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Federal Ministry of Health
Research Directorate
National Health Research Council

Research Ethics Training Manual
For Health Researchers

2010

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## Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>FMOH</td>
<td>Federal Ministry Of Health</td>
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<td>MOH</td>
<td>Ministry Of Health</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>KSMOH</td>
<td>Khartoum State Ministry Of Health</td>
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<tr>
<td>NGO</td>
<td>Non-Governmental Organization</td>
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<td>RH</td>
<td>Reproductive Health</td>
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<td>COI</td>
<td>Conflict of Interests</td>
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<td>REC</td>
<td>Research Ethics Committees</td>
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<td>IRB</td>
<td>Institutional Review Board</td>
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<td>REB</td>
<td>Research Ethics Board</td>
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<td>RD</td>
<td>Research Directorate</td>
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<td>CIOMS</td>
<td>Council for International Organizations of Medical Sciences</td>
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Preface
Introduction

Historically there have been horrible violations that accompanied the research that involved human participants. For instance, the Nazi doctors in the WWII have been abusing the prisoners in the concentration camps by literally freezing them alive to study the effect of extremely cold weather on human physiology. This was the beginning of a new era where humanity came to know that research should have guidance in terms of protecting the participants from similar abuses.

Such abuses led to the development of a series of international guidelines (the Nuremberg Code, Declaration of Helsinki, International Guidelines for Biomedical Research Involving Human Subjects (CIOMS), The Belmont Report and many others (see chapter 4)). However, there are still many violations that are being reported recently in both the developed and developing countries. For example there is the infamous Tuskegee Syphilis Study in Alabama, US (1932-1972), where more than 400 African-American men with latent syphilis were followed for the natural course of the disease rather than receiving treatment. The trial was continued even after penicillin was approved as available treatment for syphilis, leading to 40 wives infected and 19 children born with congenital syphilis.

What is research ethics?

It is that branch of ethics that works on defining, systemically analyzing, and attempting to resolve the ethical issues encountered during the conduct of a research study to ensure that both the participants and the researchers are protected and ultimately ensuring that clinical research is conducted in a way that serves the needs of such participants and of society as a whole [Weijer, 1997 391 /id].

Audience of the manual

This book targets the health researchers, especially in the clinical research done by practicing clinicians and paramedics (e.g., physicians, surgeons, nurses, dentists, therapists, etc.). It can also be invaluable to educators teaching research ethics in medical schools, hospitals, residency programs, and continuing medical education programs. As such, we also expect that the manual will serve as both: a training manual; and a textbook for courses in research ethics. Moreover, it may be of interest for public who may be interested in knowing more about research in general and research ethics in particular.

With such a variety of audience, we have worked on making the manual as readable, practical and as user-friendly as possible.

Structure of the manual

This manual is composed of seven chapters that follow this introduction. The first chapter provides an introduction to the development of research ethics, written by Dr. Huda Hamid. The second chapter is on the main concepts related to research involving human subjects, contributed by Dr. Sumaia Elfadil. The main ethical principles that regulate and guide research (with emphasis on risks and benefits) is contributed by Dr. Babiker Ahmed. Then Dr. Howeida Abusalih presents the most important national and international ethics guidelines, codes and declarations. Informed consent is presented in chapter five by Dr. Ghaiath Hussein, while Dr. Mustafa Niemri writes the chapter on RECs’ functions and responsibilities. Finally the chapter on ethical review process, conflicts
of interest and report back to the ethical committees is contributed by Prof. Suad Suleiman.

The annexes provided at the end of the manual include some basic national and international documents and forms related to the review of research by RECs or to the process obtaining the ethical approval for the research.

**Structure of the Chapter:**

Each chapter has the following outline:

- Chapter author
- Summary box: which summarizes the chapter in a memorizable abstract.
- Key points: a box with the “take home messages!”
- Introduction
- Learning objectives
- Learning methods
- Contents of each chapter
- Case studies and problems
- References and readings

**Need help?**

If you have any question, comment, suggestion or inquiry, you can either contact:

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Chapter 1: Introduction and history of research ethics

Huda Hamid, MD
Chapter 2: Research involving human subjects

Sumaia Elfadil, MD

Introduction

With increasing burden of disease and broadening of the concept of health and its social determinants, advancement of science to high impact prevention, diagnostic and treatment methods that combat disease, equally to raise community awareness on prevention and health promotion, a great demand for research arises. Since this advancement is for wellbeing of humans, it is mandatory that humans will be the subjects of research. Ethics in biomedical research ethics in now evolving as a result of the very fast growth in health research.

This module tries in simple terms to orient participants on research involving human subjects to safeguard humans against harmful practices in research.

This module will not go in-depth in many concepts, principles and processes that are expected to be addressed in other modules.

Learning Objectives

By the end of this module, participant is the expected to:

- Conceptualize and discuss what research, human subjects are
- Understand and differentiate in what conditions does research is considered as involving human subjects or not.
- Understand and is able to make boundaries between ethics in health research and ethics in medical practice.
- Understand, define and discuss the three main ethical principles of research involving human subjects: Respect for person, beneficence and justice
- Understand, define and discuss other ethical principles commonly observed in health research.

The learning methods

- Lecture and discussion
- Case studies/questions and answers
- Self reading
Module contents

Definitions and concepts

Research is defined as “systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”.

Activities which meet this definition constitutes research for purposes of guidance on “Research Involving human Subjects”, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities, such as testing information, educational and communication materials, testing interventions, surveys etc.. This is commonly practiced by different public health programmes overlooking the fact that it is research and that ethical conduct should be considered.

Human subjects are commonly participants in research on: basic biology, clinical medicine, psychology, and all other social sciences. Humans have been participants in research since the earliest studies. As research has become formalized, the academic community has developed formal definitions of "human subject research", largely in response to abuses of human subjects.

Human subject refers to “a living individual about whom an investigator (whether professional or student) is conducting research that obtains: Data through

1) intervention or interaction with the individual, or
2) Identifiable private information.

Intervention includes both (a) physical procedures by which data are gathered (for example, veni-puncture, laparoscopy, administer drug or any material etc.,) and (b) manipulations of the subject or the subject’s environment that are performed for research purposes.

Ethical conduct has to be observed both in experimental and observational studies since both are about human subjects.

What are the experimental and observational studies?

Both studies involve observation. However the fundamental difference is that an experiment requires you to observe what happens when you make some sort of changes regarding what you are experimenting (the variable). An observational study finds the relationship between changes among individuals where the variable that already exist.

The ethical consideration to be observed when you try to cause the change yourself.
Interaction includes interpersonal communication between an investigator and the person/persons being investigated under the research.

3) Private identifiable information
In order for obtaining the information to constitute research involving human subjects, the information should be about behaviour that occurs in a context in which an individual is not expecting that observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).
Private information must be individually identifiable (i.e., the identity of the subject: name, age, address and sex is or may readily be ascertained by the investigator or associated with the information).

What are the boundaries between ethics in medical practice and ethics in health/medical research?

Humans are the core objective in medical/health practice or research for health. Whenever you are dealing with humans, ethical disciplines have to be applied to maximize benefits and reduce risks threatening humans’ well being. The differences in application come when taking decisions on what strategy/process to follow to ensure ethical conduct in either of them. In order to be able to make that very fine distinct you have to know whether the protocol you are dealing with, is a protocol for practice or a research protocol. To decide whether the protocol should go for review or not you have to understand the boundaries between ethics in medical practice and ethics in health/medical research.

Medical/clinical practice is a set of protocols/standards of care designed to provide diagnosis, preventive treatment or therapy to particular individuals, based on evidence and well experimented theories that have reasonable expectation of success. Those practices include: therapies whether chemical or physical, instruments, techniques, counselling etc..

By contrast, the term “research” refers to activities/protocols designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective. Research results might end with development of a medical/clinical protocol if proved effective.

The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because
notable deviations from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined. In either situations and since we are dealing with humans attention to application of ethics and morals is mandatory. When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

Hippocrates, the father of western medicine, in Ionic Greek (late 5th century BCE) an oath and his physicians followers have historically set the primary guidance to medical ethics through the Oath of Hippocrates to practice medicine ethically. One of the famous statements is “Do no harm to the patient”. Medical ethics in the modern sense refers to the application of general and fundamental ethical principles to clinical practice situations in a broader sense but the main focus is that practitioner works for the best of his patient/client.

While Hippocrates and his followers have paved the road and set the guidance to medical ethics through the oath, Belmont report, a result of a four years endevaour of the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research in US, set the guidance to basic ethical principles that should underlie the conduct of biomedical and behavioural research involving human subjects and to develop guidelines that govern such research. This endeavour took place in February 1976 at the Smithsonian Institution's Belmont Conference Centre. The National Commission while carrying its work, it was directed to consider:

(i) the boundaries between biomedical and behavioural research and the accepted and routine practice of medicine,
(ii) the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, (will be discussed in module 3).
(iii) appropriate guidelines for the selection of human subjects for participation in such research (will be discussed in module 3)

(iv) and the nature and definition of informed consent in various research settings (will be discussed in module 5).

Later in 1993, the International Ethical Guidelines for Biomedical Research Involving Human Subjects, were developed by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), on the basis of Belmont report. CIOMS guidelines shed more emphasis on the principles of ethical biomedical research including: informed consent, standards for external review, recruitment of participants.

As for Sudan, “National Health Research Ethics” guidelines, based on international guidelines and addressing local contexts were developed by FMOH and endorsed by consensus in 2006.

**Basic ethical principles**

The expression "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**, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence/non maleficent and justice.

1. **Respect for Persons**

Respect for persons includes two ethical aspects: full autonomous should be provided to individuals and protection should be provided to persons with diminished autonomy.

An autonomous person is an individual capable of deciding for himself and of acting in line with these decisions. To respect autonomy is to:

- respect for personal self-determination and give weight to and considers one’s opinions and choices while refraining from obstructing their actions unless they are clearly dangerous to others.
- respect for privacy for persons: ensure confidentiality protections
- respect for persons with limited autonomy: some individuals lose this capacity wholly or in part because of illness, mental disability, children where you have to obtain family consent. In other circumstances that severely restrict liberty (prisoners, women in a community where culture restricts their decision) privacy and protection for persons is to be ensured.

In all cases, the extent of protection afforded should depend upon the risk of harm and the likelihood of benefit people will receive. Example is when the research is designed specially to test a hypotheses related to such group of people with limited
autonomy. It is to be noted that judgment on individual’s autonomy is to be reevaluated periodically.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. The informed consent is the first and longest principles of ethics: “The voluntary consent of the human subject is absolutely essential.” In some situations, however, application of the principle is not obvious.

2. Beneficence/non malicence

Ethics is not only about respecting decisions and protecting persons from harm, but it is also by making efforts to secure their well-being what is known as beneficence. Beneficence incorporates two general rules: do not harm and maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." To know what will benefit persons may require exposing persons to risk. It is then, very important to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks, a situation that comes always under the dilemma of how to make balance between protecting subjects and advancing knowledge for the sake of people.

The obligations of beneficence are not limited to individual benefits, but it extends to the community at large. The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. A good example is found in research involving children. Discovering effective ways of treating childhood diseases and fostering healthy development are benefits that justify research involving children, even when individual research subjects are not direct beneficiaries. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

2. Justice

The word justice stands in literature for fairness or reasonableness, especially in the way people are treated or decisions are made. It also refers to equal treatment for all: the availability of the same rights, position, and status to all people, regardless of gender, sexual preference, age, race, ethnicity, or religion. The ethical principle of justice in research is about who should receive the benefits of research and who should bear its burdens? Justice entails fairness in distribution of risks and benefits, where benefits and risks of research are distributed fairly among all groups in society and is about fairness in
selection of human research subjects by avoidance of choosing groups based on easy availability or compromised position. Do not involve groups unlikely to benefit from the subsequent applications of the research.

The scandals of prisoners of the Nazi concentration camps who were submerged in tanks filled with cold water to determine how long German pilots would survive after parachuting into the cold north sea and the Tuskegee where black Americans were deprived from treatment of syphilis while it was available were condemned as flagrant injustice.

In order to apply the three general principles of ethics to the conduct of research we have to consider the following requirements:

1. **Community Partnership**
   It is important to ensure community participation in planning, conducting and overseeing research and integrating results into the health system i.e. research must be responsive to the needs of the community.

2. **Independent review**
   To ensure research subjects protection and adhere to ethical conduct it is mandatory not to carry any research activity without being reviewed by a recognized independent review body. These are usually committees that has been formally designated to approve, monitor, and review biomedical and behavioural research involving humans with the aim to protect the rights and welfare of the research subjects.

3. **Social Value**
   To be ethical, clinical or behavioural research must lead to improvements in health or advancement in generalizable knowledge. The research must have an impact to the society.

4. **Scientific Validity**
   Research must be conducted with an appropriate methodology to ensure that the results will answer the original research questions with appropriate endpoints or statistical tests, sufficient subjects, justification of validity to avoid waste of resources and justify exposing subjects to burdens or risks.

5. **Fair Subject Selection:** The scientific objectives of the study should guide inclusion criteria and choice of targeted populations. Inclusion criteria: vulnerable groups should not be targeted, research should be applicable to diseases of vulnerable groups. Exclusion: groups cannot be excluded without scientific reasons and higher risk is a reason to exclude certain groups.

6. **Favourable risk-benefit ratio**
   Identification of risks factors include: physical, social, economic, psychological factors and minimizing risk by using best possible research design and enhancing potential benefits.

7. **Informed Consent**
   Informed consent ensures that individuals themselves decide whether to enroll in research and whether research fits with their own values, interests, and goals. Research on individuals who cannot decide: children and mentally impaired requires surrogate consent. More about informed consent will be discussed later.

8. **Respect for human subjects**
   Respecting enrolled subjects includes: protecting confidentiality, permitting withdrawal, providing new information and monitoring welfare throughout the study.
Academic Freedoms and Responsibilities
Researchers enjoy, and should continue to enjoy, important freedoms and privileges. To secure the maximum benefits from research, society needs to ensure that researchers have certain freedoms. It is for this reason that researchers and their academic institutions uphold the principles of academic freedom and the independence of the higher education research community. These freedoms include freedom of inquiry and the right to disseminate the results thereof, freedom to challenge conventional thought, freedom from institutional censorship, and the privilege of conducting research on human subjects with public monies, trust and support. However researchers and institutions also recognize that with freedom comes responsibility, including the responsibility to ensure that research involving human subjects meets high scientific and ethical standards. The researcher’s commitment to the advancement of knowledge also implies duties of honest and thoughtful inquiry, rigorous analysis, and accountability for the use of professional standards. Thus, peer review of research proposals, the findings and their interpretation contribute to accountability, both to colleagues and to society. Review of the ethics of research helps ensure a more general accountability to society.
Accountability, moreover, requires that the whole process should always be open to critical assessment and debate.

Case studies and problems
a) The norms of research ethics are driven by the principles articulated in the Hippocratic Oath.
a. True or False?
b) The most pressing issue for research performed in the International arena is how to avoid exploitation.
a. True or False?
c) Respect for persons, as manifested by the requirement for informed consent, is the essence of research ethics.
a. True or False?
d) Discuss in brief therapeutic misconception?

References and readings:
1. http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.102
2. Social Sciences and Humanities Research Council of Canada, Ethics Guidelines for Research Involving Human Subjects. Ottawa,
Chapter 3: Ethical principles – risks and benefits
Babiker Ahmed, MD
Chapter 4: The national and international ethics guidelines, codes and declarations

Howeida Abusalih, MD

Background

The first international document on the ethics of research, the Nuremberg Code, was promulgated in 1947 as a consequence of the trial of physicians who had conducted atrocious experiments on unconsenting prisoners and detainees during the second world war. The Code, designed to protect the integrity of the research subject, sets out conditions for the ethical conduct of research involving human subjects, emphasizing the human subject's "voluntary consent" to research. (1)

To give the Universal Declaration of Human Rights, adopted by the United Nations General Assembly in 1948, legal as well as moral force, the General Assembly of the United Nations adopted in 1966 the International Covenant on Civil and Political Rights, of which Article 7 states "No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation." (2)

The Declaration of Helsinki, promulgated in 1964 by the World Medical Association, is the fundamental document in the field of ethics in biomedical research and has had considerable influence on the formulation of international, regional and national legislation and codes of conduct. The Declaration, revised in Tokyo in 1975, in Venice in 1983, and again in Hong Kong in 1989, is a comprehensive international statement of the ethics of research involving human subjects. It sets out ethical guidelines for physicians engaged in both clinical and non-clinical biomedical research, and provides among its rules for informed consent of subjects and ethical review of the research protocol. (3)

The publication in 1982 of Proposed International Guidelines for Biomedical Research Involving Human Subjects was a logical development of the Declaration of Helsinki. As stated in the Introduction of that publication, the Guidelines were intended to indicate how the ethical principles embodied in the Declaration could be effectively applied in developing countries. The text explained the application of established ethical principles to biomedical research involving human subjects and drew attention to new ethical issues arising in the period that preceded its publication. The present publication, International Ethical Guidelines for Biomedical Research Involving Human Subjects, supersedes the 1982 Proposed International Guidelines. (3)

CIOMS and WHO have continued to work together to provide ethical guidance for research involving human subjects. One important outcome of this cooperation has been International Guidelines for Ethical Review of Epidemiological Studies, published by CIOMS in 1991, intended to assist investigators and institutions as well as regional and national authorities in setting and maintaining standards for the ethical review of epidemiological studies. (4)
Rationale of teaching International guidelines

The Compliance with these guidelines helps to ensure that the dignity, rights, safety, and well-being of research participants are promoted and that the results of the investigations are credible.

All international guidelines require the ethical and scientific review of biomedical research alongside informed consent and the appropriate protection of those unable to consent as essential measures to protect the individual person and the communities who participate in research.

These Guidelines are intended to facilitate and support ethical review in all countries around the world. They are based on a close examination of the requirements for ethical review as established in international guidelines, as well as on an evaluation of existing practices of ethical review in countries around the world. They do not, however, purport to replace the need for national and local guidelines for the ethical review of biomedical research, nor do they intend to supersede national laws and regulations.

2-Learning objectives

By the end of this module, the participants are expected to:

1- Describe comprehensively the important statements in the Nuremberg code.
2- Discuss the Human rights in relation to research Ethics
3- Outline skillfully declaration of Helsinki.
4- Be familiar with Belmont Report.
5- Be acquainted with International ethical guidelines for biomedical research involving human developed by CIOM
6- Be able to describe the WHO guidelines for Research ethics committee that review Biomedical Research

Module content:

3-1-Nuremberg Code:
Consist of the following

3-1-1. The voluntary consent .
This means that the person involved
• should have legal capacity to give consent.
• should be able to exercise free power of choice.
• should have sufficient and comprehensive knowledge of the subject matter involved. (1)

3-1-2. The experiment should
• yield fruitful results for the good of society.
- The experiment should be based on the results of animal experimentation.
- Experiment should be based on knowledge of the natural history of the disease or other problem under study.
- the anticipated results should justify the performance of the experiment.
- The experiment should be so conducted without unnecessary physical and mental suffering and injury.
- No experiment should be conducted, where there is a belief that death or disabling injury will occur; except in those experiments where the experimental physicians also serve as subjects.
- The degree of risk should never exceed that determined by the humanitarian importance of the problem to be solved by the Experiment.
- Proper preparations to protect the experimental subject against even remote possibilities of injury, disability, or death should be made.
- The experiment should be conducted only by scientifically qualified persons through all stages of the experiment of those who conduct or engage in the experiment.
- During the course of the experiment, the human subject should be at liberty to bring the experiment to an end.
- During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, if he believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject. (1)

3-2- The Universal Declaration of Human Rights:
The Universal Declaration of Human Rights (UDHR) is a declaration adopted by the United Nations General Assembly on 10 December 1948 at the Palais de Chaillot in Paris. The Declaration has been translated into at least 375 languages and dialects, making it the most widely translated document in the world. The Declaration arose directly from the experience of the Second World War and represents the first global expression of rights to which all human beings are entitled. It consists of 30 articles which have been elaborated in subsequent international treaties, regional human rights instruments, national constitutions and laws. The International Bill of Human Rights consists of the Universal Declaration of Human Rights, the International Covenant on Economic, Social and Cultural Rights, and the International Covenant on Civil and Political Rights and its two Optional Protocols. In 1966 the General Assembly adopted the two detailed Covenants, which complete the International Bill of Human Rights. (2)

3-3- DECLARATION OF HELSINKI.
The medical and research community realized that Nuremberg Code did not provide adequate guidance for most of the research activities carried out by medical doctors. (3)
In 1953, the WMA Committee on Medical Ethics recognized that:
1. Need for professional guidelines designed by physicians for physicians.
2. Experiments must be classified into two groups:
a) Experiments in new diagnostic and therapeutic method
b) Experiments undertaken to serve other purposes than simply to cure an individual Policy (3)

3-3-1 INTRODUCTION TO DECLARATION OF HELESINKE

- The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects.
- It is the duty of the physician to promote and safeguard the health of the people.
- In medical research on human subjects considerations related to the well-being of the human subject should take precedence over the interests of science and society.
- The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease.

- Special attention is required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
- Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. (3)

3-3-2. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

- It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
- Medical research involving human subjects must conform to generally accepted scientific principles thorough knowledge of the scientific literature adequate laboratory and where appropriate, animal experimentation.
- Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
- The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence.
- The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
- Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person.
• Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others.

• Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed.

• Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject.

• Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

• The subjects must be volunteers and informed participants in the research project.

• The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient’s information and to minimize the impact of the study on the subject’s physical and mental integrity and on the personality of the subject.

• In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject’s freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

• When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

• For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

• When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

• Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the
physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee.

- The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

- Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.(3) 3-3-3.

3. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

- The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

- The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

- At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

- The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.(3)

3.4-Belmont report:

On July 12, 1974, the National Research Act in USA was signed into law, thereby creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider:
the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine.

- the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects.
- appropriate guidelines for the selection of human subjects for participation in such research and
- the nature and definition of informed consent in various research settings.(4)

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution’s Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department’s policy. The Department requests public comment on this recommendation(4)

International ethical guidelines for biomedical research involving human subjects

Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). CIOMS, Geneva 2002.(5)

**Guideline 1: Ethical justification and scientific validity of biomedical research involving human beings**

research can be ethically justifiable only if it is carried out in ways that respect and protect, and are fair to, the subjects of that research and are morally acceptable within the communities in which the research is carried out(5).

**Guideline 2: Ethical review committees**
All research proposals involving human subjects must be submitted for review of their scientific merit and ethical acceptability to one or more scientific review and ethical review committees.

**Guideline 3: Ethical review of externally sponsored research**

An external sponsoring organization and individual investigators should submit the research protocol for ethical and scientific review in the country of the sponsoring organization, and the ethical standards applied should be no less stringent than they would be for research carried out in that country.

**Guideline 4: Individual informed consent**

For all biomedical research involving humans the investigator must obtain the voluntary informed consent of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the permission of a legally authorized representative in accordance with applicable law. Waiver of informed consent is to be regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee.

**Guideline 5: Obtaining informed consent: Essential information for prospective research subjects**

Before requesting an individual’s consent to participate in research, the investigator must provide the following information, in language or another form of communication that the individual can understand:

1. that the individual is invited to participate in research, the reasons for considering the individual suitable for the research, and that participation is voluntary;
2. that the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled;
3. the purpose of the research, the procedures to be carried out by the investigator and the subject, and an explanation of how the research differs from routine medical care;
4. for controlled trials, an explanation of features of the research design (e.g. randomization, double-blinding), and that the subject will not be told of the assigned treatment until the study has been completed and the blind has been broken;

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5. the expected duration of the individual’s participation (including number and duration of visits to the research centre and the total time involved) and the possibility of early termination of the trial or of the individual's participation in it;
6. whether money or other forms of material goods will be provided in return for the individual’s participation and, if so, the kind and amount;
7. that, after completion of the study, subjects will be informed of the findings of the research in general, and individual subjects will be informed of any finding that relates to their particular health status;
8. that subjects have the right of access to their data on demand, even if these data lack immediate clinical utility (unless the ethical review committee has approved temporary or permanent non-disclosure of data, in which case the subject should be informed of, and given, the reasons for such non-disclosure);
9. any foreseeable risks, pain or discomfort, or inconvenience to the individual (or others) associated with participation in the research, including risks to the health or well-being of a subject’s spouse or partner;
10. the direct benefits, if any, expected to result to subjects from participating in the research;
11. the expected benefits of the research to the community or to society at large, or contributions to scientific knowledge;
12. whether, when and how any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research, and whether they will be expected to pay for them;
13. any currently available alternative interventions or courses of treatment;
14. the provisions that will be made to ensure respect for the privacy of subjects and for the confidentiality of records in which subjects are identified;
15. the limits, legal or other, to the investigators’ ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality;
16. policy with regard to the use of results of genetic tests and familial genetic information, and the precautions in place to prevent disclosure of the results of a subject’s genetic tests to immediate family relatives or to others (e.g., insurance companies or employers) without the consent of the subject;
17. the sponsors of the research, the institutional affiliation of the investigators, and the nature and sources of funding for the research;

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18. the possible research uses, direct or secondary, of the subject’s medical records and of biological specimens taken in the course of clinical care;
19. whether it is planned that biological specimens collected in the research will be destroyed at its conclusion, and, if not, details about their storage (where, how, for how long, and final disposition) and possible future use, and that subjects have the right to decide about such future use, to refuse storage, and to have the material destroyed;
20. whether commercial products may be developed from biological specimens, and whether the participant will receive monetary or other benefits from the development of such products;
21. whether the investigator is serving only as an investigator or as both investigator and the subject’s physician;
22. the extent of the investigator’s responsibility to provide medical services to the participant;
23. that treatment will be provided free of charge for specified types of research-related injury or for complications associated with the research, the nature and duration of such care, the name of the organization or individual that will provide the treatment, and whether there is any uncertainty regarding funding of such treatment;
24. in what way, and by what organization, the subject or the subject’s family or dependants will be compensated for disability or death resulting from such injury (or, when indicated, that there are no plans to provide such compensation);
25. whether or not, in the country in which the prospective subject is invited to participate in research, the right to compensation is legally guaranteed;
26. that an ethical review committee has approved or cleared the research protocol.

**Guideline 6: Obtaining informed consent: Obligations of sponsors and investigators**

Sponsors and investigators have a duty to:

- refrain from unjustified deception, undue influence, or intimidation;
- seek consent only after ascertaining that the prospective subject has adequate understanding of the relevant facts and of the consequences of participation and has had sufficient opportunity to consider whether to participate;

**Biomedical research involving human subjects**

- as a general rule, obtain from each prospective subject a signed form as evidence of informed consent—investigators should justify any exceptions to this general rule and obtain the approval of the ethical review committee;
- renew the informed consent of each subject if there are significant changes in the conditions or procedures of the research or if new information becomes available that could affect the willingness of subjects to continue to participate; and,
- renew the informed consent of each subject in long-term studies at predetermined intervals, even if there are no changes in the design or objectives of the research.

**Guideline 7: Inducement to participate**

Subjects may be reimbursed for lost earnings, travel costs and other expenses incurred in taking part in a study; they may also receive free medical services. Subjects, particularly those who receive no direct benefit from research, may also be paid or otherwise compensated for inconvenience and time spent. The payments should not be so large, however, or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgement (“undue inducement”). All payments, reimbursements and medical services provided to research subjects must have been approved by an ethical review committee.

**Guideline 8: Benefits and risks of study participation**

For all biomedical research involving human subjects, the investigator must ensure that potential benefits and risks are reasonably balanced and risks are minimized.

- Interventions or procedures that hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual subject must be justified by the expectation that they will be at least as advantageous to the individual subject, in the light of foreseeable risks and benefits, as any available alternative. Risks of such “beneficial” interventions or procedures must be justified in relation to expected benefits to the individual subject.
- Risks of interventions that do not hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual must be justified in relation to the expected benefits to society (generalizable knowledge). The risks presented by such interventions must be reasonable in relation to the importance of the knowledge to be gained.

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**Guideline 9: Special limitations on risk when research involves individuals who are not capable of giving informed consent**
When there is ethical and scientific justification to conduct research with individuals incapable of giving informed consent, the risk from research interventions that do not hold out the prospect of direct benefit for the individual subject should be no more likely and not greater than the risk attached to routine medical or psychological examination of such persons. Slight or minor increases above such risk may be permitted when there is an overriding scientific or medical rationale for such increases and when an ethical review committee has approved them.

Guideline 10: Research in populations and communities with limited resources

Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:
- the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and
- any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.

Guideline 11: Choice of control in clinical trials

As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or “no treatment”. Placebo may be used:
- when there is no established effective intervention;
- when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms;
- when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.

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Guideline 12: Equitable distribution of burdens and benefits in the selection of groups of subjects in research

Groups or communities to be invited to be subjects of research should be selected in such a way that the burdens and benefits of the research will be equitably distributed. The exclusion of groups or communities that might benefit from study participation must be justified.

Guideline 13: Research involving vulnerable persons

Special justification is required for inviting vulnerable individuals to serve as research subjects and, if they are selected, the means of protecting their rights and welfare must be strictly applied.

Guideline 14: Research involving children

Before undertaking research involving children, the investigator must ensure that:
- the research might not equally well be carried out with adults;
- the purpose of the research is to obtain knowledge relevant to the health needs of children;
- a parent or legal representative of each child has given permission;
Chapter 4: The national and international ethics guidelines, codes and declarations

Guideline 15: Research involving individuals who by reason of mental or behavioral disorders are not capable of giving adequately informed consent

Before undertaking research involving individuals who by reason of mental or behavioral disorders are not capable of giving adequately informed consent, the investigator must ensure that:

- such persons will not be subjects of research that might equally well be carried out on persons whose capacity to give adequately informed consent is not impaired;
- the purpose of the research is to obtain knowledge relevant to the particular health needs of persons with mental or behavioral disorders;
- the consent of each subject has been obtained to the extent of that person’s capabilities, and a prospective subject’s refusal to participate in research is always respected, unless, in exceptional circumstances, there is no reasonable medical alternative and local law permits overriding the objection; and,
- in cases where prospective subjects lack capacity to consent, permission is obtained from a responsible family member or a legally authorized representative in accordance with applicable law.

Guideline 16: Women as research subjects

Investigators, sponsors or ethical review committees should not exclude women of reproductive age from biomedical research. The potential for becoming pregnant during a study should not, in itself, be used as a reason for precluding or limiting participation.

However, a thorough discussion of risks to the pregnant woman and to her fetus is a prerequisite for the woman’s ability to make a rational decision to enrol in a clinical study. In this discussion, if participation in the research might be hazardous to a fetus or a woman if she becomes pregnant, the sponsors/investigators should guarantee the prospective subject a pregnancy test and access to effective contraceptive methods before the research commences. Where such access is not possible, for legal or religious reasons, investigators should not recruit for such possibly hazardous research women who might become pregnant.

Guideline 17: Pregnant women as research participants

Pregnant women should be presumed to be eligible for participation in biomedical research. Investigators and ethical review committees should ensure that prospective subjects who are pregnant are adequately informed about the risks and benefits to themselves, their pregnancies, the fetus and their subsequent offspring, and to their fertility. Research in this population should be performed only if it is relevant to the particular health needs of a pregnant woman or her fetus, or to the health needs of pregnant women in general, and, when appropriate, if it is supported by reliable evidence from animal experiments, particularly as to risks of teratogenicity and mutagenicity.

Guideline 18: Safeguarding confidentiality

- the agreement (assent) of each child has been obtained to the extent of the child’s capabilities; and,
- a child’s refusal to participate or continue in the research will be respected.
The investigator must establish secure safeguards of the confidentiality of subjects’ research data. Subjects should be told the limits, legal or other, to the investigators’ ability to safeguard confidentiality and the possible consequences of breaches of confidentiality.

Guideline 19: Right of injured subjects to treatment and compensation

Investigators should ensure that research subjects who suffer injury as a result of their participation are entitled to free medical treatment for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability or handicap. In the case of death as a result of their participation, their dependants are entitled to compensation. Subjects must not be asked to waive the right to compensation.

Guideline 20: Strengthening capacity for ethical and scientific review and biomedical research

Many countries lack the capacity to assess or ensure the scientific quality or ethical acceptability of biomedical research proposed or carried out in their jurisdictions. In externally sponsored collaborative research, sponsors and investigators have an ethical obligation to ensure that biomedical research projects for which they are responsible in such countries contribute effectively to national or local capacity to design and conduct biomedical research, and to provide scientific and ethical review and monitoring of such research. Capacity-building may include, but is not limited to, the following activities:

- establishing and strengthening independent and competent ethical review processes/committees
- strengthening research capacity
- developing technologies appropriate to health-care and biomedical research
- training of research and health-care staff
- educating the community from which research subjects will be drawn.

Guideline 21: Ethical obligation of external sponsors to provide health-care services

External sponsors are ethically obliged to ensure the availability of:

- health-care services that are essential to the safe conduct of the research; treatment for subjects who suffer injury as a consequence of research interventions; and services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned(5).

3.6-Guidelines for Good Clinical Practice Developed by ICH

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration(6).

The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for
product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.(6) Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities. The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

3-6-1- THE PRINCIPLES OF ICH GCP

- Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP.
- Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
- The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
- The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
- Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
- A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee approval/favourable opinion.
- The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician.
- Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
- Freely given informed consent should be obtained from every subject prior to clinical trial participation.
- All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting interpretation and verification.
- The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
- Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
- Systems with procedures that assure the quality of every aspect of the trial should be implemented.
The document also explained in details the responsibilities of Research Ethics Committee, compositions, functions and operations as well as procedures and records.

3-6-2 INDEPENDENT ETHICS COMMITTEE RESPONSIBILITIES

- REC should safeguard the rights, safety, and well-being of all trial subjects.
- REC should obtain the necessary Trial documents such as trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates.
- REC should review a proposed clinical trial within a reasonable time and document its views in writing.
- REC should consider the qualifications of the investigator for the proposed trial.
- REC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.
- REC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

REC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects.

3-6-3 SPONSOR Quality Assurance and Quality Control

- The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).
- The sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.
- Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

3-7 WHO Guidelines for Research Ethics Committee That Review Biomedical Research

The Operational Guidelines for Ethics Committees That Review
Biomedical Research is the result of a wide international consultation begun in August 1999 at A Seminar on the Ethical Review of Clinical Research in Asian & Western Pacific Countries organized by TDR WHO in Chiang Mai, Thailand. The participants at the seminar expressed a need for international guidance on the constitution and operation of ethics committees. The Operational Guidelines for Ethics Committees That Review Biomedical Research are proposed by the WHO and CIOMS as a support for improving the organization, quality, and standards of ethical review around the world. These Guidelines take into account current practices while suggesting guidance for a harmonized state approach.

The objective of these Guidelines is to contribute to the development of quality and consistency in the ethical review of biomedical research. The Guidelines are intended to complement existing laws, regulations, and practices, and to serve as a basis upon which ethics committees (ECs) can develop their own specific written procedures for their functions in biomedical research. In this regard, the Guidelines establish an international standard for ensuring quality in ethical review. The Guidelines should be used by national and local bodies in developing, evaluating, and progressively refining standard operating procedures for the ethical review of biomedical Research.

The Guidelines described comprehensively the Role of the Research Ethics Committee, How to establish a system for ethical review, Constituting The research ethics committee in addition to the requirements of membership.

3-8 National Guidelines

The national guidelines was set by research department Federal Ministry of Health on August 2008. The national guidelines regulate the conduct of research related to health, with special emphasis on those involving human subjects in Sudan. It is composed of five main chapters followed by the annexes. The introduction goes through the main concepts of research, types of research and research ethics.

The second chapter explains the principles of ethics for research involving human subjects. This includes detailed explanation of all the three basic ethical principles, namely respect for persons, beneficence and justice in any research involving human subjects. It also enlists about other 20 principles that regulate and guide the research conduction.

The third chapter is about the National Research Ethics Committee. This includes a thorough explanation of the structure and functioning technical procedures followed within the National Research Ethics Committee. It includes the authority under which NHREC was constituted, its Membership, meetings, and quorum. It also elaborates on the independent consultants, operational cost, the record keeping and archiving together with updating of NHREC members.

Chapter four is the core of the guidelines for the researcher, as it explains all the steps and procedures for obtaining the ethical clearance in a simplified flow chart.
and detailed steps of what to prepare, ethical elements review, how to apply, review procedures and decision making.
The fifth chapter is about the Informed Consent, its definition, importance, and components. It explains the information that the research subject should know and understand before being involved in the study. (8)
It also goes through the regulations of the use of biological materials from subjects in clinical trials, the use of medical records and biological specimens. It explains some of the basic principles about the secondary use of research records or biological specimens together with some obligations to be followed by both sponsors and investigators. It covers the issues related to the possible influence on the research subject like withholding information and deception, intimidation and undue influence. It also aims at assuring the equitable distribution of burdens and benefits in the selection of groups of subjects in research. (8)

**Learning methods**
- Lectures
- Group discussions and presentations
- Case study and discussion.
- Assignment
- **Self learning.**
- Exercises

**Case Studies**

*Case study (1) Frostbite Clinical Trial*
A drug company plans to do Phase I safety study on healthy subjects for a drug designed to reduce the damage from severe frostbite. Animal and toxicological studies indicate that the drug has no serious side-effects. The researchers want to work in Egypt because it is far less expensive to run a Phase I study there than in any Western country, and in past studies, they have found it easy to recruit and retain subjects in rural areas. They have adopted culturally appropriate informed-consent procedures and will offer subjects compensation for any injury that might occur as well as payment that is generous but not extravagant by local standards. In addition, the company has committed itself to funding a network of badly-needed local health clinics in the areas from which subjects are recruited.

**Questions:**
1-How do you apply CIOMS international guidelines for this study?

*Case Study (2)*
Researchers propose a Phase III study of a new treatment for asthma in children. They wish to conduct the study in a particular region because there is a high prevalence of asthma in the region. The research participants will be children less than 10 years old, and the informed consent will be properly obtained from their parents. A modest compensation will be given to the families for participation. Political and social research has however indicated severe human-rights violations regarding the treatment of women, especially female children. Sons are much more highly prized than daughters and there have been some reports of female newborns not receiving health care and sometimes being abandoned and left to die. Local officials reject these reports as malicious, claiming that if female infant mortality is higher, it is due to female infants often being more sickly. With this information the researchers discover that parents are reluctant to allow their sons to participate in the study. They will agree only if the compensation is twice what it would be for daughters.

Question: The researchers have sufficient funds to comply with this demand, but should they? Why or why not? Answer should be based on Guidance from Declaration of Helsinki

Case Study (3)

A researcher wants to investigate a promising new drug for a virulent disease largely confined to a single country. The study will require several visits to the clinic for physical assessment and blood drawing. The disease affects both men and women, but appears to affect women more severely. The researcher, however, wants to restrict the study to male subjects, although preliminary studies suggest that safe and effective dose-levels of the drug are different for men and women. The reason for restricting recruitment is that women in that country are expected to stay in their homes and are discouraged from leaving them. While it may be possible to recruit an adequate number of women, it will require extensive negotiations with village elders, driving up the time and expense of the study and risking suspicion and hostility in the host communities. REC members disagree over the ethical acceptability of this study. What are your thoughts based on Ethical guidelines?
7-References


2- WWW.UN.org/overview/rights

3- WMA (World Medical Assembly) (1989), "Declaration of Helsinki: Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects". Adopted, June 1964 (Helsinki) and amended, October 1975 (Tokyo), October 1983 (Venice) and 1989 (Hong Kong).


Chapter 5: Informed consent

Ghaiath Hussein, MBBS, MHSc. (Bioethics)

Background and rationale:

A Definition of Informed Consent

Informed consent is a process, not a discrete event. For an informed consent to be ethically acceptable, is described as "a morally valid choice concerning the participation by a subject in research is a choice made: (1) by a competent person; (2) on the basis of adequate information concerning the nature and foreseeable consequences of the research, including all available options; and (3) without controlling influences or ulterior forms of constraint or coercion."{1998 89 /id}

The informed consent document provides a summary of the clinical trial (including its purpose, the treatment procedures and schedule, potential risks and benefits, alternatives to participation, etc.) and explains your rights as a participant. It is designed to begin the informed consent process, which consists of conversations between you and the research team. If you then decide to enter the trial, you give your official consent by signing the document. You can keep a copy and use it as an information resource throughout the course of the study.{2006 352 /id}

Learning objectives

By the end of this course, the student will be able to:

- Define the informed consent (IC)
- Discuss the ethical principles that it expresses
- Identify the uses of the informed consent
- Differentiate between the IC in research vs. IC in clinical practice
- Describe the components of the informed consent
- Describe the process of taking the consent

Learning outcomes:

By the end of the course, the students should have achieved/produced the following:
- Performed a systematic critique of different models of informed consent
- Develop at least one written model IC
- Develop a detailed plan of action for an IC taking process

**Content of the Module**

**Historical background**

All modern codes of ethics concerning research with human subjects affirm the moral importance of a principle of informed consent. It is a principle born of outrage at the atrocities committed by German physicians and scientists under the Hitler regime. As is well known, thousands of concentration camp prisoners were used as human guinea pigs against their will in experiments that were typically excruciatingly painful and generally led to death or permanent disfigurement. As a part of its written decision, the war crimes tribunal that convicted several of the notorious “Nazi Doctors” produced what has since become known as the Nuremberg Code (1949 349 /id), widely regarded as the first international code of human experimentation ethics. The code begins simply, with one statement set apart from all the rest:

“The voluntary consent of the human subject is absolutely essential."

Later international codes of research ethics, such as the Declaration of Helsinki (1964 350 /id), outline key considerations of informed consent. Most recently, the International Ethical Guidelines adopted by the Council for International Organizations of Medical Sciences (CIOMS) (2002 351 /id) reassert the primacy of informed consent. The following timeline provides an overview of some of the key events that have contributed to the development of the current system.

**1947 — The Nuremberg Code (1949 349 /id)**
Developed in response to the Nuremberg Trials of Nazi doctors who performed unethical experimentation during World War II, the Code was the first major international document to provide guidelines on research ethics. It made voluntary consent a requirement in clinical research studies, emphasizing that consent can be voluntary only if:

- participants are able to consent;
- they are free from coercion (i.e., outside pressure); and
- they comprehend the risks and benefits involved.

The Code also states that researchers should minimize risk and harm, make sure that risks do not significantly outweigh potential benefits, use appropriate study designs, and guarantee participants' freedom to withdraw at any time. The Nuremberg Code was adopted by the United Nations General Assembly in 1948. (Full Text URL: http://www.ushmm.org/research/doctors/codeptx.htm)

1964 — Declaration of Helsinki (1964 350 /id)

At the 18th World Medical Assembly in Helsinki, Finland, the World Medical Association adopted 12 principles to guide physicians on ethical considerations related to biomedical research. It emphasizes the distinction between medical care that directly benefits the patient and research that may or may not provide direct benefit. These guidelines were revised at subsequent meetings in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), Edinburgh, Scotland, October 2000, Washington 2002, Tokyo 2004 (Note of Clarification on Paragraph 30 added), and in the 59th WMA General Assembly, Seoul, October 2008. (Full text URL: http://www.wma.net/en/30publications/10policies/b3/index.html)
1974 — The National Research Act

The U.S. Congress signed this act into law, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research. The Commission was charged with:

1. identifying the basic ethical principles that should govern medical research involving people, and then
2. recommending steps to improve the Regulations for the Protection of Human Subjects.

1979 — The Belmont Report

After four years of work, the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research issued "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." The report sets forth three principles underlying the ethical conduct of research:

1. respect for persons: recognizing the autonomy and dignity of individuals, and the need to protect those with diminished autonomy (i.e., impaired decision-making skills), such as children, the aged, and the disabled;
2. beneficence: an obligation to protect persons from harm by maximizing benefits and minimizing risks;
3. Justice: fair distribution of the benefits and burdens of research.

The Belmont Report explains how these apply to research practices; for example, it identifies informed consent as a process that is essential to the principle of respect. In response to the report, both the U.S. Department of Health and Human Services and the U.S. Food and Drug Administration revised their regulations on research studies that involve people.


This policy was adopted to ensure a uniform system of protections in all federal agencies and departments that conduct research.

2002-2008 Formation of the National Health Research Council and the development of the National Guidelines for Research that Involves Human Subjects. More details are available on this link:

https://sites.google.com/site/healthresearchlibrary/HealthResearchinSudan/historyofresearch
General Principles

The conduct of experimental studies in humans is governed by a body of principles that provide the foundations for judging the ethical adequacy of such an experiment. One addresses the question of who receives the benefits of the research and who bears its burdens (justice). A second requires that the research maximize the potential benefits to the subjects and minimize the risk of harm (beneficence and non-malificence). The third, the source of guidelines for informed consent, requires that subjects enter into the research voluntarily and with adequate information (respect for persons).{Bernard Weiss, 2001 84 /id}

**Informed consent** is a process, not a discrete event. For an informed consent to be ethically acceptable, is described as "a morally valid choice concerning the participation by a subject in research is a choice made: (1) by a competent person; (2) on the basis of adequate information concerning the nature and foreseeable consequences of the research, including all available options; and (3) without controlling influences or ulterior forms of constraint or coercion."{1998 89 /id}

**Conditions of informed consent**

**Myth and Reality about informed consent** {2006 352 /id}

**Myth:** Informed consent is designed primarily to protect the legal interests of the research team.

**Reality:** The purpose of the process is to protect the participant and other participants by providing access to information that can help the participant make an
informed choice. It also is designed to make the participant aware of the participant’s rights.

*Myth:* The most important part of this process is signing the informed consent document.

*Reality:* Actually, the heart of this process is the participant’s ongoing interaction and discussions with the research team and other medical personnel—before, during, and after the trial. The document is designed to get this conversation started.

*Myth:* My doctor knows best; he or she can tell me whether or not the participant should consent to participate.

*Reality:* The participant’s doctor is likely to be a valuable source of advice and information, but only the participant can make this decision. No one—not even medical experts—can predict whether a treatment, screening, prevention, or supportive care method under evaluation in a trial will prove successful. The informed consent process is designed to help the participant weigh all of the information and make the right choice for the participant or the participant’s child.

*Myth:* Once the participant sign the consent form, the participant have to enroll and stay enrolled in the trial.

*Reality:* That’s not true. Even after the participant sign the form, the participant are free to change the participant’s mind and decide not to participate. The participant also has the right to leave a clinical trial at any time for any reason, without forfeiting access to other treatment.

*Myth:* Medical personnel are busy, so the participant can’t really expect them to keep me informed as the trial progresses or listen to my questions.

*Reality:* The research team has a duty to keep the participant informed, make sure that the participant understands the information they provide, and answer the participant’s questions. If the participant ever feels that the participant is not getting what the participant need, do not hesitate to speak up. The participant will be given the name and phone number of a key contact person who can answer the participant’s questions throughout the course of the trial. Keep in mind that people like the participant are making this research possible through their willingness to participate.

**Consent as a process**

The informed consent process provides the potential participant with ongoing explanations that will help him/her make educated decisions about whether to begin or continue participating in a trial. Researchers and health professionals know that a written document alone may not ensure that the participant fully understand what participation means. Therefore, before to the participation decision, the research team should discuss with the study’s purpose, procedures, risks and potential
benefits, and the rights of the participant. Even after participation, the team should continue to update the participant on any new information that may affect his/her situation. Before, during, and even after the trial, the participant will have the opportunity to ask questions and raise concerns. Thus, informed consent is an ongoing, interactive process, rather than a one-time information session.

It is essential that Research Ethics Committee (REC) members think of informed consent not as a form that must be signed, but as an educational process that takes place between the investigator and the prospective subject. No one can guarantee that another person has understood the information presented; one can only inform prospective subjects as clearly as possible. No one can guarantee that another's choice is voluntary; one can only attempt to remove obvious impediments to free choice by being alert to coercive aspects of the consent procedure. In cases where there is reason for special concern about pressure (e.g., when patients are invited to participate in research conducted by their physician, or when students, military personnel, employees, etc., are asked to participate in research conducted by their supervisors), the REC may require some form of monitoring (such as the presence of an impartial observer). If the research presents significant risk, or if subjects are likely to have difficulty understanding the information to be provided, the REC may suggest that investigators employ devices such as audiovisual aids, tests of the information presented, or consent advisors.

Because obtaining informed consent is an educational process, the REC should do what it can to enhance the prospective subject's comprehension of the information presented. It should consider the nature of the proposed subject population, the type of information to be conveyed, and the circumstances under which the consent process will take place (e.g., manner, timing, place, personnel involved). After answering these questions, the REC may want to suggest changes in the timing or location of an investigator's first contact with potential subjects, or changes in how others will contact subjects during or following the study. For example, some investigators may plan to release their data to a "data broker" who will in turn make the data available to other researchers. RECs should review the appropriateness of making the data available in this way, and should ensure that subjects will be informed about who will have access to the data and who might contact them.

Sometimes the information to be imparted to prospective subjects is so complex or possibly disturbing that it may require some time for it to be absorbed and appreciated. In these circumstances, the REC might suggest that the investigator either present the information and discuss the issues with prospective subjects on more than one occasion, or that a period of time elapse between imparting the information and requesting a signature on the consent form. During this waiting period, prospective subjects might be encouraged to discuss their possible participation with family members, close friends, or trusted advisors. Other approaches to communicating complex information include the use of audio-visual materials and brochures.
Chapter 5

Informed consent

Capacity

☐ Refers to the presence of a group/set of functional abilities a person needs to possess in order to make a specific decisions (Griso and Applebaum, 1998). These include the ability to:

☐ UNDERSTAND the relevant information

☐ APPRECIATE the relatively foreseeable consequences of the various available options available.

Voluntariness

Free and informed consent must be voluntarily given, without manipulation, undue influence or coercion.

The element of voluntariness has important implications. Consent must be freely given and may be withdrawn at any time. Undue influence may take the form of inducement, deprivation, or the exercise of control, or authority over prospective subjects.

The influence of power relationships on voluntary choice should be judged according to the particular context of prospective subjects. For example, the voluntariness of prisoners, members of organizations with authoritarian structures (such as the military, police, some religious groups or street gangs), or of employees or students may be restricted because their institutional context implies undue pressure. Care should be exercised in developing relationships between researchers and authorities, so as not to compromise either the free and informed consent or the privacy and confidentiality of subjects.

Conversely, situations may arise in which an organization, such as a corporation, a government, a political party or a criminal organization that may have been approached about a research project, may wish to prevent the research; however, individuals over whom the organization has some authority may be willing to participate. Researchers and REBs should not prevent such research, but should ensure that potential subjects are fully informed of the views of the organization’s authorities and the possible consequences of participation, and pay special attention to confidentiality.

REBs should also pay particular attention to the elements of trust and dependency—for example, within doctor/patient or professor/student relationships—because these can constitute undue influence on the patient to participate in research projects, especially those involving residents in long-term care facilities or psychiatric institutions.
Documentation of consent

In most cases the national regulations require that informed consent be documented, but they also provide for some important exceptions. Documentation usually involves the use of a written consent form containing all the information to be disclosed and signed by the subject or the subject’s legal representative. It should be reiterated, however, that these documents are not substitutes for discussion. The person who signed the consent form must be given a copy as a reference and reminder of the information conveyed.

In case the participant has difficulties signing, each oral presentation must be witnessed by a third person, who must sign both the consent form and a copy of the written summary of the presentation. A copy of the summary must be provided to those who sign the consent form so that they have the information available for future reference.

Waiver or exceptions of documented consent:

The REC may waive the regulatory requirement for written documentation of consent in cases where: (1) the principal risks are those associated with a breach of confidentiality concerning the subject’s participation in the research (e.g., studies on sensitive topics such as drug abuse or sexual deviance); and (2) the consent document is the only record linking the subject with the research. Written documentation of consent may also be waived when the research presents no more than minimal risk and involves procedures that do not require written consent when they are performed outside of a research setting.

National regulations on informed consent specify the information that must be disclosed to prospective subjects. The regulations do permit modifications in the consent procedure, and, under certain circumstances, informed consent may be waived entirely if the research meets certain conditions.

The REC may approve a waiver of some or all of the consent requirements provided that:

(1) the research involves no more than minimal risk to subjects;
(2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;
(3) the research could not practically be carried out without the waiver or alteration; and
(4) whenever appropriate, the subjects will be provided with additional pertinent information after they have participated in the study.

Contents of the consent

Typically, the information provided to the potential participant should include:

• TITLE
• **PURPOSE** [Why is this clinical trial being done?]

In this section, researchers explain why they are conducting the trial. Their reasons will depend on the type of condition and the trial type (i.e., whether they are investigating new prevention, screening, supportive care, or treatment methods). Researchers conduct treatment trials either because they have not found an effective treatment for a certain type of cancer, or they are not sure which treatment method works best. This uncertainty is often referred to as ‘Clinical Equipoise’, which defined as a genuine uncertainty on the part of the expert medical community about the comparative therapeutic merits of each arm of a clinical trial {Freedman, 1987 90 /id}.

In these trials, Phase the participant tests the safety and effectiveness of a new treatment, or aims to find out what dosage of a new drug can be given safely. Phase II treatment trials evaluate the effects (good and bad) that a treatment may have on people with a certain type of cancer. Phase III treatment trials compare the effectiveness of a new treatment or treatment combination with that of standard treatment. Researchers use prevention, screening, and supportive care trials to evaluate new strategies for preventing cancer, detecting it more accurately and effectively, and alleviating treatment side effects.

• **DESCRIPTION OF PROCEDURES** [What is involved in the trial?]

This section describes the procedures that the participant will undergo, how frequently the participant will have them, and where they will take place (at home, in the hospital or clinical center, or in an outpatient setting). For treatment trials, this section should include:

- procedures that are part of regular cancer care and may be done even if the participant do not join the trial;
- standard procedures being done because the participant are in the trial; and
- procedures that are being tested or evaluated by the trial.

If this is a "randomized" trial, then the participant will be assigned at random (by computer) into one of two or more study groups. People in the different groups will receive different treatments or treatment combinations, so that researchers can evaluate which is most effective. If this is the case, the document should make clear what procedures each group will undergo. It should also indicate what the participant’s chances are of being placed in any one group.

• **DURATION** [How long will the participant be in the trial?]

This section indicates how long the trial will last and whether it involves follow-up, and if so, for how long. It also includes information about any circumstances under which the researcher might remove the participant from the trial (for example, if the participant’s condition worsens or new information indicates the participant shouldn’t continue). The document should make clear that the participant has the
right to stop participating at any time, and it should describe any possible medical consequences of sudden withdrawal.

- **RISKS** [What are the risks of the trial?]

This section includes the foreseeable physical and non-physical risks of participating in the trial. A non-physical risk might be time away from work, while physical risks might include side effects such as nausea, vomiting, pain, or susceptibility to infection, among others. The document should indicate the likelihood of these risks occurring, how serious they may be, and whether they are more likely to be short-term (last only during the trial or shortly afterward) or long-term (last weeks, months, or even years after the trial is over). The document should make clear which risks are related to the investigational aspects of the trial. It also should include specific information about reproductive risks (Could participating make the participant infertile? Should the participant not get pregnant or father a child while on the trial? Can the participant nurse a child during the trial?).

- **BENEFITS** [Are there benefits to taking part?]

The document describes any benefits to the participant or to others which may reasonably be expected. A trial may or may not involve direct medical benefits to the participant, but it might lead to new knowledge that can help others in the future.

- **ALTERNATIVES TO PARTICIPATION** [What are my options if the participant don’t participate?]

For treatment trials, this section describes what care options the participant has besides participating in the trial, such as other commonly-used therapies or no treatment at all.

- **CONFIDENTIALITY**

This statement tells the participant the extent to which the participant’s information will be kept confidential. It should inform the participant about any groups or organizations that may have access to the participant’s records for quality assurance and data analysis (such as the National Cancer Institute, the Food and Drug Administration, or other trial sponsor).

- **COSTS/ ADDITIONAL EXPENSES** [What are the costs?]

This section indicates whether participating in the trial will result in added costs to the participant or the participant’s sponsor. It also covers other cost issues, such as who will pay for emergency medical treatment in case of injury or illness, whether the participant will have to pay for drugs that become commercially available during the trial (if this is a drug trial), and whether or not the participant will receive payment for participating.

- **PARTICIPANT’S RIGHTS** [What are my rights as a participant?]
The document should specify that:

1. the participant’s participation is voluntary;
2. the participant can choose not to take part or leave at any time without penalty or loss of benefits; and
3. any new information that might affect the participant’s participation will be shared with the participant.

- **CONTACT INFORMATION** [Whom do the participant call if the participant have questions or problems?]

The participant should have a contact name and phone number (usually of a member of the research team) for getting answers to questions about the study or a research-related injury. The participant also should be given a phone number for the REC or a patient representative, in case the participant has questions about the participant’s rights as a research participant.

- **SUPPLEMENTAL INFORMATION** [Where can the participant get more information?]

This section lists additional resources that may prove useful as the participant make the participant’s decision, such as NCI’s Cancer Information Service, informational booklets, community organizations, and Web resources.

- **THE SIGNATURE**

The participant’s signature represents the participant’s legal consent to participate in the trial.

If any of these sections appears to be incomplete or missing from the informed consent document, don’t hesitate to ask for the information.

Other Useful Tips

- Keep a copy of the informed consent document as a helpful resource for the duration of the trial. Ask for a copy if one isn’t offered to the participant. The participant may also request a copy of the protocol (full study plan).

- According to National regulations, no informed consent document may include any language that asks or appears to ask the participant to waive the participant’s legal rights, or that releases or appears to release the investigator, the sponsor, or the institution from liability for negligence.

- If the participant cannot understand the forms the participant are signing, don’t be afraid to let someone know that the participant are having trouble. If the participant have difficulties reading the document at first, try not to get upset. Many people feel anxious about reading and signing documents and
communicating with physicians. Just take the participant’s time and ask for help when the participant need it.

GUIDELINES FOR WRITING INFORMED CONSENT DOCUMENTS

1. INTRODUCTION

The ethical principle of respect for persons requires that subjects be given the opportunity to choose what shall and shall not happen to them. Valid informed consent requires:

1. Disclosure of relevant information to prospective subjects about the research;
2. their comprehension of the information, and
3. their voluntary agreement, free of coercion and undue influence, to research participation.

The process of informed decision-making by research subjects generally includes discussion of the research study with the Principal Investigator (PI), and others as appropriate, and signing the written informed consent document. Depending on the nature, type and duration of the research, ongoing discussion with and education of subjects about the study may continue long after the informed consent document is signed.

A goal of the NIH is to assure that all written informed consent documents are complete and clearly written so as to promote informed decision-making by subjects participating in its research activities. This information sheet provides guidance to NIH clinical researchers and RECs on the procedures and requirements for informed consent to research participation and the content and format of written consent documents.

2. REQUIREMENTS FOR INFORMED CONSENT

1. General Procedures

Unless otherwise waived by the REC, NIH research investigators should obtain valid informed consent from all research subjects (or their legally authorized representatives) who participate in their research studies. Generally, after the Principal Investigator has explained the research study to the subject, the subject’s informed consent is documented by signing the protocol’s written consent document, which an REC must have previously reviewed and approved. The NIH consent document form NIH-2514-1 (Consent to Participate in a Clinical Research Study), obtainable from REC Protocol Administrators, is used for all subjects enrolled in research conducted at the Clinical Center. Form NIH-2514-1 is also available from the Clinical Center’s Protocol Coordination Service Center (301-496-0744).

The subject is given a copy of the signed document, and, when the research is conducted in the Clinical Center, the Principal Investigator ensures that the original signed consent document is filed in the subject’s permanent medical record maintained by the Clinical Center’s Medical Record Department. In cases where
subject accrual occurs elsewhere, signed consent documents are retained according to the policies of the institution where the research is conducted.

2. **General Principles**

Unless otherwise authorized by an REC, research investigators are responsible for ensuring that informed consent shall:

- be obtained in writing from the subject or the subject's legally authorized representative;
- be understandable to the subject or her/his representative. Suggestions for writing consent documents are provided in 3., below.
- be obtained in circumstances that are not coercive and that offer the subject (or her/his representative) sufficient opportunity to decide whether she/he should participate. The consent document should not contain language that implies or suggests that the subject (or her/his representative) gives up any legal rights or releases research investigators or the NIH from liability for negligence.

3. **Basic Elements for Written Informed Consent Documents**

Unless otherwise authorized by an REC, research investigators must provide the following information to each subject in writing:

The basic elements which have an asterisk (*) are incorporated in existing language printed on form NIH-2514-1 (Consent to Participate in a Clinical Research Study). Nevertheless, to enhance comprehension and readability, investigators are strongly urged to use a format in the body of the consent form that presents information in sections, introduced by headings, and that clearly and simply identifies and describes each of the elements to be discussed, even if the sections repeat information that appears on the printed form. For an example of an effective way to use headings, see 4. below.

- A statement that the study involves research;*
- An explanation of the purpose of the research and the expected duration of the subject’s participation;
- A description of the procedures to be followed and identification of any procedures that are experimental;
- A description of any foreseeable risks or discomforts to the subject, an estimate of their likelihood, and a description of what steps will be taken to prevent or minimize them;
- A description of any benefits to the subject or to others that may reasonably be expected from the research. Monetary compensation is not a benefit. If compensation is to be provided to research subjects or healthy volunteers, the amount should be stated in the consent document;
- A disclosure of any appropriate alternative procedures or courses of treatment that might be advantageous to the subject;
• A statement describing to what extent records will be kept confidential, including a description of who may have access to research records;*

• For research involving more than minimal risk, an explanation and description of any compensation and any medical treatments that are available if research subjects are injured; where further information may be obtained, and whom to contact in the event of a research-related injury;*

• An explanation of whom to contact for answers to pertinent questions about the research and the research subject's rights (include the Clinical Center’s Patient Representative and telephone number);* and

• A statement that participation is voluntary and that refusal to participate or discontinuing participation at any time will involve no penalty or loss of benefits to which the subject is otherwise entitled.*

4. **Additional Elements**

When appropriate, and required by the REC, one or more of the following elements of information will also be provided to each research subject:

• If the subject is or may become pregnant, a statement that the particular treatment or procedure may involve risks, which are currently unforeseeable, to the subject or to the embryo or fetus;

• A description of circumstances in which the subject's participation may be terminated by the investigator without the subject's consent;

• Any costs to the subject that may result from participation in the research;

• What will happen if the subject decides to withdraw from the research and how withdrawal will be handled;

• A statement that the Principal Investigator will notify subjects of any significant new findings developed during the course of the study that may affect them and influence their willingness to continue participation;

• The approximate number of subjects involved in the study;

• The amount of remuneration/compensation, if any, that will be provided to subjects. See Information Sheet #20 “Information on Remuneration of Research Subjects in the Intramural Research Program.”

• When appropriate, a statement concerning an investigator’s potential financial or other conflict of interest in the conduct of the study.
Chapter 5: Informed consent

I am the researcher (full name and institution or organization you are affiliated with and conducting the research).

We are conducting a study or research about (explain the title and details of the study).

You have been chosen to participate in this study (or your child) and another participant (explain why you were chosen and who is with you).

We expect your participation and the participation of other participants that you will benefit (explain the expected benefits for each participant: individual, community, service provider, etc.).

During this study, I will conduct (explain the procedures you intend to conduct towards the participants: obtaining information, obtaining samples from body fluids such as blood or urine, etc. or tissues (example: bone, or giving medication or vaccine or performing a procedure such as surgical operations or medical device tests, etc.).

The procedures I will conduct towards you may have some risks or side effects (explain them if they exist or expected to occur). Or you can confirm that the research is free of any risks to participants or those incurred.

If any complications or side effects occur, we will provide medical care for you (explain the type of medical care you will receive, the body part you will receive care from, etc.).

We hope that you will participate with us in this study, we assure you of the confidentiality of your information and documents related to you, and it will not be released to the researcher and the commission for ethical research in health.

This can be done in other ways, such as filling out a personal information form, and this information will be stored in encrypted and confidential form, or we will use a code and not display your name on any form, and we will inform you of the results (in case of comprehensive medical examinations) in the way the doctor's routine, we will not collect any other information, and the information that has been collected will be used only for the purpose of this study. And we also inform you that participating in the research is voluntary, and your refusal to participate in the research does not affect your right to receive any benefits from the research (you can mention these benefits - for example, diagnosis and treatment of the disease, protection, etc.), and with the assurance that you will not be compensated for your participation in this research (except for reimbursement of travel expenses by a certain method), and your participation will be one of the volunteers and the number of volunteers is expected to be ......... participants.

We assure you that you can withdraw from the research at any time, without giving any explanation for withdrawing, and this will not affect your right to receive the benefits of the research. We will provide medical care for you in the event of any complications from conducting this research.

If you have any questions or have anything to do with the research, the participants with you, or your rights as a participant in the implementation of the research, you can contact (provide name and address of the person or organization you can contact). And if any complications occur during the implementation of the research, you can contact (provide name and address of the person or organization you can contact).
في البحث نموذج إقرار موافقة المشارك

إقرار المشارك:

لقد اطلعت على المعلومات الحالية والتي تم شرحها لي واتبعت لي طرح الأسئلة عنها كيفما شئت، وقد تلقبت الإجابات الوافية عن كل الأسئلة، وأنا أقر بالموافقة (أو أقر عن أبني) على المشاركة طوعية في هذه الدراسة. فأعلم بحق في التوقف عن المشاركة في أي وقت دون أن يؤثر ذلك على حقوقي في (مثال: تلقي العناية الطبية اللازمة في أي وقت لاحقاً).

رمز المشارك: ..................................................................................................

اسم المشارك: ..............................................................................................

توقيع المشارك: .........................................................................................

رمز من ينوب عن المشارك (في حال الطفل أو المعاق ذهنياً...الخ): ...........................................................................................................

توقيع من ينوب عن المشارك شرعاً: ........................................

عنوان من ينوب عن المشارك: ....................................................................

في حال عدم قدرة المشارك على قراءة الإقرار ويحتاج إلى من يشرح أو يترجم له:

اسم الشارح (الترجم): ..............................................................................

عنوان الشارح أو (الترجم): ........................................................................

توقيع الشارح أو (الترجم): ........................................................................

توقيع الباحث: .................................................................................................
فصل 5: إقرار بالموافقة على إجراء البحث

أنا د. [اسم الباحث] وآخرون حاليًا مع مجموعة من زملائي بإجراء دراسة عن استخدام المضادات الحيوية في عمليات استئصال السلائف الفقيرة. يهدف البحث إلى تفاوت استخدام المضادات الحيوية في عمليات الاستئصال السلائف الفقيرة. تستخدم الدراسة رؤية المشاركون بدون تصريح مسبق على مجموعة (مجموعة الدواء ومجموعة الادوية).

الفوائد المرجوة من الدراسة: تقليل نسبة ظهور الجراثيم المقاومة للمضادات الحيوية الناتجة عن استخدام غير الآلي للمضادات الحيوية، وتخفيض الأعباء المادية على المرضى من شراء مضادات الحيوية عالية التكلفة. ومع ذلك، نحن نفهم أننا سنقوم في حال حدوث أي مضاعفات لا يمكننا مواجهتها بطرق طبيعية، وسنقوم بالتعاون مع المشاركين في هذه الدراسة. سوف نتعامل مع جميع الحالات المفتوحة على المشاركين وسنقوم بالكشف عن كل المعلومات والبيانات عن المشاركون. المشارك في الدراسة طوعي ورفضه للمشاركة لا يحرم من حقه في أي فوائد من البحث، كما لا يؤثر في تلقيه العلاج من قبل المركز. من حق المشارك الانسحاب في أي وقت من الدراسة وكذلك من حق الباحث استبعاد أي مشارك من البحث في حالة أدائه غير السليم إلى ذلك.

إقرار المشاركة في البحث


توقيع [اسم المشارك]:
نموذج استمارة موافقة

الشخص المشارك في البحث أو من ينوب عنه

أنا الباحثة <<<<<<<< طالبة دراسات عليا بجامعة >>>>>>>، نقوم ببحث أو دراسة عن مرض الصرع عند الأطفال لمعرفة نوع الصرع الذي يعاني منه طفلك وتعبر عن نوع الدواء الذي يتناوله وعلى مدى فعاليته في التحكم في أعراض المرض.

يسعى البحث أيضا لمعرفة مدى التزام المريض بالوصفة الطبية وعلى العوامل التي من شأنها التأثير على التزام المريض بتناول الدواء.

لقد تم اختيارك لتشارك في هذا البحث أنت و طفلك ومعك عدد آخر من المشاركين من المداومين على هذه العادة ممن لهم أطفال يعانون من هذا المرض.

نتوقع بمشاركتك أنت و المشتركون الآخرين أن تتحصل على نتائج تمكن الأطباء القادمين على العلاج من معرفة العوامل المؤثرة على علاج المرض، وبالتالي تحسن حالة المريض من خلال التحكم في هذه العوامل مستقبلا.

خلال هذه الدراسة سأقوم بطرح عدد من الأسئلة على طفلك و سأقوم بتدوين إجاباتك على الاستمارة المرفقة. هذه المعلومات ستحفظ بطرق سرية - ولن يظهر اسمك في أي استمارة.

و نود أن نشير كذلك إلى أن المشاركة في البحث طوعية وأن رفضك للمشاركة في البحث لا تفقد الحق في المتابعة والعلاج بهذه العادة و لن تؤثر على نوعية الرعاية الصحية المقدمة لطفلك.

البحث يجتذب على أنه لن يتم منح أي قيمة تغذية مقابل المشاركة في هذا البحث، وأن بمشاركتك ستكون أحد المتزعمين الذين يشملهم البحث و عددهم حوالي 150 مشارك متطرف.

كما نؤكد لك إمكانية الانسحاب من البحث في أي وقت تشاء، و سنقوم بتوضيح لأسباب الانسحاب، وسنقوم بذلك بالتوقيع على طلب الانسحاب، و لن يؤثر ذلك أيضاً على حقك المباينة والعلاج بهذه العادة و لن تؤثر على نوعية الرعاية الصحية المقدمة لطفلك.

إذا كان لديك أي سؤال أو استفسار يخص البحث، للمشاركين معاك في البحث، أو حقوقك كمشارك أثناء تنفيذ البحث يمكنك الاتصال على 091222222978 في الرقم: >>>>>>>
نموذج استمارة موافقة

الشخص المشارك في بحث "اختبار حساسية وفاعلية مجهر شلهوب لتشخيص اللشمانيا"

Testing the Sensitivity and Specificity of the Fluorescence microscope (Shalhoub®) for Leishmania diagnosis in Eastern Sudan

انا الباحث د... ود... ود... (وزارة الصحة) وأ... (وزارة الصحة ولاية كذا)، نقوم بدراسة عن "اختبار حساسية وفاعلية مجهر شلهوب لتشخيص اللشمانيا".

لقد تم اختيارك لمشاركته في هذا البحث ومعك عدد آخر من المشاركين لأنكم شكوتم من الحمى لأن من شروط المشاركة فيها أن يكون لدى المريض حمى.

نتوقع بمشاركتك أن تتحصل على نتائج تفيد في اتخاذ القرار بشأن إدخال المجهر الجديد والاستفادة منه في فحص اللشمانيا والذي يتوقع أن يساهم في إعطاء نتائج موثوقة.

خلال هذه الدراسة سقوم بفحص عينة من دمك تفحصها بالمجهر المعروف لدينا وسنجري أخذ عينة أخرى لفحصها بالمجهر الجديد تأكد أن كل ذلك يتم بطريقة واحدة. هذا الأمر ليس له أي مخاطر وفً حالة حدوث أي أعراض جانبية من هذا الإجراء سوف نقوم بتقديم الرعاية الصحية لك بالعلاج المناسب مجانا.

ومنذ أن نأمل من مشاركتك معنا في هذا البحث نؤكد لك على سرية المعلومات والنتائج الخاصة بك وأنه لن يطلع عليها إلا الباحث المعني ولجنة أخلاقيات البحوث الصحية القومية.

نود أن نشير كذلك إلى أن المشاركة في البحث طوعية وأن رفضك للمشاركة في البحث لا يتفق الحق في العلاج بهذه الوحدة الصحية مع التأكيد على أنه لن يتم منح أي قيمة تقديرية بالنسبة المشاركة في هذا البحث ولكننا في المقابل نوفر لمرضى اللشمانيا علاج اللشمانيا مجانا وكذلك نوفر مخفض للحرارة.

شكرنا، إذا كان لديك أي سؤال أو استفسار بخصوص البحث والمشاركين معك في البحث أو حقوقك كمشارك أثناء تنفيذ البحث يمكنك الاتصال على نظرة الاستشارة >>> رقم 0122299922229

التمرين 3:

فيما يلي نموذج من الإقرارات التي قدمت للعرض على لجان المراجعة الأخلاقية، قم بتقديم استيفائها لشروط المعلومات الواجب توفرها في الإقرار، وفي حال عدم استيفائها يقوم الفريق بإعادة صياغة الإقرار ليستوفي الشروط
التمرين 4: (تمثيل دوار)

تقوم المجموعة بعد إعادة كتابة الإقرار بتقسيم نفسها إلى الآتي:

1- باحث (ومعه باحث مساعد)
2- شخص مدعو للمشاركة في البحث (وإذا لزم، معه باحث مساعد)
3- أحد أفراد أسرة الشخص المدعو للمشاركة في البحث (ابنه أو واده أو والده حسب نوع البحث)

خلال 10-15 دقيقة تقوم الباحث (ومساعده إذا لزم) بالقيام بشرح الدراسة وأخذ الموافقة المكتوبة (إذا وافق المبحوث)
• يقوم باقى المتدربين بمشاهدة المجموعة وتدوين ملاحظاتهم عن أداء الباحث ومساعده عند انتهاء الإداء التمثيلي يترك المدرب فرصة 10-15 دقيقة لإداء الملاحظات من قبل المتدربين ثم يقوم هو بإبداء الملاحظات التي لم يلاحظها المتدربون.
• يجب النتأكد أن من قاموا بالأداء التمثيلي والآخرين قد استوعبوا الفكرة واعتمدوا على قائمة مراجعة checklist التي تم التدرب عليها والدلائل الأخلاقية القوية التي تم توزيعها في بداية التدريب.

يمكن تكرار هذا التمرين حسب وقت التدريب المتاح، كما يمكن الاستعانة بأشخاص من خارج التدريب لضمان الواقعية، مثل أحد موظفي الإدارة أو العمال الموجودين في مكان التدريب.
• نماذج من أسئلة مختصرة لتقديم الإقرار:

  - هل اللغة مكتوبة بلغة مفهومة بالنسبة للمشارك في البحث؟ (هل سبق له شخّص لم يكمل الابتدائية؟ هل استعمل مصطلحات طبية؟ هل كانت الجمل طويلة؟)
  - هل شكل الإقرار جيد؟ (ستور متفرقة؟ مقاطع؟ عناوين جانبية؟ أم ستور مصفوفة لعضها خلف بعض؟)
  - هل استوفى المعلومات الواجب ذكرها للمشارك؟ (هل قدمت المعلومات بشكل مبسط ومفهوم؟)
  - هل كان من الممكن أن يكون أكثر اختصار دون أن يخل بالوضوح أو الشروط الأخرى الواجب توفرها؟

(حبر ohsr.od.nih.gov/info/sheet6.html)
Reading materials and references:


Additional websites:
Sudan’s National Health Research Library:
http://sites.google.com/site/healthresearchlibrary

Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS):

US DEPARTMENT OF HEALTH AND HUMAN SERVICES: Code of Federal Regulations, PART 46 PROTECTION OF HUMAN SUBJECTS:
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.116
Chapter 6: Research ethics committees functions and responsibilities

Mustafa Nimeri, MD

Background including rationale

The ethical and scientific standards for carrying out biomedical research on human subjects have been developed and established in international guidelines, including the Declaration of Helsinki, the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, and the WHO and ICH Guidelines for Good Clinical Practice. Compliance with these guidelines helps to ensure that the dignity, rights, safety, and well-being of research participants are promoted and that the results of the investigations are credible (1).

THE ROLE OF AN EC

The purpose of an EC in reviewing biomedical research is to contribute to safeguarding the dignity, rights, safety, and well-being of all actual or potential research participants. A cardinal principle of research involving human participants is ‘respect for the dignity of persons’. The goals of research, while important, should never be permitted to override the health, well-being, and care of research participants. ECs should also take into consideration the principle of justice. Justice requires that the benefits and burdens of research be distributed fairly among all groups and classes in society, taking into account age, gender, economic status, culture, and ethnic considerations (1).

Learning objectives

By the end of this module, the participants are expected to:

- Discuss the importance of independent ethical review of the research proposal involving human subjects.
- Describe the purposes, functions and responsibilities of the research ethics committees (Institutional review boards).
- Describe the structure, constitution, membership selection of the research ethics committees.
- Identify the barriers commonly encountered in the performance of the research ethics committees.
• Explain the ethical analysis process and the criteria for the ethical review
• Describe the mechanisms for making and communicating the decisions of the RECs and the approaches for monitoring and follow up of the approved research.
• Review ethically a research proposal through efficient application and utilization of the national format and guidelines.

Module contents

The importance of independent ethical review of the research proposal involving human subjects
What makes research involving human subjects ethical? Informed consent is the answer most US researchers, bioethicists, and institutional review board (IRB) members would probably offer. This response reflects the preponderance of existing guidance on the ethical conduct of research and the near obsession with autonomy in US bioethics. While informed consent is necessary in most but not all cases, in no case is it sufficient for ethical clinical research. Indeed, some of the most contentious contemporary ethical controversies in clinical research, such as clinical research in developing countries, the use of placebos, phase 1 research, protection for communities, and involvement of children, raise questions not of informed consent, but of the ethics of subject selection, appropriate risk-benefit ratios, and the value of research to society. Since obtaining informed consent does not ensure ethical research, it is imperative to have a systematic and coherent framework for evaluating clinical studies that incorporates all relevant ethical considerations (2).

The purposes, functions and responsibilities of the research ethics committees
Research ethics committees review proposed studies with human participants to ensure that they conform to internationally and locally accepted ethical guidelines, monitor studies once they have begun and, where relevant, take part in follow-up action and surveillance after the end of the research. Committees have the authority to approve, reject or stop studies or require modifications to research protocols. They may also perform other functions, such as setting policies or offering opinions on ongoing ethical issues in research. Review by a research ethics committee is required by international ethical standards
governing research involving human participants, as well as by local law in many jurisdictions. In international cooperative research, review may be required by the laws of the country in which the research is being sponsored, even if it is not required by the host country’s own laws. Review is also essential if the researchers intend to publish the results of their investigation, as most medical journals will not publish the results of research that has not received the approval of a research ethics committee (3).

The functions of research ethics committees include identifying and weighing up the risks and potential benefits of research; evaluating the process and materials (printed documents and other tools) that will be used for seeking participants’ informed consent; assessing the recruitment process and any incentives that will be given to participants; evaluating risks to participants’ confidentiality (and the related risk of discrimination) and the adequacy of confidentiality protections; and examining any other issues that may affect the ethical acceptability of the research. In international research, the committee represents the interests of the local population. Thus, it should ensure that the participants and their communities will receive fair benefits from the arrangement (3).

The main responsibility of a research ethics committee is to protect potential participants in the research, but it must also take into account potential risks and benefits for the community in which the research will be carried out. Its ultimate goal is to promote high ethical standards in research for health (3).

**Structure and membership of the Research ethics committees (RECs):**

**Structure of the RECs**

RECs should be constituted to ensure the competent review and evaluation of all ethical aspects of the research projects they receive and to ensure that their tasks can be executed free from bias and influence that could affect their independence. RECs should be multidisciplinary and multi-sectorial in composition, including relevant scientific expertise, balanced age and gender distribution, and laypersons representing the interests and the concerns of the community. RECs should establish publicly available standard operating procedures that state the authority under which the committee is established,
the functions and duties of the EC, membership requirements, the terms of appointment, the conditions of appointment, the offices, the structure of the secretariat, internal procedures, and the quorum requirements. RECs should act in accordance with their written operating procedures (3).

**Membership**

Clear procedures for identifying or recruiting potential EC members should be established. A statement should be drawn up of the requirements for candidacy that includes an outline of the duties and responsibilities of EC members.

Membership requirements should be established that include the following:

- The name or description of the party responsible for making appointments; the procedure for selecting members, including the method for appointing a member (e.g., by consensus, by majority vote, by direct appointment);
- Conflicts of interest should be avoided when making appointments, but where unavoidable there should be transparency with regard to such interests.
- A rotation system for membership should be considered that allows for continuity, the development and maintenance of expertise within the EC, and the regular input of fresh ideas and approaches (1).

In the light of their role in identifying and evaluating the risks and benefits of research, research ethics committees must include individuals with scientific and medical expertise. Without such expertise (supplemented, when necessary, by consultants in particular specialties), they will not be in a position to understand the procedures to be used in the study and their potential consequences for participants. In addition, committees must be able to assess the scientific validity of the study design to ensure that it is capable of producing reliable information. A badly designed study that will not result in usable data cannot support any level of risk. In some research oversight systems, the primary responsibility for scientific review rests with separate “scientific review committees”, but even when this is the case, it is important for the members of the research ethics committee to have a basic level of scientific literacy. Research ethics committees should not, however, be made up exclusively of scientific experts. Some types of
risks and benefits may be more easily identified by non scientific members, particularly those related to social, legal or cultural considerations. In addition, once risks and benefits have been identified, determining whether the relationship between them is reasonable requires value judgments as well as scientific analysis. A diversity of backgrounds and qualifications (in medicine as well as law, social sciences, etc.) can help ensure that these judgments are not inappropriately dominated by a single perspective. Social diversity and gender balance should also be reflected in the committee’s composition (3).

The membership should be designed to minimize the potential impact of conflicts of interest on the decision-making process. For example, it is important for institutional research ethics committees to have members who are not affiliated with the institution and for Government-sponsored committees to have members who are not employed by the Government. In addition, members who have a conflict of interest with respect to a particular study should not participate in the review of that study. Members should receive training in the international and local ethical and legal standards governing research, as well as in the process the committee uses to review and approve protocols. Non scientific members should be given an understanding of medical terminology and research methodology sufficient to enable them to participate intelligently in the committee’s discussions. A good knowledge of the social and cultural context is also important. Training should not be a single occurrence, but instead should be an ongoing process in which all committee members participate (3).

**Barriers commonly encountered in the performance of the RECs**

The following barriers are commonly encountered in the performance of the committees:

- External and institutional influence
- Lack of authority
- The committee decision are not always put into action
- Difficulties in monitoring of the implementation of the committees decisions
- Limited resources including human, financial, equipment, computers, photocopiers, stationary and offices
The ethical analysis process

Ethics does not prescribe a specific set of rules or policies. Instead, it provides a framework for evaluating problems and determining an appropriate course of action. Ethical analysis should reflect both internationally accepted norms and locally relevant cultural values. One approach to ethical analysis is to identify a set of governing principles and then apply those principles to evaluate the appropriateness of particular behaviour. In bioethics, the most commonly identified principles are:

1) Individual autonomy (the ability to make decisions for oneself);
2) Beneficence (the obligation to “do good” for others);
3) Non-maleficence (the obligation to avoid causing harm to others); and
4) Justice (the value of distributing benefits and burdens fairly).

These principles provide a general framework for analysis, which can then be applied to the facts of a particular ethical dilemma to reach a resolution. For example, consider a study in which researchers propose to assign individuals randomly to an experimental HIV vaccine or a placebo. The principle of autonomy suggests that, as long as the individuals are adequately informed of the risks and benefits, they should be free to decide for themselves whether to participate or not. However, the principle of beneficence might lead a research ethics committee to require that the researchers offer participants counselling about risk-reduction methods and possibly care for individuals who become infected during the study. Based on the principle of non-maleficence, the committee would have to consider whether participating in the study might harm individuals by leading them to think that they are protected from infection and therefore do not need to use risk-reduction measures. Finally, the principle of justice would require consideration whether the burdens of the study fall disproportionately on particular populations (3).

An alternative to principle-driven ethical analysis is a process known as “casuistic” reasoning. Instead of starting with abstract principles, the casuistic decision-maker begins by evaluating illustrative prior cases. Through the process of inductive reasoning, a judgment is made about the implications of these cases for resolving the particular issue at hand. For example, in evaluating the HIV vaccine trial, a research ethics committee might start by looking at other studies in analogous areas, such as vaccine trials related to other diseases, HIV studies not related to vaccines,
or placebo-controlled studies involving preventive interventions. It would then seek to identify ways in which these other studies are both similar and different from the vaccine study under consideration (3).

The criteria for ethical review

There are 7 requirements that provide a systematic and coherent framework for determining whether clinical research is ethical. They are meant to guide the ethical development, implementation, and review of individual clinical protocols. These 7 requirements are intended to elucidate the ethical standards specific for clinical research and assume general ethical obligations, such as intellectual honesty and responsibility (2). The following table is summarizing the ethical requirements as explained by Emanuel (2).

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Justifying Ethical Values</th>
<th>Expertise for Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social or scientific value</td>
<td>Scarce resources and nonexploitation</td>
<td>Scientific knowledge; citizen’s understanding of social priorities</td>
</tr>
<tr>
<td>Scientific validity</td>
<td>Scarce resources and nonexploitation</td>
<td>Scientific and statistical knowledge; knowledge of condition and population to assess feasibility</td>
</tr>
<tr>
<td>Fair subject selection</td>
<td>Justice</td>
<td>Scientific knowledge; ethical and legal knowledge</td>
</tr>
<tr>
<td>Favorable risk-benefit ratio</td>
<td>Nonmaleficence, beneficence, and nonexploitation</td>
<td>Scientific knowledge; citizen’s understanding of social values</td>
</tr>
<tr>
<td>Independent review</td>
<td>Public accountability; minimizing influence of potential conflicts of interest</td>
<td>Intellectual, financial, and otherwise independent researchers; scientific and ethical knowledge</td>
</tr>
<tr>
<td>Informed consent</td>
<td>Respect for subject autonomy</td>
<td>Scientific knowledge; ethical and legal knowledge</td>
</tr>
<tr>
<td>Respect for potential and enrolled subjects</td>
<td>Respect for subject autonomy and welfare</td>
<td>Scientific knowledge; ethical and legal knowledge of particular subject population</td>
</tr>
</tbody>
</table>

*Ethical requirements are listed in chronological order from conception of research to its formulation and implementation.

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**Decision-making mechanism**

In making decisions on applications for the ethical review of biomedical research, an EC should take the following into consideration (1):

- A member should withdraw from the meeting for the decision procedure concerning an application where there arises a conflict of interest; the conflict of interest should be indicated to the chairperson prior to the review of the application and recorded in the minutes;
- A decision may only be taken when sufficient time has been allowed for review and discussion of an application in the absence of non-members (e.g., the investigator, representatives of the sponsor, independent consultants) from the meeting, with the exception of EC staff;
- decisions should only be made at meetings where a quorum (as stipulated in the EC’s written operating procedures) is present;
- The documents required for a full review of the application should be complete and the relevant elements mentioned above should be considered before a decision is made;
- only members who participate in the review should participate in the decision;
- there should be a predefined method for arriving at a decision (e.g., by consensus, by vote); it is recommended that decisions be arrived at through consensus, where possible; when a consensus appears unlikely, it is recommended that the EC vote;
- advice that is non-binding may be appended to the decision;
- in cases of conditional decisions, clear suggestions for revision and the procedure for having the application re-reviewed should be specified;
- a negative decision on an application should be supported by clearly stated reasons.

**Communicating a decision**

A decision should be communicated in writing to the applicant according to EC procedures, preferably within two weeks’ time of the meeting at which the decision was made (1).
Follow up
ECs should establish a follow-up procedure for following the progress of all studies for which a positive decision has been reached, from the time the decision was taken until the termination of the research. The ongoing lines of communication between the EC and the applicant should be clearly specified (1).

Documentation and archiving
All documentation and communication of an EC should be dated, filed, and archived according to written procedures. A statement is required defining the access and retrieval procedure (including authorized persons) for the various documents, files, and archives. It is recommended that documents be archived for a minimum period of 3 years following the completion of a study (1).

Case studies and problems
Case (1): Case on Evaluation of Risks and Benefits

Randomized, Open-Label Trial Comparing The Safety And Efficacy Of Pegylated Interferon alfa-2a (PEG), PEG+ Ribavirin (RBV), and Interferon alfa-2a (IFN)+RBV In Patients With Hepatitis C Virus Genotype 4 Histologic Proven Chronic Active Hepatitis.

Background:
Hepatitis C virus (HCV) generally attacks the liver and, if not successfully treated, often leads to more serious complications, including cirrhosis of the liver, liver failure, and liver cancer. Of those infected, about 20-50% will develop cirrhosis.

Typically, liver damage develops gradually over a period of as much as 20 years or more before serious symptoms of the disease become apparent.

Sustained response of HCV genotype 4 chronic hepatitis cases to standard interferon (IFN) monotherapy treatment is very poor.

Clinical trials have shown the superior response of pegylated-IFN (PEG), an expensive drug made by Hoffman La Roche.

Early Phase II trials have shown that PEG + RBV or IFN + RBV are able to achieve a sustained virologic response (as measured by HCV-RNA levels).

Studies have shown that viral kinetics can predict non-responders at 12 weeks, i.e., patients who demonstrate detectable serum HCV-RNA and elevated serum liver
enzyme levels (ALT) should be considered no responders and be discontinued from therapy.

Earlier accurate prediction of response could spare considerable expense and toxicity from needless interferon therapy.

Finally, studies have shown that liver biopsy abnormalities can improve with therapy even among some patients who do not have a sustained HCV virologic response.

Study Design: Genotype 4 CHC patients will be randomized into 3 groups of 60 each as follows:

Group A: PEG (180µg) every wk.
Group B: PEG (180µg) every wk + RBV (400mgs bid).
Group C: IFN (4.5 MIU) three times a week + RBV (400mgs bid).

Treatment duration: 48 weeks

Follow-Up

Additional 24 weeks follow-up for sustained response

Study Outcome Variables:

Biochemical: ALT at 48 and 72 wks
Virological: serum HCV-RNA at 48 and 72 wks

Inclusion Criteria:

Prior liver biopsy showing chronic hepatic cirrhosis within 6 months of screening
Evidence of HCV infection genotype 4
Detectable HCV RNA and elevated ALT levels
Compensated liver disease, as designated by a Child-Pugh Class A score

Exclusion Criteria:

Negative HCV testing
 Decompensated hepatic disease (Child-Pugh Class B/C)
Active alcohol abuse
Active intravenous drug use
Anemia, hemoglobinopathies

Procedures

Patients who qualify after meeting inclusion/exclusion criteria and after signing written informed consent will undergo the following procedures:

Blood sample (15 cc) for HCV-RNA assay and serum ALT levels at 4, 8, 12 and 48 weeks.

Blood sample (15cc) for performing two types of genotyping assays: comparison of a new method of genotyping assay (sequencing-based) with a standard assay (using reverse hybridization to oligonucleotide probes).

Blood sample (15cc) for future pharmocogenetic testing to determine genetic markers for treatment response.

Liver biopsy at 72 weeks

Compensation

Patients will receive 15 LE for each study visit (weeks 4, 8, 12, 48).

Patients will receive 50 LE for undergoing liver

Major Side Effects of Drugs

Interferons:

May cause or aggravate neuropsychiatric disorders (suicidal ideation and suicide attempt)

Cardiovascular disorders (hypertension, arrhythmias, and myocardial infarction)

Endocrine disorders (including thyroid disorders/diabetes mellitus)

Autoimmune disorders (psoriasis and lupus), colitis, and pancreatitis, bone marrow toxicity

Contraindicated in patients with decompensated hepatic disease

Ribavirin:

Hemolytic anemia

Metabolites accumulate in the presence of renal failure

May cause birth defects and/or death of the fetus

PEG + RBV combination therapy:
Fatigue/asthenia, headache, pyrexia, myalgia, alopecia, neutropenia, nausea/vomiting, depressions, dermatitis.

Questions

What types of risks are involved in this study?

How can risks be further minimized?

What are the benefits of the study?

What is the risk level of the study?

What are the procedures that have potential benefits to the subjects?

What are the procedures without potential for direct benefits to subjects?

Are risks reasonable to benefits?

Case Study (2):

Introduction

In 2004, 2.3 million Africans died of HIV/AIDS and 3.1 million acquired HIV infection, bringing the number of persons living with HIV/AIDS in Africa to > 25 million. Despite recent progress, antiretroviral therapy remains out of reach for most Africans living with HIV/AIDS. In Cote D’Ivoire, trimethoprim-sulfamethoxazole (TS) prophylaxis reduced morbidity in persons with stage 2 or 3 HIV/AIDS and mortality in persons with both HIV/AIDS and tuberculosis, leading UNAIDS to recommend TS prophylaxis for 1) HIV-infected adults and children in Africa who either are symptomatic or are asymptomatic with a CED4 cell count < 500/mm$^3$ and 2) infants born to HIV-infected mothers. More recent studies in Uganda and Zambia found that TS prophylaxis provided benefit.

Trimethoprim and pyrimethamine bind and inhibit dihydrofolate reductase (DHFR), and sulfamethoxazole and sulfadoxine target dihydopterroate synthase (DHPS). Cross-resistance exists between trimethoprim and pyrimethamine and between sulfamethoxazoel and sulfadoxine, raising the possibility that use of TS prophylaxis in areas where malaria is endemic would select for Plasmodium Falciparum DHFR and DHPS mutations that confer resistance to the antimalarial combination sulfadoxine-pyrimethamine (SP). Prophylaxis with pyrimethamine was strongly and rapidly selective for DHFR mutations in children living in rural areas in Mali. If similar selection occurs with TS prophylaxis, it could accelerate the development or resistance to SP and other antifolate anti-malarials in areas where HIV infection and malaria are both highly prevalent.

Although malaria-treatment policies are increasingly recommending newer combination therapies, SP will continue to be used widely in Africa unless and until
more-expensive combination therapies are made universally available. The widespread use of TS prophylaxis in areas where malaria is highly prevalent might hasten the spread of SP resistance and introduce resistance to other promising antifolate antimalarials that are under development. More importantly, HIV-infected person receiving TS prophylaxis may be more likely to fail SP treatment when they contract malaria. If so, drugs other than SP will need to be used to treat persons receiving TS prophylaxis who develop malaria. Concerns about the impact of TS resistance on SP efficacy have contributed to reluctance to implement TS prophylaxis in areas in Africa where HIV and malaria is prevalent.

**Proposed Study**

**Participants:** The present study will be conducted at the Bandigara Malaria Project clinical research facility in Bandiagara, Mali, from Sept. through December 2000. Bandiagara is a town of 13,600 persons and is located on a semiarid plateau northeast of Bamako, the capital city. Transmission of malaria is seasonal but intense, with peak transmission occurring during the rainy season (July – October), ~ 2 episodes of clinical malaria occur per child each year. HIV seroprevalence studies have not been conducted at this site, but the overall prevalence of HIV infection in Mali is reported to be < 2%, and the clinical experience at this rural site is consistent with very low rates of HIV infection in children.

Children 5-15 years old living in Mali who are enrolled in an ongoing cohort study of the incidence of malaria will be eligible for inclusion. Exclusion criteria includes planned travel outside of the study area, severe acute or chronic illness, pregnancy, allergy to sulfa drugs, use of SP during the preceding 28 days, and use of chloroquine, TS, or other sulfa drugs during the preceding 7 days.

**Sample Sizes:** Sample sizes of 160 in the TS group and 80 in the control group are chosen, to permit detection of a difference in SP resistance of 5% versus 20% (control group vs. TS group, respectively) with 80% power, evaluated at 2-tailed $P = 0.05$.

**Objectives and Outcomes:** The primary objective is to test the hypothesis that TS prophylaxis decreases the efficacy of SP treatment of P. falciparum infection. The secondary objectives are to test the hypothesis that TS prophylaxis selects for resistance-conferring mutations in *P. Falciparum* DHFR and DHPS and to measure the prophylactic efficacy of TS.

**Treatment allocation and study intervention:** Children will be randomized in a 2:1 fashion to receive either TS prophylaxis or no prophylaxis. The choice of a prophylaxis:no prophylaxis ratio of 2:1 is based on an estimated TS prophylactic efficacy of 50%, which was, in turn based on the relatively poor efficacy of TS as a treatment for malaria in other settings. No data on the antimalarial efficacy of TS in Mali were available.
TS will be administered as a single dose on 3 consecutive days each week for 12 weeks. Thrice-weekly dosing was chosen to maximize the possibility of detecting the selection of antifolate-resistant *P. Falciparum*. Trained personnel will directly observe the administration of TS and will monitor each child for 30 min. after TS is taken. If a child vomits during the period of observation, a repeat dose of TS will be given.

Once a week, a study physician will evaluate each child. Any child who has symptoms consistent with malaria, an axillary temp. > 37.5°C, profound anemia, or jaundice will be given a full assessment, including a malaria blood smear and measurements of hemoglobin level. At enrollment and once a month thereafter, a filter-paper blood sample will be obtained form each child, and malaria blood smears will be prepared.

Study physicians will continuously be available to evaluate any medical complaints. After treatment of malaria with SP, treatment response will be assessed on days 1,2,3,7,14,21 and 28 after treatment, in accordance with the standard WHO protocol.

Uncomplicated malaria will be treated with SP. After administration, children will be monitored for 60 min for adverse reactions and vomiting. When SP treatment is administered to a child receiving TS prophylaxis, the prophylaxis will be stopped for 1 week after SP treatment. Severe malaria will be treated with intravenous quinine and parenteral SP.

SP treatment outcomes are defined as adequate clinical and parasitological response, late parasitological failure, late clinical failure, and early treatment failure, in accordance with the standard WHO protocol. Children with persistent symptoms of malaria and/or parasitemia after SP treatment will be promptly evaluated by a study physician, and children who experience treatment failure will be treated with chloroquine. At the time of this study, chloroquine is the official first-line drug for uncomplicated falciparum malaria in Mali and retained good efficacy.

**Question:** comment on any aspect of this study: study design, subject selection, safeguards for vulnerable subjects, study monitoring, risk level of the study.

**Case study (3): CONFRONTING THE STANDARD OF CARE DEBATE:**

**DEVELOPING HOME-BASED TREATMENT STRATEGIES FOR NEONATAL SEPSIS IN INDIA**

Background on India: JIM LAVERY’S BOOK
Located in the South Asian subcontinent, India borders Pakistan, China, Nepal, Bhutan, Myanmar, and Bangladesh, and sits between the Arabian Sea and the Bay of Bengal. Although the country occupies 2.4% of the world’s land area, it supports over 15% of the population, which continues to grow at about 1.8% per year. Of the billion people living in India, about 70% live in villages, and 62% depend on agriculture. More than 35% of the population lives below the poverty line, and is too poor to be able to afford an adequate diet.

Civilizations have lived in the Indus valley for at least five thousand years. Since the eighth century, the region has been invaded by Arabs, Turks, and European traders. By the nineteenth century, the British assumed political control over most Indian lands. The subcontinent gained independence in 1947, when it was divided into Muslim Pakistan and secular India—and in 1971 was further divided to create Bangladesh. The current Prime Minister, Dr. Manmohan Singh was elected in May, 2004, when India’s oldest political party, India National Congress won over the previous government in a surprise victory. The country is predominantly Hindu (80%), with a Muslim minority (12%); Christian, Sikh, Buddhist, Jain, and Parsi are also represented. Hindi is the national language and is spoken by about 30% of the population, but there are 14 other official languages.

**Neonatal sepsis in India:**

The majority of infants in rural India (83%) are born at home, and skilled birth attendants are present at only about 35% of these births. If complications arise during labor or during the first month of life, it is quite difficult for a sick baby to receive prompt, effective care, since hospitals with facilities for neonatal care tend to be inaccessible for rural populations. Moreover, parents may be unwilling to move a sick baby from home because of traditional beliefs, and as a result, most neonatal deaths also occur at home. While the national infant mortality rate is already high at 72 per 1,000 live births, the infant mortality rate in rural India is even higher at 80 per 1,000 live births. Because of serious difficulties in transporting sick neonates to hospitals, those who arrive are generally seriously ill. Hence, to reduce neonatal mortality, ways to provide neonatal care at home must be developed.

The primary causes of neonatal death are birth-related asphyxia or injury, complications related to prematurity, and infection. Hospital-based neonatal care in India is quite expensive, but alternatives to hospital-based care for treatment of the most dangerous bacterial infections (pneumonia, septicemia, meningitis, collectively known as sepsis) have not been clinically assessed.

The government-run Integrated Management of Childhood Illness program has developed several home-based child survival programs for managing pneumonia, diarrhea, and malaria in children, but these programs have never been expanded to include home-based management of sepsis in neonates.
**Rural Indian health care**

The Gadchiroli district of India, in Maharashtra state, is 1,000 kilometers from the state capital of Mumbai (Bombay). The district is extremely underdeveloped. Rice cultivation and forestry are the main sources of income. Roads, communications, education, and health services are poor. Government health services in the area are comprised of a male and a female paramedic worker for every 3,000 people and a primary health center with two physicians for every 20,000 people. The health center and paramedics provide prenatal care, immunization, family planning, control of communicable diseases, and curative medical care. Secondary care hospitals are 30 kilometers from the most remote village in each area, but specialized neonatal care is not available in these facilities, and transportation to these hospitals is exceedingly difficult. Private rural medical practitioners, herbalists, and magic healers form the main sources of curative care for the people in the villages. The Integrated Child Development Service (ICDS), run by the government in each village in the district, provides supplementary feeding to children and pregnant and lactating women, and management of diarrhea and acute respiratory infections in children.

SEARCH (Society for Education, Action, and Research in Community Health) is a non-governmental organization for community health care and research that was established in 1986. SEARCH has worked in the Gadchiroli District to develop reproductive health education programs for local adolescents, trained village health workers to manage minor health problems and has a field research area of 100 villages.

These villages are divided into an action area of 53 villages, and an adjacent control area of 47 villages.

SEARCH has been training male village health workers and traditional birth attendants to manage pneumonia in children in the action area since 1988. SEARCH also trained traditional birth attendants in the action area to administer nutrient supplements, treat common reproductive-tract infections in women, and to perform hygienic deliveries.

The government health service (ICDS) is responsible for training traditional birth attendants and management of pneumonia in children in the control area.

**The study:**

Researchers affiliated with SEARCH hypothesize that because neonatal care is not available to most neonates in developing countries, a package of home-delivered neonatal care delivered by village women, including management of sepsis (septicemia, meningitis, pneumonia), could reduce the neonatal mortality rate by at least 25% in 3 years. This hypothesized outcome result was driven in part by an
earlier study of pneumonia management in neonates in which treatment with oral co-trimoxazole led to a 20% reduction in neonatal mortality.

The study is to be conducted over five years in 100 villages in the SEARCH research area. The pre-designated action area and the control area each have about 40,000 people.

Community consent is obtained in each of the 53 villages in the action area. Women living in these villages who have 5-10 years of schooling are recruited to be trained as health workers in the action (intervention) area. Fourteen villages were eliminated from the action area because their populations were less than 300, or because not enough local women were available, leaving a total of 39 action area villages for this study.

During the baseline phase of the study, male village health workers will do census and baseline survey (including socioeconomic indicators) for the first year of the study, and record the number of live births, neonatal deaths, and infant deaths for the first two years (in all 100 villages of the field research area). Data from the first year will be used to assess baseline neonatal morbidity rates and to plan future intervention strategies. Also, a female social worker will conduct unstructured interviews and observe traditional home neonatal care in the action area.

During the second year of the baseline phase, these female health workers will be trained to take histories of pregnant women, observe labor, examine neonates, and to manage pneumonia in both neonates and children (as male health workers in the action area have been trained to do previously).

The intervention is implemented in a step-wise manner over a three-year period. During the first year, the women will make home visits to pregnant women in their third trimester, observe labor, and continue home visits routinely throughout the first month post-partum, or until the infant dies, or until the women leave the village. During the second year, the women will be trained to manage neonatal sepsis. Initially, the health workers urge parents to admit their child to the hospital if he or she shows signs of sepsis. If parents are not willing to do so, antibiotics (gentamycin intramuscular injections and co-trimoxazole syrup) are given.

In the third, final year of the intervention, the health workers will educate mothers and grandmothers about prenatal and neonatal care, including how to recognize danger signs or symptoms in infants, and the importance of seeking immediate help from a health worker.

In order to generate the kind of findings that would be persuasive to policy-makers, the investigators chose to provide no specific intervention to the control group other than existing primary care treatments available within the national health system.
The primary outcome measure is the neonatal mortality rate (in the first 28 days); the secondary outcome measures are the infant mortality rate (in the first year) and the perinatal mortality rate (five months before until one month after birth).

**Ethical issues related to the trial**

1. The sepsis trial is clearly investigating a problem of high social import, and the potential outcome of the study, i.e. development of a novel method of safe and effective neonatal sepsis treatment, would have high social value. But the trial also raises a rather fundamental question about the standard of care that should be employed in research trials. The Helsinki Document #29 would mandate that any new “method or drug should be tested against the best current prophylactic, diagnostic, and therapeutic method” for treating neonatal sepsis. Does the standard of care entail that one use the best current method in the world, in the country, or in the local community? The Indian national standard is antibiotic intravenous injection, which was not given to anyone in the trial.

Hence, was it ethical to withhold a known effective treatment from the control village?

2. Comment on the study design. Discuss the selection criteria used to select the villages in the two groups and decide whether the study will produce scientifically valid results.

3. Could another study design have been employed to answer the same question of whether village women can be trained to recognize sepsis and treat it? Could another type of control group that incorporated a higher standard of care have been used to answer the study hypothesis?

4. What kind of post-trial benefits should be given to the villages in the control group, if any?

**Exercise:**

The participants are expected to discuss extensively the review form of the National Research Ethics Committee. The aim of this exercise is to acquaint the participants with the contents and details of the forms and the applications for the review process.

The following forms are to be discussed:

1. National Application for Ethical Approval of a Research Project (annex 1)
2. Elements of informed consent (annex 2)
3. Protocol Review Checklist (annex 3)
4. Informed Consent Reviewers' checklist (annex 4)
Reading materials and references


Chapter 7: Ethical review process, conflicts of interest and report back to the ethical committees

Prof. Suad Suleiman, BSc, MSc, PhD

Introduction:
Biomedical research involving human subjects must conform to general national and international accepted scientific principles. Research should be based on adequately performed laboratory and animal experimentation and on knowledge of the related scientific literature. One of the essential components of health research is a strong set of ethical standards, well understood and applied by research teams and sponsors.

Every proposal for health and medical research on human subjects must be reviewed and approved by an independent ethics committee before it can be instigated and applied.

The main role of the ethics committee is to promote the conduct of ethical research in the institution. In particular, it contributes to safeguarding the dignity, rights, safety, and wellbeing of all actual or potential research participants and communities, as well as animals, while taking into account the interests and needs of researchers and the integrity of the institution.

The general guidelines for submission of proposals to be reviewed technically and ethically are almost standard for presenting to the committee. Details on the principal investigator, co-investigators, type of research to be conducted, procedures followed etc should be well described so that the reviewers can understand what the investigator(s) will be doing.

The national guidelines for submission for ethical approval were prepared by the Federal Ministry of Health and can be adopted and/or modified according to the needs of the institution and applicants.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol, which should be transmitted for consideration, comment, guidance and approval of the research ethics committee. The ethics committee may approve the project as presented, require changes before it can start, or refuse approval altogether.

Learning objectives:
The objectives of this module are to explain to members of the ethical committee and researchers about:

- Guidelines for the application for ethical approval of the research.
- Reviewing and approving research proposals involving human participants directly or indirectly.
- Look into the aspects of informed consent process, risk benefit ratio, distribution of burden and benefit and provisions for appropriate compensation, wherever required.
- Review the proposals before start of the study as well as monitor the research throughout the study until and after completion of the study through appropriate well documented procedures for example annual reports, final reports and site visits etc.
- Examine compliance with all regulatory requirements, applicable guidelines and laws.

**Module contents:**

**Application process to Research Ethics Committee (REC):**
The application should be in writing and dated. The REC should acknowledge receipt and have established procedures for safeguarding the confidentiality of the submitted research project. The form should specify a designated contact person responsible for correspondence and for dealing with any queries that the REC might have.

The REC must be assured that the application satisfies its requirements and those prescribed by law. Initial scrutiny should ascertain that the applicant has included all documents pertinent to ethics review of the research proposal. If all the requirements for submission have been met, the REC should inform the applicant that the assessment will begin. The information should include the anticipated timetable for review and mention the possibility that, if more documents or specific information are required, the timetable would need to be revised accordingly. The information should also make clear that if the applicant is invited to discuss the proposal in person, he or she will take no part in the decision-making procedure.

When the REC meets to review proposals, members must be asked to declare any conflicts of interest pertaining to the applications under review.

**Information to be provided to and examined by the REC:**
The information necessary for REC review can be adapted according to the nature of the research proposal.

- Description of the project
- Name of the principal researcher, qualifications and experience of the other researchers and, where appropriate, the person responsible for clinical care of participants
- Aim of and justification for the research based on the most up-to-date review of scientific evidence
- Methods and procedures envisaged, including statistical and other analytical techniques
- Comprehensive summary of the project in plain language
- Statement of previous and any concurrent submissions of the research project for assessment or approval and outcome of those submissions
- Participants, consent, and information
- Justification for involving human beings in the research project
- Criteria for inclusion/exclusion of research participants
- If appropriate, method of randomization
- Type of study: e.g. descriptive, un-blinded, single or double blinded
- Selection and recruitment procedures
- Reasons for use or absence of control groups, including justification for placebo
- Treatment of control group
- Description of the nature and degree of foreseeable risks that may happen through research participation
- Nature, extent, and duration of the proposed interventions, and details of any burden on the participants or community imposed by the research
- Arrangements to monitor, evaluate, and react to emergency that may have consequences for the present or future health of research participants and/or other persons affected by the research or its results
- Timing and details of information for proposed research participants, including proposed methods for provision of this information
- Documentation or any visual or other material to be used for seeking consent, or, in the case of persons unable to consent, authorization for participation in the research
- Arrangements to ensure respect for the private life of the research participants and to ensure the confidentiality of personal data
- Arrangements for dealing with information that may be generated during the research and be relevant to the present or future health of participants and their family members
- Proposals for health care after the end of the research project
- Funding arrangements

Other information

- Description of the research facilities
- Details of all proposed payments and rewards for research participation
- Details of all circumstances that might lead to conflicts of interest and that may affect the independent judgment of the researchers
Details of any foreseen potential further uses, including commercial uses, of the research results, other data collected in the research process, or biological materials
- When the biological material will be shipped to another institution outside the country, details of the joined agreement between the institutions and investigators on the use of the samples.
- Details of all other ethical issues as perceived by the researcher
- Details of any insurance or indemnity to cover damage arising in the context of the research project

**Description of the project**

- The application must contain sufficient information to enable the REC to conduct a thorough review and should clearly identify the principal or lead researcher. For collaborative research, the other researchers should channel all relevant information via the principal researcher, who will be the main point of contact with the REC. The REC must be satisfied that all researchers are appropriately qualified. The role of each investigator should be clearly identified.

- The REC should pay particular attention to the scientific justification for the proposed research. This information is essential if RECs are to help prevent inappropriate research. The proposed research methods and procedures should be described in enough detail for the REC to judge whether they are likely to expose participants to any undue risk – e.g., if a pharmacological substance is to be used, the REC needs to have adequate information about its safety and its pharmacological and toxicological properties.

- The requirement for a comprehensive summary of the research in plain language is important not only to aid the understanding of lay members of the REC; but also to ensure adequate comprehension by other REC members who may not be familiar with aspects of the research being reviewed.

- It is important for the REC to be aware of previous and concurrent submissions of the research project, and the outcome if known. For example, if another REC has already rejected the proposal, a new REC needs to know this to decide whether the proposal has been changed in response to legitimate concerns, whether the researchers are merely “shopping around” in the hope of finding another REC that will give a favourable opinion, or if a previous negative decision was unjustified for whatever reason.
Justification for involving human beings in the research

- The applicants must justify why they are proposing to conduct the research in human beings. The REC will need to be satisfied not only that the research holds out the ultimate prospect of improving people’s health; but also that similar results cannot reasonably be obtained by other means, for example by mathematical modeling or research in animals. It naturally follows from this principle that the REC should not approve of invasive research methods if non-invasive methods would be similarly effective.

Inclusion and exclusion criteria

- The determination of the size of study groups should depend on the project, taking into account statistical consideration. Whether categories of people are eligible to take part in research will depend on the research design. The researchers must justify their proposed inclusion and exclusion criteria. This is both to guard against inappropriate inclusion (e.g. carrying out research in people unable to consent which could be carried out in those able to consent) and to protect against inappropriate exclusion (e.g. on the grounds of gender or age). Acceptable exclusion criteria might, for example, be related to the nature or stage of disease or to concurrent medication that might interfere with a medication being studied. Particular care should be taken with women of reproductive age; but the often wholesale exclusion of women from research in the past has led to lack of knowledge about the effects of prescribed treatments in women, with potentially dangerous consequences.

Healthy volunteers

- Biomedical research may involve healthy people, for example in physiological studies, in studies of vaccines (which, being prophylactic agents, are generally given to healthy individuals), or in studies to determine the safety and pharmacological profile of potential new medicines. Researchers who plan to recruit healthy volunteers must abide by the general ethical principles pertaining to biomedical research. In addition, the REC must be satisfied that the research will entail no more than acceptable risk and acceptable burden for those participants. For safety reasons, it is advisable to restrict the number of participations for each individual volunteer.

- The researchers also need to satisfy the REC that they have procedures for confirming that the volunteers are healthy and suitable for inclusion in the research according to pre-determined criteria – e.g., in drug studies it would
be appropriate to determine whether a volunteer has any allergies or has previously received a pharmacologically related substance. The REC should pay particular attention to the adequacy of the research setting and medical supervision. Volunteer studies are often conducted in designated non-hospital-based facilities; but should nevertheless have access to an appropriate level of medical care, especially in the event of emergencies. The REC should also look carefully at any proposed payments or rewards for volunteers to ensure that inappropriate payments or rewards do not attract people simply as a means of making money.

**Specific questions relating to REC review of placebo-controlled studies**

- Is there a compelling scientific reason to carry out a placebo-controlled study?
- Is there a known treatment of proven effectiveness?
- If so, is it safe for the patients to go without such treatment for the period required by the project? In other words, is the additional risk acceptable?
- Is the additional burden imposed on the patient by unrelieved symptoms acceptable?
- Would there be an additional burden as a result of the patients’ condition on their families / care?
- Will the patients be informed about the possibility that they may be assigned to a placebo group?
- Does the study involve patients unable to consent? Is the level of the additional risk and burden within the acceptable limits for research on such patients?
- Are there measures in place for early detection of a seriously unfavourable course of the disease in patients on placebo that would necessitate appropriate intervention? Is there provision for an appropriate suitable temporary analysis?

**Benefits and risks**

For any biomedical research involving human beings, the researchers must ensure that the risks and burdens of research participation are not disproportionate to any potential benefits. Risks and burden should always be minimized. This key requirement stems from the ethical principles of beneficence and non-maleficence.

For interventions that hold out the prospect of direct benefit for the participant, a higher degree of risk and burden may be acceptable – e.g. the degree of risk and burden acceptable in research on a new treatment for a serious condition such as advanced cancer would be unacceptable in research on a minor infection. Risk and burden may not only be physical but also psychological or social, while potential direct benefits include those of a painkilling as well as curative nature.
There may also be benefits of research for advancement of scientific knowledge and society in general. When these are the only foreseen benefits, the REC must be satisfied that the research will entail no more than acceptable risk and acceptable burden for the participants.

**Recruitment arrangements**

Recruitment of research participants is governed by three important principles:

i. that the participation is voluntary;

ii. that recruitment is appropriate to the research question and methods (see inclusion and exclusion criteria above)

iii. that participants are chosen in an unbiased manner.

Biomedical research relies on the participation of volunteers, who must understand from the start that they are free to decline to participate (and subsequently to withdraw) without giving a reason and with no disadvantage to their care.

The REC application should clearly describe the means of recruitment, for example by advertisement or by personal contact connected with the provision of medical care. If planning to contact potential participants, researchers should avoid inadvertently distressing them or their families – e.g. they should ensure that contact details are correct, and that there are no special reasons for avoiding contact. The application should also outline the steps that the researcher will take to safeguard privacy and confidentiality during the recruitment process. If the researchers plan to use preliminary screening questionnaires to aid recruitment, they should supply this information to the REC. For records-based research it is accepted best practice that the initial approach should be made via a doctor or other healthcare professional familiar with the participant.

**Information for potential participants**

The REC should pay particular attention to the proposed way in which information will be presented to potential participants. The information must be given verbally, if appropriate with the help of an independent interpreter, and accompanied by written participant information, which should be included as part of the application. The information must be clearly written in plain language that is readily understandable by a lay person. For this reason, it is accepted good practice for researchers to obtain a lay opinion on the leaflet before they submit it to the REC. If there is need that information is translated into another language, the REC should be assured that the researchers have confirmed the accuracy of the information to be
presented to participants by back-translation. The participant should receive a copy of the written information leaflet and that of the signed consent form to keep.

**Typical participant information checklist**

- Title of the study
- Introductory invitation paragraph
- What is the purpose of the study?
- Why have you been chosen to take part?
- Do you have to consent?
- What will happen to him if he consents?
- What do you have to do?
- Will any tissue samples or data be used for further purposes?
- Do you have to consent now to this possible further use of the tissue samples or data
  (separate consent to be required)?
- Can you withdraw consent during the study?
- What happens if you withdraw consent?
- What are the treatment/procedure/etc being tested?
- What are the alternatives for diagnosis/treatment?
- What are the side-effects of taking part?
- What are the possible disadvantages and risks of taking part?
- What are the possible benefits of taking part?
- What if new information becomes available during the course of the study?
- What happens when the study stops?
- Will any healthcare be continued?
- What happens if something goes wrong?
- Will taking part in this study be kept confidential?
- What will happen to the results of the study?
- Will he be informed, in accordance with the national law, about the results?
- Who is organizing and funding the research?
- What is the relation between the researchers and the sponsor?
- Who has reviewed the study?
- Who has approved the study?
- Contact details of the responsible person, including names and telephone numbers,
  for further information
- Contact details of medical supervisor

**Potential unnecessary influence**

The REC must be satisfied that the researchers will place no unnecessary influence on people to encourage research participation. Such influence might be financial in nature; but might also take other forms. For example, people who are unwell and weak may feel that they have to agree to participate even if that goes against their wishes. The trust placed by patients in doctors and other health professionals may also lead to undue influence, especially when the health professional is the
researcher. In that event, it is best practice to involve an appropriately qualified neutral person in seeking consent. The REC should also pay attention to other sources of undue influence. For example, if employees were made to feel that continued employment depended on their research participation, or if a junior doctor were made to feel that career progression depended on recruitment of patients to a senior colleague’s study. Some groups of people may be especially vulnerable to coercion (being forced) – e.g. those deprived of liberty like military service personnel, or those who are vulnerable within a given society because of prevailing social hierarchy or prisoners.

**Informed consent**

Biomedical research involving interventions must not be allowed to proceed unless the potential research participant has given his or her consent. For consent to be valid it must be informed and freely given. A permanent personalized record of the consent should be kept by the researcher as part of the study records.

**Recording**

In addition to providing the participant information to the REC, the researchers must also include their proposed consent form for REC record. If the research involves people who are unable to consent or emergency situations, the documents relevant to obtaining authorization for research participation should be submitted.

**Safety and supervision**

Assessment of health status of research participants:

- The REC must be satisfied that the research protocol outlines appropriate methods for assessing the health status of potential research participants and that the assessment will be carried out by a suitably qualified clinical health professional.
- For research involving healthy volunteers, a standard clinical examination at the outset of the project may be all that is necessary e.g., medical history, physical examination, and laboratory tests or radiological examination if justified.
- Research involving patients is often linked to their healthcare and the findings acquired in the course of clinical care may be sufficient for research purposes. If not, or if the results do not satisfy the inclusion/ exclusion criteria of the research project, the need for additional examinations/ tests should be anticipated and included in the research protocol.

Medical supervision of research participants
The application must include the name of a suitably qualified and experienced person who will ensure medical supervision of the participants. In case of emergency this person (or a designated appropriate colleague) must be available for contact by research participants and those responsible for the participants’ regular health care. In addition, the medical supervisor and those responsible for the participants’ regular health care should know about all essential non-research treatments that patients are receiving. The protocol should also designate institutions for emergency treatment, describe their facilities, and note the distance, if any, from the research site.

Information to the ethics committee during the conduct of research

- It is important for RECs to keep in touch with projects that they have approved, generally by review of regular reports from the research team to establish whether, in the light of any new developments, changes in the project have become necessary or even if the research needs to be discontinued. Re-review will also establish whether additional consent needs to be sought from the participants (or further authorization from their representatives) and whether the consent form for future participants should be modified.

- For specific types of research - e.g. clinical trials of medicinal products (i.e. drug trials) the law defines the adverse events and reactions that are to be notified to the REC. Over and above these legal requirements, the REC may decide that other information is necessary and therefore ask for its inclusion in the protocol.

- The REC and the applicant should agree on arrangements for validating any events that occur, for example by means of a ‘Data and Safety Monitoring Board’ (DSMB). The REC and the DSMB should be clear about their respective responsibilities and about how they will interact.

- In the light of any events occurring during the project or if new results become available from research in the same field, the REC needs to decide whether the research design should be changed or the research stopped. The applicants must tell the REC about any proposed changes to the project, and if the research has been stopped early and why. They should also notify the REC when the study finishes as planned.

- Visits to study sites by RECs are advisable.

New information and protection of research participants
In response to events or new scientific information during the course of the research, the REC may need to revise its initial decision about the project. Research protocol and/or the official report of the REC should set out how any altered decision and resulting consequence will be conveyed to participants. The REC must be assured that this information is conveyed as soon as possible, and that participants are told whether the REC has asked the investigators to prepare revised information/new consent forms concerning modifications to the project. At this point, as at any stage during the research, participants’ right to withdraw consent must be respected. The content and clarity of information to participants is especially important when the REC has withdrawn a favourable opinion. When the investigators submit a revised protocol to the REC, they must indicate explicitly how the revision has addressed REC concerns.

Confidentiality and right to information

Data protection

- Personal information collected in the course of biomedical research must be considered confidential and protected accordingly. For this reason, the data should be stripped of identifiers, as much as possible and as soon as possible.

- The applicants must justify the nature and degree of identifiability and the corresponding protective measures to the REC. The applicant should also indicate how long they propose to keep the identifiable data. If identifiable data are to be used, the participants must be informed about the extent of identifiability and who will have access to identifiers, and agree to the use of their identifiable data.

Safety of samples collected:

- If biological materials are to be removed, and stored for research purposes, the REC must be satisfied that the researchers have made provisions to ensure their security and the confidentiality of any information which could be obtained from them. The researchers must outline their proposed methods for safe storage in the proposal. If materials removed for diagnostic purposes are also intended for research use, the specific protective provisions for research apply only during the research procedure. When
research use finishes, any other relevant provisions concerning storage of biological materials must be observed.

Right to know – right not to know

- The right to know any information collected about the health of a person applies to research. Research participants are not only entitled to have this information as acquired in the course of a research project but also to refuse this information. The REC must be satisfied that both rights are respected by appropriate provisions in the research protocol, taking into account any specific restrictions according to national law. The REC should consider whether the wish of a participant not to be informed about unforeseen results with relevance to health would justify his or her exclusion from the research.

Duty of care

- Research participants are entitled to health-related information collected during the course of research. The information could be part of the research results or acquired incidentally. The researchers should themselves evaluate the relevance of such information for the current or future health or quality of life of participants and may need to consult the REC on this issue. When information is to be offered, this must be done within a framework of healthcare or counseling so that clinical professionals can explain the nature and relevance of the results in a way that is readily comprehensible to participants, and similarly discuss the options available for prevention, treatment, or other course of action. It is important to remember that research results of clinical relevance usually need to be verified by previously validated methods. These discussions with participants must be confidential and the right of participants not to receive such information must be respected.

Availability of research results

Making research results available to the REC and the research participants

- On completion of the research the investigators must submit a report or summary of their findings to the REC. At this point, the researchers should also confirm their proposals as outlined in the application for publication of the research results in scientific journals or making them publicly available by other means.

- The conclusions of the research should be made available, in a comprehensible form, to any participant who wishes to see them. Although
provision of this information has to respect the interests of third parties such as the research sponsor or researchers themselves, this should not be used as an excuse to deprive participants of their legitimate right to know the outcome of the research to which they contributed. However a reasonable delay may be acceptable.

*Making research results available for scientific and healthcare purposes*

- It is important to make available the results of research, whether supporting the research hypothesis (“positive”), or opposite to the research hypothesis (“negative”) or being uncertain. Suppression of results not only distorts the research endeavour if other research groups are unaware of them; but also can directly affect patients, who may be recruited needlessly to take part in unnecessarily repetitive research. In addition, systematic accumulation and analysis of research results is essential for developing medical treatments – very seldom will the results of a single research project be so clear cut that they have an immediate impact on clinical practice. In fact, progress depends on new research being carried out and interpreted in the context of systematic reviews of all other relevant and reliable evidence. If some of this relevant evidence remains unpublished the totality of evidence is biased and therefore unreliable. Patients may then continue to receive treatments that are actually harmful, or conversely not receive treatments that would benefit them.

- At the end of a study a report or summary should be submitted to the REC. In the case of premature termination of a study, a report including reasons for termination should also be submitted. Furthermore, the Protocol requires that the results should be made publicly available in reasonable time, and that the conclusions of the research be made available to participants who request them. The REC must therefore be assured that the researchers have formulated a publication policy and that they have negotiated the policy with any external research sponsors so that they are not contractually inhibited from disseminating their results. A “reasonable” delay in publication is acceptable so as not to prejudice a patent application; but should not be used as an excuse to withhold results indefinitely. Only in very exceptional circumstances should a REC agree to non-publication of results – for example if the researchers could convincingly argue that publication would compromise public safety. Even in these circumstances REC members would need to be assured that the research participants had been advised about and had agreed to this unusual measure before giving their informed consent to take part in the research.
There have been particular concerns about biased publication of research results relevant to possible new treatments, especially concealment of “unfavourable” results of drug trials by pharmaceutical companies. To counter this bias and to help ensure the eventual publication of the findings, all trials should be registered by researchers when they begin. REC members can encourage this drive towards transparency by making their ethical approval conditional upon such registration. If national law does not permit conditional approval on these grounds, the REC should still use its position to request free publication of the full research results.

Circumstances that might lead to conflict of interest affecting the independent judgment of researchers

- The judgment of a researcher concerning the research must not be influenced, by financial (See Payments and rewards below), personal, academic, political, or other interests at any stage. In the application the researcher should therefore set out any circumstances that might lead to a conflict of interest.

- The REC should also be made aware of any potentially conflicting role if a clinician is involved both in the research and in the clinical care of the participants. For example, to choose a patient’s treatment or to alter it for the purpose of enhancing enrolment in a research project would be ethically unacceptable. If the roles cannot be separated, the REC may wish to ask for additional safeguards to be put in place, especially with respect to obtaining participants’ informed consent (See Potential undue influence above).

Payments and rewards to be made in the context of the research

- The REC application should give details of all payments and other rewards to be made to the researchers, their research institutions, and research participants. This information will enable the REC to judge whether or not the proposed payments and rewards are appropriate.

- The REC should be satisfied that any payment and rewards to be provided to participants are appropriate to the burden and inconvenience of the research but not at a level that might encourage them to accept a risk that they would otherwise not accept. Reimbursement for expenses and any financial loss incurred in participation would not be regarded as undue influence as long as
it does not represent a substantial proportion of income or the only source of income for the participants in the study.

- Researchers should give details of any payments, rewards or material goods that will be provided to them or their institution in return for the research so that the REC can judge whether they are appropriate.

- The REC also needs to be aware of the interplay between public and commercial funding of research – e.g., for research into the treatment of a given disease, a commercial funder might offer far larger payments per participant recruited than a public funder, whereas the research design proposed by a public funder may be far more likely to yield results of broad relevance to a particular healthcare setting.

**Foreseen potential further uses, including commercial uses, of the research results, data, or biological materials**

- The REC needs to be aware of any potential further uses of the research results that are foreseen by the researchers. For example, the researchers might already plan to make their results available for combination with results of similar research studies in a meta-analysis, or research in one disease area such as diabetes might have applications in another disease area such as heart disease. Such transparency is especially important if there are foreseen commercial uses of the research results. In addition, it is increasingly common for data and biological materials to be archived for use at a later date. As far as possible, such further use should be anticipated by the researchers since it has special relevance for way in which data/materials are stored and for the consent process.

**Arrangements for compensation for damage**

- Any research participant who has suffered damage as a result of participating in the research is entitled to fair compensation according to national law. Compensation conditions and procedures vary from country to country, but in all cases, the researchers should provide the REC with details of any insurance or indemnity to cover damage arising in the context of the research project.

**Justification for control groups**
To obtain reliable evidence, it is often essential to compare the effects of the new method with those of a control method in participants drawn from the same participant population. This is the principle of comparing “like with like”, which is fundamental for achieving unbiased results. The applicants should therefore give their reasons for the presence, and especially the absence, of control groups, together with details of the proposed control method. Participants assigned to a control group should receive a proven effective preventive diagnostic or therapeutic method. Placebo may only be used as the control method under strictly defined conditions.

**Use of placebo**

- Placebo is an inert substance or a sham procedure. Biologically, the use of placebo is similar to non-treatment. However, there is scientific evidence that placebo may in some cases produce effects similar to those of treatments both regarding benefits and adverse reactions – this is known as the “placebo effect”.

- Placebo may only be used as the control method under strict conditions – i.e. when there are no methods of proven effectiveness, or when withdrawal or withholding of such methods does not present an unacceptable risk or burden. Consequently, the REC should pay particular attention to the foreseeable risk or burden. No other reasons would be ethically acceptable.

- An ethically unacceptable reason to conduct a placebo controlled study instead of having control groups on standard treatment is that such studies tend to be cheaper and faster, since in particular the number of patients required demonstrating the effect is usually smaller.

**REC review and implications for publication of research results**

Most scientific journals, when considering submissions involving human research participants, will require that the research had been approved by a REC. In this way, RECs also contribute to the scientific and ethical quality of the research that is done.

**RECs’ roles during the research**

RECs should follow up, as appropriate and according to national practice, the conduct of research projects that they have approved and may need formally to re-examine them in view of new developments and relevant knowledge acquired during the research.
This is especially important when the research entails a considerable level of risk, or where it is expected to generate clinically relevant information which could affect—positively or negatively—the safety, health or wellbeing of the research participants.

The purpose of follow up is to establish whether, in the light of any new developments during its conduct, the research can continue unchanged according to the original proposal, or whether modifications in the project have become necessary, or, even, if the research needs to be discontinued.

Follow up can usually be achieved by REC review of project reports that the researchers (or research sponsors where appropriate) are usually obliged to provide on a regular (at least annual) basis.

RECs should also have a designated mechanism, that allows them to react as appropriate to any serious information received during the course of the research project for example concerning the safety and well being of the research participants including, where appropriate, interim information concerning the efficacy of a medicinal product being studied. This should be done promptly and duly documented.

The actions available to the researchers, sponsors, and RECs (in addition to taking immediate measures to protect the health and well-being of the research participants) include protocol amendments, or a temporary suspension or termination of the research.

**RECs’ roles after the research**

The roles of RECs after the research is completed are currently rather limited. This is not generally regarded as the most important use of REC expertise and moreover RECs seldom have the legal competence, the time and other resources to function effectively for this purpose.

One area in which RECs’ responsibilities tend to be more visible is in helping to ensure that the obligations of researchers and their institutions or sponsors of research to the research participants, and/or to the groups or society from which they were recruited, are fulfilled as specified in the original research proposal. For example, researchers’ or sponsors’ obligations may entail the offer of health-related information revealed within the research to the research participants, or provision of specific health care or other benefits. These issues may be especially prominent when research is conducted in developing countries, in vulnerable people, or in marginalized or disadvantaged population groups. Although RECs do not have any legal powers to demand that such obligations are fulfilled, their moral status and influence can help to resolve issues that arise.
Another ethical obligation of the researchers or of the sponsors of research is to make the conclusions of the research available to the research participants in a form that is comprehensible to them and to society by means of fair and adequate publication. Sometimes, for commercial or other reasons, research results, especially ‘negative’ results, are suppressed. Such biased under-reporting is not only unscientific and unethical but has also harmed patients, for example when adverse effects of treatments have been concealed. Although several mechanisms are being introduced to aid transparent reporting of research information - e. g. the requirement for pre-registration of any clinical trial on medicinal products in a public database before the trial begins - RECs can still help by being attentive to this important issue as related to projects completed under their supervision.

**Biological materials of human origin:**

The use of human biological materials is increasingly important for biomedical research. Consequently, research participants and the public should have confidence that the materials will be handled and used sensitively and responsibly. It is likewise important that any collections of human biological materials are used optimally and that unnecessary collection of new materials is avoided.

The materials that are taken from human beings for research use can be divided into two broad categories:

i. those that are to be immediately used in a specific research project;

ii. those that are to be stored for future use.

The distinction is not absolute in that part of a sample may be used straight away and the remainder kept for use later on.

The ethical issues for research involving human biological materials are two-fold:

i. issues concerning initial removal of the material, which require a physical intervention – this is the only time when the physical integrity of a person is to be considered and the general protective provisions concerning biomedical research apply as for any other research intervention;

ii. issues of consent/authorisation and confidentiality concerning use and/or storage of the materials that have been removed. These issues have been the focus of considerable attention and the subject of guidance.

Issues with respect to removal and storage of human biological materials:

- Removal confined to diagnostic and/or treatment purposes – free informed consent as for any clinical procedure; storage according to health service regulations;

- Removal for diagnostic/treatment purposes and for research purposes (dual use) – free informed consent for both types of use;
- Removal only for research purposes:
  (a) for defined research project or projects;
  (b) storage for subsequent projects with aims that are the same as or differ from those of the original research use – free informed consent for the specific project and/or for future projects that may not be expected and depending on the scope of the donor’s consent
- Removal for storage in biological material banks

**Multinational research: review by different RECs**

Every multinational research project must be submitted for ethical review to a REC in each State/country in which research activity is to be conducted and must only be carried out in States where the REC has given a favourable opinion.

The practical issue for a REC involved in reviewing research that is to be conducted internationally is to be satisfied that there is an appropriate mechanism for ensuring the research is conducted to a common set of ethical standards. This might mean getting the formal agreement of research funders/researchers that the research they fund/carry out will be governed by common ethical principles irrespective of research location. RECs in the various countries involved may also need to liaise directly with one another while bearing in mind the independent nature of REC decisions and any prevailing cultural differences particularly regarding informed consent.
Annexes

Annex 1: National Application for Ethical Approval of a Research Project

The Republic of Sudan

Federal Ministry of Health

Health Research Council

National Health Research Ethics Committee

NATIONAL APPLICATION FORM FOR ETHICAL APPROVAL OF A RESEARCH PROJECT

The application technical and ethical guidelines are to be read before completing this form to ensure that the questions are answered appropriately.

You may find it helpful to print out the application form before completing it electronically to help you to keep to the page limits allowed. No extra pages should be added, except where specified, as appendices.

The relevant paragraphs of the Operational Standard for Ethics Committees (Ministry of Health document) have been included in subject headings for reference.

Ministry of Health

Health Research Council

2007
Health Research Ethics Committee

NATIONAL APPLICATION FORM FOR ETHICAL APPROVAL OF A RESEARCH PROPOSAL

For office use only

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Please read the technical and ethical guidelines thoroughly before filling the form

Part 1: Technical proposal form

1. Principal investigator (PI) / Applicant

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2. Co-investigator (1)

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2. Co-investigator (2)

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2. Co-investigator (3)

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- Institute:
- Current position:
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- Signature:
3. Title of Proposal:

4. Purpose (tick where appropriate)
   - For a grant.
   - For national endorsement.
   - For a postgraduate degree.
   - Other, specify.

5. Introduction/ Background (Including rationale, problem statement and hypothesis)
You can use extra paper.

6. Objectives

- General objective:

- Specific objectives:

8. Methodology

- Study design:
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• Data collection technique (interviews, observation, review of secondary data, focus group discussion...etc)
• Data collection tools (including questionnaire, details of laboratory tests, detailed sample taking procedures, drug dosage, clinical case sheet, check list.....etc.)

9. Data analysis

9. Work plan:

• Place (include institutional technical facilities available)

• Time (include when study to commence, duration, if in stages the time schedule for each part)
• Collaborating individuals / institutions:
10. **Budget:** (Personnel/ consumable items/ transportation/ field expenses.....etc.)
11. References:

12. Annexe

Part Two: Ethical Considerations

1. What is an estimate of total time involved for participants in the study?

2. Who will carry out the research procedures?

3. What other research studies is the principal investigator currently involved with?

4. Where will the research procedures take place?

5. Does the project involve collection or use of human tissue?

6. If yes: will this material be used in further studies?

8. Is it intended to inform the participant’s doctor of individual results of the investigations, and their participation, if the participant consents?
9. If no, outline the reasons

10. Does the researcher, the host department, the host institution, have any financial interest in the outcome of this research? If “yes”, please give details.

**Part Two: Minimization of Harm**

11. How do the research procedures differ from standard treatment procedures?

12. What are the benefits to research participants taking part?

13. What are the physical or psychological risks, or side effects to participants or third parties? Describe what action will be taken to minimize any such risks or side effects.

14. What facilities/procedures and personnel are there for dealing with emergencies?

15. What arrangements will be made for monitoring and detecting adverse outcomes?

16. Is the trial being reviewed by a data safety monitoring board (DSMB)?

17. If yes, who will fund of the DSMB?

18. What are the criteria for terminating the study?

19. Will any potential toxins, mutagens or teratogens be used?
20. If **yes**, specify and outline the justification for their use

21. Will any radiation or radioactive substances be used?

22. Has the National Committee for atomic energy completed risk assessment?

23. If **yes**, please enclose a copy of the risk assessment, and the contact name and phone number

24. If **no**, please explain why

25. Will any drugs be administered for the purposes of this study?

26. If **yes**:
   a. is approval of the concerned authorities required?
   b. trade name of drug
   c. Chemical name of drug
   d. Pharmacological class:
   e. Pharmacological class, e.g., long half life, receptor selectivity.
   f. Recommended dose range
   g. Form of administration in the study
   h. Known or possible interactions with non-trial drugs the participants may be taking
   i. Side effects and adverse reactions

27. Does the study involve the use of healthcare resources?

28. If **yes**, please specify:

29. What effect will this use of resources have on waiting list times for patients i.e. for diagnostic tests or for standard treatments?

**Part three: Privacy and Confidentiality**

30. How will participants be recruited? (e.g. advertisements, notices)

31. Where will potential participants be approached? (e.g. outpatient clinic) If
appropriate describe by type (eg students)

32. Who will make the initial approach to potential participants?

33. How will data including audio and video tapes be handled and stored to safeguard confidentiality (both during and after completion of the research project)?

34. What will be done with the raw data when the study is finished?

35. How long will the data from the study be kept and who will be responsible for its safe keeping?

36. Who will have access to the raw data and/or clinical records during, or after, the study?

37. Describe any arrangements to make results available to participants, including whether they will be offered their audio tapes or videos.

**Part Four: Informed Consent**

Consent should be obtained in writing, unless there are good reasons to the contrary. If consent is not to be obtained in writing the justification should be given and the circumstances under which consent is obtained should be recorded. Attach a copy of the information sheet and consent form.

38. By whom, and how, will the project be explained to potential participants?

39. When and where will the explanation be given?

40. Will a competent interpreter be available, if required?
41. How much time will be allowed for the potential participant to decide about taking part?

42. In what form (written or oral) will consent be obtained? If oral consent only, state reasons

43. Are all participants able to consent themselves?

44. If no, explain why, and who will consent for them?

45. Is there any special relationship between the participants and the researchers? E.g. doctor/patient, student/teacher

46. Will there be any financial cost to the participant, e.g. travel costs? If so, will such cost be reimbursed?

47. Will any payments be made to participants or will they gain materially in other ways from participating in this project?

48. If yes, please supply details

Part Five: Declarations

1. Declaration by Principal Investigator

The information supplied in this application is, to the best of my knowledge and belief, accurate. I have considered the ethical issues involved in this research and believe that I have adequately addressed them in this application. I understand that if the protocol for this research changes in any way I must inform the ethics committee.
NAME OF PRINCIPAL INVESTIGATOR:

SIGNATURE OF PRINCIPAL INVESTIGATOR:

DATE

2. Declaration by Head of Department in which the Principal Investigator is located or appropriate Dean or other Senior Manager

I have read the application and it is appropriate for this research to be conducted in this department I give my consent for the application to be forwarded to the concerned ethics committee.

NAME AND DESIGNATION:

SIGNATURE: INSTITUTION:

DATE:

مجلس البحوث الصحية
لجنة مراجعة أخلاقيات البحوث الصحية القومية

موجهات الإقرار بالموافقة على إجراء البحوث الصحية على الإنسان

1. اسم الشخص الذي سيقوم بشرح البحث أو المشروع البحثي للمشارك في البحث.
2. عنوان الدراسة
3. الهدف من الدراسة
4. وصف الإجراءات التي سيقوم بها الباحث تجاه المشارك:
   ● أخذ معلومات من المشارك
- أخذ عينة دم
- أخذ عينة نسيج
- أخذ عينة عظم
- إجراء آخر (حدد)

4- وصف تفصيلي للمشارك عن إجراءات البحث التي سيقوم بها الباحث.

5- توضيح للمشارك عدد المشاركين في البحث.

6- وصف للمشارك الفوائد المتوقعة من البحث له أو للمجتمع أو للنظام الصحي.

7- وصف المخاطر المتوقعة من البحث للمشارك (إذا وجدت).

8- وصف الإجراءات البديلة أو العلاج المناسب للمشارك.

9- تأكيد سرية المعلومات والوثائق الخاصة بالمشارك.

10- إبلاغ المشارك بالإطلاع على الوثائق الخاصة به من قبل لجنة أخلاقيات البحوث الصحية القومية.

11- توضيح للمشارك في حالة وجود درجة من الخطورة عند إجراء البحث وهل يوجد تعويض عنه من الباحث أو الوحدة الصحية للمشارك.

12- توضيح للمشارك عن الجهة التي يمكن أن يتصل عليها للاستفسارات عن:

- المشارك في البحث
- حقوق المشارك في البحث

12-الجهة التي يتصل عليها المشارك (المحفوذ - عنوانه وتلفونه) في حالة حدوث أذى من جراء البحث.

12-توضيح للمشارك (المحفوذ) أن مشاركته في البحث طوعية وأن رفضه المشاركة في البحث لا تقف له حقه في أية فوائد.

13-توضيح للمشارك (المحفوذ) أن من حقه الانسحاب من البحث في أي وقت والتوقيع على طلب الانسحاب.

14- في حال البحث على النساء توضيح للمشارك (المحفوذ) بالمخاطر المحتملة والغير مرتبطة الآن للعقار أو الإجراء الذي سيستخدم في البحث:

- على الجنين في حالة المرأة الحامل
- أو على المرأة إذا حملت مستقبلاً

15- توضيح للمشارك (المحفوذ) أنه وفي ظروف معينة يمكن للباحث إيقاف المشارك.
16- توضيح للمشارك (المبحوث) القواعد التي سوف تجري من إستمراره في المشاركة في البحث.
نموذج موافقة المشاركة في البحث

أقر برغبت في المشاركة في البحث والذي تم شرحه لي (أعلاه) والذي سيقوم به الباحث:

..........................................................................................................

..........................................................

توقيع المشاركة.

توقيع الشاهد عن المشاركة أو من ينوب عنه شرعاً

إسم المشارك:

..........................................................

_asm.shahid condiciones

توقيع الباحث:

عنوان الشاهد أو من ينوب عنه:

....................................................................................................

..........................................................................................

فناً حال عدم قدرة المشارك أو من ينوب عنه

إسم الشارح (المترجم) .....................................................................

عنوان الشارح أو (المترجم): ..........................................................

Annexes

112
توقيع الشارح أو (الترجم): .................................................................
## Annex (2): Elements of informed consent

### ELEMENTS OF INFORMED CONSENT

Checkboxes to be completed by reviewers

<table>
<thead>
<tr>
<th>Elements of Informed Consent:</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Purpose of Research:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A statement that the study involves research</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>An explanation of the purposes of the research</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Expected duration of the subject’s participation</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>A description of the procedures to be followed</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Probability of random assignment to each treatment</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Identification of any procedures that are experimental</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>(2) Risks and Discomforts:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A description of any reasonably foreseeable risks or discomforts to the subject</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>(3) Benefits:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A description of any benefits to the subject or to others, which may reasonably be expected from the research</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>(4) Alternatives:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>(5) Confidentiality:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and, if relevant, that other agencies might</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
inspect the records

(6) Compensation for Injury:
For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained

(7) Research Questions:
An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject

(8) Voluntary Participation:
A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled

Additional Elements of Informed Consent (When Appropriate):

☐ (1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

☐ (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

☐ (3) Any additional costs to the subject that may result from participation in the research.

☐ (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
(5) A statement that significant new findings developed during the course of the research which may relate to the subject’s willingness to continue participation will be provided to the subject.

(6) The approximate number of subjects involved in the study.

**Annex (3): Protocol Review Checklist**

**Protocol Review Checklist**

**REC:**

**Title of Research Protocol:**

**PI:**

**Reviewer:**

<table>
<thead>
<tr>
<th>Purpose/Background/Justification</th>
<th>Briefly summarize the study purpose, background, and justification.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SOCIAL VALUE**

- Does the study address an important question of community/national interest?
- Does the literature review justify the study?
- If not involved, does the community need to be involved in the design, implementation, and the dissemination of the results of the study?
<table>
<thead>
<tr>
<th>STUDY DESIGN</th>
<th>Yes</th>
<th>No [If no, explain in comments]</th>
<th>N/A</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Is the scientific design of the study appropriate <em>(e.g., qualitative design, use of placebo control group, phase III, etc.)</em></td>
<td></td>
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<tr>
<td>• Are the objectives well described?</td>
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<tr>
<td>• Will the study endpoints address all of the study's objectives?</td>
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<tr>
<td>• Are the study groups clearly described?</td>
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<tr>
<td>• Is the sample size and methods of sampling adequate and is the type of statistical analysis well described?</td>
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<tr>
<td>• Can the study as described in this protocol answer the research question it is designed to answer, and thus contribute to generalizable knowledge?</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

| STUDY PROCEDURES | | | | |
| • Are the study procedures well described? | | | | |
| • Are experimental procedures clearly distinguished from standard of care interventions? | | | | |
| • Are the study visits clearly described? | | | | |

<table>
<thead>
<tr>
<th>SELECTION OF SUBJECTS AND RECRUITMENT</th>
<th>Yes</th>
<th>No [If no, explain]</th>
<th>N/A</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Considering the purpose of the research, is the selection of subjects fair? That is, are recruitment practices designed so that the research will not unfairly burden or unfairly benefit a particular population to the exclusion of others?</td>
<td></td>
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<tr>
<td>• Are inclusion criteria described?</td>
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<tr>
<td>• Are exclusion criteria described?</td>
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<tr>
<td>• Does any compensation for participation <em>(e.g., financial, prospects of free medical care)</em> represent an undue inducement?</td>
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<tr>
<td>• Does the setting of recruitment represent a coercive concern?</td>
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</tr>
</tbody>
</table>
- Are withdrawal criteria/procedures for individual subjects adequately described?

**VULNERABLE SUBJECTS**

<table>
<thead>
<tr>
<th>Yes</th>
<th>No [If no, explain in comments]</th>
<th>N/A</th>
<th>Comments</th>
</tr>
</thead>
</table>

- Does the study involve vulnerable groups and if yes, are additional protections included?
  - Additional protections for minors
  - Additional protections for people lacking decisional capacity
  - Additional protections for prisoners
  - Additional protections for students or employees of institution
  - Additional protections for other vulnerable groups

- Are the following foreseeable risks present and clearly defined?
  - Physical risks?
  - Social risks?
  - Psychological risks?
  - Legal/political risks?
  - Economic risks?

- Are risks minimized as much as possible (e.g., appropriate exclusion criteria, substitution of less risky interventions, etc)?

- Are the procedures performed at proper facilities by appropriate providers?

- Are there potential benefits to individuals, and if so, are they described?

- Potential benefits to society described?
- **FINAL ASSESSMENT:** Are risks to subjects are reasonable when compared to anticipated benefits?

<table>
<thead>
<tr>
<th>Data and Safety Monitoring</th>
<th>Yes</th>
<th>No [If no, explain in comments]</th>
<th>N/A</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are statistical stopping rules (i.e., interim analysis) adequately described?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2. Is there a data safety monitoring board?</td>
<td></td>
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</tr>
<tr>
<td>3. Are there plans to monitor and report adverse events appropriate?</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adequate?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Informed Consent</strong></td>
</tr>
<tr>
<td>1. Is the description of the informed consent process well described?</td>
</tr>
<tr>
<td>2. Are the consent forms /assent forms included? (see consent form checklist for assessment)</td>
</tr>
<tr>
<td>3. Will informed consent and/or assent be obtained from all potential subjects or legally authorized representatives?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject Privacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>1. Are provisions to protect subject privacy adequate (e.g., interviews will take place in private spaces)?</td>
</tr>
<tr>
<td><strong>CONFIDENTIALITY OF DATA COLLECTED</strong></td>
</tr>
<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td>• Are provisions to maintain confidentiality of collected data described and are adequate?</td>
</tr>
<tr>
<td>• Will there be any storage of tissue samples for future research? If yes, please answer the following:</td>
</tr>
<tr>
<td>o Will there be genetic analysis of the stored tissue samples?</td>
</tr>
<tr>
<td>o Are provisions to maintain the confidentiality of the stored tissue specimens adequate (consider whether the samples will be identifiable and whether a code will be used to link to identifiers)?</td>
</tr>
<tr>
<td>o Will subjects have the option to withdraw their samples at any time?</td>
</tr>
<tr>
<td>o Are plans to re-contact subjects regarding future research findings relevant to their health reasonable?</td>
</tr>
<tr>
<td>o Are there appropriate limits on future use of the samples to a particular institution, researchers, or area of study?</td>
</tr>
</tbody>
</table>

**OTHER CONSIDERATIONS**

•

•

**INFORMED CONSENT DOCUMENTS**

Refer to checklist

**REVIEWER RECOMMENDATION**

<table>
<thead>
<tr>
<th>Yes</th>
<th>No [If no, explain in comments]</th>
<th>N/A</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unconditional Approval</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
Conditional Approval

Defer until more information is obtained

Disapprove

CONTINUING REVIEW FREQUENCY

(Regulations require continuing review must be at least every 12 months. The review period will reflect an interval appropriate to the degree of risk. More frequent review may be considered for research when the degree of risk warrants closer monitoring.)

List determined frequency:

MAJOR CONCERNS ABOUT PROTOCOL

GENERAL COMMENTS;

________________________________________  _____________
Signature of Primary Reviewer     Date
# Annex (4): INFORMED CONSENT REVIEWER’S CHECKLIST

**Title of Protocol:**

<table>
<thead>
<tr>
<th>Introduction to the Research</th>
<th>Acceptable</th>
<th>Not Acceptable (note why)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Statement that the study involves research.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>General Information about the Research</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. General purpose of the study.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Description of the general study methods.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Approximate number of subjects involved in the study.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Procedures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Expected duration of the subject’s participation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Frequency of trips to the study site.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Procedures to be followed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Are experimental procedures distinguished from standard of care interventions?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Explanation of what drugs or products are involved.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Identification of drugs or products that are experimental.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Possible Risks and Benefits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. All reasonably foreseeable discomforts and risks to the subject. Whenever possible, likelihood, severity and duration of risks.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. When applicable: statement that the particular treatment or procedure may involve risks to the subject that are currently unforeseeable.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Benefits to subjects that can reasonably be expected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Benefits to society</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voluntary/Refusal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Participation is voluntary.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. Subject is free to refuse to participate in the study at any time without penalty or loss of benefits to which they are otherwise entitled.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confidentiality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. Statement that confidentiality will be maintained</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. Identification of organizations that may have access to the subjects’ records</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored Tissue Samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Will there be genetic analysis of the stored tissue samples?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Are the provisions to maintain the confidentiality of the stored tissue specimens reasonable (consider whether the samples will be identifiable or whether a code will be used to link to identifiers)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Will subjects have the option to withdraw their samples at any time?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Are there plans to re-contact subjects with the findings of any health-related results?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
e. Are there appropriate limits on future use of the samples to a particular institution, researchers, or area of study?

Are there mention whether subjects can share in any profits obtained from any commercial products that come about from the stored tissues?

### Payment

19. When applicable: statement about any monetary or other inducements for participation.

### Alternatives to Participation

20. Appropriate, alternative procedures or courses of treatment that may be advantageous to the subject.

### Leaving the Research

21. Participation is voluntary.

22. Subject is free to refuse to participate in the study at any time without penalty or loss of benefits to which they are otherwise entitled.

23. Reasons why subjects may be asked to leave the study with or without the subject’s consent.

24. Significant new findings developed during research will be provided to the subject.

25. When applicable: consequences of a subject’s decision to withdraw from the study and procedures for orderly termination of participation by the subject.
<table>
<thead>
<tr>
<th>Annexes</th>
<th>125</th>
</tr>
</thead>
<tbody>
<tr>
<td>If Volunteer Has Questions about the Study</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Contact information for subjects who have questions about the study.</td>
</tr>
<tr>
<td>Research Related Injuries</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Explanation and description of any compensation and/or medical treatment available if injury occurs.</td>
</tr>
<tr>
<td>27</td>
<td>Contact information for subjects who experience health problems while in the study.</td>
</tr>
<tr>
<td>29</td>
<td>If such a problem should occur and they need more help, what will happen and who is responsible for payment.</td>
</tr>
<tr>
<td>Rights of Participants</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Contact information for subjects who have questions about their rights while they are in the study.</td>
</tr>
<tr>
<td>Other Considerations</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Is the language simple and understandable?</td>
</tr>
<tr>
<td>32</td>
<td>If minors are involved, are there assent forms?</td>
</tr>
<tr>
<td>33</td>
<td>If minors are involved, are there parental consent forms?</td>
</tr>
<tr>
<td>34</td>
<td>If people with limited decisional capacity are involved, are there forms for legally authorized decision maker?</td>
</tr>
<tr>
<td>35</td>
<td>If answer is NO to any of the above questions, is there justification provided?</td>
</tr>
<tr>
<td>36</td>
<td>Is translation required? If so, is it provided?</td>
</tr>
</tbody>
</table>
Potential subjects must be given all information that might reasonably be expected to influence their willingness to participate. This information should be provided in language understandable to the subject or the representative preferably at a 6th grade level for developing countries and an 8th grade reading level for developed countries. Additionally, the document should be free of any language through which the subject or the representative is made to waive or appear to waive any of the subject’s legal rights, or releases or appears to release the investigator, sponsor, the institution, or its agents from liability for negligence.

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<table>
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<tbody>
<tr>
<td>37</td>
<td>If biological specimens are requested, is the request adequately explained?</td>
</tr>
<tr>
<td>38</td>
<td>If there are sub-studies, are they adequately explained?</td>
</tr>
<tr>
<td>39</td>
<td>If there is a sponsor of the study, is it identified?</td>
</tr>
</tbody>
</table>

Primary Reviewer’s Signature          Date