondary participants. Informed consent needs to be collected if identifiable information is being collected about the secondary participants.
- Research participant has the right to keep their **genetic information** confidential and not share it with family members especially in the case where genetic information is about non-paternity, disease carrier status, etc. This is just to avoid the possibility of domestic disputes.
- Investigators should not disclose the **genetic information** to family members without permission of research participant. Family members' information should be kept confidential from each other by the clinician/investigator if they have undergone for genetic tests. If clinician/investigator thinks that disclosure of the genetic test is absolutely warranted to provide treatment or counselling, he/she should first try to take informed consent from the family members, as otherwise the risks of non-disclosure against breach of confidentiality needs to be balanced after the approval from ERB. For example, if a female research participant happens

to be diagnosed as a carrier of X-linked or some disease conditions (hemophilia, Huntington's disease, non-syndromic deafness, etc.) affecting the fetus and may transmit such abnormality to the next progeny. It may cause marital conflict once such information is revealed to the husband or other family members, despite the fact that husband himself is a carrier of the autosomal recessive disorder. So, suitable counselling must be part of the genetic testing process.

- **Genetic information** has potential for misuse, for example, prenatal sex determination is banned by Nepali law for pre-selection of sex of the fetus. All investigators shall follow the provisions of the law/act/regulations/directives as appropriate.
- Knowledge of **genetic information** of an individual/family/community/population/ child might be misused by employers/insurers leading to psychosocial harm and discrimination. Therefore, participant's information should not be shared with anyone without obtaining their consent.
- For **future genetic research**, collected bio-samples can be stored for much longer period after obtaining consent from the research participants. Biological samples from the participants with rare genetic conditions, ethnic groups/tribes/populations on the verge of extinction, and others have huge geographical and cultural value and can be preserved for future genetic research if ERB provides the permission to do so.
- If researchers come up with gene or other related patenting concept during research process, it has to be declared in the proposal and should follow IPR policy/regulations of Nepal.
- Steps must be taken to safeguard investigators and research participants from possible inducement or coercion when the study is conducted by commercial companies.

- All genetic testing laboratories must undergo for accreditation for quality standard.
- Although researcher maintains anonymization of individual's genomic data, such data will always be associated with individual's identity at gene level. This may conflict the principle of confidentiality. So, extra efforts must be made to maintain privacy.
- **Gene editing technology** has been used to alter human genes to cure and eliminate certain genetic based diseases. This technology can be used to modify genes in a wide variety of cell types and in organisms. It may be permanent once the genetic change is introduced, and this would have long-term effects as there is a possibility of encountering errors while using this technology. If such technology has been planned to be used during embryonic state (period between 15 days and 8 weeks' post-conception of a pregnancy), number of ethical issues might have been encountered, such as the rights of unborn babies and the roles of humans in making permanent genetic changes. In this case, consent of father and mother should be taken.

## 7.8 Research in Humanitarian Emergencies and Disasters Situations

Health research might be necessary in humanitarian emergencies and disaster situations to enable and facilitate provision of efficient and suitable health response during such situations. In such circumstances, close attention must be given to the effect of increased vulnerabilities of the participants, and ethical review processes. Designing health research project in such situation is becoming challenge because of rapidly evolving ethical uncertainties. The role of ERB in this case is very critical while reviewing proposals developed for such emergency and disasters situations. Such proposals might be reviewed through expedite review process. In such situations, the ERB must determine who

could be an acceptable LAR in the absence of intended LAR. Participant's decision making capacity might be so low (they might be under traumatized conditions) that they are unable to figure out between reliefs offered and research components. Researchers must explain this during informed consent taking process and provide additional protections (counselling, psychological help, medical advice, etc.) for research participants because of their vulnerability. For children with untraceable or deceased relatives, the consent must be obtained from an individual who is not part of the study team. If investigators may need to waive the consent or get the consent from the participants at a later stage when community comes out of panic stage or the situation allows, he/she must have to provide its justification and obtain prior approval from ERB. Roles of investigators, volunteer workers and caregivers should be clarified, and potential CoI must be declared if any.

Investigators should consider fair selection of participants. There should not be over-sample, especially from vulnerable segments of the population. Participants selection criteria with proper justification must be provided in the proposal.

The inflow of visitors/members of media during emergencies may lead to a breach of privacy and confidentiality. So researchers must put extra efforts to protect the identifying information about research participants.

Investigators and sponsors must attempt to provide beneficial interventions, which may be part of the study initiative even after completing the research project and till the local social support system is restored to deliver routine services.

## **7.9 Stem Cell Research for Health**

Research on stem cell provides novel treatment of numerous incurable diseases. With appropriate approvals from ERB, stem cell research is permissible in areas of embryonic, adult and cord blood except reproductive cloning type of study. If stem cells will be used outside the domain of a clinical trial, it is considered unethical and ERB may not provide its approval. Stem cell clinical trial should be conducted with clinical grade cells processed by Good Laboratory Practice (GLP), Good Manufacturing Practices (GMP), and GCP guidelines. Investigators should keep himself/herself updated in accordance with changes in guidelines regarding use of these cells.

## **7.10 Use of Animals in Research for Health**

Large number of animals is being used for health research, and these animals have the feeling of pain and suffering as human being. So, unnecessary exposure to pain and improper handling of the experimental animals should be avoided.

The use of animals for research in medicine is decreasing and effort is being made to replace animal experiment by other laboratory experiments. However, it is not possible in all instances, so we must use animals. When it is extremely necessary to use animals, there should be a general guideline to treat them in proper manner. Care should be taken to subject the animals to as less pain as possible, and if killing is necessary, it should be done subjecting to less pain.

Research using animals is a wide field, and it is not possible to cover all aspects of animal use for experiment in one guideline. NHRC has published "Ethical Guidelines for the Use of Animals in Health Research in Nepal" in the year 2005 targeting the areas of

public health and academic institutions where animals are used for drug/vaccines trials.

The fundamental principles in animal experimentation for health should be:

- No animals should be used in human health research until written ethical approval is obtained.
- Assure the appropriate species, quality, and number of animals in health research.
- When designing the research proposal, the number of animals used should reflect the minimum necessary to yield valid answers to the research hypothesis.
- Accepted sources of animal purchase.
- Ensure that all those involved in the use of animals in health research be appropriately qualified, act humanely and be protected.
- Ensure that the use of animals in health research is justified and provided proper care.
- The species chosen for study should be best suited to answer the question(s) posed, taking into account their biological characteristics, including behavior, genetic constitution and nutritional, microbiological and general health status.
- Necessary steps to be taken to assure physical comfort, to avoid pain or distress and to assure the good health of all research animals.
- Minimize the discomfort, distress, and pain in connection with sound research.
- Before using animals, the users should submit their detail proposal illustrating steps and plans with reasonable cause and expected benefit. The person should support the need to use animals with evidence and reasons that there is no other alternative.
- At the end of each experiment, the users are responsible to euthanise all animals. In case the animals are to survive, the users must provide the reasons for such necessity in their

proposals and must be responsible for rearing the animals under conditions appropriate for the species. The animals should neither be released to nature, nor should they be abandoned at the animal unit without care.

- The use of wild/endangered/threatened animals is to be restricted to scientific research. However, these can be used only in cases of extreme necessity when no other animals can be substituted. The use of such animals for research has to abide by the law and policies for wildlife conservation. Wild animals for experimentation shall be acquired as National Parks and Wildlife Conservation Act 2029 (1977 AD) (3) and the Wildlife Farming, Breeding and Research Policy 2059 (2002 AD), Convention on International Trade in Endangered Species of Wild Flora & Fauna (CITES), Animal Health and Livestock Service Act 2055 (1999 AD) (4) and rules 2057 (2001 AD). (5).
- The means of transportation should provide safety for the animals and should have the least impact on the well-being of the animals. The animals should not be exposed to extreme environments. Adequate spaces and appropriate temperature and ventilation should be provided to avoid stress. Delivery boxes should be strong and well secured to avoid escape.
- The researcher should be qualified, have knowledge on the behavioral characteristics of the animal subjects so as to be aware of normal, species-specific behaviors and unusual behaviors that could forewarn the researcher of potential health problems.
- Animals used in health research should be housed in a separate location away from public housing. The animals should not be exposed to dust, smoke, noise, rodents, insects and birds. For avoiding infection and stress, the animal facility must be equipped with systems that can control: infection, temperature, humidity, ventilation, lighting and sound, to suit the needs of each species.

- Animal facility should be developed and maintained following nationally approved standards, particularly in term of maintaining biosafety and biosecurity.
- Animals should only be handled following standard biosecurity guideline, taking into consideration of the risk of the agents used in animal experimentation and experimental animal categories.
- Procedures subjecting animals to pain, stress, misery or death should be used only when an acceptable alternative procedure is unavailable.
- Ensure care, housing, anti-cruelty and maintenance of research animals.
- Every animal house should be managed in such a way that the direct involvement/ supervision/accountability of a qualified and trained veterinarian is ensured.
- Animals should be fed palatable, non-contaminated and nutritionally adequate food daily or according to their particular requirements unless the protocol in which they are being used requires otherwise.
- The **cages for the animals** should be made of suitable material, a suitable size and have adequate feeding, watering and movement arrangements to avoid any injury to the animals. The bedding should be appropriate for the animal. Animal bedding is a controllable environmental factor that can influence experimental data and animal well-being. The veterinarian, along with investigators should select the most appropriate bedding material.
- All **transportation of animals** should be planned to minimize transit time and the risk of zoonosis, protect against environmental extremes, avoid overcrowding, provide food and water when indicated and protect against physical trauma. Each shipment of animals should be inspected for compliance. A health certificate for the animal should be obtained at the point of transportation origin and destination. Newly received animals should be given a period for

physiologic, psychological, and nutritional stabilization before their use.

- Animals should not be used in more than one study either in the same or different projects, without the approval of the ERB.
- Animals cannot be subjected to successive surgical procedures unless these are required by the nature of the research, the nature of the surgery, or for the well-being of the animal. Multiple surgeries on the same animal must receive special approval of the ERB of NHRC.
- The return of wild-caught animals to the field can carry substantial risks, both to the free-ranging animals and to the ecosystem. Animals reared in the laboratory cannot be released. Therefore, such animals must be euthanized after the research is completed. Euthanasia shall be accomplished in a humane manner, appropriate for the species, and in such a way as to ensure immediate death. Death should be confirmed by personnel who can recognize and certify the cessation of vital signs in the particular species. A registered veterinarian shall closely monitor the method of euthanasia.
- It is understood that proper record keeping is extremely important for any animal used in health research. The record forms should be kept simple but complete. All animals used in health research must regularly be monitored and up-to-date records kept.
- The NHRC should appoint a committee, which is to be responsible for monitoring and promoting the ethical use of animals in research, testing, production of biological materials, through the ethical guidelines for the care and use of animals in health research in Nepal.

## **Section 8. Formation of Institutional Review Committees and its Regulation**

As the number of health research is increasing in Nepal, it is not possible for ERB to review and monitor all the researches being in the country. So, ERB has started to support the establishment of IRCs at the health agency, academic and research institutions. NHRC has developed IRC guidelines for regulation of such IRCs, which is a logical approach to strengthen the capacity for reviewing health research proposals.

### **8.1 Establishment and Functions of Institutional Review Committees**

Any health institution which fulfills the basic criteria as mentioned in the annex-III is eligible to establish an IRC. It should work within the framework of ethical and the scientific standards in health research. It is mandatory that the IRC must be independent, autonomous and multidisciplinary in nature. The IRC must be supplied with administrative and financial support from the institute. The IRC should outline a clear SOP, proposal registration process and fee (if any) for reviewing a research proposal.

Executive chief of the institution should not be the member of any IRC. The IRC should have the freedom to work independently and decide on the merits of research proposals without interference from within the institutional framework.

The number of members in the committee is suggested to be in between 7 to 15, with an attention to gender, age and discipline balance. The committee should include at least one member who is not affiliated with the institution.

Institutional Review Committees (IRCs) must receive approval from the ERB. Their decisions may not be considered ethically

valid without NHRC approval. The IRC must pay NPR 20,000.00 (Nepali rupees twenty thousand) as a one-time processing fee to the NHRC. The IRC approval should be renewed every three years from ERB. At a time of renewal, the IRC must pay NPR 5,000.00 (Nepali rupees five thousand) as a renewal processing fee. If the renewal process is not commenced within six months of expiry date, the IRC will be notified for termination of approval.

An IRC should inform the ERB if there are any changes in its composition and SOP. All approved IRCs should display their NHRC approval status in their letter pads.

## **8.2 Networking and Regulation of Institutional Review Committees by Ethical Review Board**

Ethical review board must organize network meeting with all the IRCs at least once a year. All IRCs will be supervised, monitored and evaluated by the ERB at least once in three years period. For enhancing the capacity of IRCs, ERB must organize ethics related training workshops.

All IRCs should forward the following research proposals to the ERB for approval:

- Research proposal at the national or international level
- Externally sponsored/funded research (*the term “externally” indicates not only outside of the country but also outside of the particular health care facility or institution*)
- Clinical trials involving human and/or animal participants

The IRC is not authorized to provide ethical clearance to any research proposals submitted from outside of the institution. All research proposals approved by the ERB may not need further approval from any IRCs existed in Nepal. “Institutional Review Committee guidelines for Health Research in Nepal” must be looked at for further details.

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## Glossary

**Accountability:** The obligation of an individual or organization to account for its activities, accept responsibility for them and to disclose the results in a transparent manner.

**Adverse Event:** Any untoward medical occurrence in a patient or participant involved in a study which does not necessarily have a causal relationship with the intervention. The adverse event can therefore be any unfavorable or unintended sign or experience, whether or not related to the product under investigation.

**Assent:** To agree or approve after thoughtful consideration an idea or suggestion to participate in research by children between 7 to below the age of 18 years who is old enough to understand the implications of any proposed research but not legally eligible to give consent. The assent has to be corroborated with informed consent of parent/ LAR.

**Audit:** A systematic and independent examination of research activities and documents to determine whether the review and approval activities were conducted, data recorded and accurately reported as per applicable guidelines and regulatory requirements.

**Autonomy:** The ability and capacity of a rational individual to make an independently informed decision to volunteer as a research participant.

**Beneficence:** To try to do good or an action which weighs the risks against benefits to prevent, reduce or remove harm for the welfare of the research participant(s) in any type of research.

**Bio-availability:** It is the measurement of the proportion of the total administered dose of a therapeutically active drug that reaches the systemic circulation and is therefore available at the site of action.

**Bio-bank:** It is a systematic collection of bio-specimens in standard laboratory/health institution for research and related activities at a later time.

**Bio-equivalence:** It is a term used in pharmacokinetics when there are two or more medicinal products (proprietary preparations of a drug), containing the same active substance that need to be compared in vivo for biological equivalence.

**Capacity:** Capacity of vulnerable population may be reduced because of their personal disability, understanding or ability to communicate, lack of power, social injustice, environmental burdens or situation that avoids them from doing so.

**Case Report Form:** It is a printed, optical or electronic document designed to record all the required information in the protocol on each study participant for reporting to the sponsor

**Clinical Trial Registry:** An official platform for registering a clinical trial.

**Cognitive Impairment:** When a person has trouble remembering, learning new things, concentrating, or making decisions that affect their everyday life.

**Compensation:** Provision of financial payment to the research participants or their legal beneficiaries when temporary or permanent injury or death occurs due to participation in health research.

**Confidentiality:** It is the duty of the investigator(s) or research agency to the research participant to protect the delivered information. It incorporates the requirement to safeguard information from unauthorized access, use, disclosure, alteration, damage or stealing.

**Contract Research Organization:** An institution or service organization which is generally recruited by the sponsor for

providing research support/services (especially vaccine trial) on a contractual basis nationally or internationally.

**Coercion:** An overt or implicit threat of harm to a participant which is intentional to force compliance.

**Collaborative Research:** An umbrella term for methodologies that actively engage national and International public/private institutions in the research process from start to finish.

**Competence:** The broad professional knowledge, attitude and skills required in order to work in a specialized area or profession.

**Deception:** It occurs when investigators provide false or incomplete information to participants to misleading them to achieve the study objectives and for larger public good. Research employing any type of deception should undergo full committee review.

**Disaster or Humanitarian Emergency:** It is an event or series of events that represents a critical threat to the health, safety, security or well-being of a community or other large group of people, usually covering a wide land area.

**Exploitation:** The action or fact of treating someone unfairly in order to benefit from their participation.

**Fabrication:** This is the intentional act of making-up data or results and recording or reporting them.

**Falsification:** This is manipulating study supplies, materials, equipment or procedures or altering or skipping/suppressing data or results without scientific or statistical explanation, such that the research is not precisely represented in the study document.

**Impartial Witness:** A person who is independent of the trial, who cannot be unfairly by influenced by people involved in the trial, who attends the informed consent process if the participant's or the LAR cannot read, and who reads the informed consent form and any other written information supplied to the participant.

**Implementation Research:** It is a type of health policy and systems research that draws on many traditions and disciplines of research and practice. It builds on operations research, participatory action research, management science, quality improvement, implementation science and impact evaluation.

**Informed Consent Document:** Written signed and dated paper confirming a participant's willingness to voluntarily participate in a particular research, after having been informed of all aspects of the research that are relevant for the participant's decision to participate.

**Inducement:** A motive or consideration that leads one to action or to additional or more effective actions without considering the harm that may occur.

**Legally Authorized Representative:** A person who, under applicable law or judicial authority, can give consent on behalf of a prospective participant who, for either legal or medical reasons, is unable to give consent herself/himself to participate in research or to undergo a diagnostic, therapeutic or preventive procedure as per research protocol, duly approved by the ERB.

**Plagiarism:** This is the direct stealing anything (including language, thoughts, ideas, or expressions) from someone's published paper/book etc. and represent these as one's own original work. Sometime duplicating one's own publication also

falls under the category of plagiarism, which may be termed as self-plagiarism.

**Pilot Studies:** A pilot study, project or experiment is a small-scale preliminary study conducted in order to evaluate feasibility, time, cost, adverse events and effect size (statistical variability) in an attempt to predict an appropriate sample size and improve upon the study design prior to performance of a full-scale research project.

**Principal Investigator:** An individual or the leader of a group of individuals who initiates and takes full responsibility for the conduct of health research; if there is more than one such individual, they may be called co-principal investigators/co-investigators.

**Privacy:** It is the participant's right to control the information that can be gathered and stored by him/her and to whom that information might be shared.

**Psychosocial harm:** Research, particularly psychology studies, can put participants in situations that may make them feel uncomfortable while learning about their reaction to a situation. The result can be psychological harm that can manifest itself through worry (warranted or unwarranted), feeling upset or depressed, embarrassed, shameful or guilty, and/or result in the loss of self-confidence.

**Quorum:** Minimum number and/or kind of ERB members required for decision making during a meeting.

**Re-consent:** It is the process of obtaining and documenting again the participant's willingness to remain in the study.

**Risk:** Probability of harm or discomfort to research participants. Acceptable risk differs depending on the conditions inherent in the conduct of research.

**Standard Operating Procedure:** Detailed written instructions in a certain format describing all activities and actions to be undertaken by an organization to achieve uniformity in performance of a specific function.

**Serious Adverse Event:** It is serious when the research outcome for the participant is death, life-threatening injury requiring hospitalization, prolongation of hospitalization, significant disability/incapacity, congenital anomaly, or requirement of intervention to prevent permanent impairment or damage.

**Social Harm:** It is a non-medical adverse consequence of study participation, including difficulties in personal relationships and stigma or discrimination from family or community. Social harm can be related to personal relationships, travel, employment, education, health, housing, institutions (government/non-government) and others.

**Sponsor:** An individual, institution, private company, government or nongovernmental organization from within or outside the country who initiates the research and is responsible for its management and funding.

**Transparency:** It implies intentional openness, communication, and accountability operating in such a way that it is easy for others to see what actions are performed.

**Undue Inducement:** Offer of disproportionate benefit in cash or kind that compromises judgment which may lead to acceptance of serious risks that threaten fundamental interests.

**Vulnerability:** It pertains to individuals who are relatively or absolutely incapable of protecting their own interests because of personal disability, environmental burdens or social injustice,

lack of power, understanding or ability to communicate or are in a situation that prevents them from doing so.

## Annexes

### Annex I: Sample transfer plan

Biological samples	For what test	Is the required test available in registered laboratory in NPHL in Nepal? Yes / No	Is the required method available in the registered laboratory? Yes / No	If no, is there any plan to make test/method available in the registered laboratory? Yes / No	Is there any plan to transfer biological sample abroad? Yes / No	Remark

## Annex II: Process and list of documents required for applying online proposal submission

<b>Screening:</b> Research related to health, national or international researcher and thesis or self-funded study.
<b>Administrative information:</b> <ul style="list-style-type: none"><li>▪ Most current version of the CV of the PI, Co-investigators and other team members with special mention of academic qualification and research experiences in pdf format or Word format</li><li>▪ Photos of PI and Co-Investigator and other team members in jpg format</li><li>▪ Scanned signature of PI and Co- Investigator and other team members in jpg format</li></ul>
<b>Financial details:</b> It includes human resource cost, field expenses, transportation cost, laboratory cost, data management cost, report writing and dissemination cost, logistic cost, monitoring and evaluation cost, miscellaneous cost, ethical approval cost, and at the end “total budget of health research to be spent in Nepal”.
<b>Technical Details:</b> Title of Research, Research area, Background, Rationale/justification, Conceptual Framework, General Objective, Specific Objective, Research Hypothesis, Study Variables, Research Method, Research Design, Description of Research Design, Study site and its Justification, Study Population, Sampling unit, Sample Size, Number of participants and Justification, Sampling Technique, Criteria for Sample Selection, Data Collection Technique, Data Collection Tools, Pretesting, Validity and Reliability of Tool, Potential Biases, Limitation of the Study, Plan for Supervision and Monitoring, Plan for Data Management and Analysis, Expected Outcome of the Research Results and Plan for Utilization of Research Findings
<b>Ethical consideration:</b> Number of human participants to be involved, frequency, responsibility, vulnerability, risks and benefits, types of informed consent, etc.
<b>Documents:</b> Data collection tools, conceptual framework, consent form, agreement letter, work plan, donor agreement letter (if any), etc. <ul style="list-style-type: none"><li>▪ Data collection tools should be in Nepali and local language (if necessary) including interviews and Focused Group Discussion guideline, observation checklist, questionnaires etc.</li><li>▪ A copy of informed consent/assent form in Nepali and local language (if required) should be included in the application. This should include a detail description of the process of giving the information to the research participants and its content, process of obtaining the consent, the person responsible for obtaining the</li></ul>

informed consent and documentation of the signature of the researcher/research participants and/witness if applicable

- Consent form should be in Nepali and local language (if necessary)
- Conceptual framework
- If the research study is to be conducted in a hospital/organization or institution, a letter of support from the respective hospital/organization or institution should be provided.
- Agreement letter with donor, if it is a funded study.
- There should not be more than one PI in a study. However, If the PI is a non Nepali citizen, one additional PI should be a Nepali citizen relevant to the study subject.
- Nepalese PI must be responsible for proposal submission and its related communication and correspondences.
- Institutional ethical clearance from his/her own country, if submitted from academic and related institution from outside the country
- If the study requires bio-samples/specimens to be transported outside of Nepal (justification needed), MTA, CVs of the bio-sample/specimens handling person, and commitment letter from the PI as the proposed tests will be conducted only for this study, must be provided. Only extracted and amplified bio-samples (in most of the cases) will be allowed to transfer. Back up bio-samples should be kept in Nepal (if possible) as otherwise PI should provide its justification.

**In case of trial, additional documents are required**

- Description about the study design, screening and eligibility assessment including randomization and blinding process (if followed)
- The phase of trial, and a detail description of the safety of the product or procedures
- Investigational Medicine Product (IMP) (IMP description, labelling, supply, its storage, etc.)
- Investigators brochure
- Safety reporting (definition, causality, procedure for recording and reporting adverse events, etc.)
- Independent DSMB
- Pharmacovigilance safety report including the pharmacological, pharmaceutical, and toxicological data available
- Provision of insurance in the event of any participant suffering harm as a result of their involvement in the research

<ul style="list-style-type: none"> <li>▪ Results of the previously conducted clinical trial (authentic reports)</li> <li>▪ Signed final copy of the previously conducted clinical trial documents</li> <li>▪ No objection letter from the regulatory authorities in Nepal; for example, in the case of drug and vaccine trial, DDA should provide such letter. There may be a need of such letter from National Committee for Immunization Program working under Family Welfare Division of Department of Health Services if vaccine trial will be conducted.</li> <li>▪ Clinical Trail Registration (CTR) number</li> <li>▪ Original Protocol</li> <li>▪ Detail of CRO</li> <li>▪ Other center's ethical approval letter</li> <li>▪ List of abbreviations /acronyms</li> <li>▪ References</li> </ul>
<p><b>For student applicants,</b></p> <ul style="list-style-type: none"> <li>▪ Approval Letter from concern Institute/University, mentioning PI, Co-investigator, collaboration and funding provision of the study</li> <li>▪ Recommendation letter from academic supervisor stating that the student is working under his/her supervision.</li> <li>▪ In case of foreign student working for academic thesis in Nepal, the local Nepali supervisor should be the co-investigator.</li> </ul>
<p><b>Ethical approval processing fee</b>  Researcher can deposit the ethical approval processing fee at NHRC Office or at Standard Chartered Bank Nepal Ltd. Kathmandu, Nepal</p> <p>Swift code: SCBLNPKA</p> <p>A/C Name: Nepal Health Research Council</p> <p>Saving A/C Number: 18-0018546-06</p> <p>Address: New Baneshwor, Kathmandu, Nepal</p> <p>Details of the ethical approval fee structure:</p> <ul style="list-style-type: none"> <li>• For Nepalese students studying inside Nepal (Thesis) <ul style="list-style-type: none"> <li>– If self-funded, NHRC fee will be NPR 1,000.00 (one thousand)</li> </ul> </li> <li>• For Nepalese students studying outside Nepal (Thesis) <ul style="list-style-type: none"> <li>– If self-funded, NHRC fee will be NPR 10,000.00 (ten thousand)</li> </ul> </li> <li>• For Nepalese researchers <ul style="list-style-type: none"> <li>– If the proposal having its total budget below NPR 200,000.00 (two</li> </ul> </li> </ul>

hundred thousand), NHRC fee will be NPR 5,000.00 (five thousand)  
– If the proposal having its total budget between NPR 200,000.00 (two hundred thousand) to NPR 1,000,000.00 (one million), NHRC fee will be NPR 10,000.00 (ten thousand)

- For International researchers/students  
– If the proposal having its total budget up to US\$ 10,000.00 (ten thousand), NHRC fee will be US\$ 200.00 (two hundred)

– If the proposal having its total budget up to US\$ 500,000.00 (five thousand), NHRC fee will be US\$ 3% of the total budget.

***For example, if the total budget will be US\$ 500,000 (five hundred thousand), researcher needs to pay US\$ 15,000 (or equivalent amount of NPR as per submission dated exchange rate)***

– If the proposal having its total budget up to US\$ 1,000,000.00 (one million), NHRC fee will be as follows: For first US\$ 500,000.00: 3% and for second 500,000: 1.5%. ***For example, if the total budget will be US\$ 1,000,000 (1 million), researcher needs to pay US\$ 22,500 (which is US\$ 15,000 plus US\$ 7,500) (or equivalent amount of NPR as per submission dated exchange rate)***

– If the proposal having its total budget above US\$ 1,000,000.00 (one million), NHRC fee will be as follows: For first US\$ 500,000.00: 3%, for second 500,000: 1.5% and for third .....: 1%.

***For example, if the total budget will be US\$ 2,000,000 (2 million), researcher needs to pay US\$ 32,500 (which is US\$ 15,000 plus US\$ 7,500 plus US\$ 10,000) (or equivalent amount of NPR as per submission dated exchange rate)***

### Annex III: Basic criteria to establish an Institutional Review Committee in Nepal.

<b>Basic Criteria to Establish the IRC</b>			
<b>S.N</b>	<b>Indicators</b>	<b>Score</b>	<b>Remarks</b>
1	Cover letter clearly marking the list of the IRC Member(Gender, discipline, age balanced) with designated IRC chair and member secretary along with their educational background and position in IRC and attached CV	3	3
2	Commitment letter from the head of institute to run the IRC with provision of Dedicated HR(1), separate Office(1) and Logistic support (1)	3	3
3	Standard Operating Procedure based on IRC guidelines published by NHRC	3	3
4	CoI form (1), Commitment letter (1) and Appointment letter to the IRC member (1)	3	3
5	Academic Institute with master degree and above	5	5
6	Number of Approved research in Last One year <b>(10*5 Researches)</b>	50	50
6.1.	Ethical Clearance from NHRC		
6.1.1	If staff, with affiliated institute (1*2)	20	-
6.1.2	If student, with affiliated institute (1*1)	10	-
6.2	Report Submitted		
6.2.1	If staff, with affiliated institute (1*3)	30	-
6.2.2	If student, with affiliated institute (1*2)	20	-
7	Fund allocation for research activities & Capacity Building	4	4
8	Published Article (IRC Chair/Member secretary)	15	15
8.1	1st Author (1*15)		
8.2	Corresponding Author (0.75*15)		

8.3	Co-Author (0.5*15)		
9	IRC Chair (Fulltime faculty member)	5	5
9.1	Professor (5)		
9.2	Associate Professor (3)		
9.3	Assistant Professor (2.5)		
10	Inspection visit by ERB (If fulfill all the requirements having with good coordination between IRC & Institution and positive environment of research culture)	9	
	<b>Total Score</b>	<b>100</b>	

#### **Annex IV: list of members of committees involved in revision of guidelines (2016-2019)**

##### **Executive Board members of NHRC**

Prof. Dr. Anjani Kumar Jha, Executive Chairman

Dr. Bhoj Raj Adhakari, Vice Chairman

Prof. Dr. Madhu Dixit Devkota

Dr. Sandhya Chapagain Acharya

Dr. Yogesh Neupane

Dr. Bhola Ram Shrestha

Dr. Shyam Kumar BK

Dr. Ramesh Kharel

##### **Ethical Review Board members (ERB) of NHRC**

Prof. Dr. Prakash Ghimire, ERB Chairperson

Prof. Chitra Kumar Gurung

Prof. Dr. Sabina Shrestha

Mr. Harihar Dahal

Prof. Dr. Lochana Shrestha

Prof. Goma Devi Niraula Shrestha

Prof. Dr. Ramesh Singh Bhandari

Dr. Satish Kumar Dev

Dr. Binod Kumar Yadav  
Mr. Bimalesh Thakur  
Dr. Ashish K.C

**Ex-ERB Board Members:**

Prof. Dr. Jeevan Sherchand (Ex- Chairperson)  
Prof. Dr. Aarati Shah (Ex- Chairperson)  
Prof. Chandra Kala Sharma  
Prof. Dr. Kedar Prasad Baral  
Prof. Dr. Deewakar Sharma  
Prof. Dr. Dharma Khanal  
Dr. Narhari Kharel  
Prof. Dr. Shankar Man Rai  
Dr. Anil Kumar Jha  
Prof. Dr. Mohan Raj Sharma  
Prof. Dr. Jyothi Sharma

**Reviewers**

Dr. Ramesh Kant Adhikari  
Prof. Dr. Kedar Prasad Baral  
Dr. Roli Mathur  
Dr. Suchita Joshi  
Dr. Angel Magar

**List of participants in National Consultation workshop for National Ethical Guideline finalization, NHRC, Kathmandu**

Prof. Dr. Anjani Kumar Jha (Executive Chairman, NHRC)  
Prof. Dr. Prakash Ghimire (Chair, ERB)  
Prof. Dr. Ramesh Kant Adhikari (Past Chair, ERB)  
Prof. Dr. Kedar Prasad Baral (Ex-ERB, Member)

Prof. Dr. Sabina Shrestha (Member, ERB)  
Prof. Dr. Dharmendra Karna (Member, ERB)  
Prof. Goma Devi Niraula (Member, ERB)  
Asso. Prof. Dr. Satish Deo (Member, ERB)  
Dr. Aashish KC (Member, ERB)  
Mr. Puskar Nepal (Invitee Member, ERB, MoHP)  
Prof. Dr. Dharma Prasad Khanal (Ex-ERB, Member)  
Dr. Mohan Krishna Shrestha (Member Secretary, Tilganga Eye Centre)  
Prof. Ganesh Dangal (IRC Chair, Phect-Nepal,  
Dr. Hari Prasad Dhakal (Chair, Nepal Cancer Hospital,  
Dr. Suchita Joshi (Nepal Medici Hospital)  
Mr. Nirbhay Kumar Sharma (Deputy Chief Admin Officer, NHRC)  
Ms. Saraswati Sharma (Member, IRC)  
Dr. Meghnath Dhimal (Senior Research Officer, NHRC)  
Dr. Rajendra Kumar BC (Research Advisor, NHRC)  
Ms. Namita Ghimire (Research Officer, Ethical Review, M & E Section NHRC)  
Mr. Ashok Pandey (Research Officer, NHRC)  
Dr. Anju Vaidya (Research Officer, Ethical Review, M & E Section NHRC)  
Mr. Anil Kumar Sah (Research Officer, Ethical Review, M & E Section NHRC)  
Ms. Jyoti Kumari Jha (Research Officer, Ethical Review, M & E Section NHRC)  
Mr. Sashi Verma (Research Officer, Ethical Review, M & E Section NHRC)  
Mr. Ashwin Karakheti (Program Officer, Ethical Review, M & E Section NHRC)  
Mr. Pukalal Ghising (Assistant Account Officer, NHRC)  
Mr. Subash Ghising (Admin. Assistant, NHRC)

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