

HEALTH RESEARCH ETHICS TRAINING MANUAL

2015



Nepal Health Research Council (NHRC)

Ramshah Path, Kathmandu, Nepal

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Research ethics provide guidelines for the responsible conduct of research ensuring that the ethical considerations are aligned with the fundamental principles: respect, beneficence and justice. It is crucial for researchers to be familiar with the basic ethical aspects of research in Nepal. Thus, development of such manual is of great significance and Nepal Health Research Council (NHRC) now owns a first Research Ethics Training manual.

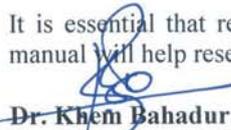
This training manual has been developed with the objective to orient health researchers and reviewers on fundamentals of research ethics, issues encountered while conducting health research and responsibilities of Research Ethics Committees/Boards, including sponsors/donors and researchers. It is based on the principles of National Ethical Guidelines for Health Research in Nepal, 2011 and other international research ethics training curriculums. It provides a basic level of training appropriate for health researchers and in general includes:

- An overview of ethical principles to be considered in research involving human participants
- Community participation in research process
- Responsibilities of Institutional Review Board

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It is essential that researchers familiarize themselves with the subject matter in this manual and I hope this manual will help researchers to follow processes to protect rights of the research participants.


Dr. Khem Bahadur Karki
Member-Secretary
Nepal Health Research Council

Abbreviations

ARI	Acute Respiratory Infection
CBO	Community-Based Organization
CIOMS	Council for International Organizations of Medical Sciences
CSWs	Clients of Sex Workers
DSMB	Data Safety Monitoring Board
ELISA	Enzyme Linked Immuno-Sorbent Assay
ERB	Ethical Review Board
FDA	Food and Drug Administration
FHI	Family Health International
FSWs	Female Sex Workers
GCP	Good Clinical Practice
GCLP	Good Clinical Laboratory Practice
GMP	Good Manufacturing Practice
GoN	Government of Nepal
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IRC	Institutional Review Committee
IWF	International Women's Forum
KABP	Knowledge, Attitude, Belief and Practice
MoHP	Ministry of Health and Population
MSM	Men who have Sex with Men
NCASC	National Centre for AIDS and STD Control
NGO	Non-Governmental Organization
NHRC	Nepal Health Research Council
PI	Principal Investigator
PLHIV	People Living with HIV
PWIDs	People Who Inject Drugs
SOP	Standard Operating Procedure
SSP	Saath-Saath Project
STD	Sexually Transmitted Diseases
STI	Sexually Transmitted Infection
USAID	United States Agency for International Development
VDC	Village Development Committees
WMA	World Medical Association

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1. Introduction

1.1 Background

The Nepal Health Research Council (NHRC), was established in 1991 by the Government of Nepal (GoN) through an Act of Parliament, is an autonomous apex body. The NHRC aims to promote the quality and ethical standard of health and medical research in the country and provides ethical approval for research in Nepal. Since the establishment of the NHRC, it has facilitated the ethical review committee and has approved 1212 health research proposals in between 1991 to 2014.

The NHRC has focused on research-capacity strengthening through training of individual researchers on research ethics as part of its regular health research methodology training workshops. This has helped to orient researchers on ethical principles and practices. The NHRC has also organizes training workshops on research ethics, and this has led to enhance skills on research ethics. Although the NHRC provides training workshops on research ethics, it does not have its own research ethics manual, which systematically guides health researchers to go for in-depth understanding on the research ethics process. This underscores the need to develop such a training manual and make it widely available to researchers and research proposal reviewers in Nepal.

Any research involving human beings needs to be scientifically valid and robust and should be conducted according to accepted ethical standards. If either condition is not met, the research should be called into question. Ethics and science go hand in hand. Research is ethically acceptable only if it relies on valid scientific methods. Research that is not scientifically valid exposes research participants or their communities to risks of harm without any possibility of benefit. In an ethically acceptable research, risks are minimized (both by preventing potential harms and minimizing their negative impacts) and are reasonable in relation to the potential benefits of the study. The nature of the risks and benefits may differ according to the type of research to be conducted.

Research ethics provides guidelines for responsible conduct of research on human beings. It educates

and monitors scientists/researchers conducting health research to ensure a high quality of ethical standard. Knowledge of ethical research is important for all people who conduct health and related research projects or use and apply the results from research findings. It is now widely accepted that all health researchers should be familiar with the basic ethical principles and have up-to-date knowledge about policies and procedures designed to ensure the rights, safety and wellbeing of research participants.

Internationally accepted standards for research ethics help ensure that research conducted at the local level meets international norms. It is important to consider ethics in international as well as local context, especially any study involving vulnerable populations. As such, information on research ethics should provide an overview of the main ethical principles to be considered in the development and conduct of research involving human beings. It should also provide guidance to assist researchers in designing studies that respect local cultures, adhere to regulations, and meet expectations, use case studies for considering real-world examples of ethical issues and ancillary reference documents on modern perspectives that shape the research ethics field.

This training manual is developed based on internationally recognized research ethics training curricula with an aim to help and inform health and related researchers on ethical aspects of the research process in Nepal.

1.2 Importance of Ethics in Research

Ethically acceptable research ensures that no particular group or class of persons bears more than its fair share of the burdens of participation in research. Similarly, no group should be deprived of its fair share of the benefits of research; these benefits include the direct benefits of participation (if any) as well as the new knowledge that the research is designed to yield. In addition, ethically acceptable research is based on a scientifically sound research question/hypothesis and the research conducted according to accepted research standards. When research ethics is followed,

it ensures the protection of rights and safety of the research participants.

1.3 Goal and Objectives

Goal

To impart knowledge and skills on health research ethics for researchers and reviewers.

Objectives

- To orient and equip health researchers and reviewers on the fundamentals of research ethics during the research process,
- To provide practical knowledge on ethical principles and issues encountered while conducting health research in different settings, and
- To enhance the knowledge of researchers and reviewers on various responsibilities of research ethics committees/boards, including sponsors/donors and researchers him/herself.

1.4 Guidelines for Use of Training Modules

This training manual as the facilitation guide for research ethics is targeted particularly to health researchers and proposal reviewers. This manual is designed for an interactive, and participatory group training but can also be used for self-study. This manual has 10 modules which is to be completed within 4 days of training.

Day 1 sessions contain introduction and development of research ethics, review process of ethical aspects of the research proposal, guiding principles for health research involving human beings, international declarations and guidelines.

Day 2 will mostly highlight importance and process of informed consent, its components and examples of case studies on its application.

Day 3 will include sessions on responsibilities of institutional review board, recruitment, care and protection of research participants.

Day 4 sessions will highlight responsibilities of sponsors and researchers. Inducement and compensation are also included.

Guidelines for Initiating the Module

This manual is designed to instruct and guide those who are seeking to improve their knowledge on

research ethics and the specific ethical review process in Nepal. The facilitator should be thoroughly familiar with the content of each module to support those receiving the training. By reviewing these materials, the facilitator will be in a better position to facilitate the training and ensuring a good learning experience for the trainees.

Guidelines for Facilitating Skills and Roles

In most training workshops, the facilitator is the determining factor for the success of the training. It is essential to consider how a facilitator should prepare and the attitude he/she must adopt during the entire training period.

The facilitator should carefully study the training schedule and its contents. He/she should be a good listener, encourage everyone to give her/his opinion, emphasize the knowledge that participants possess, strive to empower the participants, respect time-frame, deal with difficult participants without breaking the group dynamics, respect all participants equally, manage to turn criticism into constructive ideas, and able to synthesize and wrap up.

The facilitator's role is to guide the participants through the learning process on the types of skills they need by moderating discussions, dealing with group dynamics, controlling the class, mastering questioning techniques, and along with good listening skills through appropriate approaches encouraging participation and exchange of opinions and ideas. The facilitator is urged to follow the suggested module plan in this manual and highlight key messages, which helps the participants to understand and follow the information as well as retain it for later reference.

Guidelines for Participatory Approach

The participatory approach aims at achieving a behavioural change and building on participants' experience. Using this approach, the facilitator conveys the needed information while at the same time encouraging the participation of everyone and respecting their opinions in a non-judgmental way. Through questions and answers and sharing of experiences, the participants will better synthesize and internalize the knowledge. Use of cards, markers, newsprints, soft-boards and pin-boards are very useful materials while adopting this participatory approach during training workshops.

Participatory methods such as group work, group discussion and case study are used in this manual.

Group work refers to the division of participants into smaller groups using specific criteria for specific tasks. An optimum group consists of five to eight people.

Group discussion enables participants to think about and then express their opinions on an issue. Listening to others may broaden or change their opinions and eventually help them to clarify their ideas, attitudes, values and behaviour. In some cases, debating issues helps individuals to face conflicts and to reach a consensus. In group discussion, you need to ensure that everyone gets a chance to speak and feels that he/she is able to contribute to the group discussion. It is useful to elect one member to report on the main points of the discussion to the whole group (rapporteur) and perhaps a second person to facilitate the discussion.

Case study refers to a real or imaginary account meant to illustrate certain facts and lead to certain lessons. Cases can be in the form of oral narratives, written materials, pictorials or audio-visuals. When using these, the facilitator should study and understand them thoroughly, design objectives for using them and tasks for participants, allow participants enough time to understand them, guide the plenary discussion and summarize conclusions.

Notes:

Icebreakers are short games short meant to create an informal atmosphere and make participants feel comfortable with one another. They must be interactive and ensure that participants interact with one another. This is particularly important and helpful when participants have not met each other before.

Energizers are also games used during sessions to break monotony and ensure attentiveness among participants.

Class Exercises are exercises conducted within the class without forming any groups.

Group Exercises are exercises conducted in a group. The ideal size of a group comprised of people with varied backgrounds to allow active participation is generally five to eight.

1.5 Course Structure of the Training and its Schedule

This research ethics training curricula is structured to be conducted over four days.

Course Structure

The training workshop consists of 10 modules:

Day One

Module 1: Course Orientation

- Introduction of participants and facilitators
- Description of the course
- Administrative issues

Module 2: General Introduction to Research Ethics

- Meaning of research ethics, its definition and rationale
- Historical perspective of research ethics (from global to national)
- Guiding principles for health research involving human beings

Module 3: The Development of Contemporary Research Ethics

- International declarations, guidelines and other related documents on research with human beings
- National Ethical Guidelines of Nepal

Day Two

Module 4: Informed Consent-I

- Meaning of Informed Consent, its definition and rationale
- Essential elements of Informed Consent
- Types of consent

Module 5: Informed Consent-II

- Consent from vulnerable people
- Privacy and confidentiality
- Documentation process of consent and re-consent

Day Three

Module 6: Responsibilities of Institutional Review Committees/Boards-I

- Protection of rights of research participants
- Safety of research participants and quality of data
- Competent review of protocol

Module 7: Responsibilities of Institutional Review Committees/Boards-II

- Recruitment of research participants
- Care and protection of research participants
- Reviewing Informed Consent

Module 8: Responsibilities of Institutional Review Committees/Boards–III

- a. Procedure of review
- b. Review of safety data and protocol violation
- c. Documentation process of review

Day Four**Module 9: Responsibilities of Sponsors and Researchers**

- a. Responsibilities of sponsors/funding agencies
- b. Responsibilities of researchers
- c. Community/health facility participation in the research process

Module 10: Inducement/Compensation and Social Risks

- a. Meaning of inducement and compensation and its rationale
- b. Meaning of social risk and its rationale

Training Schedule Framework**1.6 Users of this manual**

All health researchers and research proposal reviewers and facilitators who would like to conduct training in the field of research ethics should use this manual.

1.7 Target Group for Training

The target group for training is health researchers and research proposal reviewers.

2. MODULES

2.1 Module 1 Course Orientation

Learning Objectives:

By the end of the session, the participants will be able to:

- Be acquainted with each other, including their training facilitators,
- Accept the training goal, objectives, its modality and various modules to be adopted during the training, and
- Become familiar about the administrative aspects of the training workshop.

Time Frame: 90 minutes

Materials: Copies of Training Schedules and Modules, Pre-test Questionnaires, Computer, Audiovisual Equipments with LCD Projector and Screen, Flip Chart, Board Markers, Name Tag holders for Participants and Training Facilitators.

Teaching Methods/Process: Lecture, Assessment/Presentation, Discussion and Brainstorming.

Course Contents:

- Introduction of participants and facilitators
- Description of the course
- Administrative issues

2.1.1 Introduction of Participants and Facilitators (Time: 60 minutes)

The opening session is started with welcoming the participants, giving remarks, and deliberation of training goals and objectives. The training facilitator asks all the participants that they need to pair up and introduce each other. It is essential to ask all the participants to spend 2 to 3 minutes with each other in order to note his/her name (including their nick name), place of origin, place of current work, their professional experience, occupation/profession, likes/dislikes, hobbies, previous research ethics-related experiences, and their expectation from the training.

The training facilitator asks each partner in the pair to introduce each other to the rest of the class following the guideline mentioned above. After the introduction,

names and affiliated institution can be written on a name badge or card and clearly displayed. The introduction should not take more than 45 minutes.

The training facilitator needs to comment on the expectations shared to confirm what will be covered (or not) during the workshop.

The training facilitator needs to establish “group norms”.

- Brainstorm what should be the guiding principles for the group and only put down what the group has agreed upon and participants commit to respect.
- Guide participants in setting the ground rules/training norms and ask participants to respect that the content of the training and the experiences of each participant are: confidential to the group, without reference to the work hierarchy, to be based on an attitude of mutual support, and disciplined but informal (using first names only, not professional titles or caste).
- Explain that the key points emerging from each day will be summarized the following morning and that the contents of each day sessions will be presented so the participants know what to expect.

2.1.2 Description of the Course (Time: 25 minutes)

The training facilitator presents the overall goal and major objectives of the training workshop and the format of the training. It should be clear to all the participants that they will each work as part of a small group on the case studies.

The training facilitator should emphasize the uniqueness of each participant’s background and experience, pointing out how important it will be for everyone to contribute their experiences about research ethics and ethical review process.

The training facilitator should distribute the training modules to all the participants and describe how the

module is structured and will be used. After this, the training facilitator should explain briefly about the 10 modules used in the training manual:

There are 10 modules for the entire period of the training workshop. There will be three modules in day one, starting with the course orientation, followed by the second module which will explain about the general introduction to research ethics (meaning of research ethics and its definition, rationale, historical perspective of research ethics [from global to national], and guiding principles for health research involving human participants).

The third module will cover the development of contemporary research ethics, wherein international declarations and guidelines on research with human participants, and national ethical guidelines will be presented.

Similarly, two modules will be covered in day two, with lots of emphasis given on informed consent and its related issues. The meaning of informed consent, its definition and rationale, essential elements of informed consent, types of consent and their examples along with case studies, consent from vulnerable people, privacy and confidentiality, documentation process of consent and re-consent will be discussed.

There will be three modules during day three, and all of these modules will focus on the responsibilities of research ethics committees/boards, including protection of the rights of research participants, safety and quality, competent review of protocol, recruitment of research participants, care and protection of research participants, reviewing informed consent, procedure of review, review of safety data and protocol violation, and the documentation process of review will be explained.

Day four is the last day of the training workshop. There will be two modules, where the discussion will focus on the responsibilities of sponsors and researchers and inducement/compensation and social risks.

After explaining all the modules in brief, the training facilitator should explain the modality to be adopted

for group work, group discussion and class exercises. It is suggested that the directions for group work and some sessions of the modules with class exercises be presented in boxes in the training manual. Case studies will be provided during the class exercises as well as group work wherever applicable during the sessions. Icebreakers and energizers will be used during the sessions as and when required.

Box 1

Training Evaluation and Feedback

During the registration process on the first morning of the training workshop, the training facilitator should give each participant the questionnaire (Annex-I). The same questionnaire will be distributed during the evaluation session at the end of the training workshop. The training facilitator will then compare the two to determine what was learned and areas that need to be strengthened or followed up. Apart from administering pre-test and post-test questionnaire, there will be a daily session evaluation (Annex – II), and one questionnaire (Annex-III) will be the overall evaluation of the training workshop. The training facilitator will provide the feedback to their trainer(s) based on daily evaluation. These can be helpful in determining the level of understanding and learning during the training workshop. The training facilitators should meet at the end of each day to evaluate the day's work and to plan and modify the style of facilitation skills during the training program without deviating from what is explained in the training manual as and when necessary.

2.1.3 Administrative Issues (Time: 5 minutes)

The training facilitator should inform all the participants about the arrangements for breaks and lunch as well as any other information relating to housekeeping, e.g., fire exit, toilets and any administrative issues.

2.2 Module 2 **General Introduction to Research Ethics**

Learning Objectives:

By the end of the session, the participants will be able to:

- Define research ethics and its rationale,
- Describe the historical perspective of research ethics, and
- State the guiding principles for health research.

Time Frame: 90 minutes

Materials: Flip Chart, Board Markers, Computer, Audiovisual Equipments with LCD Projector and Screen

Teaching Methods/Process: Lecture, Assessment/Presentation and Discussion

Course Contents:

- Meaning of research ethics, its definition, and rationale
- Historical perspective of research ethics (from global to national)
- Guiding principles for health research involving human participants

2.2.1 Meaning of Research Ethics, Its Definition, and Rationale (Time: 20 minutes)

When most people think of ethics (or morals), they think of rules for distinguishing between right and wrong, such as the Golden Rule, or a code of professional conduct like the Hippocratic Oath (“first of all, do no harm”). Most people learn ethical norms at home, at school, in religious places, or in other social settings. Although most people acquire their sense of right and wrong during childhood, moral development occurs throughout life and human beings pass through different stages of growth as they mature. Ethical norms are so ubiquitous that one might be tempted to regard them as simple commonsense. On the other hand, if morality were nothing more than commonsense, why are there so many ethical disputes and issues in our society?

The fundamental concept of the word ethics is basically derived from the Greek word “ethos”, which

means character, or a fundamental outlook influencing behavior related to customs and moral values of the people. Ethics deals with the process of determining correctness of an activity. It is a way of characterizing actions with regard to human dignity. It draws direction from the moral values existing in society. It is guided by the concept of human rights, social and professional responsibility.

Ethics in the research context is concerned primarily with safeguarding the interests of research participants and aims to safeguard their dignity and rights.

There are several reasons why it is essential to follow ethical norms in research.

- Norms **promote the aims of research**, such as knowledge, truth, and avoidance of error. For example, prohibitions against fabricating, falsifying, or misrepresenting research data promote the reality and avoid mistakes.
- Following recognized ethical standards **ensures that the rights, safety and wellbeing of research participants are protected**. For example, explaining the risks and benefits of the research to potential participants ensures that they fully understand about the study and can make an informed choice as to whether they are prepared to participate.
- Ethical principles encourage the **values that are important for collaborative work**, such as belief, responsibility, mutual respect, and justice as research involves coordination and cooperation among diverse set of people from different institutions and disciplines. For example, various ethical norms in research, such as authorship guidelines, rules for confidentiality in peer review, and policies for copyright, patenting, and data-sharing are considered to protect intellectual property rights while encouraging collaborative work. Most researchers would like to receive some type of recognition for their contributions and do not want to have their ideas stolen.

4. Many of the ethical norms help to make certain that researchers are **responsible to the public**. For example, national policies on misconduct of research, conflicts of interest, protection of the human and animal participants and their use are crucial to ensure that all researchers particularly those who receive public funds should be responsible to the public.
5. Ethical norms and standards in research also facilitate to build **public support** for research. If people or funding agencies start believing on the quality and honesty of research, they are more likely to provide fund(s) for research project(s).
6. Finally, various research norms promote a variety of other essential **social and moral values**, such as social responsibility and human/animal rights and their safety, and compliance with the law and regulations. Ethical violation in research can significantly harm human beings if incorrect research findings are generalized. For example, a researcher who fabricates data in a clinical trial may put study participants at risk of harm or even death, and a researcher who fails to abide by ethical norms and standards relating to biological safety may put at risk their health and safety including the whole study team members.

2.2.2 Historical Perspective of Research Ethics (from global to national) (Time: 40 minutes)

Research on human beings has been conducted since the time of the ancient Greeks. However, ethics related to health and biomedical research is a more recent phenomenon.

Global Context: Before and during World War II, intervention with human beings was taking place in various fields of scientific development. Thousands of human beings were subjected to scientific experimentations, which routinely led to suffering and death.

Ethical violations were also noted in the illegal experiments performed on prisoners of war in Germany during World War II. Such experiments included immersing prisoners in cold water, decompressing prisoners in high-altitude chambers until they died, and injecting many prisoners with typhus to see what happened. In many cases these experiments led to death. Such experiments were conducted in German concentration camps (Dachau) and killing camps

(Auschwitz). In 1946-47, a total of 23 Nazi German physicians were brought to trial in the subsequent **Nuremberg War Crime Trials** (Nuremberg Medical Trial) for these illegal experiments. These German physicians betrayed in some measure their duties as physicians.

Recognition of the need to protect human research subjects led to the issuance of the Nuremberg Code on 19 August 1947 in Germany. This was the first international document on research ethics. This stated that voluntary informed consent is mandatory prior to participation. The Code outlined 10 ethical principles to be followed:

- i. Voluntary consent of the participants is absolutely essential. The subject must be capable of giving consent without coercion, and full responsibility rests with the principal investigator for ensuring that voluntary consent is obtained.
- ii. The experiment must be designed to bring forth results that will benefit society, which cannot be obtained in any other manner.
- iii. Human experimentation that involves a medical intervention, e.g., giving a drug or vaccine or implanting a medical device, should be based on animal research results as well as knowledge of the natural course of events, disease, or problem.
- iv. All unnecessary mental or physical harm should be avoided.
- v. When there is reason to believe that death or disabling injury may occur, no experiment should be conducted except perhaps when the experimenting physicians also serve as subjects.
- vi. The degree of risk should never exceed the humanitarian importance of the problem to be solved.
- vii. All precaution should be taken to protect subjects from even remote possibilities of injury or death.
- viii. Only qualified personnel should be allowed to conduct experiments.
- ix. The subject must be able to withdraw from the experiment at any time if a point is reached, which may bring about physical or mental harm or for any other reason when they do not want to continue in the experiment.
- x. The principal investigator must be ready to terminate the experiment at any stage if it appears that injury or death will result.

After the publication of the Nuremberg Code in 1947, a series of international declarations, conventions and

covenants related to ethics in health, health care and research have been published.

The most prominent of these documents is the **Declaration of Helsinki**, adopted by the World Medical Association (WMA) in 1964. It has since been modified several times (1975, 1983, 1989, 1996, 2000, 2002, 2004, 2008, and 2013). It was intended to mitigate the risk that inappropriate research posed both to the truthfulness and the status of the research project. It added three major influential points to that already outlined in the Nuremberg Code. The first was a theoretical difference between clinical, therapeutic, or diagnostic research and non-therapeutic biomedical scientific research. The former type of research is justified by its benefit to the human beings and the latter type is justified so long as the interest of community does not take preference over the wellbeing of the study participants. Unfortunately, the Declaration of Helsinki did not adequately address the final right of the independent review. However, it recommends written records of informed consent, extra protection for vulnerable people and concern on the medical researcher who enrolls his/her own patients for research purposes.

Even after the formulation of Nuremberg Code in 1947 and Declaration of Helsinki in 1964, there were continuing ethical violations among human beings. One of such example was the Tuskegee Syphilis Study (Box 2).

In the U.S., the Food and Drug Administration (FDA) and the National Institute of Health had been active in formulating policies about research ethics in the 1960s, including policies mandating independent review. In 1979, the **Belmont Report** was published and it identified three basic principles of research ethics:

1. Respect for persons (treating individuals as autonomous agents and protecting persons with diminished autonomy),
2. Beneficence (minimizing harms and maximizing benefits), and
3. Justice (fairness in the distribution of the benefits and burdens of research).

These three principles were considered as meeting the fundamental requirements on legitimate research using human participants. Many official policies have explicitly identified these three principles as the moral basis of their policy.

In 1982, the Council for International Organizations of Medical Sciences (CIOMS) issued the **International**

Box 2

Tuskegee Syphilis Study (1932-1972)

The U.S. Public Health Service performed a long-term prospective study and followed long-term effects of untreated syphilis on 400 low-income African-American syphilitic black males (aged 25 to 60 years) until death. Although these males received free medical examinations (just to make them believe that they were being treated for the disease), they were not told about their disease, the real nature of the study, and they were denied treatment that could have saved their lives. The study was conducted in Macon County, Alabama, and designed to determine the natural course of untreated latent syphilis. The study continued for 40 years. Even after the discovery of *penicillin* and its becoming widely available in the early 1950s as the preferred treatment for syphilis, the black males did not receive the treatment. Only in 1972, when the study results first appeared in the national press, the Department of Health, Education and Welfare (now called the Department of Health and Human Services) halted the study and appointed an investigatory panel to look into this in August, 1972. The panel found the study to have been “ethically unjustified” and argued that *penicillin* should have been provided to the syphilitic males.

Ethical Guidelines for Biomedical Research Involving Human Subjects

to indicate how the ethical principles set forth in the Declaration of Helsinki could effectively be applied, particularly in developing countries. This introduced a new set of issues raised by research done from more developed countries on human participants in less developed countries. Proposals were put forward on how to deal with informed consent in a way that is culturally sensitive and how to avoid exploitation of less-developed countries in the research process. The guidelines were revised in 1993 and 2002. The CIOMS guidelines are designed to be used in developing national policies on the ethics in biomedical research, applying ethical standards in local circumstances and establishing or redefining adequate mechanisms for ethical review of research involving human participants. Moreover, the CIOMS guidelines take the position that research involving human beings must not violate any universally applicable ethical norms and standards but

recognize that, in certain aspects, the application of the ethical principles needs to consider cultural and societal values.

In 1991, the U.S. Health and Human Services division of the U.S. Government issued a new law under the U.S. Code of Federal Regulations that laid out the U.S. Government requirements for ethical conduct of research. This was published in 45 CFR (Code of Federal Regulations) Part 46 and has since become known as the Common Rule. This law was designed to standardize human beings protection system across U.S. federal agencies and departments. It requires prior approval from ethics review committee, which includes approval of written informed consent and its proper documentation, equitable recruitment of study participants and their justice, special provision for protecting vulnerable human beings (if recruited), and approval of research protocol.

In 1996, the International Conference on Harmonization (ICH) finalized the Guidelines for Good Clinical Practice (GCP), which was developed to standardize scientific and ethical requirements for clinical research leading to the approval of new drugs. The GCP guidelines are intended to provide standards for both ethical and scientific standards for developing, conducting, recording and reporting clinical trials. Subsequently in 1997 the USFDA adopted GCP in the Federal Register as a required standard for any research funded by the U.S. Government. In 2006, the WHO published the Handbook for Good Clinical Research Practice to aid researchers in the implementation of GCP standards in all types of human research. Since then, many countries have taken the ICH GCP guidelines and adapted it for their own setting but still include the same basic scientific and ethical principles.

In 2002, the UK-based Nuffield Council on Bioethics in its publication, the Ethics of Research Related to Healthcare in Developing Countries emphasized the need to examine the ethical issues raised when research related to health care is conducted in developing countries and funded by sponsors from developed countries. The Council's main recommendations focus on the inclusion and development of local partners in the research.

National Context: The NHRC has been involved in the research proposal review process since 1991. While doing so, the NHRC has always been stressing on the

protection and interests of human beings in research by following international declarations on research ethics, particularly the Helsinki Declaration.

In 1995, the NHRC published the first document on research ethics titled NHRC's Ethical Guidelines. This was aimed at research proposal reviewers, ethical committee members, health and medical researchers, health professionals and students of health and medical sciences. Since then, the NHRC has started to deliver one-hour lecture on research ethics in most of the research-related training workshops conducted by them.

In 2001, the NHRC published the National Ethical Guidelines for Health Research in Nepal. Since then, it has organized a series of workshops and consultative meetings on research ethics in Nepal. Similarly, in 2005, there were three publications: Ethical Guidelines for the Care and Use of Animals in Health Research in Nepal, National Guidelines on Clinical Trials with the Use of Pharmaceutical Products, and Guidelines for Institutional Review Committees for Health Research in Nepal.

The workshop on ethics in health research, organized by the NHRC on March 13-14, 2008, recommended that it was now important to revise the National Ethical Guidelines published in the year 2001. So, seven members were delegated as a taskforce committee to accomplish this task, and over the period of revision, a series of workshops was held to garner further suggestions for revisions. The revised guideline was disseminated in a workshop on April 26, 2010. With the additional suggestions from this workshop, steps were taken to finalize the ethical guidelines, and the section on the Standard Operating Procedure (SOP) was added. Subsequently, the new national ethical document has been named as National Ethical Guidelines for Health Research in Nepal and Standard Operating Procedure, 2011 and assists the Ethical Review Board (ERB) of the NHRC in the achievement of its commitment to promote, protect the dignity, rights, safety and wellbeing of all in health research involving the culture and environment of Nepal. The document is divided into three sections – Section A: Guiding Principles for Health Research Involving Human Participants, Section B: Basic Principles of Health Research Involving Human Participants, and Section C: SOP for the ERB of NHRC.

2.2.3 Guiding principles for Health Research Involving Human Participants (Time: 30 minutes)

The trainer should ask, "What are the ethical principles for health research involving human participants?"

All research involving human participants should be conducted in accordance with four basic ethical principles,

- Respect for the dignity of persons (and community)
- Beneficence (non-maleficence)
- Justice (treat individuals fairly)
- Respect for the environment (this principle is unique to Nepal)

Respect for the Dignity of Person (and Community): Researcher should respect the autonomy of persons by promoting the necessary freedom in decision-making attributable to persons based on their morals and self-respect and their capacity to decide for themselves. There should be the active protection of persons and special protections of vulnerable people against harm or abuse. This means that we should not disrespect the research participants in the study and/or breach their confidentiality or disclose any of their personnel information. Special concern must be given to persons who may have a diminished capacity to make their own choices due to physical, mental, social, or economic reasons. Researcher should also respect for the participants' culture, beliefs and their community to which they belong including their specific decision-making process within their family and community.

Beneficence/non-maleficence (do no harm): Researcher should maximize possible benefits and minimize possible harms and wrongs. Research participants must be safeguarded against possible harms (psychological and physiological) and abuses (stigmatization). There should not be more risks of

having harms and abuses against possible benefits to the research participants/community, and these aspects must be weighed. First of all, researcher needs to consider that protecting the research participant(s) is much more important than adding new knowledge to science and individual research interests. Researcher should use the least harmful methods to achieve their scientific goals.

Justice (treat individuals fairly): There should be equitable justice while treating the research participants in both the circumstances, i.e., treatment or placebo and/or experimental or non-experimental. There should be equal risks and benefits among both the groups. Researcher has the responsibility to distribute the risk and benefits in an equitable manner. It means that the participants in the both above-mentioned circumstances must be treated alike and those differences between persons due to circumstances need to be addressed appropriately. Researcher should explain about the provision of providing equitable (i.e., distribution of the burdens and benefits of research in equitable manner) and compensatory (i.e., provision of compensation for injury/harm in equitable manner) justices during the research process. This principle does not allow using vulnerable people as research participants for the benefit of privileged people. If vulnerable people will be used in the study, researcher should provide sound justification for doing so and provide special provisions for the protection of the rights and welfare of vulnerable participants.

Respect for Environment: Researcher needs to respect the physical, biological, cultural, religious, and linguistic environment of the community where the study is going to be conducted. Researcher should not disturb or damage or degrade their natural settings. Researcher must dispose properly and safely all kinds of biologically hazardous wastes from laboratory, clinical or field research.

2.3 Module 3 **The Development of Contemporary Research Ethics**

Learning Objectives:

By the end of the session, the participants will be able to:

- Trace out the international declarations relating to research ethics,
- Apply the various guidelines on research involving human beings, and
- Describe national ethical guidelines.

Time Frame: 180 minutes

Materials: Flip Chart, Board Markers, Computer, Audiovisual Equipments with LCD Projector and Screen

Teaching Methods/Process: Lecture, Brainstorming, Plenary session, Assessment/Presentation, and Discussion

Course Contents:

- International declarations, guidelines and other related documents on comprehensive human beings research
- National Ethical Guidelines of Nepal

Game

- ZIPP-ZAPP

Group Exercise:

- Case Studies
- Small Group Discussion

2.3.1 Game (Time: 30 minutes)

ZIPP-ZAPP

Objective: To improve training atmosphere, especially at the first day (after lunch) of a workshop. The ZIPP-ZAPP game is an icebreaker. After the games, the participants will know each other by names. It also helps to change seating positions. To begin, the participants need to be seated in a circle. The facilitator walks around in the circle of participants. He/she points here and there to the participants and says, "ZIPP" or "ZAPP". At "ZIPP", the participant must tell the name of his/her right neighbor, at "ZAPP", the name of left

neighbor. After a few rounds of "ZIPP" and "ZAPP", the facilitator says, "ZIPP-ZAPP" and all participants must get up and change their places. Now "ZIPP" and "ZAPP" goes on repeatedly for two to three rounds.

2.3.2 International Declarations, Guidelines and other related Documents on Comprehensive Human Beings Research (Time: 60 minutes)

After the publication of the Nuremberg Code in 1947, the most prominent declaration was the Declaration of Helsinki, adopted by the 18th WMA General Assembly Helsinki, Finland, in June 1964. The Declaration has been amended nine times since then:

- 29th WMA General Assembly, Tokyo, Japan, (October 1975),
- 35th WMA General Assembly, Venice, Italy (October 1983),
- 41st WMA General Assembly, Hong Kong (September 1989),
- 48th WMA General Assembly, Somerset West, Republic of South Africa (October 1996),
- 52nd WMA General Assembly, Edinburgh, Scotland (October 2000),
- 53rd WMA General Assembly, Washington DC, USA (October 2002),
- 55th WMA General Assembly, Tokyo, Japan (October 2004),
- 59th WMA General Assembly, Seoul, Republic of Korea (October 2008), and
- 64th WMA General Assembly, Fortaleza, Brazil (October 2013),

Declaration of Helsinki

(a) Introduction

The Declaration of Helsinki has been developed by the WMA as an enunciation of ethical principles to provide direction to clinicians and others who conduct medical research involving human beings. Medical research involving human beings includes not only intervention research but also research on particular biological samples or demographic data. It is the duty

of the clinician to promote and protect the health of the people.

The clinician's knowledge and conscience are devoted to the execution of this task. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The advancement of medical care is often based on research, which ultimately must rest in part on intervention involving human participants. The main aim of medical research involving human participants is to improve the preventive, prophylactic, diagnostic, and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. These procedures must continuously be evaluated through research for their effectiveness and efficiency. Most of these procedures involve some risks and burdens and these always have to be weighed against the potential benefit to the patient.

Ethical standards should be maintained during medical research, and it should protect the health and rights of human beings. There should be a provision of special protection for vulnerable study population. The particular needs of these vulnerable populations must be recognized and addressed. Examples of vulnerable or disadvantaged populations include those with limited income, children, women, mentally or physically incapacitated, prisoners, and others depending on cultural norms. Special consideration is mandatory for those who cannot give or refuse consent by themselves, for those who will not be able to take benefit personally and for those for whom the research is combined with care.

Researchers should know about all the ethical, legal and regulatory requirements for conducting research among human participants in their own countries. They also need to know about all of those applicable international requirements. These requirements should not be allowed to reduce or eliminate any of the protections for human participants described in this Declaration.

(b) Basic Principles for all Human-related Research

i. It is the responsibility of the researchers involved in

research to safeguard the life, health, privacy, and dignity of the human beings.

- ii. Researchers conducting research involving human beings must follow generally accepted scientific principles and must have a thorough knowledge of the scientific literature and other relevant sources of information including laboratory aspects.
- iii. Appropriate care must be exercised while conducting the research which may affect the environment and the safety of animals used for research.
- iv. The experimental design involving human beings should clearly be formulated in the protocol and must be submitted for consideration, comment, guidance, and approval to an independent ethical review committee. This committee should abide by the legislations and regulations of the country in which the study is conducted. The review committee has all the rights to monitor and supervise ongoing researches, and researcher(s) must provide all the information to the committee members, especially of any serious adverse events. During the monitoring period, the researchers should submit the information related to institutional affiliations, any potential conflicts of interest, incentives for participants, funding agencies and sponsors.
- v. The research protocol must mention a statement of the ethical aspects to be applied during the study period as per the principles of the Declaration of Helsinki.
- vi. Only qualified persons should conduct the research involving human beings and that should be done under the supervision of the Principal Investigator (PI) and co-investigators. The PI and co-investigators have all the responsibility to look after the human beings. Research participants will not be responsible by themselves even though they provide their consent.
- vii. Each and every health-related research study involving human beings must be conducted with careful assessment of expected risks and burdens in comparison with anticipated benefits to the participants/families and/or the communities. The design of all studies should publicly be available.
- viii. Medical research involving human beings should only be conducted if the objective value is more important than the inherent risks and burdens to the human being. This is considered to be important when the human beings are healthy volunteers.

- ix. Researchers should not start studies that do not follow sound scientific and ethical standards. Researchers should stop any research if the risks from the study are found to outweigh the potential benefits. Researcher must not engage in research studies involving human beings unless they are confident that the risks involved have adequately been assessed and can satisfactorily be managed.
 - x. The research participants must be volunteers and properly informed about the risks and benefits of the research.
 - xi. The right of research participants to protect their integrity should be respected. Every safety measures must be taken to respect the privacy of the research participants, the confidentiality of the participants' information and to minimize the impact of the research study on the participants' mental and physical integrity including their personality.
 - xii. Each and every eligible research participants must adequately be informed of the objectives, methods, sources of funding, any possible conflicts of interest, institution where the researcher works, the expected benefits and possible risks of the study. The research participant should be informed of the right to withdraw from participation in the study or to withdraw informed consent to participate at any time without penalty. After ensuring that the research participant has understood the information, the researcher should then obtain the participant's written informed consent. If the research participant is unable to give written informed consent, the non-written consent must formally be documented and witnessed.
 - xiii. When obtaining informed consent for the research study, the researcher should be careful if the participant is in a dependent relationship with the researcher or may consent under pressure. In such cases, a well-informed researcher, who is not involved in the research study and completely independent of this relationship, should obtain the informed consent.
 - xiv. In the case of obtaining informed consent from a research participant who is physically handicapped with lack of mental competence or legally incompetent, the researcher must obtain the consent from the legally authorized representative in accordance with applicable law(s) prevailing in the country. Such research participants should not be included in research study unless and until there is a necessity to conduct the research in order to promote the health of such population and the study cannot instead be performed on legally competent persons.
 - xv. When a research participant considered as legally incompetent (e.g., child) but able to give assent to decisions about participation in the study, the researcher should obtain that assent along with the consent of the legally authorized representative of incompetent research participant.
 - xvi. Research on participants from whom it is not possible to obtain the consent should be done only if the physical/mental condition that prevents obtaining informed consent is a needed attribute of the participants. There should be precise reasons for involving such research participants with a clause that renders them unable to give informed consent must be stated in the interventional protocol for consideration and approval of the ethical review committee. The protocol must mention that consent to join and remain in the study will be obtained as early as possible from the individual or a legally authorized representative of the research participant and certainly before any research procedures are carried out.
 - xvii. In publication of the research results, the researchers are obliged to safeguard the correctness of the findings. Positive and negative findings should be published or otherwise made available to the public. Institutional affiliations, any possible conflicts of interest, and funding sources must be declared in the publication. Reports of experimentation not in accordance with the principles mentioned in this Declaration should not be accepted for publication.
- (c) Additional Principles for Health Research Involving with Medical Care**
- i. The clinician may unite medical research with medical care, only to the extent that the study is justified by its potential prophylactic, therapeutic or diagnostic value. When such thing happens, additional standards apply to protect the research participants.
 - ii. New method must be tested against the best existing prophylactic, diagnostic and therapeutic methods for gathering the information regarding its effectiveness including risks, burdens and benefits. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method

exists. In studies of medical devices, wherever possible new devices should be compared to currently approved devices that are most similar to the new one being tested.

- iii. To the extent possible, the researchers will endeavor to ensure that research participants benefit from the research findings by having access to the most beneficial and affordable medical options after the research is complete.
- iv. The clinician must inform the research participant which aspects of the care are related to the research. The refusal of a participant to participate in a research study must never hamper the relationship between the clinician and research participants.
- v. In the treatment of a research participant, where proven prophylactic, diagnostic and therapeutic methods have been found to be ineffective or do not exist, the clinician, after obtaining the informed consent from the research participant, must be free to use unproven or new prophylactic, diagnostic and therapeutic procedures, if in the clinician's judgment it offers hope of saving life and re-establishing the health of the research participant. Where possible, these procedures must be made the objective of study, planned to evaluate their safety and efficacy. New information must be recorded in all the cases and published if appropriate. The other relevant guidelines of this Declaration should be followed.

Note: *The Declaration of Helsinki also includes expectations for scientific requirements and research protocols, ethics committees, use of a placebo, post-trial provisions, registration and unproven interventions at its subsequent revised versions.*

After the publication of the Helsinki Declaration in 1964 and with subsequent amendments, the Belmont Report was issued in 1979 and published in US Federal register in 1979. Its full title is The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report summarizes ethical principles and guidelines for research involving human subjects. Three core principles are identified: respect for persons, beneficence, and justice. Three primary areas of application are also stated. They are informed consent, assessment of risks and benefits, and selection of subjects.

Scientific research has produced substantial social and public health benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human beings in biomedical experiments, especially during the Second World War. Following Nuremberg War Crime Trials, the Nuremberg Code was drafted. This sought to set standards for conducting research on human beings and sought to ensure that the ethical violations that occurred in the German concentration camps would not occur in the future. This code became the model of many later codes which intended to ensure that research involving human beings would be carried out in an ethical manner.

The Nuremberg Code includes such principles as informed consent and absence of coercion, properly formulated scientific experimentation, and beneficence towards experimental participants.

Three principles are relevant to research involving human beings as identified in the Belmont report. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, participants, reviewers and interested citizens to understand the ethical issues inherent in research involving human beings. The aim is to provide an analytical structure that will direct the resolution of ethical problems arising from research involving human beings.

The Belmont Report

(A) Boundaries between Practice and Research: It is essential to differentiate between behavioral and biomedical research, on the one hand, and the practice of accepted medical care on the other, in order to be familiar with what activities ought to undergo review for the protection of research participants. The distinction between research and practice is unclear somewhat because they can happen together (as in research designed to evaluate a therapy) and somewhat because notable departures from experimental practice when the terms "experimental" and "research" are not carefully explained.

For the most part, the term "practice" refers to experimentations that are considered exclusively to improve the health of an individual patient or client and that have a reasonable anticipation of success. These are also sometimes referred to as Standard of Care. The intention of medical practice is to provide diagnosis, preventive treatment or therapy to particular

individuals. By contrast, the term “research” designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge. Research is usually described in a formal protocol that contains an objective and methodology designed to achieve that objective.

A doctor is free to provide alternative treatments that are not standard if they believe that it is in the best interests of the patient. But once they start providing that same alternative treatment to multiple patients to see if they can get the same improved result, then that is considered research as it is testing something new on more than one patient to determine safety and/or effectiveness. Also, any radically new interventions should not be implemented without formal research being conducted first in order to determine whether they are safe and effective.

Research study and practice may be carried on together when study is designed to evaluate the safety and efficacy of a pharmaceutical product or therapy. All the elements of research must undergo review process for the protection of human participants.

(B) Basic Ethical Principles: The term “basic ethical principles” refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles are particularly relevant to the ethics of research involving human beings:

1. Respect for Persons: Respect for persons includes that individuals should be treated as autonomous agents and protected if the persons belong to diminished autonomy. Its principle thus divides into the requirement to acknowledge autonomy and protect those with diminished autonomy.

An autonomous person is an individual capable of expressing their thoughts about their personal thinking. We should give high respect for autonomy of any person.

However, not every human being is capable of self-determination. The capacity for self-determination evolves during an individual’s life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Anyone who is not able to make self-determinations needs special protections including

having legal representatives that can act in their best interests.

Some human beings are in need of extensive protection, even to the point of excluding them from activities which may harm them. Some research participants require slight protection beyond making sure that they undertake activities freely and with awareness of possible adverse consequence. Such protection depends upon the probability of providing benefit, and risk of harm. The judgment that any person lacks autonomy should be re-evaluated from time to time and may vary in dissimilar situations.

It demands that research participants enter into the study voluntarily and with sufficient information. Sometimes involving prisoners as research participants may require a condition that prisoners not be deprived of the opportunity to volunteer for study. However, under prison conditions they may delicately be coerced or unduly influenced to take part in research activities for which they would not otherwise volunteer. Therefore, these prisoners should be protected.

2. Beneficence: The principal of beneficence states that persons are treated in an ethical manner by making efforts to secure their wellbeing. The expression “beneficence” covers kindness, acts that go beyond strict duty. It is understood in a stronger sense, as an obligation. There are two general rules for better describing the expressions of beneficent actions that are (a) do not harm and (b) minimize possible harms and maximize possible benefits.

The Hippocratic maxim “do no harm” has long been a fundamental principle of medical ethics. Others have extended it to the realm of research, saying that one person should not harm another person regardless of the benefits that might come to others. Moreover, the Hippocratic Oath requires physicians to benefit their patients “according to their best judgment”. Understanding what will actually benefit may require exposing persons to risk.

Researchers and members of their institutions are obliged to provide maximum benefits, and at the same time, risk should be minimized during the study period. Generally, a large number of society members are able to identify the longer-term benefits and risks that may result from the knowledge improvement and from the development of novel medical, psychotherapeutic, and social procedures.

There should be effective ways of treating the diseases more prevalent among children and provide benefits for their health development in order to justify research involving children – even when individual research participants are not direct beneficiaries. Research also makes it possible to keep away from the harm that may result from the application of previously accepted routine practices that on closer examination turn out to be unsafe or simply not effective.

3. Justice. This implies the sense of “fairness in distribution” or “what is deserved.” An injustice occurs when some burdens are forced unjustifiably or when some benefits to which a person is entitled is denied without proper reason. It is that equals should be treated equally. However, this statement requires further explanation. Who is equal and who is unequal? What considerations justify departure from equal distribution? It is necessary to explain in what respects people should be treated equally. In order to distribute burdens and benefits, there are various extensively accepted formulations, which are provided to each person **(a)** an equal share, **(b)** according to individual need & effort **(c)** according to societal contribution, and **(e)** according to merit.

Questions of justice are related with social practices such as political representation, taxation and punishment. These days such justice questions have not generally been associated with scientific research. During the 19th and early 20th centuries, the burdens of serving as research participants fell largely upon poor ward patients, while the benefits of improved medical care was provided primarily to private patients.

Similarly, in the 1940s, the prisoners were exploited as research participants in Nazi concentration camps. In Macon County Alabama, USA, in the 1940s, the Tuskegee syphilis study was begun, wherein rural black men were put under to study the untreated course of a disease. These populations were not given effective treatment to treat their syphilis thinking in order to continue the study. Therefore, the selection of research participants needs to be done in such a way that some classes (e.g., welfare patients, particular racial and ethnic minorities) are needed to be systematically selected, not simply because of their easy availability and manipulability.

When the study leads to the development of therapeutic devices and procedures, justice demands both that these not provide benefits only to those

who can afford them and that such study should not excessively involve participants from groups unlikely to be among the beneficiaries of the study.

After the publication of the Belmont Report in 1979, the Council for International Organizations on Medical Sciences (CIOMS) issued the International Ethical Guidelines for Biomedical Research Involving Human Subjects in 1982. This guidelines indicates how the principles of ethics expressed in the Declaration of Helsinki could effectively be applied, particularly in developing countries. The guidelines were revised in 1993 and 2002. The CIOMS guidelines are designed to be used in developing national policies on the ethics in biomedical research, applying ethical standards in local circumstances, and re-defining sufficient mechanisms for ethical review of research involving human beings.

International Ethical Guidelines for Biomedical Research Involving Human Subjects

(a) Introduction: This is the third (revision) in the series of international ethical guidelines for bio-medical research involving human subjects issued by the CIOMS since 1982. The CIOMS Guidelines emphasize that the biomedical research needs to be conducted in developing countries, with the implications for multinational research in which they may be partners.

The guidelines take the position that research involving human subjects must not breach any universally applicable ethical standards, but acknowledge the application of the principles of ethics, such as respecting for autonomy, taking informed consent, respecting socio-cultural values, while respecting absolutely the ethical standards.

Human rights of research subjects and researchers in a variety of socio-cultural contexts are considered to be an important issue. The issue concerns largely two principles: respect for autonomy and protection of vulnerable populations.

Certain areas of research are not addressed by specific guidelines. One such is human genetics. Another unrepresented area is research with products of conception (embryo and fetal research, and fetal tissue research).

(b) General Ethical Principles: As indicated by the Belmont Report, CIOMS Guidelines also highlighted the three basic ethical principles: respect for persons,

beneficence and justice. All research involving human subjects should be conducted in accordance with the three basic principles of ethics. In varying conditions they may be expressed differently and given different moral values, and their application may lead to different decisions or courses of action. The discussion about the three basic ethical principles as expressed in the Belmont Report still stands.

The CIOMS Guidelines added the responsibility of sponsors and researchers, wherein it emphasized that sponsors of research or researchers cannot, in general, be held accountable for unfair circumstances where the study is carried out, but they must cease from practices that are likely to deteriorate unfair circumstances or contribute to new inequities. They should not take benefit of the relative inability of low-resource countries or vulnerable populations to look after their own interests, by conducting research in those countries and avoiding complex regulatory systems of developed countries in order to develop products for the profitable markets of those countries.

Generally, the research project should exclude vulnerable population or low-resource countries, and if conducted, it should be responsive to their health needs and priorities in that any product developed is made reasonably available to them.

2.3.3 National Ethical Guidelines of Nepal (Time: 30 minutes)

The National Ethical Guidelines for Health Research in Nepal and Standard Operating Procedure was published in January 2011. This guideline has been prepared in line with the concepts of various international codes, declarations and guidelines and has followed accordingly.

Ethical Principles as Mentioned in the National Ethical Guidelines of Nepal

Guiding principles as adopted by Nepal are same as that appear in the Belmont Report and CIOMS Guidelines. They are the principles of respect for autonomy of an individual, beneficence, and the principle of justice. These guide health research and care in Nepal. Nepal added the principle of respect for the environment, which basically proposes to ensure respect for the community, culture, their environment, and safe deposition of bio-hazardous waste materials. Nepal considered this principle as fourth ethical principle. This came into existence in view of the increasing world movement for the protection of the environment. It is

researchers' responsibility to protect the social, cultural and natural heritage of communities and societies. Following commitments express the responsibility of researchers.

- a. To guarantee the proper and safe disposal of biologically hazardous waste materials obtained from laboratory, clinical and field research,
- b. To protect the religious, cultural, and linguistic tradition of communities and individuals, and
- c. To treat the genetic and biological tradition of the people with respect and care.

Basic Principles of Health Research Involving Human Beings

As envisaged by the Act of NHRC 1991, all health research conducted in Nepal should obtain prior approval of the ERB of the NHRC or a similar analogue body like Institutional Review Committee (IRC) or Institutional Review Board (IRB) authorized by the NHRC.

There is a review system and the process is guided mainly by the four ethical principles as adopted by the NHRC. They are the principles of respect for autonomy of person, beneficence, justice and respect for environment. Following ethical guiding principles are to be followed:

- i. **Essential Research:** In order to understand the problem or disease process, or identify preventive or diagnostic approach to a disease, research is essential and need to be conducted among human participants.
- ii. **Voluntary Participation:** Human participants should be involved voluntarily and provide their consent in such a way that they can refuse to participate at any time without any sort of penalty. They must have been provided basic information (objectives of the research, risks and benefits involved, applied methods) prior to give consent.
- iii. **Children in Health Research:** Research should not be conducted among children if it could have been done among adults. Researcher should provide an appropriate justification if there is an involvement of children in research. If so, researcher should have to take proxy consent from their parents or legal guardian.
- iv. **Pregnant Women in Health Research:** Research should not be conducted among pregnant women and lactating mothers if it could have

- been done among other women. Researcher should provide an appropriate justification if there is an involvement of such participants in research.
- v. Other Vulnerable People in Health Research:** There should be special attention if other vulnerable participants such as military personnel, mentally retarded people, prisoners, students are being recruited as participants during research process.
- vi. Potential Benefit:** Each and every research participants or community involved in the research process should derive any potential benefit.
- vii. Harm and Risks:** There should not be any harm to research participant or community. The risk should be minimal if it is involved during the research process. Researchers' should put his/her emphasis on maximizing the benefit and minimizing the risk in such a way that the risk/benefit ratio will be in favour of benefits.
- viii. Compensation:** There should be a provision for compensating the research participants or community if any harms occurs during the research process. Apart from this, a provision should be made to compensate the time and efforts of the research participants or community for the research process. Such information should be informed to the participants.
- ix. Qualifications and Competence for the Research:** The principal researcher involved in the research process should be well qualified and competent enough to carry out the research.
- x. Equal Distribution:** There should be equal distribution of the burden and benefits of participation during participants' selection process from among variety of ethnicity or socio-economic status or geographic regions.
- xi. Dissemination of Research Findings:** The findings obtained from the research should be shared with the local stakeholders. If researcher plans to publish their findings in scientific journals, it should first be published in the local scientific journals and then internationally acclaimed indexed journal. But there should not be double publications in the same research title. Researchers can use other means (such as meetings, conferences) of disseminating their findings.
- xii. Institutional Research Arrangements:** Institutions involved in the research process should have very good organizational setup conducive to research, involvement of competent researchers and research support staffs, archiving of research materials and its preservation and safety. Any research to be conducted by the institution should have received prior approval from the chief of the institution and ERB/IRC/IRB.
- xiii. Confidentiality and Disclosure:** All kinds of data related to research participants including their identity should be kept confidential. This might be disclosed only under compelling scientific and legal situations. The order from a court of law or Data Safety Monitoring Board (DSMB) or a similar body will provide the reason for such disclosure.
- xiv. Professional, Legal and Moral Responsibility:** Institution involved in research, sponsors (including funding agencies), and researchers (including his/her team) must take overall (professional, legal and moral) responsibilities to abide by the guidelines and directives prescribed by the ERB/IRC/IRB.
- xv. Transparency and Conflict of Interest:** Researchers should conduct the research with honesty, fairness, and impartiality. There should not be any kind of conflict of interest. If so, this needs to be disclosed; otherwise, it may lead to suspension of the research proposal or penalty determined by the law. Researcher will get ample of opportunities to provide their defense against the suspension/penalty decision made by ERB/IRC/IRB.
- xvi. Research and the Environment:** Researchers should obey the principle of respecting the environment while conducting research. They should take an account of respecting and safeguarding social, religious, linguistic, cultural and natural heritage of individuals and communities. They should also ensure proper and safe disposal of all kinds of bio-hazardous waste produced during the research process in laboratory or field settings.
- xvii. International and/or Externally Sponsored Research:** Externally sponsored research should be conducted only when it is considered to be relevant for the Nepali people. Such research project should have at least one co-investigator from Nepal and a provision for capacity-building

and strengthening in the field of research. Such study should take ethical approval from the ERB of NHRC.

xviii. Transfer of Biological Samples Outside of

Nepal: The principle researcher should provide convincing reasons for transfer of biological samples from Nepal. Such transfer will only be permitted if it has originally been mentioned in the research proposal. Transfer of biological samples is considered to be a sensitive issue as it is tied to the existing culture and social norms of the communities. It needs precise explanation why it is necessary to transfer such samples outside of Nepal and safety measures for shipment.

xix. Approval Required for all Health Research in

Nepal: All kinds of health research to be carried out in Nepal must receive approval from ERB/IRC/IRB. In the case of failure to do so, researchers are liable for penalty as prescribed in the NHRC Act 1991.

2.3.4 Group Exercise (Time: 60 minutes)

The facilitator should randomly divide all participants into smaller groups consisting of five to eight people. The following case study needs to be provided to each group.

Case Study: Testing a Microbicide

Background

A critical need in stemming the spread of the HIV/AIDS pandemic is to expand the range of methods that women can use for the prevention of all Sexually Transmitted Infections (STI), including vaginal microbicides. A vaginal microbicide would offer the potential for women to protect themselves from HIV and other STIs. To be truly female-controlled, the ideal microbicide would be effective, safe, acceptable, affordable, colorless, odorless, tasteless, easy to store and use and available in a variety of preparations. It should also be available in contraceptive and non-contraceptive formulations and dispense without a prescription. However, because the first microbicide to be developed is unlikely to be an "ideal" product with all these characteristics, the immediate priority is to develop a microbicide that provides protection if used consistently by those who need it most.

The protective benefits of microbicides for male partners have not been studied, but investigators believe that a woman's male partner would also be protected from infection. Microbicides have

been shown to be effective against many sexually transmitted pathogens in vitro and they appear to be most effective in vivo as prophylaxis against cervical infection by *Neisseria gonorrhoea*, *Chlamydia trichomatis* and vaginal infection by *Trichomonas vaginalis*.

The prospects for developing microbicides are promising. There is a growing consensus that developing a microbicide should be technically feasible, and there has been significant progress in microbicide research and development over the several years. Many microbicide products are still in the stages of phase I and II testing in order to establish their safety and toxicity. Currently, only one product, Nonoxynol-9 (N-9) is being tested in phase III trials to assess its efficacy in protecting women from HIV infection.

Despite the established need for a female-controlled barrier method, many scientists, pharmaceutical companies and investors remain skeptical about the feasibility of achieving this goal. In part, this uncertainty derives from the lack of conclusive scientific data demonstrating that, as a class, female barrier methods have the potential to reduce the transmission of STIs. Without results from well-controlled clinical trials that test the efficacy of female barrier methods, their potential role in an overall program of HIV prevention will remain subject to debate.

The International Women's Forum (IWF), a developed country-based non-profit research organization, with a strongly feminist agenda, is planning a study of a microbicide in Nepal. Laboratory tests show that the product blocks HIV attachment to target cells in vitro. The phase I testing of this product was conducted in five countries and results indicated that the product caused no significant signs of irritation and that the women generally found it acceptable and easy to use. It should be noted, however, that these women only used the product for 10 days and were not sexually active during this time.

The proposed trial is designed to further assess the safety and effectiveness of this product. This is the first large-scale phase II microbicide trial to be done in a population of women who are not sex workers and with a microbicide formulation that is non-contraceptive. It will be conducted by IWF with co-investigators from the selected teaching hospitals in Nepal. The project sites are two family planning clinics. The IWF has funded the renovation of the two clinics that will be

used for the study in order for the laboratory facilities to be upgraded and for more nursing and support staff to be employed.

Recruitment and site selection: Before the start of the study, the researchers from IWF and representatives from the selected teaching hospitals of Nepal hold meetings in all the clinics in which the study will take place, in order to explain the study and elicit feedback from potential participants.

To participate in this trial, women must be 18 years or older, HIV negative when they enroll, and resident in the community for at least one year prior to the study, with no intention of leaving for another year. Individual informed consent will be sought from each participant by one of the researchers with the aid of a translator if necessary. Consent will not be sought from male partners as the researchers feel that this would undermine women's autonomy. They neither encouraged nor discouraged the women from informing their partners of their involvement in the study.

Approximately 300 women will use the gel or placebo for approximately one year by applying it vaginally at least three times weekly as well as before intercourse. After enrolling in the trial, the women will come to the clinic monthly to be examined for signs of irritation and tested for STIs; every three months they will be tested for HIV and asked a series of product-acceptability questions. At these visits, the women will receive safer-sex counseling, free condoms, and counseling to ensure that they understand the trial requirements and objectives. Prior to being tested for HIV and receiving their results if they choose (women have the option not to get their results), they will undergo pre-and post-

test counselling. If a woman is found to have a treatable STD, she will receive treatment; if she is found to have HIV or another condition, she will be referred to health and support services (secondary/tertiary hospitals or social workers) available in the local area and will be encouraged to take her partner with her. Women diagnosed as HIV positive can continue to participate in the trial if they choose, so that leaving the trial does not signify HIV sero-status. All participants will receive modest monetary compensation for time and transport for each visit, as well as refreshments.

A group of women from the community health committee, a locally elected body that represents the community in health matters, raises an important concern during one of the pre-study meetings. They disagree with the decision of the researchers not to get informed consent from the male partners of women in the trial. They reason that this might place women at risk for sexual and physical abuse if their partner discovers that they are using the product without their consent. The co-investigators from Nepal, also present at the meeting, argue that men will not allow their partners to take part in the study if they are informed about the microbicide. Seeking male consent would also negate one purpose of the study, which is to test a female-controlled method.

The facilitator should give at least 15 minutes to read the text critically and ask them to discuss among themselves for 10 minutes. The facilitator should ask them to identify some pertinent ethical issues from a research perspective and raise some questions from an ethical background. This might take another 15 minutes. Immediately after that, the raised issues and ethical questions will be presented during a plenary session, which will be last for 20 minutes.

2.4 Module 4 Informed Consent – I

Learning Objectives:

By the end of the session, the participants will be able to:

- Explain informed consent and rationale,
- Describe the essential components of informed consent including various types of consents, and
- Illustrate its applications with different examples including case studies.

Time Frame: 180 minutes

Materials: Flip Chart, Board Markers, Computer, Audiovisual Equipments with LCD Projector and Screen

Teaching Methods/Process: Lecture, Brainstorming, Plenary session, Assessment/presentation, and Discussion

Course Contents:

- Meaning of Informed Consent, its definition and rationale
- Essential elements of Informed Consent
- Types of consent

Class Exercise:

- Case Studies
- Interactive Session

Group Exercise:

- Case Studies
- Small Group Discussion

2.4.1 Meaning of Informed Consent, its Definition and Rationale (Time: 10 minutes)

The facilitator should ask the participants, "What is Informed Consent, and what are its features?". Write responses on flip chart papers.

Informed consent is the process of explaining to the research participants about the nature of the research to enable them to make decision regarding their participation. The study team should also try to ensure that participants are not pressured by their family, community members, or anyone, including the researcher.

Informed consent is much more than just a form. It is a process that continues throughout the research to ensure that participants have adequate information about study participation. This process requires several steps before the participant actually agrees and signs the consent form (or makes their mark if they are illiterate).

Informed consent is not only a legal requirement, it is a communication process between the research team and the participant that starts before the research is initiated and continues throughout the study. It is essential that the information provided is understood by the potential participant and empowers that person to make a voluntary decision about whether or not to participate in the study.

Informed consent is based on the principle that competent individuals are entitled to choose freely whether to participate in research or not. The following principles must be applied to obtain the informed consent from the study participant.

- **Information:** The participant must be provided with full information regarding the research by the researcher including information about procedures, the purpose of the research, anticipated risks and benefits, and alternative procedures. Participants should have the opportunity to ask questions and withdraw at any time without fear of negative consequences.
- **Comprehension:** It is the responsibility of the researcher to make sure that the participant understands all the information provided. If the study participant is not able to understand the information because they are a minor or are in some way mentally compromised, or otherwise legally incompetent, then the participant can only be enrolled if consent is provided by their legally authorized representative according to local laws.
- **Voluntariness:** Informed consent is valid only if it is given voluntarily without any coercion, biases, or undue influences in the form of excessive, unwarranted, inappropriate or improper incentives, and the participants understands and agrees to all the consequences.

- **Obtaining consent or signature and documentation of informed consent:** The researcher must obtain the participant's signature in writing (or written consent). Documentation of informed consent should be added to the study records. A copy of the complete signed informed consent form should be offered to the participant. The consent form includes the signature of the participant as well as study team that administered consent. In case the participant is not able to provide consent, proxy consent should be obtained in writing from the legally authorized representative according to national laws.

During the informed consent process, participants must be given enough opportunity to raise their questions, concerns and queries, and have these responded to adequately before deciding to participate in the research study. This information is usually provided in an information sheet, which the person obtaining the consent can give the participant or can read to them. The consent form should be written in simple local language to make sure that the study participant can easily understand the information. Informed consent must contain all elements required by relevant international and national standards, including GCP. When conducted correctly, informed consent protects an individual's freedom of choice and respects their autonomy.

2.4.2 Essential Elements of Informed Consent (Time: 50 minutes)

There are various essential elements of Informed Consent, which are given below:

(A) Description of Research: A description of the research is commonly presented at the beginning of the informed consent process, including a description of who is running the study and who the researchers are. It should clearly explain the problem that the study is trying to address as well as the relevance of the research for the community from where potential participants are being sought. The objectives of the research study should be presented, explaining what new information is sought. The anticipated period that participants will be in the study, including the number of follow-up visits (if applicable), the total number of participants, and where the study is taking place are

also included. The participant needs to understand what is expected or what he or she will have to do by agreeing to participate in the study. The participants must agree to the procedures required by the study, particularly if those procedures are interventional or present some risk or are experimental in nature. When the study requires the use of a placebo¹, the participant must understand that he or she may receive an inactive product or actually not receive any treatment at all if they are assigned to this group. The use of placebos often requires special attention in the informed consent document. The names of the sponsors and ERB/IRC/IRB that approved the research are also commonly included. There should be a description of the provision for addressing participants' queries and complaints during the course of the study and how the research results (including laboratory tests results) will be available to the study participants.

(B) Risks and Benefits: Each and every research study must be justified on the basis of a favorable risk/benefit assessment. The term "risk" refers to a possibility that harm may occur. The term "benefit" in research refers to something of a positive value related to health or welfare. The most likely types of harm to research participants are side effects from the study procedures or treatments or psychological harm (if research is sensitive in nature and someone might become stigmatized if it is known that they are on the study, e.g., an HIV study). In the case of stigma, there is also the risk of physical harm if participants are attacked because of being identified as having a socially unacceptable condition, such as HIV. Other kinds of harms include legal proceedings (arrest, prosecution), social (disclosure to family, workplace discrimination, isolation), economic (loss of employment, travel expenses), especially in case of vulnerable people like Female Sex Workers (FSWs), Client of Sex Workers (CSWs), People Living with HIV (PLHIV), Men who have Sex with Men (MSM), People Who Inject Drugs (PWID) should also be taken into consideration. The social risks may include stigma, discrimination, loss of respect, or public ridicule. All risks involved including the risk of loss of privacy must be explained to the participants in understandable terms. All attempts should be made to minimize harm to the individuals and society at large. Special consideration for the cultural characteristics

¹ The placebo is similar to the new drug or device being tested except that it does not contain the active ingredient in the new drug or device. Sometimes, this is called a "sugar pill". Placebos usually look, feel, and taste identical to the product being tested in the research study.

of the communities that are being studied is essential to prevent any disturbance to cultural sensitivities because of the investigation. Similarly, risks or side effects that may be associated with the product under study should be presented in the informed consent process.

Note: *When the research design involves no more than minimal risk, risk that is no more likely and not greater than that attached to routine medical or psychological examination, and it is not practical to obtain informed consent from each participant, the ERB/IRC/IRB may waive some or all of the elements of informed consent.*

The design of the study should ensure that the benefits of the study are maximized for the individuals and communities taking part in the study. Benefits are commonly presented as available only during the study, which means the benefits end when the research is completed. The duration of any benefit associated or derived from the research participation must be clear to the potential participants beforehand. Benefits include the potential for better treatment, either immediately or in the future, and financial benefits in terms of compensation for being on the study and free or reduced price of medical care.

Making precise judgments about the risks/benefits ratio might be difficult in some cases. However, the potential risks/benefits should thoroughly be discussed with prospective participants. Ideally in a study, benefits should outweigh risks or at least be equivalent in all groups being studied. Risks should be reduced to those necessary to achieve the research objectives. When research involves significant risk, extraordinary insistence on the justification for the risk is necessary.

Note: *Special care is needed in determining how benefits are presented in individuals with limited access to health care services. Offering free health care to individuals who would otherwise not have access to it is a powerful incentive to participate in a research study and is potentially coercive. Researchers are responsible for ensuring that potential participants' decisions are not clouded by the promise of health care or a potentially better (but unproven) new treatment.*

(C) Available Alternatives: It is important to present to the participant the existing alternatives or choices other than participation in the study. The participant should be given information on the advantages and disadvantages of the alternatives and be allowed the

opportunity of choosing between participating in the study or the alternatives. The informed consent form must describe treatment alternatives that are available or may be made available – including other options to participating in the research. For some study, there is no alternative – the only choice would be to not participate.

(D) Confidentiality: The informed consent form should indicate the degree of confidentiality that will be provided; the names of people or organizations that may review or have access to the research records, such as sponsors or regulatory agencies; the conditions in which the information will be kept confidential; and how long the records will be kept after the study ends. Confidentiality protects participants from adverse consequences that may arise from other people knowing that they participated or their responses. For example, if information about a person's sexual preference is disclosed, he or she may suffer discrimination, stigma or even be subject to criminal charges. It may be necessary to ensure that all study staff, even the drivers, and file clerks, understand the need to protect participant identity. Potential threats to confidentiality, as well as measures taken to minimize them, should be discussed with the participants as part of the informed consent process.

The main ways to ensure confidentiality include:

- Ensuring names or other means of identification are not recorded on study records.
- Storing data safely and appropriately and ensuring restricted access to only those that need the information.
- Training research staff on the importance of confidentiality.
- Having clear disciplinary procedures for staff who breach confidentiality.
- Identifying problems and possible solutions related to confidentiality.

Note: *Confidentiality extends beyond the duration of the study. Additional counselling on any anticipated future use of the information or biological samples gathered must also be provided, including the conditions under which such information might be used.*

(E) Compensation: There should be a clear provision about any compensation that may be available to the participant if a problem arises during the study. Information must be disclosed about the treatment that would be available and who would pay for it in

the case of complications or adverse events. It is the investigators' responsibility to provide medical services to the participants. Researchers must be aware of institutional and sponsor's policies on compensation in such cases. The possible lack of compensation for research-related complications must carefully be assessed by the ERB/IRC/IRB approving the research proposal.

It is generally considered appropriate to compensate participants for their time and travel. The amount of this compensation should be reasonable, based on local costs and commensurate with the extent of participation. Incentives can consist of cash payments for participation or small gifts, or Information, Education and Communication (IEC) materials, such as T-shirts or cap. In general, incentives are considered appropriate for compensating or thanking study participants for time away from work. However, higher payments may jeopardize the voluntary nature of informed consent. They can create a situation where an individual's decision to participate is unduly influenced by money or gifts.

Additionally, using incentives may result in a sample that is not identical to the population of interest because the sample is biased towards those who have a greater need for the incentive. This needs to be balanced against the fact that not using incentives may cause the sample to be biased towards those who are more cooperative. Any incentive provided must receive approval from the ERB/IRC/IRB.

Note: *Respondent-driven sampling provides incentives to participants to recruit additional members of the high-risk population to the study. These incentives can be considered 'payment' to the participant, who in their role as recruiters acts as field workers. This part of the methodology may be controversial in some settings and may require explanation to the ERB/IRC/IRB reviewing and overseeing the research study.*

(F) Participants Contacts: There should be a contact address of a person whom the participant may contact if they have any problems during the study. If any side effects, injuries or complications may arise during the conduct of the research study, the researcher should provide the contact details to the participants. A member of the study team is the typical contact person. Regarding questions related to the participant's rights, the name and contact address of the proposal

approving agency in Nepal should be provided in the informed consent form. All the contact addresses (postal addresses, telephone numbers, e-mail address) should be current. Contact persons from the study team and approving agency should be available at all times.

(G) Voluntary Participation: It is necessary to state that participation is absolutely voluntary. This element of the informed consent should include statements such as "Your participation in this study is voluntary, and you can discontinue your participation at any time without any penalty", and "I understand that I have the right to leave this study at any time for any reason whatsoever. I may cancel my consent and withdraw from the study without penalty." Moreover, this will not result in any loss of benefits to which the participant is, otherwise, entitled including health care.

Information included in the Informed Consent (as applicable to study design):

- i. The nature of the research study (for example, who is conducting the study, purpose of the study, target population, number of participants required in the study, time that each participant will be in the study, details of the study procedures and interventions, type of questions among others),
- ii. Research participant selection method (randomization or other methods),
- iii. Trial treatment (open leveled, single or double-blinding) including informing the participants that they may receive placebo or actual drugs,
- iv. Participants' responsibility to participate in the research study as prescribed by the research protocol once agreed to participate,
- v. The potential risks/discomfort and benefits from participating in the study,
- vi. Provision of whom to contact with questions, concerns and complaints, payment or compensation of their time and travel,
- vii. Provision of a DSMB (applicable especially in the case of clinical trial), and the contact information with name of the person or people involved,
- viii. The frequency and timing of study procedures and data collection,
- ix. How their clinical and physical examination related data (once obtained) will be provided to them,
- x. How their privacy will be protected (names or addresses are not written),

- xi. Participation is voluntary,
- xii. Participants have the right to refuse to answer any questions or stop the interview at any time, especially as they may find some of the questions sensitive,
- xiii. How they could withdraw from the study once informed consent and data has been obtained,
- xiv. The collected data will be utilized only for the specific research study, not at all for other purposes,
- xv. The duration of data storage,
- xvi. Compensation for study-related injury/adverse events (if any, applicable especially in the case of drug/vaccine/device trial) occur during the study period,
- xvii. Provision of providing health care or treatment or counseling (if required) once the participants has been enrolled in the research study,
- xviii. Whom to contact for further information, and
- xix. Explanation of situations where the study or their participation might end early.

The participant involved must have the legal capacity to give consent.

That the participant or their legal representative will be informed in a timely manner of new information that might affect their willingness to remain in the research study.

That monitors, auditors, representatives of the ERB/IRC may inspect their research study data so as to verify the quality of the research and help to protect research participants.

The anticipated expenses that research participants will have to pay (if any) for taking part in the research study.

Features of Informed Consent

- Informed consent should be prepared in a language understandable to the research participant. If there are illiterate participants, literate people who speak the native language of the participant must read the informed consent to him/her.
- Study title along with its major general objective(s) of the research study needs to be mentioned. It is also essential to include who is doing the study, how participants can join the study, what will the researcher do, what is expected of the research participant to do, what are the alternatives to participation.
- Information should be provided in an understandable language about the procedure to be adopted in the study, and the potential risks, discomfort and benefits involved.
- If significant time commitment will be required, study team should compensate for time in the form of a small payment (or equivalent) for participation.
- Participation should be voluntary, which means participants are free to choose whether to join the study or not.
- The study team should explain under what circumstances participants will be compensated for study-related injury.
- Special attention needs to be given while taking consent from a vulnerable person. This requires a witness and a legal representative.
- While taking consent from a child/adolescent (aged 7 to below 18 years), to the extent possible, assent must be obtained in addition to their legal guardian giving proxy consent for their participation.
- Sometimes written consent might not be needed or appropriate for people who are literate and competent, for example, verbal consent from sex workers in a bar where having them sign a consent document would draw attention to them.
- Confidentiality and anonymity should be maintained.
- The consent form should contain a statement such as "I have been given an opportunity to ask questions concerning the procedures to be used in this research study and I have had all my questions answered. I understand if I have further questions concerning the research study conducted, I may contact the study team at any time. I also understand that I may leave the study at any time if I want to and there will be no penalty for me".
- There should be a space for a signature or thumb print by the participant and one of the study team members. A third party as a witness might be required if the participant is illiterate.

2.4.3 Types of Consent (Time: 25 minutes)

Basic types of consent are as follows:

Informed Consent: A process by which a research participant voluntarily confirms his or her willingness to participate in a particular research study. This consent should only be sought after all appropriate information has been given about the research project, its objectives, potential benefits, risks and inconveniences, and of the research participant's

rights and responsibilities in accordance with the Declaration of Helsinki. The research participant needs to understand the information given to them.

If the participant signed the consent form, the consent would be termed signed informed consent, which has legal validity as otherwise it would be termed as verbal informed consent.

Verbal Consent: It is usually not recommended but can sometimes be considered if having a documented consent process might put the study participant at risk, e.g., interviewing a commercial sex worker in a bar might draw attention to them. If verbal consent is felt to be warranted, this is only possible after obtaining ERB/IRC/IRB's approval. For example, in an HIV surveillance study, in order to ensure total confidentiality, it is usually best to obtain verbal consent. This means that the name of the respondent does not need to be recorded. There still needs to be some way of verifying consent, but rather than the participant's signature, interviewers can sign a statement to verify that the respondent has been given the required information and has voluntarily decided to participate.

Note: *Some researchers have started to use the phrase "understood consent" instead of "informed consent". The meaning is the same, but the sense of putting the word gives some clarity that the participant understood the consent and signed it accordingly. Researchers argue that only giving information does not guarantee that they have understood which might be the case while using the word "informed consent".*

Proxy Consent: This is basically a third party providing consent on behalf of the research participant. This kind of consent is taken when dealing with vulnerable populations such as children, mentally ill patients, etc.

Note: *Persons aged 7 to below 18 years need to provide written assent apart from taking written informed consent from their legal guardian (proxy consent).*

Partner's Consent: Sometime researchers need to have consent from his/her spouse as the treatment might have an effect on their partner. In this circumstance, partner's consent might need to be sought. For example, the researcher is trying to test the effectiveness of a topical sex cream which is applied to the sexual organs to see if it increases sexual pleasure. In this situation, his/her spouse needs to know about it as the cream used by one will ultimately be in contact with the other during their sexual act.

Community Consent: When the participant is culturally dependent on the decision of the head of the family or community, it is necessary to have community consent, which can be done through village leaders, tribal leaders.

Note: *Researcher must obtain informed consent in accordance with the procedures of the specific study protocol before beginning any research interventions or discussions.*

2.4.4 Class Exercise (Time: 30 minutes)

The facilitator should ask in the class, "How would you take consent in the situation outlined in the case study, and what kind of consent would be taken?" and ask them to write their responses on flip chart paper.

Case Study: Taking Consent from Children

Typhoid fever is a common infection among children in developing countries. An injectable vaccine is available for use as a preventive measure. However, children do not tend to like injections and so recruitment to a vaccine study may be difficult. Therefore, an oral vaccine would be the ideal alternative and attempts are being made in some laboratories to find a good, safe and effective one.

Existing oral vaccines which are available for prevention of typhoid infection are not very effective. The Microbiology Institute developed an improved version of this vaccine. Phase II clinical trials have shown that the vaccine is safe and appears to have some level of effectiveness in preventing the infection. The drug is now ready for phase III clinical trial.

The Children's Home was selected for the study. The Home used to report one or two cases of typhoid fever in a month. Most of these cases were seen among the new children. Children were randomly assigned to receive the new oral vaccine or placebo. The Director of the Children's home ordered that all the children should participate in the study. At the end of six months, 20 children who did not receive the vaccine were affected by typhoid fever. These were mainly among the older children in home.

2.4.5 Group Exercise (Time: 65 minutes)

The facilitator should randomly divide all participants into smaller groups consisting of five to eight people. The following case study needs to be provided to each group.

Case Study: Issues in Informed Consent

A grant has been given by a foreign university to a specific department of the MoHP of Nepal for the purpose of conducting a double-blind study to evaluate the impact of periodic doses of high-dose Vitamin A on the incidence of diarrhea and Acute Respiratory Infection (ARI) in children less than five years of age in a particular community**. A traditional leader and a group of elders govern the community in its daily affairs. The village was called together by the Chairperson and the group of elders to inform the community of the impending study. In a festive environment, the investigators of the study answered all questions from members of the community (men, women, and children) and the group. After the description and the question-and-answer period, the village Chairperson and the group met briefly and gave their approval. Shortly there after, in accordance with the guidelines provided by the IRC/IRB of the university and ERB of the NHRC, the Principal Investigator (PI) and his field staff began going from house to house to obtain signed informed consent from parents to give permission for their children to participate in the study. The mothers (usually the parent at home during the visit) said that since the Village Chairperson had already approved, they did not need to sign anything because they cannot read what they are signing.

On the second day, the field team making the home visits to the Chairperson's house where they were politely informed that approval had been given for the study and it was both unnecessary and unacceptable to seek individual signatures. The fact that the Chairperson's/group's approval was enough. When the field staff said that they were required by the ERB

of NHRC to obtain signed informed consent, they were told that they would have to leave the community if they insisted on doing so.

Questions

1. Should the Village Chairperson and the group of elders be allowed to provide informed consent for the community?
2. How critical is the requirement of individual informed consent in this setting?
3. Is informed consent culturally bound or is it a universal principle that cannot be compromised?
4. Are there circumstances when individual informed consent is unnecessary?
5. How should the field staff handle this problem?
6. What are some ways a researcher might determine how a participant has suitably been informed and obtained informed consent?

**A summary of the study design is as follows: High-dose vitamin A capsules or placebo would be administered in a double-blind fashion every four months for one year to children between the ages of six months and five years. A weekly record of morbidity (diarrhoea and ARI) and mortality would be maintained and blood samples would be drawn (less than 1ml) at 0, 6, and 12 months for Vitamin A status.

The facilitator should give at least 15 minutes to read such statements critically and ask them to discuss among themselves for 15 minutes. The facilitator should ask them to try to come up with answers of the above questions. This might take another 15 minutes. Immediately after that, these answers will be presented during a plenary session, which will be conducted for 20 minutes.

2.5 Module 5 **Informed Consent – II**

Learning Objectives:

By the end of the session, the participants will be able to:

- Define vulnerable people and their consent,
- Describe the various issues related to privacy and confidentiality,
- Describe the process of consent documentation including re-consenting process, and
- Illustrate its applications with different examples including case studies.

Time Frame: 180 minutes

Materials: Flip Chart, Board Markers, Computer, Audiovisual Equipments with LCD Projector and Screen

Teaching Methods/Process: Lecture, Brainstorming, Plenary session, Assessment/presentation, and Discussion

Course Contents:

- Consent from vulnerable people
- Privacy and confidentiality
- Documentation process of consent and re-consent

Game

- The snake

Group Exercise:

- Case Studies
- Small Group Discussion

2.5.1 Game (Time:20 minutes)

The Snake

Objective: To energize all the participants and make them laugh

The facilitator should ask all the participants to stand up and form a line. Everybody looks in the same direction and places their hands on the shoulder of the person in front of him/her. The first person is the head of the snake; the last one is the tail. Now, the head tries to catch the tail, the tail moves away in order not to be caught. It is very fast games which does not need any preparation and makes everybody move and laugh.

2.5.2 Consent from Vulnerable People (Time: 40 minutes)

The facilitator should ask the participants to discuss different categories or type of persons they think are vulnerable research participants and write their responses on flip chart paper.

The CIOMS has referred to vulnerability in the following terms: "Vulnerability refers to substantial incapacity to protect one's own interests owing to such impediments as lack of capacity to give informed consent, lack of alternative means of obtaining medical care or other expensive necessities, or being a junior or subordinate member of a hierarchical group".

Those who cannot protect themselves and their choices are basically termed as vulnerable people. These include people with certain diseases or conditions, the mentally ill (mentally impaired), children and old people, HIV high-risk groups, PLHIV, FSWs, MSM, PWIDs, illiterate, poor, pregnant women, tribal, uniform service people (military, armed-force, police), and prisoners. These group need to be taken into special consideration as they need special protection. We need to provide specific justification if we are going to include these sort of vulnerable people in research. **Proxy consent** (third party will provide the consent on behalf of the study participant) might be needed in some instances such as adolescent, children, mentally ill patients.

Note: *Countries may have laws and standards about the age at which an adolescent can participate in research without their parents' consent. You should familiarize yourself with these laws before starting the study in any given country. In Nepal, people aged 18 years and above can consent without their parents' or legal guardian's consent (proxy consent). Even though the legal guardian of an adolescent or child or a person with a mental disorder gives the actual consent for participation in research, whenever possible, the **assent** of the child/adolescent (aged 7 to below 18 years) or the person with a mental disorder, to the extent possible, has to be obtained.*

Working with HIV High-risk Groups: Some high-risk groups such as MSM, CSWs, FSWs and PWIDs may be engaged in illegal or stigmatizing behavior. If high-risk group members fear that information about their behavior or HIV status may be used against them, they may refuse to participate in the study process. So, great care should be taken into consideration when dealing with such participants, and researchers must take all necessary steps to protect their privacy.

It is important to adhere to the following rules when undertaking the process of informed consent.

- Ensure that the consent is taken in a private place.
- Consent is an individual process and only one participant should be consented at one time.
- The informed consent process should be conducted in the native language of the research participant and translator should be present if needed.
- The discussion on informed consent needs to be conducted by maintaining privacy and confidentiality.
- In particular, check that the research participant understands all of the information about the research study, what he or she is expected to do and what are the potential risks and benefits.
- Allow the research participant plenty of time to understand the information, ask questions and consider the answers.
- Allow research participant to consult with others about the study if desired.
- Offer, but do not force, the research participant to take a copy of their signed informed consent form.
- Provide adequate support to the research participant for their time only in accordance with what has been approved by the ERB/IRC/IRB.
- Do not make any statements that contradict or stretch what is written in the consent form.
- The right of the research participants to refuse to participate or withdraw from the research at any point of time needs to be ensured.

Note: When studying vulnerable populations, you may find that certain practices or diseases generate stigma, e.g., people who are HIV positive or who have TB. In other cases, some of them may be engaged in illegal activities/behaviors, e.g., injecting drugs, selling sex. In those cases, people may be unwilling to come forward for a study in case others find out about them. In these cases, assurance of total anonymity and privacy is even more important and critical. Steps that can be taken to minimize threats to confidentiality may include:

- Consent must be taken one person at a time.
- Conduct interviews in private settings that cannot be overheard or seen.
- Do not put signs outside the research study clinic about the nature of the study, i.e., do not label the building "HIV Study Clinic" or "Counselling Centre for Drug Injectors"
- Keeping study documents in a locked, limited-access room.
- Having all research study team including field staff sign confidentiality forms and undergo training in research ethics.
- Do not use the participants' name on any research study documents and only use an identifying code number. Only have one list of name versus identifying code number and keep this list under strictly controlled, limited and restricted access.

If people fear that information about their behaviour or the disease they might have will be disclosed, they may not give you accurate data. Preserving absolute confidentiality of all research participants in a research study is vitally important but particularly critical for any vulnerable or stigmatized groups. In those cases, confidentiality is also protecting them from other's learning of their behaviour and practices which could lead to social, economic, physical and personal loss.

2.5.3 Privacy and Confidentiality (Time: 30 minutes)

The facilitator should ask the participants to discuss the meaning of privacy and confidentiality and write their responses on flip chart paper.

Privacy is the protection against interference into personal affairs, while confidentiality is the trust that responsible persons to whom private information has been disclosed will refuse to share the information with others.

Note: Private information is the information which the individual reasonably expects to be unknown or the information that the individual provides to another with the reasonable expectation that it will not be shared.

The investigator must safeguard the confidentiality of research data, which might lead to the identification of the individual research participants. Data of individual research participants can be disclosed only in a court of law under the orders of the presiding judge or in some cases by a regulatory agency under a "for-cause" investigation of submitted research data. The ERB/

IRC/IRB can also request individual data if they have genuine concerns about the safety of the research participants. Therefore, it is important to maintain only one single list of research participant names against identifying code numbers, but this list must strictly be controlled and kept under lock and restricted access. This list must not be copied or given to anyone unless they have a court order or similar authority.

For example:

Confidentiality in leprosy research: Leprosy is a stigmatized disease, so lepers are a vulnerable population. Involving this population into the research study may put them into the risk of social discrimination. These risks include:

- Loss of *confidentiality* or accidental identification as a leper,
- Negative reactions/outcomes from the public or family members, and
- Loss of job.

Certain considerations must be taken into account when attempting study in this population, including the *stigma* associated with being lepers, which prevents many from being open about their disease condition.

Confidentiality protects research participants from the negative consequences that may arise from participating in a research study. We need to be aware regarding Nepal's laws requiring reporting of individuals with leprosy infection; otherwise, this may complicate participation.

Following steps can be taken to minimize potential threats to their confidentiality:

- Conducting interviews with lepers in private settings and only one person being interviewed at any one time,
- Limiting access to any identifying information to authorized personnel,
- Keeping research study documents in a locked, limited-access room, and
- Having all staff sign confidentiality forms.

Explaining these issues to them is part of the *informed consent* process.

Confidentiality in Sex Workers Research: Sex workers are a vulnerable population because sex work is *stigmatized* and often considered illegal in Nepal.

Their participation in research activities put them at risk of harm and discrimination. These risks include:

- Loss of confidentiality, accidental identification as a sex worker,
- Accidental disclosure of HIV status,
- Negative reaction/outcome in response to publicized results,
- Physical abuse by their agents or handlers, and
- Loss of income.

Consider your ability to obtain true *informed consent* when sex workers may be coerced to participate or not participate by their agents or other handlers. Confidentiality protects research participants from the negative consequences that may arise from participating in a research study. We need to be aware of any of Nepal's laws that may complicate participation.

Following steps can be taken to minimize threats to confidentiality:

- Conducting interviews with sex workers in private settings and only one person being interviewed at any one time,
- Keeping the names of the sex workers separate from the research data collected about them,
- Limiting research access to any identifying information to authorized research study personnel only, and
- Keeping research study documents in a locked, limited-access room.

Confidentiality in HIV and AIDS Research: If a person's HIV status becomes known, he or she may suffer stigma, discrimination, and/or other consequences. Be aware of any particular provisions in Nepal's laws that may complicate participation. These may include:

- Laws around age of legal adulthood, including when adolescents can consent to participate in the research studies,
- Laws prohibiting sex work or under-age sex work according to law,
- Laws prohibiting men to have sex with men,
- Laws prohibiting injection drug use, and
- Laws requiring reporting of individuals with HIV infection.

People asked to participate in a study should understand potential threats to their confidentiality. They should also understand the steps that the investigators will

take to minimize them. Explaining these issues to them is part of the informed consent process.

Ensure Interviewer Safety: Conducting HIV study among PWIDs requires face-to-face contact with drug-dependant persons who may have criminal histories, psychiatric conditions and/or violent tendencies. These persons may pose a risk to the interviewer's safety. Interviewers should be trained on how to assess intoxication and ensure their own safety.

Confidentiality in Group Discussion: Researcher needs to say "participation in this discussion will involve in a loss of privacy, but information about you will confidentially be handled. We will not reveal your full name to other participants and at no time during the group discussion will your name be written down in connection with the information you have provided. We will ask you to use only your first name or to choose a fake name. We will also ask you and the other participants not to tell anyone outside of the group what any person said during the discussion. However, we cannot guarantee that everyone will keep the discussions private. Study records will be kept as confidential as possible. All tapes and transcripts of the discussion will be kept in locked filing cabinets and only members of the research study team will have access to them. Your name or any other research data that might identify you will not be used in any reports or publications resulting from this study".

2.5.4 Documentation Process of Consent and Re-consent (Time: 20 minutes)

The documentation process starts with the consent form being signed by the research participant or his/her witness, or both, and one of the study team members. Signatures on the consent form verify that the research participant has understood the process and has voluntarily agreed to participate. In the case that the signature is not possible, the research participant may be asked to give a thumbprint or make a mark as evidence that he or she received the information and agreed to participate in the study. However, a signature does not necessarily mean that the participant has understood and given voluntary consent. The Declaration of Helsinki suggests that "after ensuring that the research participant has understood the information, the researcher should then obtain the participant's freely given informed consent, preferably in writing". Sometimes the name of the research

participant does not necessary need to be recorded, but it has to be mentioned in the coded form.

It is important to realize that the need for documentation will vary according to the setting of the research study. For some type of research – low-risk survey research, anonymous survey methods, stored tissue research, or retrospective analysis – some of the elements may not apply or require the research participant's signature, and in some locations, participants may be uncomfortable signing forms. In such cases, the ERB/IRC/IRB responsible for the research study determines and approves the method of documenting some or all of the required elements, or not documenting, informed consent.

Note: *Waiver of informed consent could also be considered during conditions of emergency. However, this would be permissible only if ERB/IRC/IRB has already approved the research study or use of the drug, and its use in life-threatening conditions. However, the patient or the legal guardian should be informed after she/he regains consciousness or is able to understand the research study.*

There are four criteria for allowing a waiver:

- Research should involve no more than minimal risk to the research participant.
- A waiver will not adversely affect the rights and welfare of the research participants.
- The research cannot be conducted without the waiver and it is not possible to obtain the consent of the research participant, e.g., testing on patient samples when the patient has already died.
- When appropriate, the research participants will receive additional pertinent information after their participation ends.

Sometimes research participants may need to be re-consented when new information becomes available about the research study like the drug/device/ intervention or new safety information becomes available. This also must be fully documented. Re-consent must take place following all the same procedures as for the original consent and no steps can be skipped or shortened.

Note: *Ethics Codes states "consent in research is a process, not a one-off event, and may require re-negotiation over time; it is an issue to which the researcher should return periodically".*

Completed consent forms and re-consent forms should be kept properly in locked file cabinet. The only people permitted to look at these documents include authorized members of the research study team, members of the ERB/IRC/IRB and study monitors sometimes representing the sponsor. Regulatory agencies can only see these documents if they have a court order or equivalent authority to review the research study data.

All of these consent forms must be retained on file for at least three years after completion of the research study. Sometimes these need to be kept longer according to the requirements of specific study sponsors/funding agencies/regulatory bodies.

Note: *Sometimes written consent from some specific population like sex workers in a bar would not be possible, so in those circumstances where having them sign a consent document would draw attention to them, verbal consent would be appropriate, wherein researcher explains about the purpose of the study and informs them how important their responses are. After assuring them absolute privacy and confidentiality, the researcher may take their verbal consent. The researcher should document this verbal consent in study records stating where and when the consent process was conducted and verbal consent was provided.*

2.5.5 Group Exercise (Time: 70 minutes)

The facilitator should randomly divide all the participants into smaller groups consisting of five to eight people. The following case study needs to be provided to each group.

Case Study: Confidentiality Issues

Leprosy, an endemic disease prevalent in some parts of Nepal, is widely stigmatized. In rural Nepal, people still believe that leprosy is contagious and ritually unclean and that the disease is a divine punishment for sins committed in previous lifetimes. This causes fear towards leprosy-affected people and can lead to exclusion, isolation and separation from family, friends and community. Literature review showed that most of the people said, "It is undesirable to marry someone who has been or is affected by leprosy". Often only the diagnosis of leprosy may carry stigma that may cause a psychosocial impact on the individual. This psychosocial impact may cause greater burden than the development of disabilities. It is estimated that 15 percent of the world's population has a disability, with 80 percent of people with a disability living in low- and middle-income countries (WHO, 2012), among which 74

percent were female population. These women and girls are facing difficulty in getting married. Females with a disability are often not considered to be "marriageable" because of fear that their children will inherit the "defect" and because of assumed incapability to perform certain roles in the house. In this context, the investigator thought that the similarities and differences between the influence of leprosy and other disabilities on prospects of marriage have not been researched, and so the study has been planned to conduct in Nepal. The researcher is trying to assess the possible influence of leprosy and leprosy-related disability on the prospects of marriage and marital relationships by comparing women affected with leprosy, women with other disabilities, and women from the general population.

Nepali or local language (wherever required) needs to be used during the interview phase. The interviews need to be conducted privately. Some local interviewers can also be hired for this purpose.

Their disability status have been categorized into seven categories, and the severity of the impairment due to leprosy has been scored as per WHO disability grading system.

All the research participants were asked to sign an informed consent. The data have been collected. Although most of the participants were interviewed only once, some were interviewed twice. This was because of the supervisor's recommendations as some of the section of the interview sheet was not filled during the interview phase and the supervisor requested the local interviewers to locate these participants and took their interview once again.

During the study period, supervisors reported the following incident to the PI:

"While observing interviewing procedures at the rural settings, I noticed that a local interviewer was trying to locate the women by name and her leprosy and disability status. In another setting, I also noticed that some interviewers allowed one of their family members to be sitting with research participant during the interview process. I was not pretty sure whether it was a demand by the research participant or not. One of the community people said to me that his neighbour has recently been found with leprosy disease. When I asked him how came he knew about it? He said to me that one of our local interviewers suddenly told him about this while searching for a woman for second-round interview."

He was not sure how to respond to this situation. The practice may be putting the participants at risk due to failure to protect their confidentiality.

Questions

1. Is it worthwhile to go for second-round interview even though some of the section of the interview sheet was not filled?
2. Is it necessary to locate a research participant by name and her leprosy and disability status?
3. Is it necessary to allow one of their family members to be sitting with the research participant?
4. What might have been lacking during training of these interviewers?
5. How serious is the situation as one of the community people knew that his neighbour has been found with leprosy disease (which was unintentionally revealed by the local interviewer)?
6. Should the PI undertake any action? If so, what should it be?
7. What advice should the PI give to the field supervisor?

The facilitator should give at least 15 minutes to read such statements critically and inform them to discuss among themselves for 20 minutes. The facilitator should tell them to come up with answers to the above questions. This might take another 15 minutes. Immediately after that, these answers will be presented during a plenary session, which will be conducted for 20 minutes.

2.6 Module 6 Responsibilities of Institutional Review Committees/Board – I

Learning Objectives:

By the end of the session, the participants will be able to:

- a. Define IRC/IRB, its main purpose and composition,
- b. Define research participants, and their rights during research process,
- c. Describe the various safety and quality issues of the research participants during research process,
- d. Enumerate the various steps of competent review of protocol, and
- e. Illustrate its applications with different examples including case studies

Time Frame: 180 minutes

Materials: Flip Chart, Board Markers, Computer, Audiovisual Equipments with LCD Projector and Screen

Teaching Methods/Process: Lecture, Brainstorming, Plenary session, Assessment/ presentation, and Discussion

Course Contents:

- a. Protection of rights of research participants
- b. Safety of research participants and quality of research data
- c. Competent review of protocol

Class Exercise:

- Case Studies
- Interactive Session

Group Exercise:

- Case Studies
- Small Group Discussion

2.6.1 Protection of Rights of Research Participants (Time: 30 minutes)

The facilitator should ask the participants, "What do you understand by IRC/IRB, and its main purpose?" and write their responses on flip chart paper.

An IRC/IRB is a group of people from different backgrounds. The main role of IRC/IRB is to conduct

independent review and approve the research proposal prior to initiation of the research projects. The main purpose of IRC/IRB is to ensure the protection of the rights and welfare of research participants participating in the research study. This is more important than the interests of the researcher or the institution in which a study will take place.

The facilitator should ask the participants, "What is the meaning of research participants, and their rights during research process?" and ask them to write their responses on flip chart paper.

The human beings selected for the research study purposes are termed as research participants. The rights include freedom, such as the right to join the research or not, the right to withdraw from the research at any time without penalty, to be free from discrimination and involuntary medical treatment. It has a particular concern for the vulnerable population.

Legally binding recognitions of the right to health have been made in several international instruments, including International Covenant on Economic, Social and Cultural Rights (1966), the UN Convention on the Elimination of All Forms of Discrimination Against Women (1979), the UN Convention Against Torture (1984), the UN Convention on the Rights of the Child (1989), and the UN Convention of the Rights of Persons with Disabilities (2008).

The protection and promotion of human rights was guaranteed by the Constitution of Nepal (1990). The Interim constitution of Nepal (2007) provides the right to health and environment as a fundamental right of the citizen of Nepal. The constitution has clearly stated : (1) Every citizen shall have the right to get free basic health services from the State, and (2) every person shall have the right to live in a clean environment. The NHRC Act (1991) has given more emphasis to regulate various kinds of health research activities in the country. This is basically to protect the rights and safety of human participants involved in the health research.

Civil Rights Act (1955) is explicit to provide civil rights and not discriminate any citizen on the ground of religion, color, gender, caste, and tribe. This Act also gives the power to provide for special provisions to the female, children and underprivileged class of citizens.

Right to Information Act (2007) was first recognized by the Constitution of Nepal in 1990 and later in the Interim Constitution in 2007. Article 27 of this Act states that every citizen shall have the right to ask for information that is of individual and common interest, and right to access required information from public institutions and agencies. Therefore, research participants have all the rights to know about the research protocol, and their rights must be protected during the research process.

For protection of the rights of the research participants, the ERB/IRC/IRB should at first document the thorough inspection of the ethical concerns of the research protocol, and review the suitability of the investigator(s) and the study site. The main responsibility of an ERB/IRC/IRB is to confirm that the research study is developed on the scientific basis which can address its study objectives and the potential benefits outweigh the risks.

In order to protect the research participants, every efforts should be carried out to minimize any kinds of risks that can occur during the research period (both by preventing potential harms and minimizing their negative impacts), and also effort should be made to maximize the potential benefits of the research participants at the same time.

The nature of risks may vary with the type of research studies. The ERB/IRC/IRB should be aware of risks that may occur in different dimensions (e.g., physical, social, financial, or psychological), which require serious considerations. Further, harm may occur either at an individual level or at the family or population level. The ERB/IRC/IRB should ensure the area that participants/communities to be invited in the research process is selected in such a way that the burdens and benefits of research will equitably be distributed.

The researcher or the sponsor of the research study is expected to ensure compensation in the case of research-related injuries. The ERB/IRC/IRB should consider these plans as a part of their review process.

Any invasions in the privacy of research participants and any breach of confidentiality are disrespectful to participants that may lead to loss of trust, as well

as tangible harms such as social stigma, rejection by families or communities, or loss of opportunities including employment and housing. Therefore, the ERB/IRC/IRB should examine precautions to be taken during the research process to safeguard research participants' privacy and confidentiality.

The ERB/IRC/IRB should protect all the rights and safety of the research participants. These include review of the protocol and consent, recruitment materials, assessing prior data on the drug/device and others.

2.6.2 Safety of Research Participants and Quality of Research Data (Time: 30 minutes)

The facilitator should ask the participants, "What is the meaning of safety and quality?" and ask them to write their responses on flip chart paper.

Usually safety and quality are considered to be two sides of a coin. Generally, it is accepted that giving quality services/products will ultimately ensure the safety of the patients, which is always not true. Quality itself does not ensure safety. So sometimes a high-quality research protocol may fail to protect safety of research participants. Therefore, a constant supervision and monitoring is required during research period.

In the same way, there should be a quality function of ERB/IRC/IRB, so that it can safely protect both the research participants and the investigators as and when necessary. It should follow accepted systems and procedures so that consistent ethical review is assured. For example, an ERB/IRC/IRB with a Federal Wide Assurance (FWA) number is known to give the same level of review as other IRBs with that number.

The entity establishing the ERB/IRC/IRB employs reliable means to evaluate whether the staff and members of the ERB/IRC/IRB routinely follow the ERB/IRC/IRB's policies, rules, and written procedures, with special attention to whether the ethical considerations articulated in international guidelines and national standards are being considered and applied consistently and coherently, or not.

Such evaluations are conducted by knowledgeable and unbiased people at regular, pre-defined intervals using a pre-defined format; internal assessments are supplemented periodically by independent external evaluations. For example, regulatory agencies such as NHRC in Nepal have the right to inspect IRBs/IRCs as well.

The entity establishing the ERB/IRC/IRB is committed to consider and, when appropriate, follow up on the findings and recommendations of the internal and external evaluations.

The results of the evaluation are of a type that can aid the ERB/IRC/IRB in reviewing its practice and appraising performance (rather than apportioning blame), while also assuring the public that research is being reviewed according to established standards.

Researchers, research participants, and other interested parties have a means of lodging complaints about the ERB/IRC/IRB; if possible, such complaints should be reviewed by an entity other than the ERB/IRC/IRB itself, and appropriate follow-up actions should be taken.

Written Policies and Procedures of ERB/IRC/IRB: The entity that creates the ERB/IRC/IRB has a responsibility to establish the necessary policies to govern the ERB/IRC/IRB. The ERB/IRC/IRB adopts its rules of procedure and—with the secretariat/staff—promulgates comprehensive, written procedures, which are distributed to all members. To the fullest extent possible, the hosting institution provides ERB/IRC/IRB with a secretariat whose staffs have the necessary knowledge, expertise and training to support the ERB/IRC/IRB in performing its review and record-keeping function. The ERB/IRC/IRB policies and rules typically address the following topics.

Membership: The ERB/IRC/IRB's policies and procedures explain the authority, the terms, and the conditions of appointment. The number of members in the ERB/IRC/IRB will, in general, depend on the number of fields from which they will be drawn. According to international law, an ERB/IRC/IRB must have at least five members in order to have a quorum. One of these five people needs to be a non-scientific person. In Nepal, in general, the IRC/IRB often have more members than this; a minimum of seven and maximum of 15 are suggested taking into consideration gender, age and discipline. The ERB/IRC/IRB should include at least one member who is not affiliated to the institution.

The composition of an ERB/IRC/IRB as constituted in Nepal is as follows:

- A person with sufficient knowledge of public health/epidemiology/research methodology.
- A person with expertise in bio-medical/laboratory science.

- A person with expertise in clinical science.
- A person with expertise in nursing field.
- A person with expertise in behavioral and social science.
- A person with expertise in statistics.
- A person with expertise in pharmacy/pharmacology.
- A person with expertise in legal matters and/or ethics.

One of the above must be a non-scientist. Members can fulfill more than one role.

Governance: The ERB/IRC/IRB's policies and procedures define how the ERB/IRC/IRB will establish its offices (e.g. Chair, Vice-Chairs). The Chair is someone respectful of divergent views, able to encourage and help achieve consensus, and with the time to prepare adequately for meetings. The Chair is not a person who has a supervisory relationship toward other members.

Independent Consultants: The ERB/IRC/IRB's policies and procedures define the circumstances under which an ERB/IRC/IRB may call upon independent consultants to provide special expertise to the ERB/IRC/IRB on specific issues of the research protocols. Such consultants cannot decide anything during ERB/IRC/IRB meeting, but he/she may provide his/her opinion. Moreover, the consultant is never considered as a voting member of the ERB/IRC/IRB.

Submissions, Documents Required for Review, Review Procedures, and Decision-making: The ERB/IRC/IRB's policies and procedures describe the requirements for submitting an application for review, including the forms to be completed and the documents to be submitted. They also specify the process and procedure for review, process for coordinating review with other committees, process for setting up meetings, circulating documentation for the meetings, inviting non-members of the ERB/IRC/IRB, approving the meeting minutes, and any related process issues. Procedures for deliberation and decision-making are clearly established and described. Specific quorum requirements for reviewing and making decisions or taking actions are clearly established in the standard operating procedures (SOPs).

Communicating a Decision: The ERB/IRC/IRB's policies and procedures describe procedures for communicating the decisions of the ERB/IRC/IRB and specify the maximum amount of time between the

decision about the application and when the applicant is informed. Decisions should be made by a meeting that has a proper quorum. All relevant documents must be present before a decision can be made. The ERB/IRC/IRB members should arrive at a pre-defined method for arriving at a decision and this could include unanimous vote, majority vote, closed or open voting. In some situations when the members cannot meet in person but perhaps 'meet' by phone, then votes can still be taken if a quorum exists and systems have been established and documented for phone-voting.

Follow-up Reviews and Monitoring of Proposed Research:

The SOPs describe the process by which ERB/IRC/IRB's will follow up the progress of all approved studies—from the time that the approval decision is taken until the termination or completion of the research. The date that the ERB/IRC/IRB approves the protocol initially is the date when, at a minimum, the study should be re-reviewed every year. In their approval letter, the ERB/IRC/IRB should specify the approval period which can be no greater than one year but can be less if the ERB/IRC/IRB feels that earlier review is needed to ensure the safety of the research participants. For example, if annual review is required and the protocol was first approved on March 3, 2014, but researcher could not able to initiate the study even within one year period from the date of approval, re-approval must be sought and granted not later than March 2, 2015. If re-approval is not obtained by the required due date, all study procedure must stop until re-approval has been obtained. On the completion of a study, a close-out report must be submitted to the ERB/IRC/IRB.

Documentation and Archiving: All of the ERB/IRC/IRB's documentation and communication is dated, filed, and archived according to the written procedures. Records may be kept either in hard copy or electronically. In either case, sufficient safeguards are established (e.g., locked cabinets for hard copy files, password protection and encryption for electronic files) to maintain confidentiality. The ERB/IRC/IRB staffs are sufficiently trained to understand their responsibilities related to record-keeping, retrieval, and confidentiality. There should be a procedures who is authorized to access the files and documents.

2.6.3 Class Exercise (Time: 30 minutes)

The facilitator should ask the participants to read the

following case study and discuss on the questions as stipulated.

Case Study: HIV-positive Man and His HIV-negative Wife

Suppose a study is ongoing to find out the HIV infection in the suspected cases residing in a rural community. A 50-year-old man was admitted to the hospital with multiple non-specific symptoms for investigation. His HIV test turned out to be positive. Without informing the man about the test or its outcome, the investigator (doctor) discussed the situation with the patient's wife and encouraged her to undergo HIV test. She turned out to be negative. Though the wife was quite upset about the situation, she showed that she was a bold woman. She asked the doctor several questions on the disease transmission, treatment and curability. Later, she came to the doctor and made just one request, since the husband and wife were living with the wife's brother, "please don't tell my brother that my husband is HIV-positive. We are laborers without any land and need my brother's help for shelter and survival. If he finds out about this, he may ask us to leave the house."

Questions

- The test was carried out without his knowledge and consent. Describe the ethical problems involved in this action.
- Consider the fact that no counseling can be done without informing the patient of the diagnosis. Do you think that not obtaining informed consent is a barrier for counseling? Discuss the ethical implications.
- Can you think of any situations where HIV testing is justifiable without the consent of the patient? Explain why, and identify ethical problems.
- Do you think that the doctor in this case was justified in adopting this testing procedure and managing the information in this way?
- What would you do next in this case?

2.6.4 Competent Review of Protocol (Time: 40 minutes)

Generally the proposal reviewers should hold an appropriate educational degree and trainings in health-research process, but there might be reviewers who review the protocol from a faith-based perspective. They should be capable and interested to review the research proposals. These experts/consultants could be a specialist in specific diseases, particular health

problem/condition, health systems, health-research methodologies or legal or ethical aspects or member of special interest/minority groups so that they can provide special expertise to ERB/IRC/IRB on proposed research protocols.

In order to go for competent review of the research protocol, the experts should look at the following basic items:

Title of the Research Proposal: The ERB/IRC/IRB should review the title of the proposal, which should be brief, self-explanatory and clearly indicative of the purpose of the study.

Introduction: The ERB/IRC/IRB should review the introductory part of the research proposal, which should appear in a logical sequence with appropriate scientific background citing relevant literature, particularly of similar studies.

Statement of the Research Problem, Justification and Literature Review: The ERB/IRC/IRB should review the clarity and definitive statements on the core research problem and explanation on why the proposed research study needs to be conducted.

They should also look whether there is a clear statement of the justification for the study, its significance in development and in meeting the needs of the country/population in which the research is carried out or not. Are references drawn from the recent literature provided and citations accurate, or not, need to be looked critically.

Objectives and Research Hypothesis (if relevant): The ERB/IRC/IRB should review the clarity of research objectives (general and specific or primary and secondary), whether such objectives follow the criteria of SMART (i.e. Specific, Measurable, Achievable, Relevance/Realistic, Time bound) and are phrased in operational terms with the use of action verbs. Similarly, clarity of research hypothesis needs to be reviewed whether it really tries to test it and also try to establish the relationship between two or more variables. It should also review resultant endpoint.

Priority of Health Research: Whether the research proposal focuses on a problem of priority importance as identified by the NHRC or not needs to be reviewed.

Study Variables: Identification of the variables is the essential things while developing the research

proposal. Are these clearly identified and defined? These aspects need to be reviewed critically.

Study Site: A brief description of the site(s) where the research is to be conducted, including information about the adequacy of facilities for safe and appropriate conduct of the research, and the demographic and epidemiological information (if relevant) about the selected site needs to be reviewed.

Sample Size and Sampling Method: What is the number of research participants needed to achieve the study objective, and how has such number of participants been calculated? How will the participants be selected? What kind of sampling methods will be adopted? Are the types of sampling methods including sampling frames appropriate and compatible with the desired statistical confidence limits (if relevant)? These aspects will be reviewed. Inclusion and exclusion criteria of samples will also be reviewed along with the methods for blinding (if applicable).

Study Design: A detailed description of the design of the trial or study needs to be reviewed. How the researcher is trying to explain the appropriateness of the relevant study design needs to be looked at critically. How is the researcher trying to control confounding effects? How is the researcher planning to maintain external and internal validity of the selected study design and whether assignment to treatment groups will be randomized (including the method of randomization), and whether the study will be blinded (single-blind, double-blind), or open? What criteria will be used for inclusion and exclusion of participants and what is the justification for the exclusion of any groups (such as age, sex, social or economic factors, or for other reasons)? What is the justification for involving vulnerable participants in the research (if relevant)? What are the procedures for follow-up of patients, methods of control group selection, response rate, compliance (if relevant)? Is there any explanation regarding the measures being taken to reduce bias, minimize risks, balancing against the benefits and increasing the validity and reliability in the design including the specificity and sensitivity of the techniques (if relevant)? What measures are considered in relation to the nature and uses of the data? These aspects will also be taken into consideration.

Description and explanation of all interventions (the method of treatment administration, including route

of administration, dose, dose-interval and treatment period for investigational and comparator products used). These include the process of recruitment, e.g., advertisement, and the steps to be taken to protect privacy and confidentiality during recruitment; plans and justification for withdrawing or withholding standard therapies in the course of the research, including any resulting risks to participants; any other treatment that may be given or permitted, or contra indicated during the study; clinical and laboratory tests and other tests that are to be carried out.

Data-Collection Methods and Techniques: The relevancy of the data-collection methods and techniques including measurement devices and data-collection instruments such as case report forms, questionnaire, etc. need to be reviewed for its appropriateness for the purpose and nature of data that are to be collected.

The ERB/IRC/IRBs committee should review the best research practices including internationally accepted Good Clinical Practice (GCP) Guidelines, Good Clinical Laboratory Practice (GCLP) Guidelines, and Good Manufacturing Practice (GMP) Guidelines (if relevant) to be adopted during the study period.

The following aspects will also be reviewed: Methods of recording and reporting adverse events or reactions, and provisions for dealing with complications; the known or foreseen risks of adverse reactions/events, including the risks attached to each proposed intervention and to any drug, vaccine or procedure to be tested; for research carrying more than minimal risk of physical injury, details of plans, including insurance coverage, to provide treatment for such injury, including the funding of treatment, and to provide compensation for research-related disability or death; provision for continuing access of research participants to the investigational treatment after the study, indicating its modalities, the individual or organization responsible for paying for it, and for how long it will continue; for research on pregnant women, a plan, if appropriate, for monitoring the outcome of the pregnancy with regard to both the health of the woman and the short-term and long-term health of the child; the potential benefits of the research to study participants and to others; the expected benefits of the research to the population, including new knowledge that the study might generate.

Ethical Consideration: Following ethical aspects will be taken into consideration while performing review:

- a. The means proposed to obtain individual informed consent and the procedure planned to communicate information (description of the study, the risks and benefits of participation, the right to quit or withdraw from the study at any time, place of consent, privacy issues, special consideration for vulnerable participants) to prospective participants, the study staff person and their position of the person responsible for obtaining and documenting the informed consent; when a prospective participant is not capable of informed consent, satisfactory assurance that permission will be obtained from a duly authorized person, or, in the case of a child/adolescent who is sufficiently mature to understand the implications of informed consent but has not reached the legal age of consent (7 to below 18 years), an assent will be obtained as well as the permission of a parent or a legal guardian or other duly authorized representative will also be obtained.
- b. An account of any economic or other inducements or incentives to prospective participants to participate, such as offers of cash payments, gifts, or free services or facilities, and of any financial obligations assumed by the participants, such as payment for medical services; plans and procedures, and the persons responsible, for communicating to participants information arising from the study (on harm or benefit, for example), or from other research on the same topic, that could affect participants' willingness to continue in the study;
- c. Plans to inform participants about the results of the study;
- d. The provisions for protecting the confidentiality of personal data and respecting the privacy of participants, including the precautions that are in place to prevent disclosure of the results of a participant's special tests to immediate family/relatives without the consent of the participants; information about how the code, if any, for the participants' identity is established, where it will be kept and when, how and by whom it can be broken in the event of an emergency; any foreseen further uses of personal data or biological materials.
- e. Plans for monitoring, the continuing safety of drugs or other interventions administered for purposes of

the study or trial and, if appropriate, the appointment for this purpose of an independent DSMB.

Data Management and Analysis: The ERB/IRC/IRB should review the explanation how the collected data from field or laboratory setting will be kept in files and entered into computer. The process of coding system and maintaining the data safety process at every level, the methods to be applied for data analysis (including the statistical software to be used in analyzing the data), the relevancy of the appropriate statistical tests and plan for interim analysis will also be reviewed.

Capacity of PI and his/her Team: The ERB/IRC/IRB should review the relevant competency of the PI and his/her study team whether their ability to conduct the study (considering their experience and training and the time allotted to the study) is justifiable or not.

Capacity Strengthening: The ERB/IRC/IRB should review the statement in what way the research project will contribute towards the development of capacity for health research in the host institution/individual researcher/community people of Nepal.

Project Administration: Suitability of the administrative arrangements (including the specific plans for monitoring and evaluation) to facilitate overall aspects of research project needs to be reviewed. The ERB/IRC/IRB should also review the appropriateness of identified staff, equipment and logistics for the study.

2.6.5 Group Exercise (Time: 50 minutes)

The facilitator should randomly divide all participants into smaller groups consisting of five to eight people. The following case study needs to be provided to each group.

Case Study: Evaluating the Use of Traditional Medicines for Diarrhea

A plant common to Nepal, 'brahambuti' (*Hydrocotyle asiatica*), is reported to be effective in the treatment of bloody diarrhea when dried, ground up, and added to water. One paper suggesting that 'brahambuti' has an effect on decreasing bloody diarrhea has appeared in the grey literature from the Department of Ayurveda in Nepal. 'Brahambuti' is the main ingredient of a popular traditional medicine 'Brahami', which is produced by a local company. This medicine is widely available, very popular, and quite inexpensive. No clinical studies have been conducted on this product and the specific chemical composition has not been determined. An

investigator at an international research institution in India is intrigued by this product and wishes to evaluate its clinical effectiveness. The present treatment for dysentery (by far the most common cause of bloody diarrhea in the country) is fluid and Ampicillin, an antibiotic that is clinically effective and bactericidal. Ampicillin, however, is often unavailable outside the major cities (80 percent of the population is rural) and, even when it is available, is too expensive for many people to afford. The investigator reasons that if the traditional medicine proves effective, therapy will be more accessible to everyone because of availability and cost.

The researcher submits a proposal to the ERB of the NHRC for a double-blinded study that compares the clinical effectiveness and bactericidal properties of 'Brahami' against Ampicillin. Adult patients admitted or monitored seen on an outpatient basis with a history of dysentery will randomly be assigned to one of the treatment groups after a rectal swab has been taken for a bacteriological diagnosis. 'Brahami', which is in a powdered form, will be formulated in a capsule dosage form so that it is indistinguishable from the antibiotic.

The ERB meets and decides not to approve the proposal for the following reasons: (1) the specific chemical composition of 'Brahami', (i.e., 'Brahambuti') is not known; (2) the prior reports of effectiveness have been for "bloody diarrhoea" which might include any number of diagnoses including dysentery and amoebiasis; and (3) there are no studies reported in any kind of peer-reviewed scientific journals that have indicated that the traditional medicine is effective or have suggested a mechanism for its reported effectiveness. The investigator notes that it would be next to impossible to define all of the ingredients of this traditional medicine and, if attempted, would be a costly undertaking. Lastly, researcher argued that those on the research review panel who expressed their opinion against approval are biased against traditional medicines, denigrating the indigenous science of the country, and trying to impose their own "Western biases" on scientific research.

Questions

1. In your opinion, was the ERB/IRC/IRB correct in its assessment? Why or why not?
2. Is the investigator correct in his accusation that

those members of the ERB/IRC/IRB who expressed their opinion against the approval of the study are showing a “Western bias” in their decision?

3. If the study were approved as presented above, would the ERB/IRC/IRB have used a double standard in its assessment of the ethics of the design?
4. In these circumstances, where the researcher and the ERB/IRC/IRB disagree, how might the situation be mediated?

The facilitator should give at least 10 minutes to read such statements critically and inform them to discuss among themselves for 10 minutes. The facilitator should tell them to come up with answers to the above questions. This might take another 10 minutes. Immediately after that, these answers will be presented during a plenary session, which will be conducted for 20 minutes.

2.7 Module 7 Responsibilities of Institutional Review Committees/Board – II

Learning Objectives:

By the end of the session, the participants will be able to:

- Explain the procedure for recruiting research participants,
- Describe the care and protection of the research participants, and
- Enumerate the various steps of reviewing informed consent.

Time Frame: 90 minutes

Materials: Flip Chart, Board Markers, Computer, Audiovisual Equipments with LCD Projector and Screen

Teaching Methods/Process: Lecture, Assessment/presentation, and Discussion

Course Contents:

- Recruitment of research participants
- Care and protection of research participants
- Reviewing informed consent

Game

- The Major Says

2.7.1 Game (Time: 20 minutes)

The Major Says

Objective: Reactivation

The training facilitator needs to tell all the participants to stand in a circle. If s/he says, "Do this", you do it; if s/he says, "Do that", you don't do it. Then the facilitator does some gymnastic exercises like bending knees, waving arms, turning head and comments with "this", where everybody is supposed to do the same, or s/he says "that" where everybody is supposed not to do it. Somebody is always out of step, which ends up in great laughter.

2.7.2 Recruitment of Research Participants (Time: 15 minutes)

The system of justice requires that there be fair procedures and outcome in the selection of research

participants. Individual justice in the selection of participants requires that researchers exhibit fairness. Thus, they should not offer potentially beneficial research only to some who are in their favour or select only "undesirable" participants for risky research. Social justice requires that distinction be drawn between classes of research participants that ought and ought not to participate in any particular kind of research. Thus, it is a matter of social justice that there is an order of preference in the selection of classes of research participants (e.g., institutionalized, mentally retarded or prisoners may be involved as research participants, if at all, only on certain conditions). Special attention should be taken in research involving uniform service people (army, police, etc) because of their potentially vulnerable situation.

A new drug or appliance developed elsewhere can only be tested among Nepali participants after Phase I and II clinical trial have been conducted/approved elsewhere.

Note:

Phase I: These are the first trials of a new active ingredient or new formulations in human being, only carried out in healthy volunteers. Their purpose is to establish a preliminary evaluation of safety, and a first outline of the pharmacokinetic and, where possible, a pharmacodynamic profile of the active ingredient in humans. This phase also aims at the determination of appropriate dose ranges or regimens or exposure to device and (if possible) clarification of dose-response or device-response relationships in order to provide an optimal background for the design of extensive therapeutic trials.

Phase II: These trials are performed in a limited number of human beings and may be a comparative (e.g., placebo-controlled) design. Their purpose is to demonstrate extended safety and early indications of therapeutic activity of the active ingredient or device in patients suffering from a disease or condition for which the active ingredient or device is intended.

In Nepal, prisoners must not be made participants of intervention research that involves more than minimal

risk, as the consent given by them may have been unduly influenced by expectations of reward. Other types of research involving prisoners will fully be reviewed by the ERB/IRC/IRB.

Pregnant and nursing women should not be participants in a clinical trial except those that are designed to protect or advance the health of pregnant or nursing women or fetuses or nursing infants and for which they are the only suitable participants.

Children cannot be considered “mini-adults”, and, therefore, any new drug/device intended for use in children has to be studied in children for its rational and scientific use and to understand how new drugs and devices work differently in children. However, before undertaking research in children, it has to be ensured that (a) children will not be involved in research that might be carried out equally well in adults, and (b) the purpose of the research is to obtain knowledge relevant to the health needs of the children.

Before undertaking research in mentally disadvantaged persons, the following has to be ensured: (a) such research cannot be carried out satisfactorily in person in full possession of their mental faculties (i.e., persons capable of consent), and (b) the purpose of the research is to obtain knowledge relevant to the health needs of persons with mental disorders.

2.7.3 Care and Protection of Research Participants (Time: 15 minutes)

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

The researcher should make provisions for making compensation to the research participants. The level of compensation should not be coercive as when third parties are paid for another subject’s participation. In addition, the researcher should make provisions to compensate the efforts and time of the participant for the purpose of research. The information related to the provision for compensation should be communicated to the research participant.

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

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

Note: A DSMB is a committee that is created to review the data from randomized clinical trials to determine whether it is safe for the study to continue. Its primary role is to review the progress of the study, with access to interim analysis and adverse event reports. This may include review of interim effectiveness analyses, safety data by blinded treatment arm, and when necessary, unblinding of the study arms. It operates according to a strict plan that includes criteria for ending a research study while in progress, if continuation of the study exposes participants to risks that are not reasonable in relation to potential benefits. In this way, a DSMB complements the work of the ERB/IRC/IRB in protecting participants in research studies from unnecessary risk.

When women take investigational drugs for HIV infection, special precautions are often needed. Women who are not pregnant when they begin to take such drugs should be counseled about reliable contraception. Nursing mothers who ask to be treated with investigational drugs for HIV infection should be advised that they must discontinue breast-feeding while taking such drugs. In each case in which an investigational drug is administered to a pregnant or nursing woman, there should be careful monitoring and reporting of the effects, if any, on the fetus or child.

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

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

Note: *In addition to the oversight of ERB/IRC/IRB, ongoing research may be subject to monitoring from several different groups such as sponsor of the research, contracted monitoring agencies, regulatory agencies among others. These groups want to ensure that the study is being conducted correctly. Monitoring may consider issues related to the safety of research participants.*

2.7.4 Reviewing Informed Consent (Time: 40 minutes)

The ERB/IRC/IRB should review the overall description of the process for obtaining informed consent including the description about who is responsible for obtaining the informed consent. This description may include process of communication with the research, objectives, methods, risks and benefit of the research, obtaining consent from the vulnerable research participant (e.g., children, elderly, disabled, prison population, people in uniform services), description about the provision for the participants to queries and complaints during the course of research. Following key things need to be reviewed:

Obtaining consent from the research participants:

It is important to know who will explain the research questions, and who will receive the informed consent from the research participant. The time allotted for this important matter needs to be considered. Apart from these, where the consent will take place, procedures for use of witnesses as well as legal representatives need to be taken into consideration.

Is there any coercion or deception? The consent form must clearly indicate that the participants volunteer of their own free will for the research. There should be no coercion or deception during the process of obtaining consent. The amount of compensation (in necessary) should be reviewed.

Type of consent: The type of consent (e.g., informed, proxy, assent) and who (people aged 18 years and above, people aged 7 to below 18 years, people aged below 7 years, vulnerable people) is going to give what kind of consent need to be reviewed.

Language of consent form: The consent form should be prepared in English as well as the relevant local language (Nepali and other) using simple language, avoiding clinical jargon, and should include the following information:

- The nature of the study—whether investigational, in terms of the use of drugs or procedure, or whether information-seeking, or if questionnaires or interviews are to be used,
- The number of research participants,
- The major objective(s) of the study,
- The expected duration of the research study and the frequency of the participants' involvement,
- The research participant's responsibility,
- A statement that the research participation is voluntary,
- A statement that the participant can withdraw from the study at any time without giving any reason, and without fear,
- A statement guaranteeing confidentiality of records identifying research participants,
- A statement of any re-imbursement/compensation for the research participant (if relevant),
- A statement on exactly what is expected of the research participant
- In the case of a clinical trial, the following information should be included:
 - The trial treatment and the probability for random assignment to different treatments,
 - A detailed explanation of the trial procedures including all invasive procedures,
 - The potential or direct benefits (if any) from participation,
 - The alternative procedure(s) or treatment(s) that may be available,
 - The risks, discomforts, and inconveniences associated with the study,
 - The provisions for management of adverse reactions/events,
 - Transfer of any biological samples from the country (if relevant) ,
 - The provision of insurance coverage for any permanent disability or death caused directly by the investigational treatment or procedure,
 - That a study participant will be given the information that may be relevant to his/her willingness to continue participation,
 - Anticipated expenses,
 - Direct access to records by authentic officials,

- Circumstances when the research participant may be removed from the study,
- Duration of the research study,
- The name and address, including telephone numbers, of the person to be contacted in case of adverse reaction/events or for any information related to the clinical trial or research study,
- Sentence indicating that the research participant has understood all the information in the consent form and is willing to voluntarily participate in the research,
- Signature space for the research participant, study team member, a witness (if relevant) and the date.

Note: *For reviewing the waiver of written informed consent (i.e., a signature on an informed consent form) from the research participants, the ERB/IRC/IRB should look at whether the researcher is able to justify this request by providing an explanation of why obtaining written informed consent would add additional risk to the research participants and their alternative provisions for informing them about the study or not. If a waiver is being requested because the research participants cannot be contacted for any reason, e.g., died, moved away, lost contact, this should also be explained in writing to the ERB/IRC/IRB.*

2.8 Module 8 Responsibilities of Institutional Review Committees/Board – III

Learning Objectives:

By the end of the session, the participants will be able to:

- a. Describe the review process,
- b. Define expedited review and conflict of interest during review process,
- c. Define safety data,
- d. Describe the review process of safety data and protocol violation,
- e. Describe the documentation process of review, and
- f. Illustrate its applications with different examples including case studies.

Time Frame: 90 minutes

Materials: Flip Chart, Board Markers, Computer, Audiovisual Equipments with LCD Projector and Screen

Teaching Methods/Process: Lecture, Brainstorming, Plenary session, Assessment/presentation, and Discussion

Course Contents:

- a. Procedure of review
- b. Review of safety data and protocol violation
- c. Documentation process of review

Group Exercise:

- Case Studies
- Small Group Discussion

2.8.1 Procedure of Review (Time: 15 minutes)

Procedure of Initial Administrative Review

The ERB/IRC/IRB should provide independent, competent and timely review of the research proposals. In Nepal, the ERB/IRC/IRB secretariat needs to go for initial review of the proposal. First, whether the basic format of the research proposal (as prescribed by the respective institution) has been completed or not needs to be checked initially to confirm that the proposal meets the document requirements of the ERB/IRC/IRB. Once it has been confirmed that all the required documents have been submitted, the actual documents are sent

for review process. There might be internal and external review system depending upon the institution's rules and regulation. Generally, one proposal is reviewed by at least two reviewers (internal and external). The person who does initial review will review overall proposal including its associated documents, the PI and his/her study team's competency and relevancy of budgetary provision to carry out the study. The review of the budget is a Nepal-specific step to check that the budget is sufficient to cover the work proposed. This is unique to Nepal and is not the role of a traditional ERB/IRC/IRB. External reviewers (not affiliated to the institution) will review the proposal anonymously. In the later reviews, reviewers will not be informed about the name of PI and budgetary provision of the study. Generally external reviewers will judge the content validity of the study proposal.

Depending upon the nature of the research proposal, it can be reviewed by more than two reviewers. This is solely at the discretion of the ERB/IRC/IRB for a particular proposal. All of this is an administrative review to make sure that the proposal is complete before going for the full ethical review by the ERB/IRC/IRB.

A scoring checklist or format is sometimes used by some ERB/IRC/IRB as it helps to ensure that the reviews are consistent and maintain the objectivity of the review process.

Full ethical review process:

In Nepal, the research proposal is critically reviewed adopting the criteria of a scoring format by the reviewers nominated by the ERB/IRC/IRB, and their comments and five-point scales (poor, fair, good, excellent and outstanding) scores are tabulated during ERB/IRC/IRB meeting. All the members of ERB/IRC/IRB review the proposal and judge the comments and scores provided by the reviewer in the following way.

An evaluation score of 1 to 5 is allocated for decision-making with 1.0 – 1.9 (below standard) being the lowest score, 2.0 – 2.9 (fair but below the standard for approval), below and fairly above midpoint score, 3.0

– 3.9 (good and possibly worthy of consideration for approval) above midpoint score, 4.0 – 5.0 (certainly of a standard) highest score.

If evaluation score comes in between

- 1.0 – 1.9 = Certainly ask for total proposal revision,
- 2.0 – 2.9 = May ask for proposal revision and give comments,
- 3.0 – 3.9 = May ask for clarification, and
- 4.0 – 5.0 = May be sufficient for approval.

Once the overall evaluation process has been completed, ERB/IRC/IRB assesses the relevance of evaluation scores and takes the final decision upon the technical aspects of the research proposal.

After reaching general consensus on the technical aspects of the research proposal, the following ethical issues are properly evaluated during the review process:

- Whether the potential risk to research participants is reasonably less than the anticipated benefits?
- Is the selection of research participants equitable? Is there additional safeguards provided in the research protocol if the study involves vulnerable population?.
- Is there a provision to take informed consent in an appropriate language understandable by the research participant? Can the participant withdraw from the study at any time without explanation?
- Is there an adequate provision to protect the privacy of research participants and maintain confidentiality of data?
- Is there an adequate provision for monitoring the data collected to ensure the safety of research participants?
- Any mechanism for compensation in case of injury/harm (if relevant)?

After reaching general consensus on the technical and ethical aspects of the research proposal, minutes are prepared and maintained in a confidential manner.

Communicating decision: In Nepal, the authorized person of the institution where ERB/IRC/IRB functions will communicate the decision of ERB/IRC/IRB in writing to the principal applicant, and this includes at least the following:

- The exact title of the research proposal reviewed,
- The name and title of the principal applicant,
- The name of the site(s) for the research,

- The date and place of the decision,
- A clear statement of the decision reached,
- Any suggestion by the ERB/IRC/IRB concerning the research study.

Note: *The authorized person is the person who is the executive chief of the institution as well as the member-secretary of the ERB/IRC/IRB.*

In the case of a conditional decision, any additional requirements sought by the ERB/IRC/IRB, including suggestions for revision and the procedure before having the application re-reviewed will be provided.

In the case of approval of the study, the communication should include: **(a)** the need to notify the ERB/IRC/IRB in case of protocol amendments, **(b)** the need to notify the ERB/IRC/IRB in the case of amendments to the recruitment of research participants, or the informed consent form, **(c)** the need to report serious and unexpected adverse events related to the conduct of the study, **(d)** the need to report unforeseen circumstances, the termination of the study and the information the ERB/IRC/IRB expects to receive in order to perform ongoing monitoring and supervision of the research study, and **(e)** the final report and research article published in scientific journals.

If the proposal is either rejected or recommended for amendment, clearly stated reason(s) should be provided.

The facilitator should ask the participants to discuss about the meaning of expedited review and conflict of interest and ask them to write their responses on flip chart paper.

Expedite Review: There are some studies that do not pose any ethical or safety concerns and have also no more than minimal risks, i.e., no risk of distress or injury, physical or psychological, to the human beings as a result of the research may undergo expedited review process. Similarly, under exceptional circumstances of urgency (e.g., a patient with some rare or ill-understood condition, epidemics) the chairperson in consultation with ERB/IRC/IRB member(s) may allow to go for expedited review process by following the scoring checklist criteria. This needs to be reported to the next ERB/IRC meeting.

Note: *Expedited review is the review of proposed research proposal by the ERB/IRC/IRB chair or a designated voting member or group of voting members rather than by the entire ERB/IRC/IRB. Wherever there is doubt, an application should go to the full committee review.*

Note: *Minimal risk means that the probability and magnitude of physical or psychological harm expected in the study are not greater in and of themselves than those normally encountered in daily life, or in routine physical or psychological examinations or tests.*

Exemption from Review: Ethics review may not be required for studies that amount to quality control and method validation. These are studies that do not involve individual participants or review of data from individual participants unless certain conditions apply. Only an ERB/IRC/IRB can determine if an evaluation is exempt or not and the researcher cannot make this determination.

Conflict of Interest: In the case when the ERB/IRC/IRB members are investigators/advisors/researcher to/with an agency whose research proposal is being put forwarded for review process, the member(s) should disclose conflict of interest and should not review the research proposal as it interferes with ability to make an objective evaluation of the proposal. However, the principal researcher can be present at the discussions, but they cannot vote or influence the vote. Conflict of interest needs to be documented and disclosed.

2.8.2 Review of Safety Data and Protocol Violation (Time: 10 minutes)

The facilitator should ask the participants to discuss the meaning of safety data and protocol violation and write responses on flip chart paper.

The data about adverse events during the research process that might affect the safety of research participants is called safety data. The ERB/IRC/IRB needs to review such data and determine if it is safe to continue the study and/or modify it or terminate it. Such data might be associated with the research intervention, and this needs to be reported to the ERB/IRC/IRB.

Note:

Adverse event: *Any untoward occurrence in research participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.*

Once such adverse events are identified, the researchers need to report these events to the ERB/IRC/IRB within 24 hours of the investigator first learning of the event. Immediately after that, a full follow-up report needs to be submitted within seven days (drugs/vaccines) or

five days (devices). The ERB/IRC/IRB generally reviews the following point in the reports:

- Adverse event's details, and its association with the study,
- Researcher's opinion regarding the severity and causality of such events,
- Current status of the event: whether it is resolved or still persists, and
- Researcher's immediate actions towards such adverse events.

Sometimes, sponsor collects the report submitted by principal research and sends a safety alert/letters about such issues. Researchers should immediately submit this safety alert report to ERB/IRC/IRB. The ERB/IRC/IRB should review safety alert report. While reviewing such reports, the ERB/IRC/IRB needs to consider the following points:

- Seriousness about the event,
- First time or repeatedly occurring events,
- Raising new concerns about the research study,
- Suggesting changes in the study design or stopping it, and
- Additional information needed to evaluate such event(s).

Note: *As part of continuing review, all safety data collected since the last approval should be reviewed again by the ERB/IRC/IRB.*

The ERB/IRC/IRB may take following actions once such reports have been reviewed.

- Suspend the study until some amendments are made.
- Terminate the ongoing study.
- Permit the study to continue with no changes.
- Allow the study to continue unchanged but suspend further participants enrolment in the study.

The facilitator should ask the participants to discuss the meaning of protocol violation. Write responses on flip chart paper.

Protocol violations and deviations may be serious situations that require immediate investigation by ERB/IRC/IRB chair and reporting to the head of the institution for further action. Protocol violations arise when something takes place that does not agree with the protocol such as enrolling a patient that does not meet the inclusion criteria or a protocol required test not being performed. In general, violations are those

instances where the safety of the research participant and/or the integrity of the study data is affected. Deviations are cases where safety and data integrity is not affected, but there is still a departure from the protocol. For example, missing informed consent would be regarded as a protocol violation and very serious, whereas a participant not showing up for a scheduled visit would be regarded as a protocol deviation as it was not caused by the study team. Protocol deviations give you information about the quality and ease of the study and indicate areas where perhaps the protocol should be amended to make it more practical and prevent less error.

Continuing Review: There should be periodic review process once the protocol has been approved by the ERB/IRC/IRB. The ERB/IRC/IRB needs to monitor the research study at least annually or more frequently if necessary to observe whether it is safe to continue the research or not. The head of the institution where ERB/IRC is located generally informs the PI to submit their study status report. After submission of a study status report including all adverse events (if any), protocol violations/deviations, this continuing review (which is a documented submission of a study status report) has to be reviewed by the full committee unless it was expedited before in which case it can be expedited again unless the protocol has changed such that it no longer qualifies for expedited review. Continuing review includes not only a study status update but also other documents required by ERB/IRC/IRB.

Note: *In case of amendments, prior approval needs to be given before the amendment can be implemented. Just because a protocol was approved by expedited review initially does not automatically mean that an amendment also qualifies for expedited review. This is because an amendment may include the addition of procedures that increase risk or reduce safety. Amendments should be presented to the ERB/IRC/IRB and they will decide if it qualifies for expedited review or not.*

2.8.3 Documentation Process of Review (Time: 5 minutes)

Once the proposal has been reviewed, the filled scoring format including its comments and suggestions need to be documented properly and attached in the same file where the proposal has been kept. The ERB/IRC/IRB secretariat needs to check whether the exact title of the research proposal, name and signature of the reviewer including date, have been written appropriately or not.

All the documents (i.e., filled reviewers' format, copies of all correspondences letters between reviewers and institution, institution and PIs) need to be kept in the order decided by the ERB/IRC/IRB. Apart from these, a clear statement of the decision (positive or negative) reached by the ERB/IRC/IRB as evident from its minute need to be attached into the same file. All the files including a copy of the original approval letter need to be locked in a file cabinet with top security. Such files need to be kept at least for 25 years, which is the requirement in Nepal.

All documentations and communication of the ERB/IRC/IRB should be dated, filed and archived according to written procedures. Proper storage space should be provided for this in each institution. A statement is required defining the access and retrieval procedure (including authorized persons) for the various documents, files and archives.

2.8.4 Group Exercise (Time: 60 minutes)

The facilitator should randomly divide all participants into smaller groups consisting of five to eight people. The following case study proposal needs to be provided to each group.

Case Study Proposal

Description of Research

Brief Summary

Female sex workers (FSWs) in the city "X" of country "Y" are a group particularly vulnerable to Sexually Transmitted Diseases (STD) and HIV infection. They are not the only or the most important party in spreading HIV infection, but they contribute to the imminent AIDS epidemic in the city "X". Since HIV prevalence is still relatively low and limited to a highly sexually active population, and most importantly, since the FSWS have little power to protect themselves, a program targeted for them is justifiable.

The city has very strong power over its citizens, and the vast majority of the population is Hindu. AIDS is still not considered a problem here. A cumulative total of 200 HIV positive, including 55 AIDS cases, were reported. There are few HIV and AIDS prevention programs being conducted in this country "Y".

This study will take place in the tourist areas of the city "X". The purpose of this study is to develop an STD, HIV and AIDS prevention training model for FSWS that is effective, practical and culturally accepted.

A randomized controlled intervention trial will be conducted among 2500 FSWs residing in some centers for FSWs in the city. This intensive training program will use a contextual approach to the prostitution problem and an adult education method; this new approach has not yet been validated.

General Purpose

The goal of this study is to contribute to the STD/AIDS prevention and control efforts in this city by implementing and evaluating an intensive training program for FSWs. This training program will attempt to improve FSWs' knowledge of the health risks in their profession, especially STD/HIV/AIDS infections, and increase condom use as a means of prevention.

Study Goals

(a) Improving STD/HIV/AIDS-related knowledge, attitude, belief and practice (KABP) of the FSWs. It is thought that, after the intervention, 1) STD/HIV/AIDS-related knowledge, attitude, belief and intention among the training group will significantly be improved compared to that of the control group, which receives only a mass educational campaign; 2) the increase in condom use practice among the training group will significantly be higher than the increase among the control group; and 3) the STD rate of the training group will significantly be lower than it is for control group.

(b) Studying the personal (individual characteristics), professional (related to their involvement in sexual activities), and contextual (larger socio-economical factors) determinants of STD/HIV/AIDS related high risk behaviors among the city's FSWs.

(c) Studying the factors that may support or impede the success of an intensive training program.

Experimental Procedure

(a) The study population is approximately 2500 FSWs located in a cluster in the city. Their ages ranges from 18 to 35 years. More than half of the women are illiterate, and only 10 per cent are educated beyond elementary level. FSWs tend to work in this place for two to three years.

This place is a center for low-paid FSWs. Here the FSWs and their caregivers are allowed to carry on their profession with limited restrictions and regulations. Prostitution is illegal in the city, so the FSWs and the caregivers are registered but not licensed. This vague

arrangement makes the moralists happy, while also making it easier for the government to implement health and social programs for the FSWs.

(b) Sample Size: A total of 225 (75 for the training group and 150 for the control group) will be the sample size. The participants will be selected using two-stage random sampling. First, the area will be divided into four symmetrical areas. Randomly, two areas will be chosen for the training and the control population. From the training population, 75 women will be selected randomly. A matching two controls for each trainee will randomly be selected from the control population. The matching factors are age, education attainment, and length of stay in this prostitution area.

The inclusion criteria are working as FSW in this cluster. There are no exclusion criteria.

(c) Intervention Design: The intervention is an intensive training program for the FSWs that take into account the determinants that brought the women to choose prostitution as their profession. Existing government training is intended as rehabilitation and re-socialization for the FSWs, and these programs are given in isolation of one another. Sewing, cooking, literacy and general knowledge classes have little or no relationship to each other. Furthermore, the information provided is out of context for the women's lives as FSWs. Therefore, it is not surprising that after the city training is over, the women have not gained skills that would help them to leave the sex trade.

Our training program will use the specific adult education principles, which assume that adults are able to decide their needs and the ways to achieve them by themselves. The combination of contextual and adult education approaches is hoped to empower the FSWs to make an informed and practical decision whether or not to stay in prostitution. FSWs will be empowered to understand the benefits, while also seeing the risks and the ways to avoid or reduce them, for any decision they make. By identifying STD/HIV/AIDS as the biggest health threat for the FSWs to consider, it is hoped that they will be motivated to practice safer-sex behaviors.

Discussions, demonstration, lectures and study trips will be used. The training will be given twice a week for 14 weeks, and each meeting will last approximately 3 hours. Class size will be kept at around 25 people to facilitate interaction among participants.

Data Collection

Quantitative Data

Baseline data will be obtained before the training. The FSWs condom use rate and their STD/AIDS-related knowledge, attitude, belief and practice will be assessed through an interview-administered questionnaire. The questionnaire was developed from a small pilot conducted recently. It took into account the low literacy level among FSWs.

Tests for gonorrhea, syphilis, chlamydia and HIV will be conducted in collaboration with the city hospital and the government health office. Nurses from the city hospital will take blood and swab from the study women on a designated day, and the tests will be done in the STD department of the city hospital.

Shortly after the training is complete, the same questionnaire will be administered to determine the condom use rate and STD/HIV/AIDS-related KABP. STD test will also be administered again at this time. Five months after the training, STD and HIV status will be obtained again for the last time. Overall, data about STD and condom use rate will be obtained three times, while data about HIV status will be obtained only twice due to high cost.

The health office has been testing annually for STDs, HIV and AIDS in this cluster for several years. Hence, what this study proposes to do is not new for the FSWs, except that the frequency would be higher and test for chlamydia would be added.

All interview and laboratory samples will be coded and names will be maintained in a separate log. This log will not be computerized nor will any copies be made. The PI will manage the log and keep it in a locked cabinet.

The city's best hospital has an AIDS team and will provide counseling for any HIV-positive FSWs found during the study.

Qualitative Data

Interviews, in-depth interviews, and focus group discussions will be scheduled separately from the training time and will be done outside the class. Individuals including those involved in sex work and those working at the center, FSWs, caretakers, clients, existing vocational teachers, guards, and cluster workers/officials will be approached for interviews. Quotes will be recorded anonymously to maintain confidentiality and anonymity.

Outcomes Measures

Before and after testing of condom use rate, KABP and STD/HIV rates will be used to measure the impact the training has on the FSWs. These data will be obtained prior to the training, at the conclusion of the training, and 5 months later. The STD/HIV rates will be examined in a laboratory using standard methods. For HIV, the pool Enzyme Linked Immuno-Sorbent Assay (ELISA) test will be used. The Western blot test will only be performed to confirm HIV-positive results of an ELISA test. For quality control, some samples of each test will be examined in the city's best hospital.

Plans for Data Analyses

Statistical Analyses

The questionnaire has five parts: questions about knowledge, belief of susceptibility, belief of self-efficacy, attitude, and sex and other STD/HIV/AIDS-related practices. Most of the questions are closed-ended, while some will use Likert scale. Univariate analyses will be used to show before and after results for some characteristics of the training and control group. Then, using the 'before-intervention' data only, three models for each of the training and the control group will be developed. The purpose is to see what factors predict a preferable KABP (using multiple linear regression), condom use and STD/HIV status (both using multiple logistic regression) for each group. Examples of possible predictors are age, education attainment and number of clients among others.

To test whether the STD/HIV/AIDS-related KABP improved, multiple linear regression analysis will be used and carried out to assess the relationship between increases in KABP and being in the training group, controlling for other confounding factors (number of clients, income, and newcomer). For the other study goals, the relationship between increase in condom use rate and being in the training group, controlling for other co-factors, will be assessed using multiple logistic regression analyses.

Previous studies reveal that the current condom use rate among FSWs in this cluster ranged from 12 percent to 25 percent. The lowest rate (12 percent) will be used as the reference for condom use rate. It is expected that condom use among the control group will change four percent due to the measurement effect. In the training group, the intervention is expected to increase condom use practice as high as 25 percent. To detect a significant difference at the 0.05 alpha level

with 80 percent power between these four percent increase in the control group and 25 percent increase in the training group, Epi-Info computer program yields a sample size of 36 and 69 for the training and control group respectively. Anticipating a 50 percent loss to follow-up, these numbers are expanded to 75 and 150 for the training and control group respectively.

Investigator Experience

Although the PI has no prior research experience, she has worked in training groups with health workers, nurses and female community health volunteers. She is also familiar with the laboratory tests, having worked in a hospital and in community health centers for several years. She has professional relationship with the city's best hospitals and with officers in the cluster itself.

Benefits or Advantages

This study will contribute to the STD/HIV/AIDS prevention and control efforts in this city. The result of this study will be used to build a training model proposed for all FSWs in FSWs' centers in this city. Since it will try to empower them, in the long run the FSWs will receive a direct benefit from the study.

The study offers the FSWs in the training group useful knowledge about STD, HIV, AIDS, and the prevention methods. We will also provide free STD and HIV tests, counseling (in collaboration with the city's best hospital), further STD examination, and limited STD treatment (in collaboration with the city hospital), if necessary.

Discomfort and Risks:

Questionnaire: It is possible that some questions may provoke psychological stress to the FSWs. To minimize this, the interviewers will be trained, and the FSWs will be told that they are free not to answer any questions they do not want to answer. This is written in the questionnaire and will be mentioned to the interviewees before the interview begins.

Training: Some training materials may have a psychological impact on participants, but whether it is beneficial or adverse is unclear. Nevertheless, we will provide referrals to the city best hospital counseling team, when needed.

Since this place is government-run, and other training programs are routinely carried out, there is little likelihood that the FSWs managers will object to the women joining the training.

Although we will not provide training for the control group, they are not restricted from getting STD/HIV/AIDS information from other sources. In this cluster, there is another HIV/AIDS-related mass campaign; hence, our intervention is basically an enhanced intervention. Moreover, after the study, we will propose to the government that the control group be given the first opportunity to join the next health training.

Blood Samples and Vaginal/Cervical Swabs: The FSWs may feel minor pain as a result of vein-puncture blood sampling. A few individuals may develop a small transient bruise, and, rarely, some individuals faint. The attending nurses will inquire about previous experiences to avoid these problems. Necessary advice and medical attention will be provided, if needed. The FSWs may also feel a little discomfort when their vaginal and cervical swabs are taken. Only experienced nurses will carry out these procedures, and a qualified obstetrician-gynecologist from the city hospital will supervise the procedure.

Another potential risk is STD transmission through shared medical equipment. Though disposable equipment is not always available, sterility issues will be addressed very carefully. In addition, nurses and laboratory technicians will be taught the risk of STD and HIV infection and will be trained to effectively protect themselves.

HIV Test Result: Positive results by ELISA will be confirmed using Western blot assays. The counselling team will inform HIV-positive participants of their status, stressing that this result does not imply the certainty of getting AIDS but prevention measures need to be taken.

Participant Recruitment: Two hundred twenty-five participants will be recruited using maps and census data available in this cluster. These women will be notified and invited to participate in an individualized manner. If some FSWs who are selected at the first batch refuse to participate, the random and matching selection will be continued until we get 150 participants.

Informed Consent: The FSWs who agree to participant will sign or thumb-print an informed consent form. Since most of the women are illiterate, researcher or literate friends will read the consent document for them.

Alternative Procedure: Not applicable.

Participant Inquiries: Researcher will answer participant's inquiries. She will be available in this cluster everyday during the training session, three times a week after the training is complete. Participants will have her office address and phone number.

Participant Rights: The FSWs rights to withdraw consent and discontinue participation will be explained orally. They may have a copy of their consent if they wish.

Anticipated Design Changes: If it is too expensive, the chlamydia test will be omitted.

Adverse Affects: Not applicable

Drug/Biological: Not applicable

INFORMED CONSENT FORM

Name and Address of Researcher

The investigator would like permission to enroll you as a participant in a research study. The purpose of this study is to develop a Sexually Transmitted Diseases (STD), HIV and AIDS-related training model for female sex workers (FSWs), like you, in the city. Together we will learn some preferable and feasible ways to prevent FSWs from getting STD and/or HIV infection.

Your participation would involve answering a questionnaire and having some STD (i.e., gonorrhea, syphilis, chlamydia) and HIV testing. You would be asked to do all of these things three times over an eight-months period.

Procedures

- i. Before the special training begins, we will ask you general questions about your work as FSWs. We will also ask you specific questions about what you know, feel, and do about STD, HIV and AIDS. In addition, doctors and nurses from the local hospital will come to this cluster to take a small amount of your blood, and vaginal and cervical swabs for HIV, syphilis, gonorrhea and chlamydia tests.
- ii. We will hold a special class for three months. At this time, we will train only 75 participants in three separate batches. We are hoping that the government health office or another organization

will include this special training for one day in their regular programs for FSWs in this cluster. In this case, the other 150 participants will be given first priority to join the next health class.

- iii. Immediately after the training, we will interview you again using the same questionnaire that we used before the special training. The team from the local hospital will again come to take blood samples and vaginal-cervical swabs for the same STD testing. Due to budget limitation, the HIV testing will not be done this time.
- iv. Finally, five months after the training session ends, we will interview you for the last time. Blood samples and vaginal swabs will be taken again by the local hospital team for STD and HIV tests.

Risks or Discomforts

Some of the interview questions are very personal and may make you feel uncomfortable. You are free not to answer any questions that you do not want to answer. We will skip these questions and continue the interview with the next questions. You may also choose to withdraw from the study altogether at any time.

Experienced nurses from local hospital will take blood from your arm. During this procedure, you may feel minor pain. There is also a slight possibility of bruising. Although it is very rare, some people faint when their blood is drawn.

Experienced nurses will take your vaginal and cervical swabs. You might feel a slight discomfort during these procedures. The nurse will pay attention to the sterility of the instruments to reduce the possibility that you could get STD infection through shared instruments. A qualified obstetrician-gynecologist from local hospital will supervise all procedures.

Benefits

- i. You will get three free laboratory examinations during the study period. Information about the results will be available to you.
- ii. During the study time, you will also be entitled to have further free examination for syphilis, gonorrhea and chlamydia in local hospital, if you wish. STD medication available at the local hospital will also be available to you free of charge during this time. Furthermore, you are entitled to free AIDS counseling in the city's best hospital.
- iii. To help compensate for your time, after the interview, we will give you a small cosmetic gift. You

- will get three gifts if you complete the study.
- iv. We will also give you a small pack of food after each blood-drawing and swabs-taking. Hence, you will get three food packages if you are willing to complete the study.

For the training group only:

- v. If you are a training group participant, you will receive useful information about STDs, AIDS, and prevention methods. During training sessions, you will get free snacks in each class.

To protect your confidentiality, we will use codes for the interview sheets and the tests. Only the PI will have access to the complete data that list your name. Confidential information contained in your medical record will not be furnished to anyone except to those who are members of the research group or to others who must be involved professionally to provide essential medical care. No information from the study will be presented or published in any way that will expose your identity. The PI will maintain individual laboratory results, which you may obtain whenever you wish.

In the event that at any time during the course of this project, you feel that you have not adequately been informed as to the risks, benefits, alternative procedures, or your rights as a research participant, or feel under pressure to continue against your wishes, the Ethical Review Board (ERB)/ Institutional Review Committee (IRC) administrator is available to speak with you at (telephone number). In the event of a research-related injury, you should contact (researcher's name) at (local telephone number).

The participant, _____, has been fully informed of the nature and purpose of the procedures described above including any risks involved in its performance. The participant has been asked if any question have arisen regarding the procedures and these questions have been answered to the best of the investigator's ability. A signed copy of this consent form will be made available to the participant

Investigator's Signature and Date:

I have been informed of the above-noted procedure(s) with its possible benefits, risks, and consequences. I,

hereby, agree to become a participant in this research study.

Furthermore, I recognize that I am free to withdraw my consent and to discontinue participation in this project at any time without affecting such matters as my compensation.

Participant's Signature and Date

Participant ID Number

Interviewer's Name

Date (YY/MM/DD)

Time (HH/MM)

AM

PM

Training Form for Female Sex Workers

Confidential: *No information shall be presented or published in any way that would permit identification of any individual.*

This interview is part of the research conducted primarily by the researcher regarding the STD/HIV/AIDS-related high-risk behavior among the FSWs in the cluster. The purpose of this study is to develop a training model for an STD/HIV/AIDS intervention program geared towards FSWs in the city.

I will interview you using the questionnaire. The process should take less than one hour. To help compensate for your time, I will give you a small gift at the end of this interview.

Before we start, I want to remind you of a few things.

1. Your answers will be kept confidential. I will not write down your name, only a code number. Reports will combine the answers from the 225 participants we will be interviewing. Nothing will be attributed to you personally.
2. It is very important that your answer as accurately as you can. If there is any question that you cannot answer accurately, please tell me so. If there is any question that you do not want to answer, just tell me and we will skip it.
3. The questions are about what you know, think and

do, with regards to STDs, HIV, AIDS, and your work as a FSW in general.

4. Do you have any questions?

Date _____

1. The first section asks for background information about the participant's age, place of birth, education status/years of schooling, marital status, religion, and children. It further asks about the participant's family members (the number of brothers and sisters, whether either parent is living, and their occupations).
2. Next, there are questions about the participant's work as FSWs. The questions include when the person became an FSW, how old she was, where she started, how long she had been part of this cluster, whether she had ever left the cluster for any length of time and, if so, what she did do while she was away. It goes on to ask who influenced her to become an FSW, whether she ever has other types of jobs, whether she did anything now in addition to FSW to make additional money. Regarding money, the questionnaire also asks how much money she gives to her caretaker, how much money it costs her to live in the cluster, whether she sends money to her family and, if so, how much and to whom.
3. The next section deals with the participant's knowledge about STDs, HIV and AIDS. It asks her to identify STDs and then answer knowledge questions about their level of danger, signs of infection, causes, transmission, curability, treatment methods, and prevention methods. Question about HIV/AIDS include how the participant heard about the disease and similar questions to those asked about STDs.
4. The questionnaire goes on to examine how the participant feels about these diseases. Included are questions about her perceived likelihood of

getting these diseases, acceptable prevention methods, cures, expectation of others with regard to protection against spreading disease, condom use.

5. The next section deals with the participant's beliefs about STDs and AIDS.
6. The next questions ask about the participant's sexual life. The questions explore how old the participant was when she first had intercourse and who she had it with. There are also questions about current practices including what types of intercourse and how frequently she has it.
7. The questionnaire goes into depth about current sexual activities including the number of clients she has had in the past month, what practices were performed and their frequency, how often condom was used, whether she asked her partner to use a condom, whether her caretaker provided condoms, where she or her customer may get condoms, and how much condoms would cost.
8. The next part asks about a variety of unrelated things such as contraceptive use, abortion, smoking, drinking, drug use, blood donation, history with STDs, practices while infected with an STD, medical check-ups.
9. The last section asks about the participant's ability to prevent herself from getting STDs. Several questions relate to her ability to influence customers and other partners to use condoms.

_____ (Researcher's Name)

The facilitator should give at least 20 minutes to read the case proposal critically and inform them to review ethical aspects of the research proposal, which might take another 20 minutes. Immediately after that, these reviews will be presented during a plenary session, which will be conducted for 20 minutes.

2.9 Module 9 Responsibilities of Sponsors and Researchers

Learning Objectives:

By the end of the session, the participants will be able to:

- Describe the responsibilities of researchers,
- Define the meaning of sponsors/funding agencies,
- Describe the responsibilities of sponsors/funding agencies,
- Define the meaning of community,
- Explain the role of community/health facility participation in the research process, and
- Illustrate its applications with different examples including case studies

Time Frame: 90 minutes

Materials: Flip Chart, Board Markers, Computer, Audiovisual Equipments with LCD Projector and Screen

Teaching Methods/Process: Lecture, Brainstorming, Plenary session, Assessment/ presentation, and Discussion

Course Contents:

- Responsibilities of researchers
- Responsibilities of sponsors/funding agencies
- Community/health facility participation in the research process

Class Exercise:

- Case Studies
- Interactive Session

Group Exercise:

- Case Studies
- Small Group Discussion

2.9.1 Responsibilities of Researchers

(Time: 15 minutes)

The facilitator should ask the participants "What sort of quality a researcher should possess?" and write responses on flip chart paper.

Researchers possessing qualities, such as integrity, respect, compassion, professionalism, courtesy, and

sensitivity, should undertake only such research that according to their understanding will be useful to human beings or community or for the furtherance of knowledge on the subject.

Persons who are familiar with the ethical standards pertinent to their research as prescribed by the National Ethical Guidelines for Health Research in Nepal can perform health research. Such persons should hold an appropriate qualification to carry out the research project. Following criteria needs to be taken into consideration while conducting the research:

Conduct of Research: The PI is responsible for getting written approval from the ERB/IRC/IRB and the ethical conduct of research as per approved protocol. The research should be conducted as per the ethical norms and standards as prescribed in the National Ethical Guidelines for Health Research in Nepal. Whenever there is a need of changing certain things in the protocol, researcher immediately needs to submit such changes to the ERB/IRC/IRB by providing proper justification. All amendments to an approved protocol must be approved by the ERB/IRC/IRB before implementation.

Relationship among Researchers: The PI has a responsibility to provide proper training and guidance regarding all aspects of research. The PI should delegate to the juniors and assistants only those responsibilities that they are reasonably capable of performing on the basis of their education, training or experience, either independently or under supervision. However, regardless of responsibilities delegated to colleagues, the PI holds ultimate accountability for the conduct of the study irrespective of what responsibilities s/he has.

Maintaining the Resources: The PI must ensure that they have adequate resources such as human resource, time, and money. The researcher has a responsibility to maintain the list of human resources, who have delegated study duties. Not only this, the researcher needs to maintain all the required essential study documents.

Safety Reporting: The researcher needs to report all unanticipated problems involving risks to the participants and unexpected adverse events/reactions associated during the study period to the ERB/IRC/IRB. The responses given by ERB/IRC/IRB towards such reporting need to be implemented promptly by the PI.

Ongoing Reporting and Follow-up: The PI needs to report the status of their research project to the ERB/IRC/IRB periodically (every three months) as prescribed in its approval letter. The PI needs to inform the ERB/IRC/IRB once the study is completed or prematurely suspended/terminated. The researcher informs the ERB/IRC/IRB of the reasons for suspension/termination whenever the study is being early suspended or terminated. The researcher needs to inform all the enrolled participants for such suspension or termination and prepare a plan for caring of the participants before they will be released from the study.

Information to Research Participants and Community: Researchers have a responsibility to make all necessary efforts to bring the research and its findings to the research participants and communities in an appropriate manner using understandable language at suitable time-frames.

Obtaining Informed Consent: After explaining the exact nature of the study and ascertaining that the prospective research participant has adequate understanding of the relevant facts and of the consequences of participation, the researcher needs to take informed consent from each participant. The researcher needs to explain about the probable, anticipated and potential benefits and/or harms (direct/indirect, immediate/long term) of research to the participants.

Complain System for Research Participants: There must be a system to complain in case of any adverse effects experienced by research participants. This clause must be incorporated in the consent form.

Equitable Compensation and Free Medical Treatment: The PI should ensure that research participants who suffer injury or other related events as a result of their participation are entitled to get free medical treatment for such injury. In case of adverse effects/side effects to participants during research such as drug trial, the patient is entitled to suitable compensation (medical services/rehabilitation). They should get such treatment equitably.

Selection of Study Participants: The researcher is responsible for ensuring unbiased selection. An adequate number of suitable research participants according to the protocol needs to be selected.

The Investigational Product(s): The PI should thoroughly be familiar with the properties, effects and safety of the investigational product(s), e.g., pharmaceutical products, placebo products that appears during the study.

All the records of trial drugs/vaccines (quantity received, supply/delivery made for the study, manufacturer, batch number, manufacturing and expiry dates, and quality control reports) should be maintained and it is the responsibility of the PI. The PI should keep the stock of the trial drugs and vaccines at the site (or any other suitable places) where the study is going to be started.

The PI has to maintain all the procedure for ensuring proper and safe handling of the investigational product(s). Moreover, such products need to be used only for the research participants as described in the protocol.

Monitoring, Supervision and Inspection: The researcher should be available at the field and laboratory settings during monitoring, supervision and inspection visits by the responsible health authorities or the persons appointed by the sponsor for quality assurance.

Accuracy and Completeness of Data Entry: The researcher has the responsibility to ensure that the findings are recorded accurately and completely in the data collection format. Such formats need to be signed by the responsible person designated in the protocol. Data entry needs to be regularly reviewed. Furthermore, test instruments, equipments, and computerized systems need to be validated and kept up-to-date.

Confidential Data: The researcher has the responsibility to maintain all the collected data in a confidential manner. Anonymous identifiers can be used to conceal the identity of the study participants. The researcher must keep all the data sets for a sufficient period of time for any kind of follow-up study (delayed toxic reactions) and inspection which might be initiated in future.

Strengthening Local Capacity: If the PI is coming from abroad, he/she should have a component of

local capacity-building as a part of their study. This may include providing training to local research staff, enhancing research capacity such as creating infrastructures. Apart from this, foreign researcher(s) should include at least one Nepali co-investigator into their core study team.

2.9.2 Responsibilities of Sponsors/ Funding Agencies (Time: 10 minutes)

The facilitator should ask the participants, "What is the meaning of sponsor?". Write responses on flip chart paper.

Individual or entity or agency that pledges to donate (in part or in full) a certain amount of resources (financial or non-financial) required to conduct the research study is termed as sponsor/funding agency. The sponsor may be an individual or an independent institution or company or an organization which takes responsibility for the initiation, management, and/or financing of a research study.

Sponsors have a number of important responsibilities in research. While sponsors may delegate the implementation of certain aspects of the research, such as contracting research organizations, they cannot delegate responsibility.

The sponsor's responsibility is to have a local representative to fulfill the appropriate local responsibilities, which needs to be discussed with local partners (if any) about the importance of the research to the local health needs and priorities. The sponsor has to indicate the potential benefits of such research once conducted in the local areas. Sponsoring agency may ensure the availability of health care services during the study period. Sponsors should require that researchers go through the local ERB/IRC/IRB and take ethical approval as well as follow the local ethical guidelines.

The sponsor needs to select and recruit suitable qualified investigators that design the study protocol and are able to carry out the study in the field or laboratory settings. The sponsor may also select appropriate number of staff including medical/health personnel to carry out the study. Their task and responsibilities needs to be assigned once recruited.

The sponsor is responsible for facilitating the study proposal (prepared by its investigators) submission process to the regulatory authorities for its approval. However, the applicant must be the PI, NOT the sponsor.

The sponsor's responsibility is to provide the quality investigational products (drugs/vaccines/device) including the information regarding its safe use during the study period. The sponsor is also responsible for ensuring that the study must be conducted by adopting the standards of ICH/GCP including relevant field activities.

The sponsor's responsibility is to provide well-labelled and properly packed investigational products in compliance with the approved protocol. The information written in the investigational product brochure should be understandable to the research participant and state that the product is for research purposes only.

In order to provide protection in the event of trial-related injury or death, the sponsor needs to ensure compliance with applicable legal, ethical and regulatory requirements regarding compensation for research-related injuries. The sponsor also needs to secure compliance with the protocol and take action if non-compliance persists.

In order to ensure the availability of healthcare services that is essential during the study period, external sponsor should specify the healthcare services that will be made available, during and after the research, to the research participants or nearby community and state the covered period and services covered by the research. The details of these arrangements should be specified in the consent process and document.

The sponsor's responsibility is to agree on the research protocol including data management, processing and analysis, breaking of the trial code (if any), preparation of study reports that are submitted to the ERB/IRC/IRB, and the Department of Drug Administration (if relevant) in writing prior to the initiation of the study.

The sponsor is responsible to provide all the available accurate and sufficient chemical, toxicological, pharmacological and clinical data regarding the investigational product.

The sponsor's responsibility is to establish the data management systems with appropriate security checks and audit trails and systems to prevent deletion of data. The sponsor is also responsible for ongoing safety evaluation.

For managing, supervising and verifying the data obtained from the study, the sponsor must appoint

suitable, qualified and appropriately trained monitors and research support persons from outside the research team.

If required, the sponsor should establish DSMB and written SOPs to monitor the safety of participants being studied. As part of this, the sponsor should establish systems for emergency unblinding of participants if required. The sponsor is also responsible for establishing all quality systems to ensure the compliant conduct of the study.

The sponsor should retain all required essential research documents and facilitate preparation of the final study report and its submission to regulatory authorities through the PI.

2.9.3 Class Exercise (Time: 20 minutes)

The facilitator should ask the participants to read the following case study and discuss on the questions provided.

Case Study: Trial in Whose Interest?

Background: India has the second-largest population of HIV-infected people in the world. Eighty-five percent of the infections are due to sexual transmission. Consistent and correct use of condoms by the male partners can prevent the infection from spreading during sexual intercourse. Women are at a disadvantage as they cannot protect themselves if their partners fail to use condoms. A drug (Reovir) used in treatment of HIV infection has been shown to prevent sexual transmission of the infection and has been found to be safe in HIV-infected patients. Its side effects are mainly flatulence, and, rarely, it can produce Fanconi syndrome-like picture.

Study Design: A randomized placebo controlled study is to be conducted in a specific clinic. All FSWs attending the clinic will be offered the opportunity to participate in the study. A total of 300 FSWs will be enrolled in the study on a first-come-first-basis.

Inclusion Criteria: All FSWs who volunteer for the study will be screened for HIV/Hepatitis B/Hepatitis C and VDRL. Participants who are negative for these tests will be further screened to rule out any other STDs. All healthy participants will be included in the trial. The research participants will sign a written consent form before the study begins.

The research participants will randomly be assigned into placebo group or treatment group consisting of Reovir 300 mg/day. Participants will undergo medical check-up every month to check for toxicity or side effects of the drug. Participants will undergo laboratory testing for hematological and renal functions on a quarterly basis. At the end of one year, all the research participants will be tested for sero-conversion using the standard protocol. During the visits, participants will be urged and asked to promote safe sex. Free condoms will be distributed to the participants during each visit. The investigators will provide standard treatment for the side-effects of the drugs for a period of one year.

Questions:

1. Is the study ethical?
2. Is there exploitation of women?
3. Are the participants protected?
4. How can this study be improved upon?
5. What are the responsibilities of the researcher?
6. What are the responsibilities of the sponsor?

2.9.4 Community/Health Facility Participation in the Research Process (Time: 15 minutes)

The facilitator should ask the participants, "What is community and how should it be defined?" and write responses on flip chart paper.

A group of people with various characteristics connected by social ties who share common perspectives and engage in shared action in certain geographical locations is called community. This can be a particular area, e.g., a city, a village, a neighborhood. Each member within a community shares their values, norms, joys, worries, needs and religious beliefs with other members. Community brings people together in the form of family and friends.

There are some studies which may target special community participants, such as PLHIV, people living with TB infection, people suffering from Cancer, health care providers, teachers, FSWs, adolescents, prisoners, PWIDs, MSM, urban people, rural people and indigenous people.

Although there are varieties of communities, their representatives might be involved in the conduct of the research and share their better views regarding the welfare of their communities. This is considered important during the study confined towards community settings.

While the risks and benefits of conducting the study, sometimes the whole community might be affected rather than the individual research participants. For example, the whole community might benefit once the health care settings have been improved due to the research study. Contrary to this, some type of research study, sensitive to their culture, might put them at the risk of their being stigmatized and discriminated.

There are many partners involved in the research process in a community. Basically, there might be three main partners:

- The community with their representatives,
- The researcher, persons involved in the research study, and sponsor(s) of the research project, and
- The national or institutional research-approving agency (ERB/IRC/IRB)

These all need to work together to ensure that research is conducted with the community concerned. These three partners have specific responsibilities and need to interact with one another during the research process. It is anticipated that the research will be conducted for the benefits of the local community, and this is possible when these three partners have the adequate information and training needed to meet their responsibilities.

Once the community representative will be involved in the research project, it optimizes the protection of participants and enhances researcher's perceptions towards the whole research process and improves the design of the study. These community representatives might also be helpful for disseminating the research outcomes to the community.

These community representatives may capture the voice (queries and concerns) of the local people, which can be communicated through well-established Village Development Committee (VDC) and Community-Based Organizations (CBO). Sometimes these committees and organizations may advise the study team for smooth running of the research project to be carried in their community settings.

Community representative might be involved during various phases of the research study:

- Before the research study: Community representatives need to internalize that the proposed research project will address their needs or problems and the study will bring some benefits

to the community without disturbing their local norms and culture.

- During the research study: Community representatives need to impart knowledge to others about the research process by highlighting major issues or concerns about the research.
- After the research study: Community representatives may help to disseminate the research results within their community once the study is completed. They may apply the major outcomes of the research study into their whole community.

Community representatives might be considered as exponents for the wellbeing of participants selected from the community. These representatives may work with the study team during the informed consent development process to ensure that the process is culturally appropriate, voluntary and complete. These representatives might ask:

- Will the treatment and health care services be made available to the participants selected from the community?
- Under what conditions such treatment and services are made available, and by whom?
- Until when such treatment and services will be made available for the participants selected from the community, and where?
- Will the existing health care service available in the community or improve once the research outcomes have been disseminated?
- Will the outcomes of the research bring about desirable behaviour change in the community?
- What types of other benefits will the community receive during and after the research process?

The participation of community representative groups during the research process will alert the study team about the types of misunderstanding (if any), ensures that the research responds to health needs and expectations of the community people and application of culturally appropriate informed consent, and provides access to research benefits. Therefore, community participation improves the research process and ensures that the research is being conducted and implemented in the best interests of community people and science.

When health facility participates in the research process, all the people working under the facility need to be informed. This will facilitate the research team and improves the research process.

2.9.5 Group Exercise (Time: 30 minutes)

The facilitator should randomly divide all participants into smaller groups consisting of five to eight people. The following case study needs to be provided to each group.

Case Study: Clinical Trial of Trovan

A multinational company sponsored a clinical trial of Trovan, an antibiotic for the treatment of meningococcal meningitis in Nepal.

Background:

Cerebrospinal meningitis caused by infection with *Nisseria meningitis* occurs in Nepal. Meningococcal disease is potentially fatal and should always be viewed as a medical emergency. The disease occurs in epidemic form in some southern parts of Nepal and thousands of cases occur over a very short period. Admission to a health facility is necessary. A range of drugs may be used depending on antibiotic susceptibility: Penicillin G, Ampicillin, Chloramphenicol, Ceftriaxone, and others. However, the WHO recommends Chloramphenicol, an oil-based injection, as an effective antibiotic, which has some serious side-effects. This injection is considered to be the drug of choice in areas with limited health facilities because a single dose has been shown to be effective.

Meningococcal meningitis is characterized by sudden onset of intense headache, fever, nausea, vomiting, photophobia, and stiff neck. Neurological signs include lethargy, hallucination, coma, and/or convulsions. Infants may have illness without sudden onset and stiff neck. Even when the disease is diagnosed early and adequate therapy given, the case fatality rate is between five percent and 10 percent and may exceed 50 percent in the absence of treatment. In addition to the mortality associated with *Meningococcal meningitis*,

15 percent and 20 percent of those who survive will suffer with neurological sequelae (e.g., Deafness, mental retardation) as a result of their illness.

A company wanted to test the drug (Trovan) for use against meningitis, including an epidemic strain. The company could not find enough patients in their own country, so its investigating team has come to Kathmandu. The trial has been initiated after obtaining ethical approval from the NHRC.

- During the study period, it has been discovered that almost half of the research participants (people aged 7 to below 18 years) did not sign the assent; however, their legally authorized guardian has signed in the consent form. The study is still ongoing and enrolling the participants. What should the sponsor do?
- During monitoring and supervision, it has also been revealed that one of the co-investigator has not been present at all when research participants are being enrolled. Only the research staffs are there. The study is ongoing and enrolling the participants. What should the sponsor do?
- The sponsor discovers that data from one study site cannot be confirmed against source data. What should the sponsor do about the data already recorded in the Case Report Form and how should the study proceed?

The facilitator should give at least 5 minutes to read such statements critically and ask them to discuss among themselves for 5 minutes. The facilitator should tell them to come up with answers to the above questions. This might take another 5 minutes. Immediately after that, these answers will be presented during a plenary session, which will be conducted for 15 minutes.

2.10 Module 10 **Inducement/ Compensation and Social Risks**

Learning Objectives:

By the end of the session, the participants will be able to:

- a. Define inducement and compensation, and describe its nature,
- b. Describe the social risks during the research process, and
- c. Illustrate its applications with different examples including case studies.

Time Frame: 60 minutes

Materials: Flip Chart, Board Markers, Computer, Audiovisual Equipments with LCD Projector and Screen

Teaching Methods/Process: Lecture, Brainstorming, Plenary session, Assessment/presentation, and Discussion

Course Contents:

- a. Meaning of inducement and compensation and its rationale
- b. Meaning of social risk and its rationale

Class Exercise:

- Case Studies
- Small Group Discussion

2.10.1 Meaning of Inducement and Compensation and its Rationale (Time: 20 minutes)

The training facilitator should ask the participants to discuss about the meaning of inducement and compensation, and its nature and write responses on flip chart paper.

The payment of any amount might influence a people's decisions or behaviour regarding research participation. If compensation is excessive, it becomes an undue inducement either to join the research or stay in the research when they would rather leave. Sometimes the offer of payment makes them participate in the study when they otherwise would not like to participate. So, greater acceptance of payment indicates that they are coerced.

Note: *Compensation is not just giving money; it is also free treatments, refreshments, and even the inducement of potentially a new treatment.*

Whenever we conduct research on human participants, the wellbeing of research participants must be our top priority. The research question is always of secondary importance. This means that if a choice must be made between doing harm to a participant and doing harm to the research, it is the research that is sacrificed.

The Nuremberg Code (1947) states that no pressure of any kind should be put on research participants. A particular concern is that participants from financially disadvantaged groups may be more vulnerable to this kind of coercion—because they need the money or the free treatment or other benefits offered, and so their consent is not truly 'freely given' if payment is involved. If payment or compensation represents an inducement to participate, the question we have to address is whether it represents an undue inducement:

- Could it distort people's judgments of the risks and benefits of participation?
- Does it interfere with their freely given and fully informed consent? How will we ensure it does not?

Concern must be taken when some or all of the research participants are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons. Additional safeguards should be included in the study to protect the rights and welfare of these people.

Payment should not over-ride the principles of freely given and fully informed consent. Research participants should know—before they start the research—that they can refuse to answer questions or withdraw from the study at any time without losing their payment. If we propose to make any kind of payment to research participants in our research project, we need to think carefully about why it is necessary, what level of compensation is provided and how reasonable it is, and how it is done. It is generally felt reasonable

to compensate people for their time and expenses involved in study participation but that this should not be excessive vis-a-vis real expenses. Generally following things need to be taken into consideration:

If payment will be given,

- Develop guidelines for when and how payment is made,
- Ensure researcher has a clear and explicit justification for paying participants,
- Ensure that participants who choose to withdraw from the research will still receive payment,
- Consider carefully any cases where there is concern that people are consenting because of payment and not because they wish to take part, and
- Develop a general policy on describing payments in terms of benefits in the consent process.

If non-financial incentives will be given,

- Develop guidelines for when and how non-financial incentives will be provided,
- Modality to provide free medical treatment,
- Modality to provide lunch vouchers for having lunch,
- Modality to provide free transportation,
- Ensure that there is a clear reason for providing non-financial incentives to participants,
- Consider carefully any cases where there is concern that people are consenting because of non-financial incentives and not because they wish to take part, and
- Develop a general policy on describing non-financial incentives in terms of benefits in the consent process.

Note: *Once someone leaves a study, all benefits end and so research participants would not receive compensation of any kind after leaving the study.*

Sometimes, it can be very difficult to assess what kind and what degree of incentive (financial and non-financial) is appropriate. Researchers must ensure that whatever incentive is offered to research participants is not unreasonably large; otherwise, these could be viewed as undue inducement. Therefore, the researchers must strike a balance between two objectionable outcomes, namely exploiting participants by providing too little by means of incentive and unduly inducing their participation by means of a incentive that is unreasonably high.

Note: *A coercive offer is an offer that a prospective participant is likely to be unable to decline because of the magnitude of what is on offer, or because of a lack of alternative courses of action. One example of coercion in research would be where a physician threatened to stop providing care to a patient unless they joined a clinic trial.*

Generally, it is considered appropriate to compensate the research participants for any expenses (e.g., transportation, lost wages) associated with their participation in the study. It is considered ethically acceptable by most of the ERB/IRC/IRB's. The research participants need to sign in the receipt once they receive incentives, and this should be mentioned in the informed consent form. Signed receipts must carefully be archived as they contain identifying information. They should be stored with the same level of protections for confidentiality as signed informed consent forms. These procedures should be worked out by the PI prior to beginning of the study as per approved protocol as prescribed by the ERB/IRC/IRB.

2.10.2 Meaning of Social Risk and its Rationale (Time: 10 minutes)

The facilitator should ask the participants to discuss about the meaning of risk and social risk, and its nature. Write responses on flip chart paper.

Risk is the probability that an event, or adverse effect, will occur within a defined time interval. Social risks are risks of harm due to loss of status, privacy, reputation, legal or financial risk as a result of confidentiality breaches including psychological risks such as depression, anxiety, stress.

Researchers have an obligation to themselves and to co-workers under their direction to maintain awareness of social risks or potential dangers and to take steps to diminish these.

The main dimensions of social risk to researchers are:

- Emotional distress in response to participants' disclosures,
- Arousal of mistrust from the place where researcher is collecting the data.

Risks may be exacerbated when conducting research in unfamiliar cultures or settings. When working in a dangerous area, it is sensible to develop some local knowledge, including such things as transport links and locations of police stations. Consideration should also be given to clothing, as it may be undesirable to be

noticeable as an outsider. Travel plans should be made in advance and the itinerary for travel and interviews should be given to someone who can function as a 'base'. Researchers should carry mobile phones in order to stay in contact with the base and to inform of any rearrangements. Personal alarms can also be carried.

Similarly, the main dimensions of social risk to research participants are:

- Finding out illegal or other behaviors that are not socially acceptable,
- Being kicked out of families or rejected by friends because of an identified disease or behavior,
- Dimensions associated with social stigma,
- Loss of income or job due to the discovery of suspicious behavior ,
- Women being hurt by their male partners for trying new drugs or devices without their partners knowledge, and
- Finding out the research participants have an incurable or communicable diseases.

2.10.3 Class Exercise (Time: 30 minutes)

The facilitator should ask the participants to read the following case study and discuss on the questions given.

Case Study: Standard of Care and Undue Inducement

A seven-year trial of anti-retroviral treatments for couples where one person is HIV-positive is being conducted in multiple semi-urban communities in Kenya, Malawi, Zimbabwe, and South Africa. The study will provide a range of medications that are not presently available to the communities where the

study is being conducted for treatment of AIDS and opportunistic infections.

Each site will have 10 to 20 couples enrolled in the study, which represents about 10 percent of those who are eligible to participate. Most of the medications that will be studied have been proven effective in other settings, and a few of the medications need follow-up care after the study is over. Two of the most promising study medications are very expensive and are known to cause resistance to future use if the treatment is stopped or interrupted. The researchers who developed the trial have indicated they believe the price of medications and availability of anti-retroviral medications will increase greatly by the end of the study.

Questions:

- (a) Given that the research participants will have access to medications while the rest of their community will not, what do you think will be some of the concerns a community advisory group may have about the study?
- (b) As a community advisory group member, what concerns would you have about the ability of participants to decide if they want to participate? If some of the medications have some painful or potentially harmful side effects, how might your response be different?
- (c) What are some responsibilities of the researcher to the participants in the study regarding access to medications and positive study results from the different treatments? What are some responsibilities of the researcher to the communities where the research is being conducted?

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4. Annexes

4.1 Annex – I (Pre-test and Post-test Questionnaire)

1 = No knowledge

3 = Some knowledge

5 = A lot of knowledge

Pre-Test (Circle before starting the training)					Self-assessment of Your Knowledge and Skills Related to	Post Test (Circle after participating in the training)				
1	2	3	4	5	Able to define research ethics	1	2	3	4	5
1	2	3	4	5	Having knowledge of historical perspectives of research ethics	1	2	3	4	5
1	2	3	4	5	Having knowledge of guiding principles for health research involving human beings	1	2	3	4	5
1	2	3	4	5	Having knowledge of international declarations and guidelines on research	1	2	3	4	5
1	2	3	4	5	Having knowledge of Nepali national ethical guidelines	1	2	3	4	5
1	2	3	4	5	Able to define informed consent	1	2	3	4	5
1	2	3	4	5	Able to enumerate essential elements of informed consent	1	2	3	4	5
1	2	3	4	5	Able to tell the types of consent	1	2	3	4	5
1	2	3	4	5	Able to define vulnerable people	1	2	3	4	5
1	2	3	4	5	Able to explain how to take consent from vulnerable people	1	2	3	4	5
1	2	3	4	5	Able to describe issues related to privacy and confidentiality	1	2	3	4	5
1	2	3	4	5	Able to describe the process of consent documentation	1	2	3	4	5
1	2	3	4	5	Able to define Institutional Review Committee/Board	1	2	3	4	5
1	2	3	4	5	Able to define rights of research participants	1	2	3	4	5
1	2	3	4	5	Having knowledge of various safety and quality issues of the research participants	1	2	3	4	5
1	2	3	4	5	Having knowledge of various steps of competent review of research protocol	1	2	3	4	5
1	2	3	4	5	Able to explain the procedure for recruiting research participants	1	2	3	4	5
1	2	3	4	5	Able to describe the care and protection of research participants	1	2	3	4	5
1	2	3	4	5	Having knowledge of various steps of reviewing informed consent	1	2	3	4	5
1	2	3	4	5	Having knowledge of the researcher's responsibility	1	2	3	4	5
1	2	3	4	5	Having knowledge of the sponsor's responsibility	1	2	3	4	5
1	2	3	4	5	Able to define community participation in the research process	1	2	3	4	5
1	2	3	4	5	Able to define inducement	1	2	3	4	5
1	2	3	4	5	Able to define compensation	1	2	3	4	5
1	2	3	4	5	Able to describe the social risk during research process	1	2	3	4	5

4.2 Annex – II (Session Evaluation)**Daily Session Evaluation****Title of Session:**

Please indicate your impression of the items listed below. If it is highly favorable, circle 9 and circle 1 for least favourable.

C	Content	Low					High				
C1	The session met my expectations	1	2	3	4	5	6	7	8	9	
C2	Applicability of gained knowledge in my working area	1	2	3	4	5	6	7	8	9	
C3	Enhancement of knowledge	1	2	3	4	5	6	7	8	9	
C4	Clarity and usefulness of audiovisual materials (if presented)	1	2	3	4	5	6	7	8	9	
F	Facilitators										
F1	Presentation skills	1	2	3	4	5	6	7	8	9	
F2	Quality of theoretical instruction	1	2	3	4	5	6	7	8	9	
F3	Quality of examples/case studies given	1	2	3	4	5	6	7	8	9	
F4	Encouragement of class participation and interaction	1	2	3	4	5	6	7	8	9	
F5	Opportunity for raising the participants' questions	1	2	3	4	5	6	7	8	9	
F6	Satisfaction with facilitator's clarification on asked questions	1	2	3	4	5	6	7	8	9	
F7	The facilitator's management of the class	1	2	3	4	5	6	7	8	9	
F8	The facilitator's management of the group/class work (if conducted)	1	2	3	4	5	6	7	8	9	
Q	Other Questions (if conducted)										
Q1	Session Length (Please indicate "✓" in the parenthesis)	Too short ()			Just right ()			Too long ()			
Q2	Your recommendation to improve this session										
Q3	Any other comments related to this session										

4.3 Annex – III (Overall Training Evaluation)

Please indicate your overall impression of the items listed below.

If it is highly favorable, circle 5. If not so favorable, give your opinion by circling from 4 to 1.

M	Module Contents	Low			High	
M1	The training course orientation	1	2	3	4	5
M2	General introduction to research ethics	1	2	3	4	5
M3	The Development of Contemporary Research Ethics	1	2	3	4	5
M4	Informed Consent – I	1	2	3	4	5
M5	Informed Consent – II	1	2	3	4	5
M6	Responsibilities of Institutional Review Committee/Board – I	1	2	3	4	5
M7	Responsibilities of Institutional Review Committee/Board – II	1	2	3	4	5
M8	Responsibilities of Institutional Review Committee/Board – III	1	2	3	4	5
M9	Responsibilities of Sponsors and Researchers	1	2	3	4	5
M10	Inducement/Compensation and Social Risk	1	2	3	4	5
F	Facilitators	Low			High	
F1	Overall presentation skills	1	2	3	4	5
F2	Overall quality of theoretical instruction	1	2	3	4	5
F3	Overall quality of examples/case studies given					
F4	Overall encouragement of class participation and interaction	1	2	3	4	5
F5	Overall opportunity for raising questions by participants	1	2	3	4	5
F6	Overall satisfaction with facilitator's clarifications on asked questions	1	2	3	4	5
F7	Overall management of the class	1	2	3	4	5
F8	Overall management of the group/class work					
O	Other questions	Low			High	
O1	Overall rating of the training	1	2	3	4	5
O2	This training is worthwhile and should be conducted on a regular basis	1	2	3	4	5
O3	Appropriateness of training venue and physical setting	1	2	3	4	5
O4	Overall rating of tea/coffee arrangement	1	2	3	4	5
O5	Overall rating of lunch arrangement	1	2	3	4	5

1. How did you get the information about this training ?
2. Which of the training modules were the most useful to you ?
3. Which of the training presentations or topics did you find the least useful ?
4. What presentations in the modules were you expecting to hear but were not presented ?
5. What topics of modules of this training would you like to learn in detail ?
6. Other comments and suggestions (if any).



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