National Ethical Guidelines for Health Research in Nepal 2022

Nepal Health Research Council (NHRC)
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Foreword

Message from the NHRC

It is indeed a great pleasure and privilege for NHRC to be able to revise a document entitled 'National Ethical Guidelines for Health Research in Nepal.' NHRC is currently exploring new ideas to overcome the challenges confronting health research. We hope this guideline builds on these very initiatives. NHRC has always been at the forefront of setting standards for ethics in health research. The council published the Ethical Guidelines in 2001, which underwent further revisions in 2011, 2019, and 2022.

National Ethical Guidelines for Health Research in Nepal 2022 is an outcome of in-depth discussions and debates with the experts, involving diverse stakeholders, NHRC Executive Committee, Ethical Review Board (ERB) Chairperson, former chairperson, and ERB members. 'This revised edition of the guideline has addressed many emerging ethical issues, keeping in view the social, economic, cultural, legal, and religious aspects of Nepal, the revised version also aims at sensitizing the government authority, health care institutions, policymakers, planners, research institutions and social scientists of Nepal on ethical obligations and best practices. We believe NHRC's revised ethical guidelines will be acknowledged and used as a reference by the researchers in Nepal and beyond.

With the concerted efforts and collaboration of Government, private, public, and other relevant organizations, we believe that our goal of preparing National Ethical Guidelines will ultimately result in the development of sound ethical practices in Nepal. We expect that the researchers will be able to enhance clarity about ERB of NHRC requirements, understand clarity about ERB of NHRC requirements, understand the standard templates, checklists for submission, and monitoring compliance needs, among others. We are confident that the government, health care institutions, and individuals will contribute to the guideline's success.

We would like to express our sincere gratitude to the NHRC Executive Committee members, especially to Prof. Dr. Mohan Raj Sharma, Prof. Dr. Prakash Ghimire former ERB Chairperson (2018-2021), ERB Members, and the ERB secretariat. In addition, we would like to express gratefulness to everyone who has kindly contributed to the development and completion of the National Ethical Guidelines for Health Research in Nepal 2022.

We would also like to thank USAID's Suaahara II Program for helping us edit the guideline.

Dr. Pradip Gyanwali
Member Secretary, NHRC

Prof. Dr. Gehanath Baral
Chairperson, NHRC

Preface

Nepal Health Research Council (NHRC) has been entrusted and mandated with the responsibility of promoting quality health research in the country. 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 of experts to develop and update ethical guidelines over different periods of time.

NHRC has developed and published a variety of Guidelines, including National Ethical Guidelines for Health Research in Nepal-2001 (first edition), 2011 (second edition), 2019 (third 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 (IRC) for health research in Nepal-2005 and 2016.

Realizing the need for timely revision to incorporate newer developments in medicine, science, and technology, NHRC executive committee formed a team of ERB members and secretariat staff to update the existing version of the Ethical Review Guideline in 2018. The current version of the guideline is based on the basic principles of the Nuremberg Code, 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, the World Health Organization (WHO), International Conference on Harmonization (ICH) and Guidelines for Good Clinical Practice (GCP). This version has attempted to address new concepts, guideline topics, and recommendations in medicine, science, and technology. The guideline has specific separate sections on basic and general ethical principles, 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, and research involving experimental animals and insect vectors.

This revised version of Ethical Guidelines has envisioned separate standard operating procedures (SOPs) for each component, including the functioning of the Ethical Review Board (ERB), review process and reviewer's roles and responsibilities, and Material Transfer Agreement (MTA) for transferring biological materials addressing intellectual property rights of the research organizations/researchers within the country. This document also incorporates various sections, including the conceptualization of and strategies to mitigate conflict of interest for the reviewers/ERB members while performing their assigned duties, o requirements for externally funded research monitoring of ethical conduct of research, bio repository, animal handling, research using genetic materials/embryos, and research during emergencies.

ERB expects all the researchers and institutions involved in health research to familiarize themselves with and adhere to the principles and guidelines as laid down in this document. Finally, ERB acknowledges the contribution of subject experts, former NHRC Chairperson Prof. Dr. Anjani Kumar Jha, ERB chairperson and members, and all who have directly and indirectly contributed to the completion of this guideline.

Prof. Dr. Ramesh Kant Adhikari
ERB Chair, NHRC

Abbreviations

AE	Adverse Events
AMR	Antimicrobial Resistance
BA	Bioavailability
BE	Bioequivalence
CIOMS	Council of International Organizations of Medical Sciences
CoI	Conflict of Interest
COPE	Committee on Publication Ethics
CTR	Clinical Trail Registration
CV	Curriculum Vitae
DDA	Department of Drug Administration
DSMB	Data Safety and Monitoring Board
DTA	Data Transfer Agreement
E-consent	Electronic Informed Consent
EC	Ethics Committee
ERB	Ethical Review Board
FERCAP	Forum for Ethical Review Committees in the Asian and Western Pacific Region
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GIS	Geographical Information System
GCLP	Good Clinical Laboratory Practice
GMP	Good Manufacturing Practice
GoN	Government of Nepal
HIV	Human Immunodeficiency Virus
ICD	Informed Consent Document
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICMR	Indian Council of Medical Research
IMP	Investigational Medicine Product
IP	Investigational Product
IPR	Intellectual Property Rights
IRB	Institutional Review Board
IRC	Institutional Review Committee
LAR	Legally Authorized Representative
LGBT	Lesbian, Gay, Bisexual, and Transgender
MoHP	Ministry of Health and Population
MTA	Material Transfer Agreement
NHRC	Nepal Health Research Council
PI	Principal Investigator

PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RNA	Ribonucleic acid
SAE	Serious Adverse Events
SOP	Standard Operating Procedure
TB	Tuberculosis
TSC	Trial Steering Committee
ToR	Terms of Reference
UN	United Nations
WAME	World Association of Medical Editors
WHO	World Health Organization
WMA	World Medical Association

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Section1. Introduction

Nepal Health Research Council (NHRC) has developed National Ethical Guidelines for Health Research in Nepal 2022 for researchers, reviewers, research sponsors, and regulatory authorities to ensure that the proposed studies involving human subjects are ethically justifiable and conform to the internationally accepted ethical principles. The main goal of the guidelines is to protect the rights and the dignity of the research participants as well as to ensure essential research of high social and scientific value. NHRC's Ethical Guidelines for Health Research is cognizant of and based on national, regional, and international guidelines and research practices.

1.1 Historical background

Nepal Medical Research Committee (NMRC) was established on 15 April 1982, under the Ministry of Health as the first regulatory body for health research in Nepal. Nearly a decade after being involved in regulating Health Research in the country, an Act of Parliament established (NHRC) on 12 April 1991 as an autonomous institution of the Government of Nepal. NHRC is primarily tasked with promoting and coordinating health research to improve the health status of Nepalese people. The Ministry of Health and Population (MoHP) is designated as a line ministry for reporting for the NHRC.

In 1995, the first NHRC's 'Ethical Guidelines' was published, which was revised in 2001 as 'National Ethical Guidelines for Health Research in Nepal.' Since then, the NHRC has been regularly organizing workshops and consultative seminars on research ethics to educate researchers and understand their difficulties in following the global ethical norms and standards. In 2005, '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' were published. The senior researchers' consultations in 2008 recommended updating the 'National Ethical Guidelines-2001' and related documents. The 'National Ethical Guidelines 2001' was thereafter reviewed, revised, and published in 2011 as 'National Ethical Guidelines for Health Research in Nepal and Standard Operating Procedure (SOP).'

The country's significant political and socio-cultural changes in the last decade and subsequent division of responsibilities among federal and provincial governments raised some ethical issues, demanding revision of the Ethical Guidelines of 2011, eventually leading to the development of 'The National Ethical Guidelines for Health Research in Nepal-2019'. The Ethical Review Board (ERB) of NHRC, accredited by the Forum for Ethical Review Committees in the Asian and Western Pacific Region(FERCAP) in 2019 recommended that the national guidelines should be in alignment with the practices endorsed by FERCAP. In addition, there were also growing concerns regarding the exigency to address newer areas of research, such as research in public health emergencies, bio-banking, and animal experimentation. Similarly, the need for the transparency of the informed consent process was

equally felt in order to protect the welfare, rights, and safety of research subjects. Likewise, the formation and functioning of Institutional Review Committees (IRCs) and their SOPs were also missing in the former ethical guidelines. All these issues mentioned above have been addressed by the 'National Ethical Guidelines for Health Research in Nepal 2022.'

1.2 Scope of the Guidelines

National Ethical Guidelines for Health Research in Nepal 2022 have been developed to assist researchers, sponsors, reviewers, regulatory authorities, and beneficiaries of research outcomes. The document underscores legal and ethical issues as well as standard procedures that the researchers are required to consider while undertaking ethically sound and justifiable health research in Nepal.

The guidelines provided in the document are applicable to all types of health research in Nepal involving human beings, their biological specimens, health-related data, and experimental animals.

Overall, the document offers ethical guidelines and rules on a broad range of topics for

- Researchers while developing research proposals;
- Ethics committee and reviewers while reviewing research proposals for approval, monitoring of ongoing research, and dissemination and utilization of research funding;
- Sponsors while approving, funding, and utilizing the findings from research;
- Regulatory authorities while reviewing the proposals and monitoring the research process to assess the comprehensiveness of their guidelines;
- Policymakers to review the research funding and possible use of research funding in policies and programs.

Section 2. Ethical Principles

The four ethical principles fundamental to research involving human subjects include autonomy, beneficence, nonmaleficence and justice. These internationally accepted four ethical principles are also the cornerstones of ethically valid health research. In addition, being respectful of research participants' environment is equally important to safeguard their wellbeing, as well as the community's dignity.

2.1 Basic Ethical Principles

a) Respect for the Autonomy of Participants

The researcher should respect participants' autonomy throughout the research process. This principle of autonomy is based on the premise that an individual participant, when fully informed of involvement, benefits, and possible harm/inconvenience of research activities, can independently decide on a correct course of action i.e., whether to participate or refuse to participate in research activity. The basic requirements to ensure research participants' autonomy include their right to decide what is best for her/him.

Researchers must safeguard the interests of individuals with impaired or diminished autonomy and ensure that the vulnerable persons are protected against any harm, abuse, or exploitation.

Respect for human rights and human dignity should take precedence, not withstanding the scientific value of research. Practices that violate human dignity should be prohibited or halted immediately.

Provisions for human subjects' autonomy in health research should be implemented primarily through the process of 'Informed Consent.'

b) Beneficence and Nonmaleficence

Beneficence refers to the ethical obligation to maximize benefits and minimize possible harm to individual participants. This ethical principle requires that all health research proposals/projects be reviewed in the light of potential benefits and risks to the human subjects and their environment, without discouraging the participation of volunteers in health research. However, in all cases, health research should promote the well-being of human subjects as upheld by the principle of nonmaleficence (do no harm).

c) Justice

Justice requires individuals in similar circumstances to be treated equally, and the differences between persons due to circumstances should be acknowledged and addressed. For example, individuals with similar health complaints should be treated equally. Likewise, justice requires an equitable distribution of the burdens and benefits of research participation. Differences in such distribution are justifiable only if they are based on morally relevant distinctions between individuals, as reflected in cases where it is essential to protect the rights and welfare of vulnerable persons.

The principle of justice incorporates an ethical obligation to protect the rights and welfare of vulnerable participants or participants exposed to vulnerable situations. People in vulnerable situations include those who are unable to express or protect their interests fully or partially. People in vulnerable situations are deemed to lack the capacity to give consent adequately and/or lack the ability to obtain quality and effective health care. These individuals could also be juniors or subordinate members of a hierarchical group or legally incompetent. Thus, special provision is mandatory to protect the rights and welfare of all participants in vulnerable situations. Vulnerabilities should be seen broadly in terms of individuals' adaptive capacity, exposure, and sensitivity which their economic status, position as migrants, age, and gender among other factors may determine.

d) Respect for the Environment

This principle requires researchers to be sensitive toward the community (e.g., adopting a culturally and environmentally appropriate approach) while undertaking health research. This principle is reinforced by the World Medical Association (WMA) Declaration of Helsinki, which focuses on special precautions for protecting the environment while conducting research. Every researcher is accountable for safeguarding the social, cultural and natural environment, biodiversity, and historical heritage of communities and societies. This includes commitments to ensure proper and safe disposal of any hazardous waste and leftover investigational products (IP) from laboratory/clinical/field research, which should be returned to the sponsor according to standard guidelines and notified to ERB.

In addition to the above mentioned four core ethical principles, health research involving human subjects should also incorporate general (extension of core principles) ethical principles as outlined in Section 2.2.

2.2 General Ethical Principles

(i) Principle of essentiality: With due consideration to all the options within the existing knowledge, the use of human participants in health research is justifiable only when it is inevitably indispensable for the advancement of knowledge that is valuable for the research subjects, community, environment etc. The essence of the proposed research should be assessed by the competent Ethical Review Board/Institutional Review Committee.

(ii) Principle of voluntariness: Research participants' right to decide whether or not to participate in the research should be respected. Documented (written/visual/audio) informed consent guarantees that the rights of participants are protected. In other words, research participants are free to withdraw from the research at any time without being penalized.

(iii) Principle of non-exploitation: The principle of non-exploitation ensures that the research participants are not subjected to exploitation or abuse. Appropriate precautions are required to be in place to safeguard the rights, wellbeing, and safety of vulnerable individuals.

(iv) Principle of social responsibility: Health research needs to be planned and conducted so

that it does not destroy the social fabric of communities. The research outcome must also benefit the community/society as a whole.

(v) Principle of ensuring privacy and confidentiality: Researchers are required to maintain participants' privacy: the identity and records of the participants should be kept confidential, and access to such information should be limited to authorized individuals only. However, the privacy of certain information such as suicidal ideation, homicidal tendency, and risky behavior of participants with a positive status of infectious diseases (HIV, TB, Influenza, COVID-19, etc.) can be breached only in consultation with the ERB and judicial bodies (if necessary). In other words, breach of privacy and confidentiality is justified only when supported by valid scientific or legal reasons. Individuals' right to life is considered more important than the research participants' right to privacy and confidentiality.

(vi) Principle of risk minimization: During the research process, all stakeholders (researchers, ERB/IRC members, regulators, sponsors etc.) should identify the potential risks and take precautionary steps to either minimize or eliminate the risks. In addition, any kind of inconvenience or distress experienced by the research subjects should be met with fair compensation.

(vii) Principle of benefit maximization: During the research process, the researcher should make decisions that work in the best interests of the research participants. This principle of benefit maximization maintains that the researcher should take steps to maximize possible benefits to the research participants and society.

(viii) Principle of professional competence: Health research involving human subjects should be conducted by qualified (in terms of education, training, and experience) and competent persons who can plan, execute, and monitor the research process with due consideration to research ethics.

(ix) Principle of institutional arrangements: Institution(s) where the proposed health research will be carried out should ensure research governance which also includes the capacity to make proper institutional arrangements (e.g., provision of essential infrastructures, including storage of the IP, human resources, funds, opportunities for training etc.) for high-quality research.

(x) Principle of transparency and accountability: Transparency and accountability are two important ethical considerations in health research. In health research involving human subjects, researchers are ethically obliged to bring their work into the public domain by disseminating databases, reports, and publications while equally protecting their research subjects' right to privacy. Stakeholders (researchers, ERB/IRC members, regulators, sponsors etc.) involved in particular research should disclose any existing CoI and manage it properly. Besides, researchers should maintain impartiality, sincerity, justice, and transparency while conducting health research to ensure accountability. Preservation of

valuable sources of information such as records and notes for the specified research period is essential for possible external inspection/audit or other purposes.

(xi) Principle of the totality of responsibility: All stakeholders (researchers, ERB/IRC members, regulators, sponsors, etc.) involved in health research should be wholly accountable for their engagements as they are bound directly or indirectly by national ethical guidelines and related protocols.

(xii) Principle of environmental protection: Researchers are ethically obliged to ensure that their work does not violate the existing guidelines and protocols pertaining to environmental protection. In other words, researchers should ensure that the safeguarding of the environment and resources should be taken into consideration throughout their search process.

(xiii) Principle of dissemination of research findings: Researchers are ethically obliged to bring their research findings or any further research (conducted using the same research findings) into the public domain through publications. The research findings should be shared with the local stakeholders, preferably through publication in local scientific journals. If the researcher plans to publish a scientific paper in an internationally acclaimed indexed journal, a summary of the research paper must be published in the local scientific journal. Publications resulting from the research should be subject to such rights as are available to the researcher and her/his associates as determined by the laws(s) in force at that time.

Overall, the individual researcher or the research team must abide by four core and 13 general ethical principles (as mentioned above) while undertaking health research in Nepal.

Section3. Responsible Conduct of Health Research

Researchers has a significant role and responsibility to prevent possible scientific fraud and research misconduct. While researchers are expected to be guided by the standard ethical norms, values, and relevant laws, research teams are expected to maintain high ethical standards and fundamental values of research. The Responsible Conduct of Research (RCR) needs to address:

- Social values of research;
- Policies and priorities that influence health research;
- Issues that emerge during research planning and conduction;
- Professional, legal, and moral responsibilities of researchers, sponsors and institutions;
- Research monitoring, reviewing, and reporting;
- Authorships in research publications;
- Handling of scientific fraud and research misconduct; and
- Clinical trials registration (if needed);
- Collaboration and networking.

Academic/Research institutions should establish a research department within their institution to facilitate and manage research, grants, and all aspects of (RCR). Any health research involving human participants must obtain ethical approval from the ethics committees approved by NHRC. IRCs are allowed to review and approve research carried out within the institute as per the latest Ethical Guideline published by NHRC.

3.1 Social Values of Research

It is the responsibility of the researcher to make sure that the research topic holds adequate social values in accordance with the prevalent norms and standards. While considering social values, the following issues need to be addressed:

- Relevance to the needs of the people/society/community/country where the study is to be conducted;
- In compliance with the contemporary ethical norms and standards; and
- Sensitivity and responsiveness to the locals' socio-cultural and ethnic values.

3.2. Policies and Priorities that Influence Health Research

Health research must be guided by the National Health Policy of the Government of Nepal, National Health Research Strategies published by NHRC, and National Health Research Policy and priority areas set by NHRC. Researchers and research institutions should develop SOP based on the ethical guidelines of NHRC for the protection of human participants' rights and wellbeing. Researchers should also follow all the existing policies and guidelines for the safety and welfare of animals used in health research.

3.3 Issues that Emerge during Research Planning and Conduction

To avoid or mitigate the possible CoI at every step of research (e.g., designing, site selection,

ethical review, participant enrollment/follow up, data collection & interpretation, etc.), research institutes should develop and follow clear policies, strategies and SOPs.

3.3.1. Identifying, Mitigating, and Managing Conflict of Interest

(a) At the level of researchers: The researcher must identify and disclose any financial and/or non-financial conflict of interest between the researcher and the bodies representing the ethical oversight. The researcher should also express his/her commitment to time and resource investment in conducting the research.

(b) At the level of reviewers: The reviewer should declare CoI during the review process if any of his/her close friends, family members, and/or students have submitted the research proposal to obtain research grants and approval. The reviewer should declare CoI if any of his/her close friends, family members, and/or students are directly or indirectly involved in the research study.

(c) At the level of research institutions: The institution must communicate and declare CoI with transparency during the research process and develop SOP to manage and mitigate said CoI. Particularly when the institutions like NHRC are involved in research implementation, CoI should not interfere in any process of the ethical review, implementation, monitoring, data analysis, and recommendation to the government for policymaking. The process of managing CoI should be clearly documented in the SOP.

(d) At the level of ECs: 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 follow directives from the ERB.

3.3.2. Data Acquisition, Management, Sharing, and Ownership

- Researchers are ethically obliged to use a 'cultural by sensitive approach' while dealing with their research subjects. In other words, researchers should be mindful of participants' socio-cultural context while collecting information. In addition, since particular information requires informed consent or prior permission, researchers should have knowledge about the process, method, and the whereabouts of obtaining informed consent. Given the importance of reliability of the information in research ethics, it is equally essential for the researchers to exhibit 'research competence' in acquiring credible information. Hence, researchers' qualifications and training hold paramount importance. Researchers should also have an understanding of key issues, key concepts, and the importance of data protection. For data protection, researchers should refer to the European Union's General Data Protection Regulation (GDPR), 2018, Nepal's Privacy Act, 2075 (2018), and the National Civil (Code) Act, 2017 (2074) of Nepal. Researchers should also be able to develop research protocols, tools, and SOPs. Research information and findings should accurately be recorded, interpreted, and reported by the researchers to ensure the reliability of the information.
- Collected data should be archived and analyzed (appropriately) using appropriate software.

The analyzed findings should be reported to IRC/ERB and concerned authorities, as required. The research roles and responsibilities framework should be clearly outlined. Moreover, researchers should clarify the ownership and publication rights relating to research data before data collection starts. A Memorandum of Understanding (MoU) (if needed) should also be signed between investigators and institutions or sponsors in advance. This also applies to any biological samples collected/stored during the study period to achieve the study objectives.

- Appropriate precautions should be taken to avoid or reduce the risk of damage, loss or theft, fire, flood, and other disastrous events. Data/biological sample files should properly be archived and stored in a secured place along with the creation of a back-up system.
- Researchers should be aware of important ethical challenges threatening 'protection of data' while processing and analyzing information involving human subjects such as:
  (a) Any personal information or identifiers such as ethnic origin, political opinions, religious or ideological conviction, union membership, sexual orientation, biological samples, health status etc., and unique identification such as genetic and biometric data;
  (b) Personal data of children, pregnant women, persons with disabilities, vulnerable people, and those who have not given their consent to participate in the study;
  (c) Data processing procedures and methods that potentially risk violating research participants' rights and freedoms;
  (d) Large-scale personal data processing, large-scale systematic surveillance of a publicly accessible area, and merging and analyzing multiple data sets;
  (e) Data fabrication and falsification, i.e., research misconduct;
  (f) Inaccurate data collection, management, or analysis which lead to skewed results that are used by others; and
  (g) Domestic (from one institution to another) and/or international (from one country to another) transfer of data.
- Given the potential risks of abuse of data, researchers should be familiar with data protection measures that include:
  (a) Anonymization of personal data;
  (b) Data minimization, i.e., collection of required data (sufficient enough to fulfill the study objectives); and
  (c) Use appropriate software or techniques or service providers (as per the available resources) for data storage and archival.
- If the data processing methods risk violating the rights and freedoms of research participants, such risks must be disclosed during the process of obtaining informed consent. Without obtaining prior permission/approval from the relevant authorities such as ERB of NHRC or IRCs of the institutions (where the proposed study is to be carried out), it is unethical to collect data for certain types of study such as:
  (a) Health research involving human subjects;
  (b) Health research involving experiments on animals;
  (c) Biological specimen collection;
  (d) Use of data sets from the bio-samples stored in the bio-bank for future research;
  (e) Data from hospital/medical/police records, some institutions/libraries, databases, and archives;

(f) Photographs, recorded messages and notes; and
(g) Other copyrighted or patented processes or materials.

- Research protocols, tools, and SOPs must be prepared, and research data and results should accurately be recorded, interpreted, and reported. If required, research protocols or tools should be modified to fit into the local context of Nepal.
- Data governance mechanisms should be in place. If projects are conducted with international collaboration where samples require transferring, there should be backup storage of samples in the country.
- Data sharing/ dissemination plan (when, how, and with whom) should be mentioned in the research proposal, which the competent ethical review committee should approve before implementation.
- All cleaned data related to international collaboration should be submitted to the Nepal Health Research Council/Concerned organization in a standard format after publication in Journal or as a report.
- Research team should include at least one statistician or someone who has adequate knowledge and experience in study design, data management, and statistical analysis.

3.4 Professional, Legal, and Moral Responsibilities of Researchers and Sponsors

Study team (that conducts the research), sponsor (that funds the research), and institution (where the research is conducted) should take respective professional, legal, and moral responsibilities to follow ethical principles and guidelines. Researchers involved in a collaborative study should work in tandem throughout the research process, from the early stage of proposal development to the completion of the study. The same study protocol and SOPs signed and dated by National and International PI should be followed in each site in case of multi-centric studies. The sponsor should uphold unbiased contract negotiation. While conducting collaborative research, a clear mechanism should be established for benefit sharing. There should also be a regulatory mechanism that discourages the use of unauthorized bio-specimens, data, and human resources.

The sponsor should also have provisions for the capacity building of the institution/research team/local community involved in the study.

3.4.1 Roles and Responsibilities of the Researchers/Investigators

National Ethical Guidelines for Health Research in Nepal 2022 defines a researcher or investigator as an individual or group of individuals who conceptualizes, initiates, and conducts a study. The 'Principal Investigator' is an individual or leader of a group of individuals who initiates and takes full responsibility for health research. If there is more than one such individual, they may be called co-principal investigators/co-investigators. Co-Investigators (Co-Is) are individuals who make significant contributions but are not entirely responsible for and/or have full authority over the project. All investigators share common responsibilities of protecting the rights and welfare of the research participants and ensuring the credibility of data. However, despite sharing common ethical responsibilities and obligations, investigators

perform their respective tasks based on the principal investigator's clear delegation of responsibilities.

Investigator's Roles and Responsibilities:

Qualifications: Investigators should-

1. Be qualified by education, training, and experience to assume responsibility for the proposed study.
2. Provide evidence of qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the ERB.
3. Ensure the selection of and maintain a list of appropriately qualified persons (co-investigators and research staff) to whom she/he has delegated duties related to the study.

Adequate resources: Investigators should-

1. Assume responsibility for assessing and ensuring the availability of adequate resources including human resources, funding, facilities, equipment, and supplies. In doing so she/he should:
2. Have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the study.
3. Provide training to the research team to ensure adherence to appropriate safety procedures and protocols. In the case of clinical trials, training on Good Clinical Practices (GCP)/Good Clinical Laboratory Practice (GCLP)/General Data Protection Regulation (GDPR) (valid for three years) should be provided.
4. Arrange for a Site Initiation Visit to ensure that the appropriate infrastructure and resources are in place in case of clinical trials.
5. Demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.
6. Have sufficient time to properly conduct and complete the study within the agreed time frame.

Medical care of study participants: A qualified physician or appropriate health worker (e.g., dentist, psychologist, etc.) who is an investigator should be responsible for all study-related medical decisions during the duration of the study. In doing so she/he:

1. Should ensure that adequate medical care is provided to a study participant for any adverse events
2. Inform a subject when medical care is needed for inter-current illness (es) the investigator becomes aware of.

Communication with ERB: The investigator is responsible for

1. Development of the proposal in the prescribed format of the ERB through the online portal.
2. Applying and obtaining ethical approval from the ERB following the submission of all the required documents.
3. Disclosing and documenting all the financial and non-financial CoI and ensuring good practice and documentation of the mitigation measures where there is any possibility

of CoI.

4. Informing the ERB/IRC and the sponsor, should she/he terminate or suspend a study along with a detailed written explanation of the termination or suspension.
5. Adhering to existing national and international law/regulations/guidelines.

Compliance with the study protocol

1. Using the ERB-approved version of the documents i.e. protocols, SOP, informed consent documents, data collection tools, etc. for the implementation of the research
2. Conducting research within a specified timeline as mentioned in the ERB approval letter and approved protocol
3. Submitting an amendment request and obtaining ERB approval if any changes are required in the original approved protocol before its implementation.

Investigational products

For studies using investigational products (IP), responsibility for their accountability rests with the investigator/institution. Investigators should:

1. Maintain an IP accountability log
2. Ensure IP is stored as specified by the sponsor's protocol and in accordance with regulatory requirements
3. Ensure IP is used only in accordance with the approved protocol.
4. Plan for returning to the sponsor or alternative disposition (destruction/disposal) of unused IP using an SOP, specially developed for the purpose
5. Informed consent of study participants
6. The investigator should comply with the applicable regulatory requirement(s) in obtaining and documenting informed consent as outlined in Section 5.
7. The investigator should have the ERB's written approval of the written informed consent form and any other written information to be provided to study participants. This also applies to any revision of content in the consent form and written information.
8. In emergency situations, when prior consent of the subject is not possible, the consent of the participant's legally acceptable representative, if present, should be taken. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the participant should follow measures described in the protocol, documented as approved by the ERB/IRC, to protect the rights, safety, and wellbeing of the participants and to ensure compliance with applicable regulatory requirements. The participant or the legally acceptable representative should be informed about the study as soon as possible and consent to continue or other consent as appropriate should be requested.

Records and reports:

The investigator should-

1. Maintain adequate and accurate study records and source documents that include all pertinent observations on each of the study site's participants
2. Take measures to prevent accidental or premature destruction of study-related

documents

3. Retain study-related documents for a period of at least five years after the end of the study. However, these documents should be retained for a more extended period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the sponsor's responsibility to inform the investigator as to when these documents no longer need to be retained.
4. Provide direct access to all study-related records upon request of the ERB/IRC, or regulatory authority
5. Submit written summaries of the study's progress, especially in the case of clinical trials, to the ERB annually or more frequently, if requested by the ERB.
6. Submit a review report at least one month prior to the expiry of the study's timeline as stated in the approval letter from NHRC, accompanied by an application for approval to continue the study.
7. Submit a written report to the ERB upon completion of the study.
8. Report all serious adverse events (SAEs) immediately to the sponsor and ERB except for those SAEs that the protocol identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify participants by unique code numbers rather than the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to reporting unexpected serious adverse drug reactions to the regulatory authority (ies) and the ERB.
9. For reported deaths, supply the sponsor and the ERB/IRC with any additional requested information (e.g., autopsy reports and terminal medical reports).
10. Take accountability for the content of all study-related documents submitted to the ERB and ensure all documents are submitted in a timely manner.

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

3.4.2 Roles and Responsibilities of the Sponsor

Sponsor in the document refer to the individual/company, institution, or organization responsible for the initiation, management, and/or financing of a clinical trial. The sponsor's role is to initiate the research, including protocol development. In general, the sponsor should:

1. Ensure that the ethical and technical competent research is receiving support;
2. Ensure that the study site is ready in terms of infrastructure, human resources, logistics, and supply before the initiation of the study. Monitor the study before, during, and after completing the research activities.
3. Ensure that the release of funds to carry out the research is timely and regular;
4. Justify the inclusion of vulnerable groups in the proposal and make provisions to safeguard them;
5. Justify the exclusion of some specific participants (if any);
6. Facilitate monitoring by ERB and ensure that the Quality Assurance (QA) and Quality Control (QC) procedures are in place;

7. Ensure that the research participants and the study team are well protected, especially when the study is on sensitive topics;
8. Select investigator(s), ensure availability of study site(s), and assure relevant qualification of the study team to conduct the study;
9. Develop, maintain, modify, and ensure the availability of research support systems and tools; and
10. Avoid exerting influence on research design, data collection, data analysis and publication of research findings.

3.5 Research Reporting

1. Submission of the final report by the sponsor/ Principal Investigator to ERB/IRC within three months of completing the study is mandatory. The research report should be in a standard format as available in an online system. It should also contain information in accordance with the study objectives, with clear scientific analysis ensuring transparency and credibility.
2. Upon submission of the final report, ERB/NHRC should arrange a review of the report by the subject expert within two weeks with due attention to maintaining confidentiality, integrity, and honesty. The reviewer should provide feedback and comments within four weeks. The researcher or sponsor may be asked to present the revised reports with incorporated feedback/comments within a month to subject experts, NHRC, MOHP, and other relevant people with similar research interests.
3. Researchers should duly acknowledge the contributors in the report.
4. Investigators should follow international and national requirements and guidelines, including National Ethical Guideline and ICMJE Guideline when publicizing the raw or analyzed data.

3.6 Authorships in Research Publications

1. Research institutions should follow the authorship policies and guidelines of the International Committee of Medical Journal Editors (ICMJE), Committee on Publication Ethics (COPE), and the World Association of Medical Editors (WAME).
2. The authorship should be defined before the start of writing the research article. No one should be offered or should accept gift authorship without substantially contributing to the research process or writing of the article.
3. The principal author should do most of the research work related to the manuscript submitted for publication. To fulfill authorship criteria, all efforts should be made to provide the researchers an opportunity for authorship based on national and international guidelines of ICMJE/COPE/WAME. While doing so, one should also adhere to the rules and regulations of their university/institution.

3.7 Handling of Research Misconduct

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

ERB/IRC should institute fair investigation of the complaints/claims for misconduct through the formation of a specific committee with reference to its ToR, investigate the misconduct, and suggest appropriate mitigation measures. This process should take priority based on the risks associated with and/or sensitivity of the misconduct as per the SOP.

3.8 Clinical Trials Registration

Clinical trials involving human participants (e.g., trials of vaccines, drugs, herbal products, complementary medicine products, medical devices, surgical procedures, alternative medicine procedures, etc.) and public health interventions involving clinical procedures should be registered in the WHO accredited clinical trial registries. Researchers should provide the registration number to the ERB while submitting the proposal for ethical approval.

In addition to ethical approval from ERB, permission from the national regulatory authority (DDA permission as per Drug Act 1978) needs to be obtained before the implementation of the trial.

3.9 Collaboration and Networking in Research

To conduct multi-centric research, collaboration and networking can be done with colleagues/experts/institutions. Such collaboration may entail sharing of tools & techniques, research products, samples, specimens etc.; following the same SOPs; co-owning copyright of research materials and research data, sharing the final product of the study, publication etc.; collaboratively managing CoI, and commercializing the results/products by the collaborating centers.

All parties involved in the MoU should provide detailed information on the nature of collaboration prior to submitting the MoU to ERB/IRC for review and Ethical approval of the proposal.

3.9.1 Externally Sponsored Research: Externally sponsored research should fulfill the following conditions-

1) Research should be based on local needs and priorities.
2) Researchers should be aware of and sensitive towards the locals' socio-cultural, religious and environmental norms and values.
3) Researchers should provide a scientific evidence-based rationale for selecting the study site in Nepal. The sponsor should also provide evidence that the same research cannot be carried out in the sponsor's country due to a lack of disease burden of the same scale as in Nepal.
4) Researchers should submit ethical approval of the responsible IRC in the sponsoring country.
5) The proposal should contain information on how the proposed research would significantly contribute to enhancing the research capacity in Nepal.

6) Research process should be transparent and ensure a high ethical standard, as approved by the competent EC.
7) Sponsors should ensure research participants of insurance/compensation in the context of research involving more than minimal risks.
8) If the biological specimens need to be transferred to a laboratory outside Nepal, an MoU or MTA should clearly address IPR, roles, responsibilities, and obligations of each partner organizations/investigators, including publication roles, data confidentiality, and post-study benefit sharing. The ERB should evaluate the feasibility of the testing in the country's laboratories and its risk and benefits on a case-by-case basis before granting a permit to transport biological specimens to another country. Once approved, a letter of transfer approval could be issued to facilitate customs clearance/courier clearance in line with the International Air Transport Association Guideline.

3.9.2 Institutional Research Arrangements

Any research activity should only be started after ensuring appropriate institutional arrangements. An effective institutional arrangement includes the involvement of competent researchers and support staff; formation of an organizational set up according to the requirement of the research; assurance of research participants' safety; protection of confidentiality of data; effective dissemination of research findings among others. Institutional arrangements also involve providing a secure place for preserving and archiving research materials, data, and reports. Such institutional arrangements should be ensured before applying for the ethical review of the study. Institutions undertaking a collaborative study should also follow the same standard of the protocol and procedures. The research conducted in any institution should obtain a no objection letter from the institution. In case of an investigator-initiated trial, a commitment letter from the institution for the management of AE/SAE should be obtained/provided.

3.9.3 Special Considerations in Collaborative Research

1. The ERB should approve any changes in partnership before the initiation of the study.
2. There should be one Nepalese PI and site Co-Principal Investigators relevant to the research project for international collaborative research. Also, the Nepalese PI should take all the legal, technical, and ethical responsibilities of the project in Nepal.
3. International collaborators should strengthen their institutional capacity in terms of human capital and infrastructure.

Section 4. Ethical Issues in Health Research

Ethical challenges are inevitable in health research on account of various reasons, including the involvement of human subjects. Some of the key ethical challenges confronting health research include ensuring the safety and wellbeing of the participants, markedly the vulnerable groups; effective assessment of risks and benefits; maintaining transparency, privacy, and confidentiality; compensating and paying participants for their time; managing CoI; collection, storage and transfer of samples; promoting fair and equitable benefit sharing; etc. In addition to ensuring participants' safety and benefit, the research team should also improve their efficiency/capacity in conducting research.

4.1 Research Involving Vulnerable Populations

Vulnerable populations include subjects who are likely to be susceptible to coercion or undue influence to participate in research due to relative (or absolute) incapability of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests. Moreover, a researcher may consider the selected individual as vulnerable provided that he/she has the following characteristics.

1. Person's autonomy is compromised, or the person is incompetent of making a voluntary informed decision for himself/herself. For example, an individual who is unconscious or /cognitively impaired or mentally challenged
2. The person is able to provide informed consent but his/her understanding is compromised because of the circumstances, unjustifiable influence (such as intimidation from the third party), the anticipation of benefits etc.
3. Person is susceptible to exploitation due to his/her disadvantaged position relating to his/her social, economic, and political settings.

Although there are many methods of assessing vulnerability, ERB primarily considers an individual's social status and physical/mental condition to assess vulnerability. However, the status of an individual's vulnerability is subject to change in accordance with the changes in his/her social status/environment, or physical/mental conditions.

Social Status

1. Individuals at risk of social exclusion, affected by inadequate housing conditions such as refugees, immigrants, migrant workers, sex workers, slum dwellers, orphans, homeless etc.;
2. Women and sexual minorities (LGBTQ+ community) such as lesbian, gay, bisexual, transgender etc.;
3. Individuals who are at the lower echelons of hierarchical structures such as prisoners, public forces (armies, armed forces, police forces), students, employees, etc.

Participant's Condition:

Children (minors or individuals under the legal age of consent, i.e., less than 18 years); elderly;

pregnant and lactating women; differently-abled person; juvenile delinquents under legal trial; victims of traumatic events, disease outbreaks, natural disasters, and conflict; 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, and individuals who have poor decision-making powers/poor access to healthcare.
Note: This list of vulnerable populations is not exhaustive, and in case of uncertainty, the Ethical Review Board/Institutional Review Committee may decide whether or not the research participant meets the criteria for vulnerability.

If vulnerable populations are to be included in the research, the researcher/institution is required to follow specific procedures and ethical obligations to protect such research participants. In other words, the research team must ensure that additional steps will be taken to protect the rights, dignity, safety, and well-being of vulnerable participants. The researcher must capacitate vulnerable individuals in order to enable them to make decisions regarding whether or not to participate in health research. If vulnerable individuals lack the ability to consent, a legally authorized representative (LAR) must be involved in the decision-making procedure. Throughout the process, the researcher should ensure that the privacy and confidentiality of vulnerable populations are maintained to safeguard their rights, safety, and wellbeing.

4.1.1 Additional Safeguards/Protection Mechanisms

Vulnerable populations are at high risk of being manipulated or easily affected by external factors and circumstances. Therefore, additional precautions should be taken to avoid putting the vulnerable population at a greater risk of abuse, exploitation or situations likely to undermine their voluntariness and wellbeing when recruited as research participants. Key points to be considered to ensure protection for vulnerable populations include:

1. Inclusion of vulnerable populations in the study must be justified;
2. Benefits and risks must be assessed;
3. Risk mitigation strategies should be outlined;
4. The absence of coercion, force, threat, undue influence etc. must be ensured;
5. Assured incentives for participation must be disclosed;
6. Information about the research, benefits, risks, and alternatives (if any) should be communicated in the language prospective participants understand;
7. Any possibility of CoI between the vulnerable participant and LAR should be addressed;
8. Efforts to address issues where participants may be susceptible to discrimination and stigmatization must be ensured; and
9. Support systems to deal with the associated medical and social problems of research participants should be in place.

4.1.2 Research Involving Children

If a research question can be answered with adults as participants, research should not involve

children. Research involving children should be carried out only after taking informed consent from their parents or LAR. Children who can understand information about participation in the study are asked to provide assent, as mentioned in Section 5. Conditions in which Health Research can be carried out with children:

1. For diseases only seen in children;
2. The information that cannot be obtained by alternative means;
3. Health issues that are significantly different for adults and children;
4. Instances where adverse effects of drugs/vaccines need to be checked or investigated in children; and
5. In cases where drug delivery formulations are required to follow precise, safe, and age-appropriate routes of administration.

Note: This list of conditions is not exhaustive. Ethics Committees shall ensure that the research with children is ethically justified.

4.1.3 Research Involving Pregnant and Lactating Women

Interventional research involving pregnant women and lactating mothers should not be carried out unless the study is related to their physiological condition and the required information cannot be generated from other means.

Justification for the inclusion of pregnant and lactating women in the clinical trials needs to be provided. Similarly, for some groups of women, informed consent can be challenging because of socio-cultural reasons. In such cases, with due respect to the woman's autonomy, the researcher must also follow the requirements of local cultural practices to not disturb the harmony in the household/family/community.

Researchers should provide proper justification for the 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 Human Immunodeficiency Virus (HIV) infection from mother to child, trial of a device for detecting fetal abnormalities etc.

Women of reproductive age should be informed of the potential 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 talk about the options available in case of failure of contraception. In case of unexpected pregnancy, they should not be automatically removed from the clinical trial unless there is evidence showing potential harm to the fetus. However, even if clinical trials are expected to be harmless for pregnant women, they must be offered the option to withdraw or continue to participate in the trial. If women agree to continue with the trial, researchers and sponsors should monitor such women participants comprehensively and offer the necessary support to the women for a specific time period.

4.1.4 Research involving Sexual Minorities and Sex Workers

Sexual minorities and sex workers may face challenges such as violence, stigmatization, discrimination, exploitation, and confidentiality issues among others. Given the unique nature of the challenges, the researcher needs to be responsible and respectful in ensuring that the research participant's rights and wellbeing will be safeguarded without any compromise. Moreover, research participants should be assured that the research practices and the outcomes will not further reinforce discrimination or stigmatize an already vulnerable population.

4.1.5 Research Involving Tribal and Indigenous Population

Research targeting tribal and indigenous populations is justified only if it is precise, diagnostic, therapeutic, and protective in nature, with suitable benefits to the tribal and indigenous population. For any research utilizing tribal/indigenous knowledge that has potential for commercialization, these details should be mentioned clearly and shared with the tribal groups through community engagements. However, gatekeeper consent should be obtained prior to approaching research subjects for community engagements.

4.1.6 Research Involving Individuals with Mental Illness or Cognitive Impairment

Research involving individuals with mental illness or cognitive impairments should be carried out only when the study is related to their condition and the required information cannot be generated from other means.
In case research participants pose potential harm to themselves or others, confidentiality may be breached for reporting to family members, and relevant authorities including and police may be involved, details of which should be included in the proposal.

4.1.7 Research Involving Members of a Group within a Hierarchical structure

For members of such groups including prisoners, public forces (armies, armed forces, police forces), students, and employees amongst others, the research process and protocol should include additional safeguard mechanisms so that their participation is free of coercion, without negative repercussions for denial or withdrawal from research.

4.1.8 Research Involving Terminally Ill Person

Patients who are in search of new interventions after having exhausted all available therapies, may be ready to provide consent for any new intervention that is not yet authenticated. In such circumstances, there should be appropriate consent procedures addressing the benefit and risk of the intervention, 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 person, the ERB should carefully review post-trial access to the medication.

4.2 Assessment of Risks and Benefits

Risk refers to a situation that involves exposure to harm or danger. In health research, risk

refers to the chance or probability that a person will be harmed or experience an adverse health effect because of participation in the research. Vulnerable participants are at higher risk than non-vulnerable participants. Investigators/sponsors should incorporate a risk-benefit assessment matrix in the submitted protocol. ERB/IRC should evaluate the proposed risk-benefit matrix/information. ERB/IRC may grant approval for the trial on human subjects once it is convinced that the benefits of the trial outweigh the risks. If there is any risk, mitigation measures should be incorporated by the researcher/sponsor. The document classifies different categories of risk in health research as outlined in Box 1.

BOX 1. Risk Categorization and its Descriptions

Types of Risk	Descriptions
Less than minimal risk	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.
Minimal risk	Probability of harm or discomfort anticipated in their search is not greater than the one encountered in normal everyday activities performed by an average healthy individual or general population or, during the performance of routine tests where the occurrence of serious harm or an adverse event (AE) is unlikely. Examples include research involving routine questioning or history taking, observing, obtaining body fluids, hair, saliva, urine etc., without invasive intervention.
Minor increase over minimal risk or Low-risk	Increment in the probability of harm or discomfort is slightly more than the minimal risk threshold. This may be present in the situations such as routine research on children and adolescents; research on persons incapable of giving consent; 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. The use of personally identifiable data in research also poses indirect risks such as social risks *(stigma, workplace discrimination, loss of respect, disclosure to family, isolation, etc.),* economic risk (loss of employment), psychological harm *(if the research is sensitive in nature and the participants risk being stigmatized if it is known that they are on the study, e.g.an HIV study)* and discomfort. .
High risk or more than minimal risk	Probability of harm or discomfort anticipated in the research is invasive and greater than minimal risk. Examples include research involving any interventional study. E.g. 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 favorable outcome (direct or indirect) of the research. Benefits include the potential for better treatment, either immediately or in the future, and financial benefits in terms of compensation for being in the study and free or reduced price of health care. Participation in a research process should be of potential benefit to the participant or his/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 with or derived from the research participation must be clear to the potential participants beforehand. Special attention 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 are available to judge research proposals. Therefore, systematic, non-arbitrary analysis of risks and benefits should be adopted as far as possible. For this purpose, a thorough collection and assessment of information about all aspects of the research should be done, and alternatives should systematically be considered.

Relevant risks and benefits should clearly be spelled out in the proposal and informed consent document. When research involves significant risk, there should be an extra justification for such risk, and ERB should review this aspect and record it in the ERB meeting report. ERB should ensure a favorable balance of benefits and risks and assess the plans for decreasing the risks or mitigating the effects 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

Protection of confidential information provided by the participants and the community should be ensured to protect the individuals' rights and to avoid stigmatization and/or discrimination. It may not be possible to keep participants' identities confidential in certain situations such as compelling scientific and legal requirements, where disclosures could be made with the permission of ERB (Box 2).

The researcher should not publish any information or photographs that may disclose the participant's identity without obtaining his/her fully understood/informed consent.

4.3.1 Data Privacy and Security

When the research-based data is outsourced or shared for commercial gain, data privacy, data security, and the possibility of legal liability should be safeguarded. There should be a mechanism (like data auditing by NHRC) to detect misuse of research-based datasets.

Research data sets, whether in paper or in electronic format, should be stored without compromising security. Appropriate measures to be adopted for the protection of participants' privacy and confidentiality are outlined in Box2.

BOX 2. Measures for Protecting Participants' Privacy and Confidentiality

Ensure physical safety and security of the involved devices and computer servers (Firewalls, etc.).

Take data security measures such as password protection, etc.

Provide differential and role-based controlled access to data elements for members of the research team.

Ensure use of data encryption when data is transferred from one location/device to another.

Ensure compliance with national regulations such as Nepal Statistical **Act-2015 BS** and Individual data Privacy-2076 and **Data Act-2015.**

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

Third-party sharing and data privacy? protection from the commercialization of data sharing?

4.4 Equitable Distribution

The selection of research participants should be such that there is a fair distribution of the burden and benefits of participation among population groups (geographical differences, ethnicity, socio-economic status, etc.) as far as possible. There should be specific criteria for participants' selection, and efforts must be taken to guarantee that participants are not exploited or over-sampled during their search process.

4.5 Compensation and Payment

Provisions to reasonably compensate the participants for any harm, including compensating for the participants' effort and time should be ensured. The information on such compensation should be communicated to the participants through an informed consent document.

4.5.1 Payment for Participation

Research participants need to be reimbursed for expenses such as travel costs, food, lost wages, and other compensations where applicable. The research participants should not be required to pay for any expenses incurred beyond routine clinical care and research-related investigations, interventions, or therapy. If participants are offered free medical care for non-research-related conditions during the study period, such ancillary care should not amount to undue inducement and such compensation needs to be thoroughly reviewed by EC. When consent is given on behalf of a participant by the LAR, payment should not become an unjustified incentive.

4.5.2 Compensation for Research-related Harm

Research participants, 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 monetary compensation in the event of death.

1. The researcher is responsible for reporting all potential SAEs to the ERB prior to commencing the research and within 48 hours of the event occurrence and detailed report within the 2 weeks of its onset. SAEs can be reported by the online ERB platform or e-mail or fax communication (including non-working days). The trial should be halted until further notice in case of a series of SAEs.
2. After receiving the SAE report, the ERB is responsible for (i) reviewing the SAEs associated with the research; and (ii) suggesting the kind of support provided to the participants if required.
3. It is the responsibility of the sponsor to incorporate insurance coverage or provision for possible compensation for research-related injury or harm. All the adverse events (AE) should be documented and reported.

Note: *The investigator/institution where the research is conducted becomes the sponsor in investigator-initiated research.*

4.6 Qualification of the Researchers

The researcher conducting the study should have relevant qualifications, experiences in the related field, the relevant number of publications, education, and training (on research methodology and research ethics). In the case of clinical trials, training on GCP is required.

Criteria for PI for the studies having more than minimal risk, multi-centric, externally funded collaborative and national level:

1. PhD in a subject related to the field of research with relevant experience of having worked as a principal investigator; or worked as a co-investigator and similar type of publication in a scientific journal.
2. Master's degree in a subject related to the field of research with relevant experience of having worked as a principal investigator; or worked as a co-investigator in a minimum of two researches and one publication in a scientific journal.
3. Bachelor's degree in a subject related to the field of research with relevant experience of having worked as a co-investigator in a minimum of three researches and two publications in a scientific journal.
4. In the case of an academic thesis, there should be a competent supervisor in a team.
5. Investigator shall be involved in up to five researches as PI at a time (not exceeding three in trials), as PI should have sufficient time to properly conduct and complete the study within the agreed time.

4.7 Transparency and Conflict of Interest

Transparency is fundamental to ethical research, with registration being the first step toward research transparency. Research transparency requires researchers to follow mechanisms that

enable them to effectively inform participants and the public about the study procedures and research outcomes without breaching confidentiality. There should also be a provision for making data available for further/future research if applicable

Besides study procedures and research outcomes, researchers are also required to declare COI, if any. Failure to disclose the same is liable to result in corrective actions or punitive measures. In case of suspension of the study, the researcher should inform such a decision to the ERB at the earliest.

4.8 Data/Bio-sample Collection, Storage, Biosecurity, Transfer, and Bio-banking

Investigators should ensure compliance with relevant standards for personnel information confidentiality. Investigators are also required to follow data safety regulations/guidelines for biosafety & biosecurity to ensure that the collection, testing, archiving, and transportation of the bio-samples and data are done in conjunction with the safety guidelines and ethical standards.

4.8.1 Data Collection, Storage, Security, and Transfer

It is always important to define tools/sources of primary and secondary data collection. Primary data collection tools comprise observations, questionnaires, Pro-forma, personal interviews, experiments, surveys, etc.. In contrast, secondary data collection tools include journal articles, internal records, government/non-government publications, books, websites, etc. Once data is collected, researchers must explain how such data will be stored and what storage medium (paper or electronic-based) will be adopted. Even after processing/analyzing the data, the researcher needs to set the storage retention period.

The study proposal should have details of measures to secure research-based data in the field, laboratory, and office settings. There are wide-ranging measures to secure research-based data which include physical security of equipment (if any); digital security mechanisms, such as system, program, and file pass-wording; file cabinet security process, e.g. lock & key that can only be accessed by the authorized person; data storage and a back-up plan, etc. Failure to address security issues in health research may be considered breaching research ethics.

While accessing the sensitive data from the medical records of the people living/suffering from 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., the researcher needs to obtain official permission from the concerned authority. The researcher is also expected to meet ethical requirements in handling such records, from retrieving of data to its incorporation in reports and publications.

Data Transfer Agreement (DTA) between the host and the collaborating institution(s) must be

submitted to the concerned authority. Prior approval is required to ship any data outside the country, even for valid scientific reasons. On transferring the data, a copy of such data should be stored in the host institution in Nepal, making it accessible to the authorized persons or investigating authorities, when required. Breaching the code is punishable in line with the Data Act and Privacy Act 2018 of Nepal.

Note: *GoN's Privacy Act, 2018 is applicable in providing guidelines on protecting privacy during the data storing and transfer process.*

4.8.2 Biological Specimen Collection, Storage, Security, and Bio-banking

Biological specimens may be any biological materials from human beings (whole blood, cord blood, dried blood spots, serum, naso-pharyngeal swabs, sperm, semen, tumor cells, embryos, urine, hair, tissues, organs, cerebrospinal fluids, etc.) or extracted products from the biological materials (DNA, RNA, Genes, Proteins, etc.). Researchers need to mention the quantity, quality, and frequency of collecting such samples from each participant, with a strong rationale for the minimal amount and frequency.

The proposal should have a clear explanation of how, when, and where such biological specimens will be stored/processed with a power backup plan and coding (bar/manual coding) strategy. The proposal should clearly mention biosafety and biosecurity, physical security, including access control provisions and assurances for maintaining standards according to applicable guidelines/rules/laws. Failure to address the above-mentioned points may not be considered ethically competent.

In collaborative studies, part of the study is undertaken within the country. In contrast, ERB may allow advanced research (in case of non-availability of tests) to be carried out in advanced labs abroad on valid grounds. In such circumstances, the researcher should store duplicate biological specimens in Nepal for at least 5 years upon completing the study.

The biological specimens are precious resources that could be stored in a bio-bank for an extended period of time. Such long-term storage enables long-term future research (when broad consent is obtained from the participants).

4.8.2.1 Biobank and Types of Biological Specimens

Biobanks 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, RNA, etc. All the ethical issues concerning bio-banking, viz. ownership, access, benefit sharing, etc., should be addressed with greater responsibility. Suppose researchers would like to conduct any further study with the stored bio-samples. In that case, the researcher must obtain prior ethical approval from the ERB and may also need to obtain an individual's informed consent, if personal identifiers are required. When personnel identifiers are not used, only ERB approval (based on bio-bank agreement of confidentiality and anonymity of the samples) should be obtained prior to conducting the study.

BOX 3. Types of biological specimens stored by biobanks:

<table>
<tr><td>Anonymous or unidentified</td><td colspan="2">No identifiers are present from the start, or if collected, are not maintained. Such samples are received by biobanks without any identifiers and supplied to researchers.</td></tr>
<tr><td rowspan="2">Anonymized</td><td colspan="2">This involves systematic de-identification, reversible or irreversible; the Link of samples/data to personal identity is reversibly or irreversibly cut.</td></tr>
<tr><td>Coded or reversibly anonymized:

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.</td><td>Irreversibly anonymized:

Link to the participant's identity is removed and cannot be re-linked.</td></tr>
<tr><td>Identifiable</td><td colspan="2">A direct link of sample/data to the participant’s identity exists.</td></tr>
<tr><td colspan="3">Source: ICMR, 2017, National Ethical Guidelines for Biomedical and Health Research involving Human Participants, Page129.</td></tr>
</table>

4.8.2.2 Key Aspects in Maintaining Confidentiality and Privacy of Donors Related to Biological Specimens and /or Data

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

4.8.2.3 Biological Specimen Transfer

When the study involves the transfer of biological samples to other countries, there should be a strong justification for such transfer in the research proposal, particularly if the tests are available in the country’s laboratories. Through an expert reviewer, ERB will evaluate the justification for the non-availability of the tests/labs performing such specialized tests with specified standards in the country. Based on expert members’ recommendations, ERB may approve transferring only processed bio-samples/extracted products (e.g., DNA, RNA, serum, plasma, etc.) to non-commercial laboratories for specific purposes (e.g., quality assurance). However, for academic collaboration with non-commercial interests (e.g. Nepali PhD student working in an advanced country lab, collecting and analyzing specimens from Nepal for his/her degree purpose), the researcher may request ERB’s approval for transferring such human

biological samples. ERB may approve a transfer of biological samples based on such non-commercial academic collaboration documentation.

Note: *Shipping of biological specimens from Nepal to other countries requires that the specified criteria and requirements are met in compliance with existing laws, rules, regulations (including protection of the country's bio-diversity and genetic materials), etc.*

Research involving an exchange of biological materials/specimens between collaborating institution(s) must sign the MTA and/or MoU with clear information on the purpose, quality, quantity, confidentiality, data sharing, publication policy, IPR, benefit-sharing, post-analysis reporting mechanism, handling of the left-over bio-samples, bio-safety, and bio-security norms, etc.

4.9 Research Benefits Sharing

If the research is about the development of a product (e.g. drug, vaccine, device, etc.), researchers must identify the ways (resources, infrastructure, and technical assistance) to ensure the availability of the product to the research participants and/or to the community from where participants are enrolled.

Sometimes, the benefits of the study may not be direct. Community people may be indirectly benefitted by establishing health facilities or schools or by providing education on good health practices. Participants 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.

In the condition where participants are not prepared to utilize the research outcome, the researcher needs to prepare an enabling environment or develop an appropriate mechanism (wherever possible) to communicate their findings. Sometimes, participants would like to have an aggregate report of all the study results, which could become a shared benefit for the community. The study team may put all the results in a publicly accessible website in this condition.

If possible, investigators and sponsors should continue to offer beneficial interventions (which were part of the research initiative) even after the completion of research, i.e., until the local administrative and social support system are restored and capable enough to provide regular services.

If the researcher thinks that the data and/or biological materials have possible commercial value, this must evidently 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 by which the researcher approaches prospective participants before enrollment. It is the researcher's responsibility to inform the participant about the aims and objectives of the research, the participant's roles, and responsibilities, research procedures, potential benefits and risks of such participation, etc. After communicating information in the best way a participant can understand, it is the researcher's responsibility again to allow the participant to be fully involved in the decision-making process. The researcher must also ensure that the prospective participant has fully understood the information provided. Adequate time should be given to the participant to comprehend the process. The researcher has to clearly emphasize that the participant is being asked for permission to participate in the study voluntarily and hence, is entitled to withdraw from the study at any time without any prejudice. The participant should also be assured that the refusal to participate will not affect the way he/she is getting treatment now or in the future. Research details should be outlined in the Informed Consent Document (ICD) in a manner and language the prospective participant can easily understand. Sufficient time should be provided for him or her to think and decide whether to participate or not to participate.

5.1 Requisites

It is mandatory to document voluntary informed consent before the commencement of research involving human participants. It is also necessary to maintain the privacy and confidentiality of the participant's personal information during all stages of the study. The prospective participant must be provided with detailed information on the research subject elaborate enough to make a fully informed decision. Such detailed information may include potential risks and benefits, nature of involvement, discomfort, compensation for time, travel, lost wages, etc. Participants should be medically competent to give valid, well-informed, and voluntary consent. Some of the legal and ethical considerations of informed consent are mentioned as follows.

1. Consent to participate in the research should be voluntary, without any pressure, coercion, and/or undue inducements.
2. Written informed consent must be obtained from the participants above 18 years of age.
3. For children above 12 years and under 18 years, in addition to LAR's written consent, a written assent must be obtained from the participating child. The assent form shall be written in simple language which is understandable by a child.
4. For children above 7 years and under 12 years, in addition to LAR's written consent, a verbal assent is required. The entire process of obtaining informed consent should be recorded in audio/video and well documented in written form.
5. In the case of children below 7 years old, the researcher must obtain written informed consent from parents or LAR (assent not required).
6. The prospective research participant must be given sufficient time to read and comprehend research-related information and weigh the risks and benefits of the study before providing voluntary consent to research participation. The prospective participant should also be allowed to ask for clarification from the research team and/or

discuss with family and friends if he/she has any fear or doubt about the research.

7. The child's refusal to participate or continue in the research should be respected.
8. The child's age should be determined by the child's birth certificate/ school record or competent documentary evidence.
9. In the case of the elderly (who are not in a mental/physical state of making a decision themselves or are not capable of providing voluntary informed consent) and individuals with impaired cognitive functions/mental disability, the consent of LAR must be obtained.

5.2 Information

Participants should be given sufficient information about the proposed research, including information on procedures, purpose, risks/discomforts, anticipated benefits, alternative procedures, etc. Participants should also be provided with a statement that clearly mentions participants' right to question and withdraw from the research at any time without any penalty. Information about the research should be provided in the best way and in the language that research subjects are able to understand.

5.3 Comprehension

The researcher's responsibility is to ascertain that the participants have comprehended the information. If a research participant cannot comprehend the information, the proxy consent of 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 not be coercion or undue inducements while obtaining informed consent from the research subject.

5.5 Process for Obtaining an Informed Consent

To obtain informed consent, the following aspects must be considered:

(i) Obtaining consent from participants: Prior to obtaining informed consent from the participant, an individual who obtains informed consent must be able to explain the entire research process, including risk/benefits, obligations, discomforts, etc., to the prospective participant. It is also worth estimating the time for obtaining consent from the participants. Informed consent should not be obtained by the health practitioner that the participant has been consulting for the treatment to avoid undue influence. Instead, informed consent should be taken by someone (for instance, assisting a nurse or research assistant) who is not the investigator and has no conflict of interest in the research. Similarly, in the case of vulnerable populations (e.g., Uniformed personnel, prison inmates, etc.) who are bound in a hierarchical relationship (reflecting power differences), consent should not be obtained by someone who already has an undue influence over the participant. Undue influence and coercion are some of the barriers to obtaining genuinely informed consent.

(ii) Coercion, inducement, and informed consent

The consent form should clearly indicate that the prospective participants agree to participate in the study voluntarily, without coercion or undue inducements. Efforts to manipulate potential research into consenting through coercion/intimidation or undue inducements (e.g. offering a large amount of money, inappropriate gifts, etc.) should be avoided. In addition, an individual, who has the upper hand in his/her relationship with the prospective participant, should not be asked to obtain consent from the research subject. Consent must also be taken to use biological specimens (collected for routine diagnostic purposes) for which the participants have had to pay.

(iii)Deception and informed consent

Any consent obtained through deception (e.g., incomplete disclosure, misleading information, etc.) cannot be considered fully informed consent. During the process of obtaining informed consent, it is crucial for the researcher not to withhold from the prospective participants any information about the research that the research subject is entitled to know. Obtaining consent from the prospective participant through incomplete disclosure, false promises of benefits (to the participant and/or community), stonewalling, etc. is considered to be against the research ethics. Deception or incomplete disclosure is only justified under the circumstances where 'incomplete disclosure' is indispensable to conducting research of essential value. However, the researcher should follow the review committee's directives while opting for non-disclosure of information to the prospective participant. In addition, the consent form should also specify beforehand that some information is being deliberately withheld from the participant, and s/he will be debriefed at the end of the study, for instance, with regards to psychological research.

(iv) Language: Consent should be written in a language that participants can comprehend. In collaborative research, consent may be written in the local language and English.

(v) Information required in the consent document: The consent document should start with a statement implying the nature of the research study in order to distinguish it from routine clinical care. It should further be followed by other statements mentioned as follows.

a. The nature of the study, whether investigational drugs/vaccine/devices/products, etc. are being used or procedures being performed; or if information-seeking through questionnaires or interviews is used;
b. Objectives and methodology of the study;
c. Estimated number of participants to be enrolled, expected duration of the study and frequency of participant's involvement;
d. A statement that the participation is voluntary and the participant can withdraw from the study at any time without explanation, penalty, fear, and/or loss of benefits;
e. A statement on exactly what is expected from the research participant, and direct or indirect benefits to the participant and community;
f. Type, amount, frequency of collection, and period of storage of biological specimens/data and possible use of stored biological specimens/data in future or to be

used for secondary purposes, including sharing with others (if any);

g. The risks, discomforts, and inconveniences associated with the study, e.g., risk of further stigmatization of individuals living with HIV resulting from their participation in the study;
h. A statement suggesting that all records will be kept confidential; however, it should also mention whether it is possible or not to guarantee absolute confidentiality. If absolute confidentiality is not possible, explain why. Also, explain the extent to which the confidentiality of participants' information will be protected and how. In case of breach of confidentiality, state the possible consequences;
i. A statement clarifying any reimbursement/compensation/provision of management of AE or SAE/free treatment/incidental expenses/insurance coverage for the participants depending on the type of study;
j. A statement on the post-research benefit-sharing, if research on biological specimens and/or data has scope for product commercialization;
k. A statement indicating the participant has understood all the information in the consent form is willing to participate in the study and may leave the study at any time without any obstruction to his/her regular treatments;
l. Contact details (name and address including telephone numbers and e-mails) of the responsible person(s) of the research team (usually PI) and NHRC/ERB secretariat focal person for any complaints/queries related to the study; and
m. Signature space for the research participant, LAR, Researcher (if required), and the date and place.

5.6 E-consent

Electronic informed consent (E-consent) uses electronic formats (online, SMS, video, audio, etc.), which can be used to generate information related to the study and also to document the consent using digital signatures. E-consent must contain all elements of the informed consent, as mentioned in section 5.5. E-consent could also be taken during public health emergencies, including disease outbreaks, where taking consent in person by the researchers is not possible or feasible.

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

5.7 Re-consent: Re-consent needs to be obtained in the following situations-

1. Discovery of new information related to the study, which may affect participants or has implications for participants, or may influence the risk-benefit ratio;

2. A participant enrolled using the consent of LAR regains the ability to consent for him/herself. For example, a researcher might have to obtain a re-consent when an

unconscious participant suddenly gains consciousness during the trial; when a participant who lacks medical competence becomes medically competent; and when a child turns into a competent adult during the longitudinal trial; etc.)

3. The study requires an extension for a long-term follow-up;
4. Modification in research methods, duration of participation, treatment modality, and study sites may impact participants' decisions on whether or not to continue participating in the study. Besides, re-consent should also be obtained if there is a probability of revelation of the participant's identity through publications or data presentation; and
5. In some cases, additional re-consent of partner/spouse may also be required. Examples of scenarios where re-consent is taken have been discussed in Box 4.

BOX 4: Examples of Scenarios where Re-consent is taken

Secondary or extended use 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 a 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 usage of her/his tissue or sample. In pediatric bio-banks or bio-banks with pediatric samples, it is essential to address the issue of children reaching the legal age of consent. Sometimes re-contact may lead to withdrawal, resulting in limited data analysis. This may lead to bias, or 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.

5.8 Waiver of the Consent

For certain conditions, as mentioned in Box 5, the ERB/IRC may consider granting a waiver of consent if the researcher applies for a waiver and the waiver request is justified scientifically and ethically, based on ERB/IRC evaluation. 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, the researcher must justify the waiver request by providing an explanation of why obtaining signed consent would add additional risk to the research participants. In addition to justifying the waiver request, the researcher must provide alternative provisions/options for informing prospective participants about the research details. Conditions for granting a waiver of consent are discussed in Box 5.

BOX 5. Conditions for granting Waiver of Consent

1. Research cannot practically be carried out without the waiver, and the waiver is scientifically and ethically justified;
2. Retrospective studies, where the participants are de-identified or cannot be contacted;
3. Research on anonymized biological samples/data;
4. Research on data available in the public domain; Research during humanitarian emergencies and disasters, when the participant may not be in a position to give consent. However, attempts should be made to obtain the participant's consent at the earliest possible dates, even after collecting information from participants is complete.

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

Conditions that are applied for waiver of informed consent in adults may also apply for a waiver of assent in children. Waiver of assent may be allowed when the available intervention is anticipated to benefit the child but would be possible only if the child participates in the study. However, this condition may be accepted only in exceptional cases where all assent forms have failed, but the LAR provides the consent. In such circumstances, ERB/IRC approval should be obtained.

5.9 Obtaining consent in Special Situations

In certain conditions, investigators need to take consent from the group leader, community leader, Legally Authorized Representative (LAR), etc., as described below:

(a) Consent from Gatekeepers: Sometimes, on behalf of a group, the permission of the gatekeepers, who are usually the head or leader of the political/social/cultural/professional group may be obtained. The process of obtaining gatekeeper consent should be recorded in audio, visual, and/or written forms. Obtaining gatekeeper consent is applicable during natural disasters when the participants are not mentally ready to provide informed consent. Besides, gatekeeper consent is also obtained while studying tribal or isolated indigenous groups, where tribal members are suspicious of outsiders and are also hesitant to share their culturally sensitive information with strangers.

(b) Community Consent: In certain population groups (e.g., ethnic minorities, marginalized populations, mobile migrants, etc.), who are incapable of protecting their own interests because of their limited exposure to the outside world, some participants may not be able to participate in the research without community's consent. In such situations, the community's consent is required. When permission is obtained from an organization that represents the community, the quorum required for representation in such a committee must be met i.e., the number of members needed to be present while giving the consent. However, individual consent must also be obtained even after taking the community's consent.

(c) Consent from Vulnerable Groups: Vulnerable persons are those individuals who are relatively or absolutely incapable of protecting their own interests due to disability; environmental burdens; social injustice; lack of power, understanding, or ability to communicate; and/or, being in a situation that prevents them from working in their best interests. The common characteristics of the vulnerable groups and the example of

vulnerable populations are provided in detail in section 4.1. If vulnerable populations are to be included in the research, all stakeholders must ensure that additional protections are in place to safeguard the dignity, rights, safety, and well-being of these individuals. Because of their inability to consent, LAR must be involved in the decision-making process. Also, since vulnerable people are at an increased risk of being further marginalized or discriminated against measures must be taken to safeguard vulnerable participants' privacy and confidentiality.

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

In some types of research, the partner/spouse of the prospective research participant may be required to give their consent; whereas, in genetic research, other family members 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 the case of illiterate participants, the consent process should be witnessed by an impartial witness (who is not a relative of the participant, is not associated with the research and has no CoI). Such an impartial witness could be the other patient in the ward who is not involved in the study, staff from the social service department, and/or a counselor. The witness, however, should be a literate person who can read the participant information sheet (PIS) and informed consent form (ICF). The witness should also be able to understand the language of the prospective participant so that he/she can read as well as communicate the information to the participant or LAR effectively for them to make an informed decision.

5.10 Consent for Studies using Deception

Deception is defined as an untrue falsehood or the act of lying to or tricking someone. Deception in terms of consent for research refers to the intentional misleading of subjects or withholding of complete information about the nature of the experiment. Investigators may mislead or omit information about the purpose of the research, the role of the researcher, or what procedures in the study are experimental. According to Whaley, every deception comprises two parts: dissimulation (covert, hiding what is real) and simulation (overt, showing the false). An example of deception is when an individual reports to be 30 years old when in fact, they are 40.

Deception is allowed only when alternative procedures are unavailable and when participants are debriefed at the end of the study. Although deception is not permissible, approval should be taken from the ERB/IRC in circumstances where some information must be withheld for validation until the completion of the study. A two-step procedure may be necessary, including

an initial consent and a debriefing after participation. In such instances, an attempt should be made to debrief the participants/communities after the completion of the research. However, the deception cannot conceal participants' real risk or danger.

If the participants refuse to allow the use of their data during debriefing, the researcher should not include the data. These types of research may carefully be reviewed by the ERB/IRC before implementation, and the possibility of unjustified deception, undue influence, and intimidation should be avoided at all costs.

5.11 Procedures after the Consent Process

After obtaining the consent, the participant should be provided with a copy of PIS and signed 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.

5.12 Documentation of the Consent

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

Section 6. Ethical Review Process

NHRC established under the act of the parliament in 1991, is mandated to review, approve, and monitor the research involving human participants and ensure the social and scientific value of the study and its ethical conduct. Consequently, all the research proposals involving human participants need to be reviewed and approved by ERB/NHRC or IRC as per the NHRC Act, which states, “a person or organization who intends to do research works on health after the commencement of this Act has to obtain the permission of the Council” (section 11, Requirement of approval to do health-related research). Suppose any person or organization does research work without obtaining approval pursuant to Section 11 or does not observe the direction given by the Council in doing research work after obtaining approval. In that case, the Council may warn such person or organization or restrict such research work for a certain period of time (NHRC Act section 12, "Special powers of Council").

6.1 Formation and Terms of Reference of Ethical Review Board (ERB)

An Ethical Review Board (ERB) is formed by the Executive Committee of NHRC with an objective to review, approve and monitor health research involving human participation. The membership and terms of reference are periodically reviewed by the NHRC Executive Committee. The process of formation of ERB, tenure of its chairman and members, working procedure, the process of maintaining confidentiality, and avoiding conflict of interest and/or, measures to manage CoI (if present) are outlined as follows:

6.1.1 Formation of the ERB

1. ERB is formed under the provision of the NHRC Act, section 10.

2. A name list of prospective candidates, interested in ERB membership is prepared by the member secretary of the NHRC. The list has to be prepared before the appointed deadline. The proposal for the new chairperson for ERB, along with the name list of candidates for board members is then submitted to the NHRC executive committee. NHRC executive committee selects the chair and the members of ERB based on candidates’ academic qualification, experience in conducting research, past contributions to the research ethics committee, integrity, non-partiality, independence, and decision-making capacity.

3. Modality of the selection of the ERB members and its composition should be endorsed by the Executive Committee of NHRC.
4. NHRC should prepare a roster of experts representing different areas in health science (Physician, Surgeon, Bio-medical scientist, Public Health expert, Social scientist, and Legal expert for the selection of chair and members.
5. NHRC Executive Committee selects 11 to 15 members, including the chair, affiliated and non-affiliated members. A balance of experience and gender is maintained in the

process.

6. Member Secretary of NHRC will function as the Member Secretary for ERB. However, in the absence of the NHRC Member Secretary or when the NHRC Member Secretary becomes Executive Chief of the organization, the Chief of Ethical Review Monitoring and Evaluation Section shall be the acting Member Secretary for ERB.
7. The tenure of the ERB members will be of three years.
8. Standard Operating Procedures (SOP) provide the details on the selection process of ERB members and the chair and its procedure.

6.1.2 Appointment of the ERB Chair/Members and Conditions of Appointment

6.1.2.1 Appointment of the ERB Chair/Members

With the approval from the NHRC executive committee, the NHRC executive chief will appoint the ERB chair, affiliated and non-affiliated members, which will be notified to the respective appointees by an appointment letter. ERB chair shall be an independent senior health professional not affiliated with NHRC. The tenure of appointment will be of three years which could be extended for one more term based on the performance and needs of the organization. ERB members, including the chair's term, will not be extended for a third consecutive term.

6.1.2.2 Conditions of Appointment

ERB members shall be appointed under the following conditions:

1. If he/she entirely agrees to make his/her profile public, as a member of ERB;
2. If he/she is able to read meticulously, understand what constitutes a conflict of interest for ERB members, and declare CoI, if any;
3. If he/she signs a confidentiality agreement regarding ERB meetings, discussions, and research proposals applied for ethical review.
4. If he/she agrees that the remunerations paid to him/her in the course of ERB work will be recorded and made available to the public on request;
5. If he/she provides a recent CV and relevant training certificate(s) related to health research ethics, GCP, GCLP, etc. (as applicable); and
6. If he/she is aware and ready to abide by relevant national laws, NHRC guidelines, and regulations

6.1.3 Qualification of the ERB Chair/Members:

6.1.3.1 Chairperson

An individual is eligible to be ERB chair if he/she is a senior and well-respected person with a post-graduate qualification in health-related sciences. He/ She must also have significant research experience as evidenced by his/her original research publications in international/national peer-reviewed indexed journals. Furthermore, the ERB chair is expected to be trained in research methods, research ethics, and GCP/GCLP with prior experience

serving as an IRC or ERB chair/member. Given ERB Chair's roles and responsibilities, the ERB chair should be independent while simultaneously exhibiting ethical leadership ability.

6.1.3.2 Member-Secretary

NHRC Member Secretary is appointed as the Member Secretary of the ERB. When NHRC Member Secretary assumes the role of Executive Chief of the organization, Chief of Ethical Review M & E Section shall be the acting Member Secretary for ERB, to minimize possible CoI for the Executive Chief.

6.1.3.3 ERB Members

A person is considered eligible for the membership of ERB, if s/he has a postgraduate qualification in health-related sciences (basic and bio-medical/clinical/public health/ Epidemiology / Biostatistics /nursing) with knowledge and experience in the ethical conduct of the health research. In addition, a person with a post-graduate degree in law and legal expertise in the health sector and a sociology/anthropology post-graduate with experience related to social health research can also be eligible to be an ERB member. Each member should be self-motivated to maintain basic ethical principles (beneficence, non-maleficence, autonomy and justice). ERB should have members representing each of the following experts:

- Clinicians (MD)
- Basic & Bio-medical scientists (MD/PhD)
- Allied Health Professionals
- Public Health experts/ Epidemiologist / Biostatisticians (MPH/MD/PhD)
- Social scientists or Ethicist (MA/PhD)
- Legal (LLM/LLB)

Note: *For some specific research related to ethnic/vulnerable communities, a layperson should be included as an invited member of ERB, based on the nature of the proposal, to represent community concerns on benefits/risks and socio-cultural barriers. A layperson should be a literate person selected from the public or community who has not pursued a health science-related career in the last five years but has been involved in social and community welfare activities. Such members may be representative of the community from where the research participants will be taken. Such a person must be aware of the local language, culture, and moral values of the community.*

6.1.4 Disqualification, Resignation, Cancellation, and Renewal of the ERB Chair/Members

1. If an ERB member is found acting contrary to, or breaching the conditions of

appointment, he/she may be disqualified by the NHRC Executive Committee. Legal prosecution against a member shall also lead to that member's disqualification. If any member–including the ERB chair does not attend three consecutive ERB meetings without prior notice with valid reasons, he/she shall be disqualified as a member of ERB.

2. ERB chair or a member may resign from his/her position by submitting a letter of resignation to the member secretary. Member secretary shall forward this to the chairperson and executive chief of NHRC. The Executive Chief shall forward this to the Executive Committee of NHRC. On acceptance of his/her resignation by the Executive Committee, he/she will no longer be a chair/member of ERB.
3. NHRC Executive Committee has the right to replace the ERB chair/members in case of their resignation/disqualification and sudden death. While replacing the ERB chair/member for the remaining tenure, NHRC Executive Committee shall follow the same procedure mentioned in the conditions of appointment of a new ERB chair/member. Such an appointment should be done as early as possible and not later than three months.
4. If the ERB chair/member is nominated as a member of the executive committee of NHRC, the existing membership in ERB will automatically be canceled.
5. At least 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 should not exceed two consecutive terms.
6. The appointment letter for ERB Chair/Member should specify the following:
    a. Subject area representing specific roles and responsibilities for each member of the committee;
    b. Duration of appointment; and
    c. Conditions of appointment.

6.1.5 Responsibilities of Ethical Review Board:

1. To ensure the protection of rights, dignity, safety, and well-being of the participants and monitor the compliance of the implementation process in line with the national and international guidelines. This is achieved through proposal review, monitoring of the implementation of approved research protocols, and review of non-compliance and final reports;
2. Recommend appropriate compensation package for research-related injuries based on scientific evidence and requirements;
3. Deliver constructive feedback with a frame of reference to help approve or disapprove the submitted research proposal;
4. Maintain confidentiality of all the documents at different steps starting from submission to review, feedback, monitoring, approval, reports review and writing of ERB minutes;
5. Facilitate the researchers in conducting research in compliance with the ethical guidelines, rules, and regulations. Facilitation should also include making researchers aware of the importance of respecting the local culture and traditions of the community where the study is conducted;

6. Organize periodic/annual review meetings/workshop/training programs for IRCs;
7. Interact with proposal reviewers on the ethical and technical review process and invite them to the ERB meeting if required;
8. Organize a joint review meeting if the study is multi-centric in nature among institutions that have their own IRC;
9. Organize reviewers' training periodically for the ethical and technical review process; and
10. Monitor approved studies to ensure that the research is conducted in accordance with the approved protocols.

Special conditions z: *In order to carry out its roles, ERB needs to function regularly, even in the absence of the NHRC executive committee. In such a condition, the ERB chair and members are mandated to function as per the assigned ToR in the appointed tenure.*

6.2 Office of the ERB Secretariat and its Functions and Responsibilities

6.2.1 Office of ERB Secretariat

1. NHRC should set up a separate ERB secretariat office with necessary administrative and resources support such as phone, internet, photocopy machine, scanner, printer, computers, file cabinets, desks, chairs, projector, meeting tables, shredder, online proposal submission, and review portal and its database management system, etc.
2. NHRC should assign a senior officer with an academic qualification, training and experience in research ethics as the chief of the ERB secretariat to support ERB Chair and member secretary in coordinating all the activities, including organization of ERB meetings, monitoring, and oversight of the implementation and investigation of complaints. ERB secretariat should have an adequate number of qualified and trained staff in different areas of health research.
3. The names of the ERB chair, member-secretary, and members should be displayed in front of the ERB office and NHRC website. Their duties and responsibilities should clearly be stated and documented in the ERB office.
4. NHRC should allocate adequate financial provision for effective functioning of ERB and strengthening of the capacity of the secretariat and ERB members, utilizing the revenues generated through proposal review.

6.2.2 Functions and Responsibilities of ERB Secretariat

The ERB secretariat should work in close coordination with the ERB chair, ERB member-secretary, and executive chief of NHRC and is responsible to:

1. Develop a roster of subject-specific expert reviewers with approval from ERB, whose review service could be obtained by the ERB/NHRC and could also be invited for meetings either virtually or in-person;
2. Collect and archive CVs, confidentiality agreements, and CoI from ERB chair, member-secretary, members, and reviewers;
3. Validate the financial section of the proposal in line with the grant agreement for payment of the ethical review processing fee;

4. Maintain the electronic database of the proposals, archiving and tracking procedures, including preliminary screening and verification of the submitted proposals as per the checklist;
5. Prepare, maintain, and distribute proposals to primary and technical reviewers. Communicate with the reviewers and investigators for clarifications, and responses; revise until the final approved proposal is archived;
6. Prepare the meeting agenda in consultation with ERB Chair and member-secretary, communicate with the ERB chair/member secretary/members and coordinate/organize ERB, and expedited review committee meetings regularly;
7. Prepare and present the summary of the proposals (Title, PI, Sponsor, Site, Risk assessment Matrix, etc.) for discussion in the ERB and expedited review sub-committee meetings;
8. Draft the meeting minutes, share with members, member-secretary, and chair for review/revision/editing and final approval. The final minute should be signed by the Chief of the ERB secretariat, Member Secretary, and ERB Chair before further communication;
9. Prepare the decision letter according to the approved minute. Obtain signature from member secretary/executive chief of NHRC/any designated officer of NHRC and communicate the decision to the researcher. If NHRC authority is the applicant for obtaining ethical approval from ERB, a decision letter should be signed by the ERB chair;
10. Organize ERB documentation, communication, and archiving;
11. Plan and organize monitoring site visits of the ongoing studies;
12. Update and share relevant and contemporary ethical issues to the ERB;
13. Facilitate to organize meetings/workshops/training related to research ethics capacity building and IRC periodic review;
14. Carry out the additional responsibilities given by ERB chair/member-secretary and NHRC chief executive;
15. Organize IRC accreditation sub-committee meetings and inspection visits for accreditation of IRCs; and
16. Organize the complaint handling meeting and communicate with members and concerned stakeholders.

6.2.3 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 twice a year. Such training programs will provide opportunities for a hands-on experience of reviewing the research proposals and responsible conduct of research. ERB members and ERB secretariat staff should be oriented with the ethics-related guidelines and SOPs upon appointment and each time there is any update/revision.

6.3 Submission and Review Procedures

ERB secretariat is responsible for managing proposal submission, review, feedback, and approval through an online submission portal and maintaining the archival database. Investigators planning to conduct health research in Nepal should submit their research proposals through the online ERB portal (http://erb.nhrc.gov.np or http://nhrc.gov.np/erb) for ethical review and approval.

6.3.1 Application Submission

Principal Investigator or an assigned team member should submit the proposal and attach all the administrative and technical documents mentioned below. The Investigator should first register with their details. An automatic email will be sent to the investigators with login details upon successful registration. With these login details (username and password), the investigators can enter into the researcher's login portal.

The administrative and technical documents to be submitted:

1. Dated cover letter signed by the Principal Investigator, mentioning that he/she has sufficient expertise to conduct the research and will take full responsibility for the research from recruitment to the completion of research;
2. Informed Consent Document (ICD) in Nepali language and in case of internationally collaborative research both English and Nepali language should be submitted in addition, this can include a translation copy in a local language if relevant;
3. Document with clear information on any compensation to be given to the research participant (e.g., any transportation costs, food, free health care or insurance coverage, etc.);
4. In the case of an interventional study, and institutional acceptance letter indicating that the institute is a collaborating partner and any SAE/AE during the course of research will be managed by the institute;
5. Sponsors grant agreement;
6. IRB approval from other collaborating institutes if it is a multi-national and multi-centric study;
7. A signed statement by the researcher stating that he/she will abide by the ethical principles of research; and
8. A declaration of the CoI and its mitigation measures, as applicable.

Only those applications fulfilling the requirements will be accepted for review and further process. Incomplete submission will not be processed further. Upon successful completion of submission of the required documents, including the proposal, an auto-generated acknowledgment email containing the proposal registration number (for future follow-up) will be sent to the researchers. A verification email will be automatically sent by the online portal, which needs to be verified by each investigator, for further processing. For any additional documents required during the review process, the researcher will be notified by the ERB secretariat. Process and list of documents and ethical review processing fee required for applying online proposal submission could be accessed in Annex – II and relevant SOP

6.3.2 Elements of the Review Process

Once the research proposal is submitted and screened for completeness of reference documents by the ERB secretariat, primary and technical reviewers will be assigned in consultation with the ERB chair and/or member secretary, based on technical expertise and experience in research ethics. The review will be based on the provided checklist. Secretariat will coordinate communication of the feedback/revision between the reviewer and the investigators while maintaining the confidentiality and mitigating CoI. Upon reviewing and revising the proposal, the proposal in consultation with the ERB chair and/or member secretary will be further processed depending on the category of risk. It will be reviewed in the Expedited Review Subcommittee or by the full ERB (Section 4, Box 1).

Basic requirements of review process

1. Relevant qualification (academic degrees, training, and experience) of the PI and other investigators in the subject area of the research in line with national rules and regulations;
2. Infrastructure (human resources, equipment, bio-safety/data safety, and supplies) and other facilities in the institutions (if any);
3. Description of the population from which the research participants will be drawn;
4. Assessment of possible risks, inconveniences, and anticipated benefits of the research to the participants;
5. Clearly articulated rationale and justification for exclusion and inclusion in the study;
6. Provisions for Data Safety Monitoring Board (DSMB)/Data Safety Monitoring Committee (if relevant for the study). For any trials, the formation and functioning charter of DSMB needs to be evaluated;
7. Provision of insurance or indemnity to the participants in case of adverse drug reaction and/or adverse events (if relevant for the study);
8. The mechanism for reporting and management of any adverse drug reaction and/or adverse event (if relevant for the study);
9. Plan for dissemination or publication of research results; and
10. Assurance of the availability of research products for the use of the participants and the community/country, if relevant.

6.3.3 Joint Review

Joint review shall be organized for the multi-centric studies being conducted in institutions that have IRCs. This is initiated to increase institutional ownership, reduce the additional burden on IRCs and monitor the implementation process. In such studies, ERB shall call on relevant IRC representatives to attend the meeting and provide their opinion for decision-making.

6.3.4 Exemption from Review

Researchers can apply for exemption from review in certain situations. Based on the risk categorization, the ERB secretariat will put forward the proposal to the Expedited Review Subcommittee meeting for the necessary decision.

Conditions for exemption from the review:

1. Research that involves accessing and analyzing data available in the public domain;
2. Research on anonymous or non-identified data/samples;
3. Observation of public behavior when information is recorded without any link and disclosure of the person under observation; and
4. Quality assurance and quality control audit in the institution.

6.3.5 Expedited Review

The Executive Chief of the NHRC shall form an expedited Review Sub-committee (consisting of affiliated and non-affiliated members). ERB chair will be the coordinator and others will be the sub-committee members. Emphasis will be laid on balancing gender and discipline while forming the Expedited Review Sub-committee. The Expedited Review Sub-committee's recommendations are presented to ERB for final approval. Expedited Review Sub-committee only reviews proposals that are grouped into 'less than minimal', 'minimal risk', and 'low risk' categories, as discussed in Box1. Proposals, which are grouped into the 'higher risk' category, are sent to ERB to decide upon further actions on the approval process as per SOP. Urgent implementation of the protocols during public health emergencies and disasters, requiring fast-track approval may also be considered for expedited review as per the following procedure:

1. Secretariat prepares the list of proposals for Expedited Review Sub-Committee meeting in consultation with Member Secretary and Expedited Review Sub-Committee Coordinator.
2. Secretariat prepares and presents the summary of the proposals (Title, PI, Sponsor, Site, Risk assessment, etc.) for discussion in the Expedited Review Sub-committee meetings.
3. Secretariat drafts meeting minutes and submits them for review/editing and approval by Expedited Review Sub-Committee coordinator.
4. Secretariat prepares a list of proposals approved by the Expedited Review Sub-Committee meeting and forwards them to ERB full board meeting for endorsement.

6.3.6 Re-submitted Proposal Review

For proposals requiring major revision, researchers may re-submit the proposals according to the decision of the ERB. The re-submitted proposal with significant revisions will follow the same process which is used for a new proposal.

6.3.7 Review of Amendment of the Approved Proposal

The researcher should submit a request for amendment through an online portal and get

approval within a valid timeline before implementation. The rationale and justification for the amendment should be scientifically strong, without deviating much from the main objective and methodology of the approved proposal. Minor revisions on the approved proposal shall be cleared through the Expedited Review Sub-Committee meeting process; however, major revisions shall be reviewed by the full board.

6.3.8 Review of the Final Report

The researcher should submit his/her final report upon completion of the study through the online ERB portal. The report will be reviewed by the relevant Secretariat staff, an expert member of the ERB, or the subject expert (as applicable), before issuing an acknowledgment letter.

6.4 ERB Meetings

ERB meetings shall be organized at regular intervals, based on the number of proposals and urgency in conducting the research, which requires swift review and approval. ERB Member-Secretary or chief of the ERB secretariat, in consultation with the ERB Chair, will organize the meetings. The following points should be considered for organizing an ERB meeting:

1. Agenda for the meeting needs to be shared with the members at least a day before the meeting.
2. If ERB feels it necessary, the PI or co-investigator, or study team members, as mentioned in the research proposal, can be invited to the meeting to present the proposal or elaborate on specific issues in the meeting. However, the study team member shall not participate in the decision-making process.
3. ERB meeting will be considered valid only if the quorum (>51%) is fulfilled
4. The ERB member(s) should declare their CoI, if any, before the meeting. The chair should institute appropriate management or mitigation measures to address the declared CoI. In the case of CoI management measures adoption, the member, who declares CoI, may be asked to leave the ERB meeting while the specific proposal is being discussed. He/she also may not be a part of the decision-making process. The Secretariat should ensure the quorum requirement in each proposal is discussed.
5. The related subject experts could be invited to the meeting for expert opinions about the proposal (if required) and their views should be recorded in the minute. However, the final decision is made by ERB members after evaluating the proposal and incorporating the opinions of the invited expert.
6. The ERB can allow the virtual presentation of the proposal by the researcher(s) if needed.
7. The decisions and procedures of the meeting should be recorded in the meeting minute.
8. Attendance sheet should record the name of all those who are present and absent in the meeting.
9. The meeting minute of the previous meeting, recommendations for expedited review sub-committee, and proposals for review exemption should be shared and approved by

the full board meeting.

10. ERB minutes should be drafted by the secretariat and verified and approved by both Member-secretary and ERB Chair.

6.4.1 Quorum requirements for ERB

1. At least 51% of ERB members must be present to form a quorum in order to make a valid decision.
2. The quorum should include medical and non-medical and technical and/or non-technical, affiliated, and non-affiliated members.
3. Presence of members representing only one gender does not constitute a quorum.
4. The proposed proposal under discussion should have been reviewed by at least one ERB member or subject expert.
5. No decision is valid without fulfillment of the quorum.
6. Invited experts should not be counted in meeting quorum requirements.

6.5 Decision Making

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

1. ERB meeting has met quorum requirements.
2. Normally, decisions can be taken by consensus; if consensus is not possible, the voting process can be initiated.
3. All ERB members present during the meeting have the right to express their opinion or vote to decide.
4. Decision must be taken either by consensus or majority votes and should be recorded. A dissenting view or opinion (if any) should be recorded with reasons.
5. If any member has CoI related to a particular proposal, he/she should declare CoI in advance. Anyone, who declares CoI, will not be part of the decision-making process.
6. The ERB can a) fully **approve** to start the study as presented, with no changes required; b) **approve** with minor modification, requiring minor changes/corrections to the item(s) noted at the convened meeting, to be followed-up by the ERB Chair and Member Secretary after the researcher makes changes/corrections/modifications as per the suggestions; c) ask for the **resubmission of** the proposal, requiring major changes/corrections to the items and a full committee review of the materials; or d) completely **disapprove** the proposal, rejecting the study and stating the reason for disapproval.
7. Reason for the proposal's disapproval will be clearly stated and communicated to the researcher.

Note: *If the Board votes not to approve the study and if the investigator wishes to appeal this decision, he or she may do so by contacting NHRC Executive through the ERB secretariat, or directly within 35 working days from the date of receiving the letter.*

6.6 Communicating a Decision

On behalf of the ERB, the ERB secretariat will communicate its decision to the applicant in a written form through online systems within two weeks of the ERB meeting. ERB should give an initial decision within 6 to 8 weeks of submitting the proposal.

Note: *Application will not be entertained and put on a pending list if the researcher investigator does not respond to the queries from the secretariat for more than 3 months. Such studies will be permanently closed, and the researcher(s) will have to reapply with a new protocol for further processing.*

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

1. The exact title of the research proposal reviewed;
2. The precise registration number of the protocol of the proposed research or amendment, date, and version number (if applicable) on which the decision is based,
3. The names and where possible, specific identification numbers (version numbers/dates) of the documents reviewed, including the potential research participant information sheet/material and informed consent form;
4. The name and title of the applicant;
5. The date of the decision;
6. A clear statement of the decision reached; and
7. Any advice, suggestions, and recommendation by the ERB.

6.7 Continuing Review

Approved ongoing research with more than a one-year study duration should be reviewed regularly, at least once a year. For that, ERB can establish a follow-up procedure (continuing review) to keep itself updated with the progress of all approved research (right from the approval of the research to its completion). The researcher should apply for a continuing review at least one month before the expiry date. The communication for continuing review will be entertained if initiated before the expiry date and will be valid if only applied within the approval time. The follow-up review intervals shall be determined by the risk category, nature, and the research proposal review schedule.

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

1. Any protocol amendment,
2. Serious and unexpected adverse events related to the conduct of the study or study product and the response taken by investigators, sponsors, and regulatory agencies;
3. 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; and
4. In case of the premature suspension/termination of a study, the applicant should notify the ERB of the reasons for the suspension/termination, including the submission (to the ERB) of a summary of results obtained from a study prematurely suspended/terminated.

The procedure for continued review considers the following aspects:

1. Documents to be reviewed such as progress reports, safety reports (if any), technical audit reports (if any), final reports, etc.;
2. Experiences of the research participants (e.g., independent observation of the discussion being held during the informed consent-taking process, independent surveys of participants' experiences, etc.); and
3. Notification from the applicant with regard to suspension/premature termination or completion of the study.

6.8 Site Monitoring Visit

ERB secretariat (in consultation with ERB Member Secretary and ERB Chair) prepares the list of proposals for a monitoring visit and forms a team including ERB member, subject expert, and secretariat.

6.9 Documentation and Archiving

All documents, including administrative and technical documents should be archived. Administrative records include ERB members' nomination decisions by the NHRC executive committee, name lists of ERB members, appointment letters, CV and CoI declaration letters of the ERB members and secretariat staff, registration, and accreditation, academic certificates, training records, international and national guidelines, ERB agenda and minutes. ERB secretariat should archive all communications with members and reviewers and/or experts along with the technical documents, including copies of the proposal submitted by an applicant; ERB decision letters; amendment; SAE/AE report; safety reports; protocol deviation and violation report; continuing review report; site monitoring visit report; documents received during follow-up; progress and final reports; complaints; audit reports; signed CoI form of the researcher; and, other required documents submitted by the researchers as per the checklist. The records (electronic/hard copy) should be kept in an appropriate storage facility. An authorized officer of the ERB secretariat should sufficiently be trained to understand their responsibilities related to record keeping, retrieval, and maintaining confidentiality.

ERB secretariat should inform the researcher/research organization that documents including research-based data (filled questionnaire/Pro-forma/electronically filled data set, etc.), filled informed consent forms, collected bio-samples (back-up) should be archived for at least five years (or more for some cases) after the completion of the study.

Section 7. Specific Requirements for Specialized Research:

There are some specific requirements that investigators and sponsors need to fulfill while conducting specialized types of research, e.g. clinical trials of drugs, vaccines and devices, synthetic biology, radioactive materials, X-rays, bioavailability, bioequivalence, public health, social and behavioral science, human genetics, humanitarian emergency, stem cell research and, use of animals in health research. Whilst conducting different phases of a clinical trial,

the investigator and sponsor must adhere to and comply with the international GCP guidelines along with the followings:

7.i. Human resources and infrastructure

Qualified human resources with clinical trial experience should be available for conducting clinical trials. Similarly, infrastructure like a laboratory, equipment, devices, space for ICF, and intervention along with other prerequisite work should be ensured. These should be in line with international guidelines for conducting different phases of clinical trials. Before initiation of the trial, the investigator should submit the site verification report to ERB.

7.ii. Contract Research Organization (CRO)

There should be a qualified local CRO for planning, developing, and implementing the clinical trial as per the protocol.

7.iii. Declaration of conflict of interest and mitigation measures:

Investigators (principal and co-investigators), sponsors, and the implementing institution involved in the clinical trial should declare any existing CoI. A statement of declaration of the trial product should be used only for research purposes without any direct/indirect financial benefit to the investigators and implementing institutions. The fact that the investigators will ethically perform professional duties maintaining equity for all, whether they are participants or not, should also be clearly mentioned.

7.iv. Insurance, Indemnity, and Medical Coverage of the Participants

Clinical trials sometime may pose threats to the participants. In order to mitigate the harmful effects of the trial, the sponsor of the study and the principal investigator should evidently cite the benefits and possible harms of participation in the informed consent document. And, if there is any harm, details about the compensation/insurance policies, provisions, and coverage should be outlined. In addition, the role of the implementing institution (undertaking the research project) in case management related to the trial effect should also be distinctly stated. The sponsor, research implementing institution, and the investigator should submit an insurance policy clearly mentioning what will be covered by the insurance and what not, how the insurance claim will be approved, and the role of investigators and participants in the insurance coverage approval process.

7.v. Independent Data and Safety Monitoring Board (DSMB)

Sponsors of the study should form an independent Data and Safety Monitoring Board (DSMB) before initiating the trial. DSMB should consist of independent subject experts (representing different research subject areas) such as clinicians, bio-statisticians, and, an epidemiologist with prior DSMB experience representing the country where the study is being implemented. For international multi-centric trials with research sites in many countries, it should have at least one DSMB member representing Nepal. However, it would be preferable to have a

national DSMB. PI should submit a DSMB charter with clarity on DSMB members' roles and responsibilities outlined as follows.

1. Interim review of the trial's progress, including updated figures on recruitment, data quality, adherence to protocol treatment and follow-up, and primary outcomes and safety data;
2. Monitor evidence for treatment-induced harm (e.g., toxicity, SAEs and ADRs, deaths, etc.);
3. Monitor evidence for treatment differences in the primary efficacy outcome measures;
4. Assess the impact and relevance of external evidence;
5. Decide whether to recommend continuation of participants' recruitment in trial or, termination of the trial (for everyone/some treatment groups/some participant subgroups);
6. Decide whether the trial should be stopped earlier;
7. Assess data quality, including completeness (and by so doing, encourage the collection of high-quality data);
8. Maintain confidentiality of all trial information;
9. Monitor recruitment figures and losses to follow-up;
10. Monitor compliance with the protocol by participants and investigators;
11. Monitor planned sample size assumptions, preferably with regards to
    a) A priori assumption about the control arm outcome; and/or
    b) Emerging differences in clinically relevant subgroups, rather than un-blinded differences between treatment groups.
12. Suggest additional data analyses if necessary;
13. Advice on protocol modifications (e.g., on inclusion criteria, trial endpoints, or sample size) proposed by investigators or sponsors; and
14. Monitor continuing appropriateness of patient information.

7.vi. Trial Steering Committee

Sponsor of the study should form an independent Trial Steering Committee (TSC) consisting of independent subject experts representing different research subject areas (not directly involved in the trial other than as a member of the TSC). A representative from the Ministry of Health and Population, Department of Drug Administration, and Nepal Health Research Council can also be a member of the TSC.

The role of the TSC is to provide overall supervision for the trial to ensure that the trial is conducted to the rigorous standards set out in the Medical Research Council's (MRC) Guidelines for Good Clinical Practice. Notably, the TSC should concentrate on the progress of the trial, adherence to the protocol, patient safety, and the consideration of new information.

7.vii. Community Engagement

Before initiating the trial, the investigator should clearly mention how the community engagement will be done. The detailed procedure should be described in the protocol, and a report of the community engagement should be submitted to ERB during the implementation

of the trial.

7.1 Clinical Trials of Investigational Products (Drugs, Vaccines, Devices and other Investigational Products in Traditional Medicine)

Clinical trials are experimental and usually well designed, where the investigational products (IP) (modern allopathic medicines/vaccines/devices or traditional ayurvedic/alternative medicine products or procedures) related intervention(s) are done to evaluate the safety and effectiveness of the interventions on participant's health outcomes. Such trials usually involve healthy participants to evaluate the outcomes of the IP. Such IPs could also be used in sick patients to verify their effects and possible adverse events in establishing their safety, reactogenicity, immunogenicity, and efficacy.

Clinical trials compare the effectiveness of the interventions in test group participants (treated with an investigational product/intervention - IP) versus the control group (receiving a placebo or an active comparator). Such investigation will distinguish between the effects of IP and placebo, concomitant treatment, spontaneous change, etc. When using a placebo in a trial, the participants should be informed and also be able to comprehend that they are randomized to a test or a placebo group and may receive IP or an inert drug during the trial period. If found effective in test group participants, Placebo group participants should be offered post-trial access to the IP. During the clinical trial period and even for a longer period, based on the pharmacokinetic properties of the IP, the safety monitoring follow-up and clinical case management of all participants must be ensured by the implementing institution (or through sponsor support). Long-term safety monitoring must be considered based on the pharmaco-kinetic & pharmaco-dynamic properties of the IP.

Clinical trials are classified into Phases I to IV. In certain special conditions like public health emergencies (requiring early development and validation of the effects of the IP in different population groups in a very short period for protection/treatment of the population), NHRC may permit even a Phase II trial of the IP developed outside Nepal, with sufficient scientific and ethical discussion and justification in ERB full board.

NHRC may only permit Phase-I clinical trials in Nepal where the institutes planning to conduct such trials have adequate infrastructures and resources in addressing any events related to IP and after-effects. In such a situation, sponsors should develop infrastructures and capacitate human resources as stipulated in international guidelines while complying with the Drug Act 1978. In addition, investigators institute should produce sufficient evidence of pharmacological, microbiological, and toxicological safety of the IP in non-human models.

The ERB should review the evidence of Phase-I and Phase-II results published in peer-reviewed international professional journals, demonstrating that the IP is suitable for continuation to Phase III. The research institute and the Principal investigator proposing to conduct Phase III clinical trial should submit the signed copy of the previously conducted Phase I and II clinical trial documents, clinical trial registration, and publications to ERB for

review and approval process. Upon approval of the clinical trial research from NHRC, the implementing institution should obtain an IP import license from DDA as per the existing Drug act of the country and regularly report to DDA as per the Drug Act provisions.

An investigator brochure should be made available with information about its product, the intended purpose of use, safety profile, registration, and approval from the regulatory authority in the manufacturing country, which should clearly show its usefulness, limitations, potential risks/hazards, and mitigation measures as applicable.

7.2 Clinical Trial involving Vulnerable Participants:

A clinical trial involving vulnerable populations will only be allowed when a strong justification for the need for
such a trial in a vulnerable population is provided, ensuring effective participant protection measures by the institute implementing the trial. The clinical trial involving vulnerable people must be undertaken with caveats mentioned as follows:

1. Women of childbearing age must be counseled for possible adverse effects of the trial on the pregnant woman and her fetus during the period of study. Women participants also need to use effective contraceptive methods during the period in order not to conceive and mitigate the possible adverse effects of the trial on the fetus.
2. 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, ensuring sufficient participant protection/effect mitigation measures in place.
3. Lactating women should not be encouraged to discontinue nursing for the sake of participation in the study except in the condition where breastfeeding is harmful to the infant. If a lactating woman decides to stop breastfeeding, the harm of cessation of such breastfeeding to the nursing infant should adequately be evaluated, and the effects should be mitigated.
4. Terminally ill patients may be recruited in the clinical trial if their clinician thinks that the IP may be the last hope for a cure or a way to get free treatment for their disease, which may otherwise be beyond their reach. In such cases, the treating doctor should only recommend such therapy if it is helpful to the participants.
5. Clinical trial is permissible in people living with HIV, if the drug under the study cannot be tested in healthy participants due to predictable toxicity of the IP. When a preventive HIV vaccine trial is conducted, it can result in positive serological tests 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 an HIV vaccine trial and provide an explanation for 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 the confidentiality of HIV infected person.*

7.3 Clinical Trial Involving Devices/Instruments/Implants:

Clinical trial incorporates the use of wide-ranging devices, such as an instrument, implant, material, etc. Such devices may also be used alone or in combination with another device. Besides, devices can be used both internally and externally, for human beings or animals, and, for one or more specific purposes (e.g. treatment, detection, diagnosis, prevention of disease or disorder, monitoring, etc.). Such device trials should be conducted following similar steps of ethical principles as applicable for drugs or vaccine trials and should be considered in the same way as for a new drug/vaccine licensing procedure adopted by the Drug Act1978. It may not be possible to remove the internal device if the research participant would like to withdraw from a trial after the installation of the device. This should be explained clearly through a comprehensive informed consent document to the participant prior to their enrollment. It is also important to ensure that the participant fully understands what is being explained to him/her before participating in the trial. When a device is implanted within the human body, its follow-up period would be long enough to find the late onset of its adverse reactions/events.

Based on the type of medical devices, the levels of risk may range from low to high. For example, the use of thermometers/bandages/tongue depressors may put participants at lower risk, and/or the use of hypodermic needles/suction equipment may give low-moderate risk. However, the use of a lung ventilator/bone fixation plate may put the research participant at moderate-high risk, and similarly, heart valves/pacemakers/defibrillator may pose an even higher risk.

7.4 Surgical Intervention/Trial:

For conducting a trial that includes surgical intervention, investigators should provide references for the process and define the most probable difficulties (if any) in the proposal for the ERB to review and perform a risk-benefit assessment. Such surgical intervention must be guided by ethical principles applicable to drug trials. Mock surgery must not be incorporated in the design of the surgical intervention (trial), except in the situation where the researcher can develop strong scientific reasons for it.

7.5 Community Trials

Community trials are carried out at the community level and the intervention is targeted to communities rather than individuals. The randomization procedure can also be adopted at the community level, and the method of such a trial is helpful in studying disease prevention or public health intervention models, including behavior change interventions. Ethical review of the community trial proposal may be treated differently, emphasizing more how specific measures are established to protect the welfare of community members who are not participating in the trial.

7.6 Traditional and Complementary Medicine Clinical Trials

To conduct clinical trials on traditional and complementary medicines developed within the country, each product must go through various pharmacological, toxicological and

microbiological testing (heavy metal contamination, toxicity, microbiological testing, etc.) from the recognized laboratory, ensuring the safety of the product. The reports of such testing should be submitted to ERB along with the scientific proposal. In addition to the requirements for a clinical trial of allopathic medicine, investigators must follow 'NHRC Traditional and Complementary Medicine Research Guideline.'

7.7 Research in the area of Synthetic Biology

Synthetic biology is the field of science that involves the application of science, technology, and engineering to facilitate and accelerate the design, manufacture, and/or, modification of genetic material of living organisms. The investigator should follow ethical and legal aspects pertaining to impacts/potential risks of synthetic biology on biosafety, biosecurity, IPRs, environment (physical and social environment) etc.

Safety provisions in the Environmental Protection Act, Biomedical Waste Management Rules, and other relevant laws of the country need to be followed by the researchers working on synthetic biology. Appropriate safety training (like safe handling of the product) must be provided to researchers and staff working in the area of synthetic biology. Their periodic health screening should be done as they are at potential risk of harm from exposure to occupational health hazards.

Biomaterials have the potential for both use and harm. Notwithstanding potential benefits, there are also a number of ethical concerns about synthetic biology vis-à-vis both physical (safety and security) and non-physical harms. To ensure safety, it is important for the researchers involved in synthetic biology to weigh the benefits of research against potential risks. Researchers should also adhere to ethical principles (beneficence, non-maleficence, equity, justice, etc.) while working on synthetic biology. Besides, to avoid misuse of research, researchers are required to work in accordance with the ethical guidelines, policies, regulations, and acts pertaining to research on synthetic biology. There also must be an effective partnership between policymakers and researchers to generate a secure system.

Biomaterials and biocompatibility testing in a certified laboratory must be done as per the relevant regulatory standards of GoN.

7.8 Research in an Area of Radioactive Materials, including X-rays

If the radioactive substance is to be tested in health care, it should be considered in the same way as a new drug/vaccine in line with Drug-Act 1978 and relevant DDA regulations. Radioactive materials comprise radioactive isotopes with diagnostic or therapeutic uses. When such materials are used in research, their permissible radiation limits must comply with regulatory authority guidelines, and this exposure must be within acceptable limits. The research site must have obtained authority for the storage, handling, and dispensing of such materials. Only trained researchers with appropriate safe handling training for radioactive materials should be involved in carrying out the study. Radiation workers or anyone who has

received more than the permissible amount of radiation in the past year and vulnerable populations (particularly women of childbearing age and children) should be excluded from the study involving radioactive materials or X-rays. Sufficient provisions should be in place for identifying pregnancies and preventing exposure risks to the embryo. Information about possible genetic damage to the offspring must be included in the ICD/ICF.GCLP, Good Manufacturing Practice (GMP) and GCP, should be observed when conducting clinical trials.

7.9 Research for Bioavailability and Bioequivalence Study

Bioavailability (BA) 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.

Bioequivalence (BE) is a term used in pharmacokinetics when two or more medicinal products (proprietary preparations of a drug) contain the same active substance that needs to be compared in vivo for biological equivalence. These comparative studies are used to assess if the new version (generic) produces the same concentration in the systemic circulation when given to human participants. If two products are said to be bioequivalent, it means that they would be expected to be the same for all intents and purposes.

BE studies are used as surrogates for clinical effectiveness data for generic drugs, where no clinical difference is anticipated between the two products. All bioavailability and bio-equivalence studies should be conducted scientifically in compliance with the ethical code of conduct described earlier for Phase-I clinical trials. Ethical conduct of BA/BE study requires evaluation of the benefit-risk profile of:

- The reference (comparator) and investigational (generic) product; and
- The study procedures include indoor stay, fasting, screening, and blood sampling.

BA/BE studies are usually conducted with healthy volunteers. Hence, they have no direct benefit to the participant but may pose risks due to the adverse effects of the drug. Therefore, all safeguards to protect participants must be in place.

The EC must carefully review the recruitment methods, payment for participation, and consent procedures.

The volume of blood drawn must be within physiological limits irrespective of the study design. The ERB should take precise note of 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.

7.10 Public Health Research

Defining boundaries between public health practice and research remains a challenge in public health ethics as the purpose or intent of the investigation may overlap. Public health practice

involves data collection through surveillance, vital statistics, disease reporting and registries; investigation of outbreaks including contact tracing, use of preventive interventions, and health promotion; monitoring and program evaluation; and enforcing of mandatory requirements, such as screening, treatment, immunization, notifying diseases and, sometimes, quarantine depending upon the situation.

Using epidemiological designs, sampling techniques, and analysis, some of these activities could create generalizable knowledge, which is the primary research intent.

The benefits and risks of public health research may influence populations, communities, and the environment and are not restricted to a person.

ERB should differentiate between public health practice and research in order to determine its role with more clarity. It is also vital to ensure that the population-based data from secondary sources do not violate any ethical principles (as mentioned hereunder) of public health research as the Principle of social justice, the Principle of reciprocity, the Principle of solidarity, and the Principle of accountability and transparency.

ERB should consider the following aspects while reviewing public health research proposals:

1. Are the objectives of the study scientifically sound and linked to the achievement of public health goals?
2. Is individual written informed consent required?
    a. If not, is gatekeeper consent/permission sufficient?
    b. Who is a gatekeeper and how is this decided?
    c. Is it a two-stage process- initially a gatekeeper consent/permission followed by individual consent?
3. If applicable, is respect for the community applied through community engagement?
    a. If so, is the methodology appropriate?
4. Which segments of the population are likely beneficiaries?
    a. What are the expected benefits?
5. Is individual harm overriding the potentially more significant societal benefit?
    a. If so, is it justified?
    b. What are the different types of potential harm?
    c. Who would be harmed?
    d. What, if any, measures can be taken to mitigate/minimize this?
    e. Is the harm fairly distributed?
    f. How do societal benefits outweigh individual harm?
6. Is social justice given due consideration while designing, implementing and assessing outcomes of the study?

7.11 Implementation Research

Implementation research facilitates informed decisions about health policies, programs, and clinical practices. It is co-designed and co-implemented with end-users to understand and encourage uptake of completed research. The analysis is intended to explain how best to scale an intervention, introduce/expand public health innovation, and how and why a policy works. It is adaptive in nature and builds on operational research and implementation science framework. The implementation research proposal should have clear and accurate pre-defined interventions, delivery mode, outcome measurement and the role of implementers and research participants. ERB needs to understand the flexibility requirement while assessing stakeholder engagements, roles, and responsibilities of the investigators to scale up, advocate, promote uptake, or sustain the public health intervention and harms to investigating team members related to interventions. ERB needs to ensure that the investigators provide the available standard of care and health benefits resulting from the research to the research participants. The results of the study are disseminated at the local level, enabling local authorities to develop future health programs/interventions.

7.12 Socio-behavioral Research

Socio-behavioral research includes, but is not limited to, anthropology, sociology, psychology, philosophy, political science, economics, history, communications, and education and is different from public health, bio-medical and clinical research. Many of these research initiatives are relevant in the mid to long term for knowledge production, science, and society (social equity and intersectionality of populations), providing a deeper understanding of explanatory factors for policymaking.

This kind of study generally focuses 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 for planning the interventions. ERB should consider the diversity in practices of the societies due to religion, caste, social class, gender, indigenous groups, and geo-ethnic variations, which are essential characteristics of society in socio-behavioral research proposals, and the mechanisms to protect vulnerabilities similar to those for public health and biomedical research.

When the researchers plan to observe some technically questionable practices and behavior of the study participants, researchers should not interrupt such practices and behaviors. They must document these in their research findings. ERB needs to review the investigator's obligation not to interrupt social harmony, 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 a researcher thinks that they might come up with sensitive incidental findings during the 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 counseling centers,

rehabilitation centers, security force protection, etc. In such circumstances, individuals with the necessary domain knowledge and experience need to be invited as external subject experts or as reviewers during ERB meetings, with the viewpoint to provide technical expert advice to ERB in the decision-making process. 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. Sponsors and local research institutions should take full responsibility for such safety concerns.

If a researcher would like to conduct a study within communities, he/she should not hire a local person from the same village as an interpreter, to avoid possible conflict of interest. In such cases, the interpreter must be from a nearby village, so that his/her potential conflict of interest, vulnerability, and the threat from participants can be mitigated. Research agencies must develop SOPs for handling deteriorating/unforeseen situations (trauma, humiliation, and threats of violence) which might happen either to participants or study team members.

For audio/visual recording of research participant 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 resulted from participating in a study.

If research participants feel that they are not autonomous in decision making, informed consent should be obtained only with the permission of the spouse/family head/community head/leader/culturally appropriate local authority/health care provider or institution. The consent-taking process should respect local cultural customs and practices. However, such permission does not substitute for individual consent unless ERB has approved a waiver. In certain situations, where the power differences between investigators and research participants are clearly visible, it would be difficult for the participants to refuse to participate explicitly. Investigators must be sensitive to cultural signs of refusal, such as silence, body language, uncommunicative replies, etc., and should not continue the interview in those cases. ERB may consider these contexts during the review process. Sometimes, ERB may waive the requirement for individual informed consent if it is convinced that the study is very important for scientific evidence generation for policy-making and would not be possible without a waiver, for example, a study on harmful practices.

7.13 Research on Molecular Genetics

Investigators need to consider the following issues while conducting research on molecular genetics:

1. **Genetic test** results may put research participants into psychological stress, which may be in the form of anxiety, depression, and sometimes, disruption in family relationships. There may be a possibility of social stigma and discrimination (in schooling,

employment, health care, and general insurance). Thus, it is imperative to maintain confidentiality in genetic testing and follow appropriate communication skills during genetic counseling.

2. 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 could be tackled in due course.
3. Study team should comprise clinicians, geneticists, genetic counselors, and laboratory personnel.
4. **Genetic testing** among vulnerable participants like children, individuals with mental illness, people with rare diseases, cognitively impaired individuals, etc. should ensure core ethical principles for the protection of the participants. ERB should provide such protection measures in the proposal and its institutional arrangements.
5. **Genetic counseling** should be done only by qualified (in terms of academic qualification, training, and experience) personnel with comprehensive information in the language comprehensible/graspable for a layperson. At times, following genetic testing results, a participant may be required to terminate the pregnancy to avoid a genetically abnormal fetus. In such circumstances, choices must be provided to the family, enabling 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 precautions should be taken so as not to break families. Such type of counseling should be done with extreme caution and patience so that participants' psychosocial harm is minimized.
6. Genetic research at times demands the collection of family members' details. Such family members will be regarded as secondary participants. Informed consent must be obtained if identifiable information is collected about the secondary participants.
7. Research participants' genetic information is confidential, and investigators should not share it with family members without their permission, especially in case genetic information is about non-paternity, disease carrier status, etc. Sharing such confidential information may at times induce family disputes. Family members' information should be kept confidential from each other by the investigator if they have undergone genetic tests. If the clinician/investigator thinks that disclosure of the genetic test is absolutely warranted to provide treatment or counseling, he/she should first try to take informed consent from the family members, as otherwise, the risks of non-disclosure against breach of confidentiality need 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 subsequent progeny. It may cause marital conflict once such information is revealed to the husband or other family members, even though the husband himself is a carrier of the autosomal recessive disorder. Thus, suitable counseling must be an integral part of the genetic testing process.
8. **Genetic information** has the potential for misuse. E.g. prenatal sex determination is banned by the law to restrict the pre-selection of fetal gender. All investigators shall

follow the provisions of the country's relevant guidelines, directives, regulations, and laws.

9. Knowledge of **genetic information** of an individual/family/community/ population/child might be misused by employers/insurers, leading to psychosocial harm and discrimination. Therefore, participants' information should not be shared with anyone without obtaining their consent.
10. For **future genetic research**, collected bio-samples can be stored for a more extended 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 upon approval of the same by the ERB.
11. If the investigators discover a new gene or product during the research, which could be patented, they should follow country law/regulations and the proposed mechanism in the approved proposal.
12. Steps must be taken to safeguard investigators and research participants from possible inducement or coercion when commercial companies sponsor the study.
13. The laboratories performing genetic testing should follow standard protocols and should have a legal standing through registration.
14. Extra efforts should be ensured to maintain privacy, and confidentiality of the genomic data, in addition to the anonymization of the personnel identity.

7.14 Molecular Testing on Biological and Environmental Samples related to Human Health:

Molecular studies on micro-organisms from biological samples (body tissues, biopsy materials, body fluids, etc.) related to human health are included in molecular diagnosis and genomic research. This also includes biomarkers testing in human tissues.

Investigators should obtain informed consent from the prospective participants while collecting the specimens, fulfilling standard ICD requirements for further analysis using genetic tools.

When the anonymized specimens/ isolates/tissues are obtained from a repository/ hospital, without any direct/indirect linkage with the participant identification (mostly retrospective assessment specimens), there is no need to obtain individual ICD; however, hospital/repository approval for using such specimens needs to be obtained before processing any specimens for study.

7.15 Research in Humanitarian Emergencies and Disasters Situations

Heath research might be necessary for humanitarian emergencies and disaster situations to collect, analyze and recommend scientific evidence-based health responses in a timely manner. In such circumstances, utmost care must be taken not only to protect/minimize harm to vulnerable participants but also during ethical review processes. Designing health research in such a situation is becoming a challenge. Ethical uncertainties are rapidly evolving and the role of ERB is very critical for fast-tracking/expediting the review process while ensuring that the

research protects the vulnerable participants and abides by the ethical norms and standards. ERB must determine who could be an acceptable LAR in the absence of the intended LAR. Participants' decision-making capacity might be so low (they might be under traumatized conditions) that they are unable to figure out the difference between benefits in the forms of relief offered Vs. autonomy, justice, and non-maleficence as participants of the research. Researchers must explain this while taking informed consent and provide additional protections (counseling, psychological help, medical advice, etc.) to research participants because of their vulnerability. For children with untraceable or deceased relatives, consent must be obtained from an individual from the same community who could represent the parents and is not a part of the study team. Suppose investigators may need to waive the consent or get the consent from the participants at a later stage when the community comes out of the panic stage or the situation allows. In that case, he/she must have to provide its justification and obtain prior approval from ERB for obtaining gatekeeper consent and individual consent at a later stage. Roles of investigators, volunteer workers, and caregivers should be clarified, and potential CoI must be declared if any.

Investigators should consider a fair selection of participants. There should not be over-sampling, especially from vulnerable segments of the population. Participant selection criteria with proper justification must be provided in the proposal. The inflow of visitors/members of media during emergencies may at times lead to a breach of privacy and confidentiality. So, researchers must put extra effort into protecting participants' personal data or identifiers. 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.

7.16 Stem Cell Research for Health

Research on stem cells provides a novel treatment for some incurable diseases. With appropriate approvals from ERB, stem cell research is permissible in embryonic, adult, and cord blood areas as clinical trials except in the area of reproductive cloning. A clinical trial should follow all the requirements as mentioned in ICH/GCP and the Clinical Trial section in the guideline. It should be conducted with clinical-grade cells processed by GCLP, GMP, and GCP. The investigator should keep himself/herself updated in accordance with the changes in guidelines regarding the use of these cells.

7.17 Use of Animals in Research for Health

Animals are being used for health research, and these animals feel and experience the same emotions as humans do. Therefore, inflicting redundant suffering or harm on animals by abusing and mistreating them during their involvement in health research should be avoided. The use of animals for research in medicine is in gradual decline, and efforts are being made to replace animal experiments with other laboratory experiments. However, in case of an absolute need, the use of animals in health research could be approved by NHRC/ERB provided that the researcher complies with 'Ethical Guidelines for the Use of Animals in

Health Research in Nepal- 2005'.

The fundamental principles in animal experimentation for health research:

1. No animals should be used in human health research until written ethical approval is obtained.
2. Ensure that the number, type, species, etc., of animals selected for the health research, are appropriate and justified.
3. When designing the research protocol, the number of animals used should reflect the minimum necessary to yield valid answers to the research hypothesis.
4. Ensure that the animals used for the health research are not purchased from illegal sources.
5. Ensure that the researchers involved in the use of animals in health research are qualified, responsible, and respectful of animals' worth and rights.
6. Ensure that the use of animals in health research is justified.
7. 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.
8. Necessary steps should be taken to ensure that the animals used in health research are well sheltered (with the provision of food, water, etc.) and protected (from abuse, cruelty, exposure to contamination, etc.);
9. Proper care should be taken to minimize animals' discomfort, distress, and pain;
10. Before using animals for research purposes, a detailed proposal illustrating the research plan, design, and procedures should be submitted to the concerned authority. The researcher should also be clear as to why the use of animals in the research is indispensable.
11. Upon completing research involving animals (that cannot be rehabilitated or returned back to their natural habitat), the researcher is obliged to euthanize animals. The decision to not euthanize animals should be backed by valid scientific reasons. If the researcher decides not to kill animals, it is the researcher's responsibility to take care of the experimental animals.
12. Use of wild/endangered/threatened animals is generally restricted. However, for research of essential value, the use of such restricted animals must abide by the law and policies for wildlife conservation. Wild animals for experimentation shall be acquired under the National Parks and Wildlife Conservation Act 2029 BS (1977 AD) (3) and the Wildlife Farming, Breeding and Research Policy 2059 BS (2002 AD), Convention on International Trade in Endangered Species of Wild Flora & Fauna, Animal Health and Livestock Service Act 2055 BS (1999 AD) (4) and rules 2057 BS (2001 AD) (5).
13. Experimental animals should be housed safely in adequate spaces with the appropriate temperature, ventilation, and stress-free housing, without exposure to extreme environments. Transfer delivery boxes should be strong and well secured to avoid escape.
14. The researcher should be adequately qualified, and have knowledge of the behavioral characteristics of the animal subjects to be aware of normal, species-specific behaviors and unusual behaviors that could forewarn the researcher of potential health problems.

15. Animals used in health research should be housed in a separate location away from public housing. In addition, animals involved in research should not be exposed to dust, smoke, noise, rodents, insects, and birds. In order to avoid infection and stress, animal facilities must be equipped with systems that can control infection, temperature, humidity, ventilation, lighting, and sound to suit the needs of each species.
16. Animal facilities should be developed and maintained following nationally approved standards, particularly in terms of maintaining biosafety and biosecurity.
17. Since experimental animals are at high risk of being exposed to pathogens and/or hazardous agents, the researcher needs to adopt safety measures in line with biosafety and biosecurity guidelines to reduce the risk of spreading animal-related diseases/infections.
18. Procedures subjecting animals to pain, stress, misery or death should be used only when an acceptable alternative procedure is unavailable.
19. Ensure that the animals involved in research are taken good care of, have a well-managed house, and is not subject to cruelty. safe
20. Animal housing should be managed in such a way that it reflects the effective involvement/supervision/accountability of a qualified and trained veterinarian.
21. Animals should be fed palatable, non-contaminated, and nutritionally adequate food daily or according to their requirements unless the protocol in which they are being used requires otherwise.
22. Cages for animals should be made of suitable material and size. Cages should also have adequate space to avoid any injury to animals. Since bedding can affect animals' well-being as well as the research outcomes, the researcher should provide clean and comfortable bedding for the animals involved in the research. For comfortable bedding, the researcher (in consultation with the veterinarian) should select bedding materials suitable for animals.
23. 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.
24. Same experimental animals should not be used in more than one study, either in the same or different projects, without the approval of the ERB.
25. Animals cannot be subjected to successive surgical procedures unless 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 from the ERB, NHRC.
26. Releasing captivated animals back to their natural habitat can pose substantial risks both to the captivated animals and other animals in the wild. Animals that are not suitable for rehabilitation must be euthanized upon the completion of the research. However, the selection and use of methods of euthanasia on animals should ensure less suffering and immediate death. Death should be confirmed by the person who can recognize and

certify the cessation of vital signs in the species. A registered veterinarian should closely monitor the method of euthanasia.

27. It is important for the investigators to maintain records of the animals in research. These records should include the type of species, birth profile, sex, identifier, behavior profile, etc. Animals' records should also be kept simple and comprehensive. All animals used in health research must regularly be monitored and have updated records.
28. The NHRC may form a committee responsible for monitoring the ethical use of animals in research, testing, and production of biological materials in line with the Ethical Guidelines for the Care and Use of Animals in Health Research in Nepal-2005.

Section 8. Establishment of the Institutional Review Committees

8.1 Establishment and Functions of Institutional Review Committees (IRC)

The ERB, NHRC cannot possibly review and monitor all research conducted in the country. So, NHRC has been supporting the establishment of the IRCs at different health facilities and academic institutions. An IRC is a committee established within an institution for ethical review of proposals with less than minimal and minimal risk submitted by students, faculties, staff, etc. The purpose of IRC is to function as an ethics committee as its actions primarily contribute toward ensuring the protection of rights, safety, and well-being of human participants in the research.

IRC gets its official recognition from NHRC. Hence, it is vital for IRC to take accreditation from NHRC immediately after its formation. IRC's job is to ensure that research proposals are ethical and within the Guidelines for IRCs for Health Research in Nepal. Given the nature of its work, IRC should be multidisciplinary and independent, autonomous to maintain ethical and scientific standards. Institutions that IRC represents should have a research department/section, appropriate physical infrastructures, and administrative and financial provisions/arrangements for IRC to function independently. Besides working independently, IRC should operate transparently based on the SOP without any interference. The SOP should be developed for IRC's effective functioning. Any institution that undertakes at least 10 health-related research in a year is eligible to establish an IRC. The members should be given an initial orientation and periodic refresher training on basic principles of research ethics and the IRC's proposal review and approval process.

While selecting the members of IRC, the institute may follow a similar procedure as for ERB, which includes 7-15 members with a balance in gender and discipline (clinical, bio-medical, legal, social sector, etc), affiliated and non-affiliated. An individual shall serve up to two Ethics Committee at a time. The administrative chief and Executive Committee members of the same institution should not be a member of IRC, to minimize potential CoI. IRC should display the organogram of the institution and its working procedure. IRC should inform ERB of any changes in IRC composition and SOP and submit annual progress reports to NHRC.

8.1.1 Renewal of Institutional Review Committees

IRC should be renewed every 3 years. IRC should apply to NHRC at least one month before the expiry of the approval timeline, along with the required documents and processing fee as per the NHRC rules. If not renewed in time, registration will be terminated after 6 months of the renewal deadline.

8.1.2 Withdrawal of Institutional Review Committees

Non-compliance with the 'Guidelines for Institutional Review Committees for Health Research in Nepal, 2016', unjustified approval of research projects against national and

international laws/guidelines of research ethics, non-renewal, and inability to conduct at least 10 research studies in a year may result in the withdrawal of IRC.

8.2 Networking and Regulation of Institutional Review Committees

Nepal Health Research Council (NHRC) has established IRC Accreditation Sub-committee, with a mandate to monitor and evaluate IRC's activities. NHRC organizes IRC/ERB network meetings at least once a year to review IRC's performance and keep abreast of national/international guidelines and SOPs (related to IRC) changes. The performance of IRCs will be evaluated annually based on the annual reports, while physical site visits of the IRCs will be done frequently. In order to strengthen the capacity of IRC, ERB should organize training/workshops on ethical principles, risk categorization, GCP guidelines, proposal review, monitoring the implementation of the research, and reporting procedure to ERB.

Research proposals reviewed and approved by the ERB do not require further review, approval, and ethical review processing fee by any IRCs. However, researchers should obtain the acceptance letter from the institution or IRCs for multi-centric studies and submit it to the ERB. ERB also organizes joint review and monitoring visits.
The guidelines are as follows:

Do's

- Proposal having less than minimal and minimal risk that are self-funded by the institute's students, faculty, and staff and/or national funding up to two lakhs
- Thesis submitted by the students from the any university of Nepal (i.e., bachelor and masters)
- Single centered study submitted by another institute faculty with less than minimal and minimal risk, if there is an academic collaboration.

Don'ts

- Research proposals in a high-risk category (trial using drugs, vaccination, an invasive procedure involving humans)
- Externally sponsored/funded multi-centric studies at the national and international level (the term "externally indicates sponsored from outside and within the country in case of more two lakhs")

Note: Please refer to Institutional Review Committee Guidelines for Health Research in Nepal-2016 for further details on IRC.

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Glossary

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

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

Assent: To agree or approve after thoughtful consideration of an idea or suggestion in order to participate in research by children (above7 years and under18 years), who is old enough to understand the implications of any proposed research but are not legally eligible to give consent. The assent has to be corroborated with the informed consent of the parent/LAR.

Audit: A systematic and independent examination of research activities and documents in order to determine whether the review and approval activities were conducted, and, 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 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 institutions for research and related activities in the future.

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 needs to be compared in vivo for biological equivalence.

Capacity: The capacity of the vulnerable population may be reduced because of their personal disability, lack of understanding or ability to communicate, lack of power, social injustice, environmental burdens and/or situation that prevents the vulnerable population to work in the best of their interests.

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, to be reported 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, and/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 not disclose any personal or confidential information of the research participant to protect their rights, safety, dignity and well-being. Hence, maintaining confidentiality incorporates the requirement to safeguard information from unauthorized access, use, disclosure, alteration, damage or stealing.

Conflict of Interest: Conflict of interest is a set of conditions in which professional judgment concerning a primary interest like a patient's welfare or the validity of research tends to be or appears to be unduly influenced by a secondary interest like non-financial (personal, academic or political) or financial gain.

Contract Research Organization: An institution or service organization that is generally recruited by the sponsor for providing research support/services (especially vaccine trials)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 the start of the research to its completion.

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 the participants in order to manipulate them into consenting. Deception is sometimes committed to achieving the study objectives and for the larger public good. Research employing any type of deception should however 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, and/or 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 influenced by people involved in the trial, who attends the informed consent process if the participant 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 participant's willingness to voluntarily participate in 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 of anything (including language, thoughts, ideas, or expressions) from someone's published paper/book, etc., and representing these as one's own original work. Sometimes 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 the 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 the 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 anxiety (warranted or unwarranted), distress or depression, embarrassment, shame or guilt and/or, 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 ensuring the participant's willingness to remain in the study by re-obtaining and documenting his/her consent.

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 the performance of a specific function.

Serious Adverse Event: It is a serious adverse event when the research outcome for the participant is death, a 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, and/or government or non-governmental organization (within or outside the country), who initiate the research and are also 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 the actions being 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, and/or, are in a situation that prevents them to act in best of their interests.

Annex I: Sample Transfer Plan

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

Annex II: Basic requirements and list of documents required for applying online proposal submission

Screening: Research related to health, national or international researcher and thesis or self-funded study.
Administrative information: ● 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; ● Photos of PI and Co-Investigator and other team members in jpg format; and ● Scanned signature of PI and Co-Investigator and other team members in jpg format.
Financial Details: 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 review cost, and 'total budget of health research to be spent in Nepal.'
Technical Details: 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
Ethical Consideration: Number of human participants to be involved, frequency, responsibility, vulnerability, risks and benefits, types of informed consent, etc.
Documentation: ● Documents: Data collection tools, conceptual framework, consent form, agreement letter, work plan, donor agreement letter (if any), etc. ● Data collection tools should be in Nepali and local language (if necessary) including interviews and Focused Group Discussion guideline, observation checklist, and questionnaire sets. ● A copy of the informed consent/assent form in Nepali and the local language (if required) should be included in the application. This should include a detailed description of the process of giving the information to the research participants and its content, the process of obtaining the consent, the person responsible for obtaining the 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 with date and version number.

● 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. ● If the PI is a non-Nepali citizen, one additional PI should be a Nepali citizen relevant to the study subject. Nepalese PI should be responsible for all the activities to be done in Nepal. S/he is also responsible for 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 (stating that 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). Or else, 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, labeling, supply, its storage, etc.); ● Investigational 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; ● Results of the previously conducted clinical trial (authentic reports); ● Signed final copy of the previously conducted clinical trial documents; ● '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; ● Clinical Trail Registration (CTR) number; ● Original Protocol (which was submitted to sponsor) ; ● Details of Contract Research Organization (CRO) (required if it is a clinical trial proposal); ● Other center's ethical approval letter or support letter;

- List of abbreviations /acronyms; and
- References.

For student applicants:

- Approval Letter from concerned Institute/University, mentioning PI, Co-I, collaboration and funding provision of the study;
- Recommendation letter from academic supervisor stating that the student is working under his/her supervision; and
- In case of foreign student working for academic thesis in Nepal, the local Nepali supervisor should be the co-investigator.

Ethical review processing fee:

Ethical review processing fee will be as per the NHRC rules and regulations as described in SOP which can be deposited at NHRC office or designated bank account.

Annex III:
List of participants in Residential Workshop on Revision and Updating National Ethical Guideline for Health Research in Nepal (Dhulikhel, Kavre on 30-31 July 2021)

Prof. Dr. Gehanath Baral, Chairperson, NHRC
Dr. Pradip Gyanwali, Member Secretary, NHRC
Prof. Dr. Prakash Ghimire, Chair, ERB, NHRC
Prof. Dr. Sabina Shrestha, Member, ERB, NHRC
Prof. Dr. Dharmendra Kumar Karn, Member, ERB, NHRC
Prof. Dr. Sudha Basnet, Member, ERB, NHRC
Prof. Dr. Dinesh Kumar Lamsal, Member, ERB, NHRC
Prof. Dr. Nisha Jha, Member, ERB, NHRC
Dr. Amit Bhandari, Member, ERB, NHRC
Prof. Dr. Rajeev Shrestha, Member, ERB, NHRC
Mr. Paban Ghimire, Member, ERB, NHRC
Mr. Narayan Prasad, Member, ERB, NHRC
Dr. Meghnath Dhimal, Chief, Research Section, NHRC
Mr. Bijay Kumar Jha (Training Officer, NHRC)
Ms. Namita Ghimire, Research Officer, Ethical Review M&E Section, NHRC
Prof. Dr. Mohan Raj Sharma (Institute of Medicine, Maharajgunj, Kathmandu)
Prof. Dr. Sunil Kumar Joshi (Chair, IRC, Kathmandu Medical College and Teaching Hospital, Sinamangal, Kathmandu)
Dr. Hari Prasad Dhakal (Chair, IRC, Nepal Cancer Hospital and Research Centre, Harrisidhi, Lalitpur)
Prof. Dr. Deepak Shrestha (Chair, IRC, Kathmandu University School of Medical Sciences, Dhulikhel, Kavre)
Prof. Dr. Jeevan Bahadur Sherchand (Former Chairperson, ERB, NHRC)
Dr. Rajendra Kumar BC (Expert, NHRC)
Prof. Dr. Reetu Sharma Baral
Mr. Shashi Verma, Research Officer, Ethical Review, M & E Section, NHRC
Ms. Richa Acharya, Research Officer, Ethical Review, M & E Section, NHRC
Ms. Rojina Basnet, Research Officer, Ethical Review, M & E Section, NHRC
Ms. Santoshi Adhikari, Research Officer, Ethical Review, M & E Section, NHRC
Dr. Subhanshi Sharma, Research Officer, Ethical Review, M & E Section, NHRC
Mr. Subodh Kumar Karn, Account Chief, NHRC
Mr. Sudip Gyanwali, Administrative Officer, NHRC
Ms. Kamala Luitel, Store Assistant, NHRC
Mr. Pukka Lal Ghising, Assistant Account Officer, NHRC
Mr. Subash Ghising, Office Assistant, NHRC, NHRC

List of participants in National Consultation Workshop for National Ethical Guideline Finalization, (NHRC, Kathmandu, 24-26 September 2019)

Prof. Dr. Prakash Ghimire (Chair, ERB, NHRC)
Prof. Dr. Sabina Shrestha (Member, ERB, NHRC)
Prof. Dr. Dharmendra Karna (Member, ERB, NHRC)
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. Shashi Verma (Research Officer, Ethical Review, M & E Section, NHRC)
Dr. Hari Prasad Dhakal (IRC Chair, Nepal Cancer Hospital,)
Prof. Dr. Sunil Kumar Joshi (Chair, IRC, Kathmandu Medical College and Teaching Hospital, Sinamangal, Kathmandu)
Prof. Dr. Ramesh Kant Adhikari (Former Chair, ERB, NHRC)
Prof. Dr. Kedar Prasad Baral (Former Member, ERB)
Ms. Namita Ghimire (Research Officer, Ethical Review, M & E Section, NHRC
Dr. Subhanshi Sharma (Research Officer, Ethical Review, M & E Section, NHRC)
Mr. Shashi Verma (Research Officer, Ethical Review, M & E Section, NHRC)
Ms. Santoshi Adikari (Research Officer, Ethical Review, M & E Section, NHRC)
Ms. Richa Acharya (Research Officer, Ethical Review, M & E Section, NHRC)
Ms. Rojina Basnet (Research Officer, Ethical Review, M & E Section, NHRC)
Mr. Pukalal Ghising (Assistant Account Officer, NHRC)
Mr. Subash Ghising (Admin. Assistant, NHRC)

List of participants in Residential Workshop on Revision and Updating National Ethical Guideline for Health Research in Nepal (Balthali, Panauti, Kavre on 16-17 November 2019)

Prof. Dr. Anjani Kumar Jha (Executive Chairman, NHRC)
Prof. Dr. Prakash Ghimire (ERB Chairperson, NHRC)
Dr. Sandhya Chapagain Acharya (Executive Board Member, NHRC)
Prof. Dr. Ramesh Singh Bhandari (Member, ERB, NHRC)
Prof. Chitra Kumar Gurung, (Member, ERB, NHRC)
Prof. Dr. Sabina Shrestha , (Member, ERB, NHRC)
Mr. Harihar Dahal (Member, ERB, NHRC)
Dr. Satish Kumar Deo (Member, ERB, NHRC)
Mr. Bimalesh Thakur (Member, ERB, NHRC)
Mr. Paban Ghimire (Member, ERB, NHRC)
Dr. Nisha Jha (Member, ERB, NHRC)
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Prof. Dr. Ramesh Kant Adhikari (Former Chair, ERB, NHRC)
Prof. Dr. Jeevan Bahadur Sherchand (Former Chair, ERB, NHRC)

Prof. Dr. Mohan Raj Sharma (Chair, IRC, IOM, Maharajgunj, Kathmandu)

Ms. Nanimaya Kaway (member, IRC Paropkar Maternity and Women Hospital)

Ms. Pratima Manandhar (Member Secretary, IRC Scheer Memorial Hospital Medical Institute College of Nursing)

Dr. Julia Chitrakar (Member, IRC Tilganga Institute of Opthalmology)

Prof. Ramjee Prasad Pathak (Chair, IRC, Nobel College)

Prof. Dr. Shiba Bahadur Karkee (Chair, IRC, Central Institute of Science and Technology)

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Ms. Namra Kumar Mahato (Research Officer, Ethical Review, M & E Section, NHRC)

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Mr. Anil Kumar Shah (Research Officer, Ethical Review, M & E Section, NHRC)

List of participants contributed in finalization of national Ethical Guideline for Health Research in Nepal

Prof. Dr. Aarati Shah (Former Chair, ERB, NHRC)

Prof. Chandra Kala Sharma (Ex-ERB Member)

Prof. Dr. Kedar Prasad Baral (Ex-ERB Member)

Prof. Dr. Anil Kumar Jha (Ex-ERB Member)

Dr. Yogesh Neupane (Ex-Executive Board Member)

Dr. Bhola Ram Shrestha (Ex-Executive Board Member)

Dr. Shyam Kumar BK (Ex-Executive Board Member)

Dr. Ramesh Kharel (Ex-Executive Board Member)