BANGLADESH MEDICAL RESEARCH COUNCIL (BMRC)
Mohakhali, Dhaka, Bangladesh

Ethical Guidelines for Conducting Research Studies Involving Human Subjects

Bangladesh Medical Research Council

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01. ETHICAL PURSPECTIVE OF BMRC

Bangladesh Medical Research Council (BMRC) was established in 1972 by the Father of the Nation Bangabandhu Sheikh Mujibur Rahman as an Autonomous Body under Ministry of Health and Family Welfare (MOH&FW). As per resolution of the Government, BMRC is the focal point for Health Research. The objectives of BMRC are to identify problems and issues relating to medical and health sciences and to determine priority areas in research on the basis of health care needs, goals, policies and objectives.

BMRC organize and promote scientific research in various fields of medicine, public health, reproductive health and nutrition with specific references to primary health care needs for the application and utilization of the results of health research.

Bangladesh Medical Research Council (BMRC) is the Secretariat for the National Research Ethics Committee (NREC). According to BMRC Policy each and every Project Proposal approved by the Scientific Review Committee must get ethical approval before funding. Scientific validity should be approved by a valid Scientific Review Committee before submission of a research project to NREC.

BMRC has National Research Ethics Committee (NREC) for Ethical Clearance of research works. The Ethics Review Committee of BMRC was established in 1979. The Committee consists of 9-13 Members (Lawyer, Female Representative, Religious Leader, are included as Member). The Committee is formed by the Council under Guidelines for formation of Ethics Review Committee for "tenure of 3 Years. The Committee is registered in OHRP as an official IRB (lRB No. 0001494) and has FWA (#00006444). The Committee has given ethical approvals to investigators of numerous International Agencies and academic Institutions (e.g. WHO, UNICEF, UNFPA, Harvard, Johns Hopkins, Columbia, Cambridge Universities, Intl. NGOs etc.)

1.1 Role of BMRC:

As per National Research Strategy (Memo No: MOHFW/ Hospital -2 / Misc-16/07/06, date: 05 January, 2009) the followings are the Role of BMRC on ethical issues.

1. Co-ordinate health research by liaising with all research stakeholders.

2. BMRC will assist the government in the development of health research priorities.

3. Review of preliminary and final research reports and give advice on strategic implications of completed research projects and send review reports to the Directorate General of Health Services and Directorate General of Family Planning.

4. Provide advice on all health research related matters to government departments and international agencies.

5. Facilitate co-ordination among the organizations and institutions at various levels so that the health research strategy operates in a coherent manner rather than a collection of fragmented and uncoordinated activities.

6. Any health research to be conducted in Bangladesh has to be registered with BMRC as a pre-requisite for any funding (national or international).

7. BMRC would advise Government on the gaps, synergies and overlaps that exist as well as on the appropriateness of the research work, its budget, achievements and emphases.

8. The National Research Ethics Committee-NREC (functioning under the BMRC & previously named as Ethical Review Committee), should set standards, advise the Departments and the Ministry of Health and Family Welfare on the management of research ethics for Bangladesh and arbitrate on the matters of ethics.

9. The NREC will be responsible to review all clinical trials of both non-registered medicinal substances in Bangladesh and new indications of already registered medicinal substances.

10. The NREC will advice the Drug Administration in ensuring that the drugs available in the country fulfill the necessary requirements for safety, quality and efficacy and that the decision to register a drug is in the interests of public health.

11. Research issues having religious or social sensitivity should be approved by NREC.

12. International collaborative research involving Bangladeshi population will have to get ethical approval by the NREC, while the administrative approval shall be given by the Government.

13. BMRC will sponsor and co-ordinate multicentric commissioned research on areas of national importance.

14. Establishment and further strengthening of BMRC sponsored research institutions and centers for conducting research studies on national priority research areas.

15. BMRC will take initiative to enhance its in-house human capacity, create appropriate physical facilities & logistics and strengthen linkages with all stakeholders involved in health research.

1.2. Objectives of the ethical approval:

As part of good research governance, research requires ethical approval.

a. To safeguarding the dignity, rights, safety and well being of all potential research participants.

b. To protect the rights of a researcher to carry out legitimate investigation, as well as the reputation of the institution.

c. To minimize potential for claims of negligence made against the researchers, the institution concerned and any collaborating individual or organization.

d. To require evidence of ethical approval in refereed journals.

e. To influence the research design with ethical consideration.

f. To avoid potential problems letter on, by trail to ensure that the main ethical issues are address before the research starts

1.3. Research requires ethical approval if it involves:

a) Human participants (including of observation or questionnaires).
b) Accessing personnel, sensitive of confidential data.

1.4. Background:

Ethical Issues in Health Research is becoming more and more important now-a-days. Several international documents are available in this area. But due to cultural and socioeconomic diversity these international guidelines need to be adopted by specific country. The World Health Organization developed Operational Guidelines for Ethics Committees that Review Biomedical Research in 2000. Many countries have developed their own Ethical Guidelines for example in India, the Indian Council for Medical Research (lCMR) has developed "Policy Statement on Ethical Considerations Involved in Research on Human Subjects" in 1980. This document was modified and published in 2000 as Ethical Guidelines for Biomedical Research on Human subjects, this document further updated in 2006. Similarly Nepal health Research Council (NHRC) has recently developed their own Guidelines "Nepal Health Research Council Ethical Guideline" which was adopted in 1995 and revised in 2001, Sri Lanka developed national Ethics Review Committee Guidelines in 2007. Other

neighboring countries have also formulated Ethical Guidelines or putting their efforts in development of Ethical Guidelines. Bangladesh Medical Research Council (BMRC) updated the Guideline in 2009. However in 2013 it has been felt that it needs further updating. Present Guideline was formulated after deliberations by groups of experts in different fields.

1.5. Definition of Ethics

The word "ethics" is derived from the Greek word "ethicos". Ethics is a branch of Philosophy that deals with morality, moral problems and moral judgments, in fact the whole science of moral principles. For simplicity Ethics can be defined as a system of normal standards or values. Standards and values may differ from country to country, society to society.

Bioethics:

Bioethics is the understanding of right, responsibility, justices and moral interaction in living being. It includes medical ethics, environmental ethics and ethical, legal and social issues arising from biotechnology. Bioethics teaches how to balance between different benefits, risks and duties. In the 1970s it emerged as a discipline of academic in USA due to the increasing complexity of medical advances. Now-a-days, bioethics has gained immense important in whole of the world due to rapid advancement in science and technology, drastic changes in macroeconomic planning and globalization. Furthermore, clinical decisions involving the system of values (pluralism, moral autonomy, democracy and human rights**)** which shapes the meaning of life, the meaning of suffering, and the meaning of death which go beyond the strictly medical horizon. In addition, biomedical field has become the place where the various moral approaches present in our pluralistic society are most directly confronted. The most critical situation is an ever-increasing range of health care professionals (personalized response to the needs of each patient) that create a new demand for ethics in the health care system. Another important critical situation is that the process of reordering health care systems to cope with scarce resources. As this scarcity forces reorganization on the basis of an analysis of the priorities, it becomes increasing vital to determine the ethical criteria on which to base such an analysis. Medical professionals face dilemma with advancing science and technology along with enormous health and environmental problems. Bioethics may make bridge between science, technology, social, cultural and spiritual values.

1.6. General Ethical Principles are:

Respect for persons:

Respect for autonomy

Beneficence:

Maximize benefits and minimize harms

Non-malfeasance (Do no harm):

Holds a central position in the tradition of medical ethics. It guards against avoidable harm to research participants.

Justice:

Refers to the ethical obligation to treat each person in accordance with what is normally right and proper.

Ethical Issues are involved in different fields of Health, such as Health Care, Medical Education, Health Administration and Health Research etc. The present document will deal with Ethics in Health and Biomedical Research.

1.7. Important issues in ethical consideration

During development of a research proposal to be implemented in Bangladesh the investigator (both national and international) should consider the following issues:

- Respect for human dignity and protection of rights and welfare of human subjects.
- Risk of research should be reasonable in relation to expected benefits.
- The investigators should be competent enough to safeguard the welfare of the research subjects (research participants).
- Research design should be sound and the researcher should be complement enough to conduct the study.
- Researcher should oversee whether prevailing legal provisions and administrative arrangement ensure that the human rights and welfare of subjects involved in health research are adequately considered and protected in conformity with the ethical principles.

1.8. Vulnerable population (Special attention should be provided by the investigator in development of research studies when the study involves the following category of subjects):

- Children
- Pregnant and Nursing Women
- Mentally ill and mentally defective persons
- Other vulnerable social and ethnic groups
- Subjects in rural communities
- Prisoner

02. International Guidelines on Ethics in Health Research

In 1947, the **Nuremberg Code** the first International document on the ethics of medical research using human subjects was formulated**.** The Code was developed as a consequence of the trial of physicians who had conducted cruel experiments on prisoners and detainees during the Second World War. The code emphasized on voluntary consent. The Nuremberg Code is annexed (Annex-I).

Universal Declaration of Human Rights adopted by the United Nations General Assembly expressed concern about involuntary maltreatment. In 1966, the International Covenant on Civil and Political Rights stated, *'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 consent to medical or scientific treatment'.* (Article-7).

The Declaration of Helsinki is considered as the fundamental document in the field of ethics in medical research. This document was adopted by the World Medical Association in 1964 and subsequently amended in1975, 1983, 1989, 1996 and 2000. The Declaration made an important distinction between therapeutic and non-therapeutic research and it made informed consent a central requirement for ethical research, and allow for surrogate consent when the research participant is minor and incompetent of giving consent. The Declaration of Helsinki is appended (Annex-2).

In 1979, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research wrote their report, "Ethical Principles and Guidelines for the Protection of Human Subjects of Research", commonly called the **Belmont Report**. In this report the Commission identified and described the basic ethical principles that underlie research and protect the certain vulnerable research participant's e.g. pregnant women, prisoners and children. The Commission considered the boundaries between biomedical and

behavioral research. The report also describes the assessment of risk-benefit criteria and introduced the written informed consent. CIOMS Guideline (Annex-3).

In 1993, **Council for international organization of Medical Science (CIOMS)** in collaboration with World Health Organization (WHO) developed international ethical guidelines for biomedical research with special attention to developing country in response to common research e.g. HIV / AIDS. CIOMS took 20 years to develop guidelines involving participants from developing and developed country. Any intervention or product or knowledge generated by research will be made available for the benefit of the population or community of the research country is the cornerstone of the CIOMS. It also justifies the placebo control and includes a section on compensation for research injuries not found in other documents.

International Conference for Harmonization–Good Clinical Practice (ICH-GCP) was promulgated in 1996 by international conference for harmonization of technical requirements for registration of Pharmaceuticals for human use. It depicts the standard for review committee, investigators, and sponsors. It is specific for research on drugs or devices seeking regulatory approval. It opposes the active control trial. ICH-GCP is agreed by Europe, USA and Japan as well as those of Australia, Canada, the Nordic countries and WHO. WHO has developed GCP Guidelines, known as WHO-GCP. (Annex-4)

03. ISSUES IN ETHICAL CLEARANCE

3.1. Informed Consent of participants

Informed Consent of participants refers to having consent of participants by informing detail particulars of the study. For all research involving human participants, the investigator must obtain the informed consent of the prospective participant. In case an individual is not capable of giving informed consent, the proxy consent of a properly authorized representative must be obtained. The form which is used to take the consent of participants is called the Informed Consent Form (lCF). The information should be given in language that is capable of understanding by the participants e.g. for Bangladeshi subject the Informed Consent Form should be written in "Bangla" along with its English version. The Informed Consent Form be attached with Research Proposal and shall get Ethical clearance from NREC.

Informed Consent Form shall include following information:

- Aim and method of the research
- Criteria for selection of the participant
- Duration of participation

- Expected benefits from the research
- Risks/discomfort involved during participation
- Measures to be taken to minimize risks
- Confidentiality of records
- Medical Services to be provided by the investigators
- Provision for compensation for injury, disability or death of subjects
- Statements mentioning 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. Address of contact person in case of queries be provided.

Obligations of Investigators Regarding Informed Consent

To obtain consent from the participants in implementation of a research study in Bangladesh the investigator shall:

- Communicate all relevant information to the participants
- Provide complete and comprehensive information
- Provide opportunity and encouragement to ask question
- Participate needs to provide sufficient time and opportunity in the research.
- Exclude possibility of unjustified deception
- Exclude possibility of intimidation and undue influence
- Consideration of financial inducement should be based on poverty level of Bangladeshi population
- Inform consent form must have sign by participant/legal guardian.
- In case of a clinical trial / experiment informed consent is to be signed by the participant in presence of witness.
- For a study without any intervention (Non-intervention type of study) involving large community it is necessary to have the consent of the community.
- In case of illiterate participants the investigator shall verbally discuss the content of the Informed Consent Form in presence of a witness who is literate and capable of understanding.
- Ensure that an individual or group or community is enough competent to understand and assess information about the research.

- ❖ See that the consent is voluntary. The decision of a subject or group or community not biased by improper influences.
- ❖ Ensure that the participant of group or community is given the detailed truthful information necessary to make a considered judgment about whether to participate.
- ❖ Renew informed consent in case of any methodological change in the research.

Consent is an important area and one that the reviewer and the committee will focus when reviewing the application. Consent must be informed and freely given. There must be no coercion. Participants must have the capacity to consent and the right to withdraw without penalty and providing an explanation. It must be ensured that all relevant information is included and it must be explained clearly what the participants will be asked to do on the participant information sheet. Participants should be told why they have been selected to take part and how many people have been approached.

As part of the information given to the participants, it must be stated that the research study has been approved by the ethical committee of the BMRC. Participants must be informed of any risks. There will always be some, is not acceptable to say there are no risks. Participants must also be informed of their legal rights, the storage and destruction of data and right to withdraw from participation in research at any time, without giving a reason. Participants must also be provided with contact details for further information, which should include a postal address and a telephone number where a person will be available at certain time to answer questions. Taking consent must be viewed as a process, not just the person reading the information sheet and signing a consent form. There is evidence that people understand much less than what they are thought to understand. The participant information sheet should therefore be checked for readability.

The committee will also want to be assured that the participants are being adequate time to decide whether they wish to take part and have the opportunity to discuss the research with family and friends. If direct quotes from participants is going to be used for dissemination, or recording using audio or video equipment, this must be stated on both the participant information sheet and as one of the statements on the consent form. If personally identifiable information is going to be used for dissemination for example photographs, participants must be given the opportunity to be contacted on each occasion that these will be used, in addition to taking their consent.

It is good practice to notify all participants regarding the last approximate date it will be possible to withdraw their data (for example, prior to

publication). It will need consideration whether participants data will still be useful if they decide to withdraw. If this is the case, they will need to consent for its use, they can therefore be given the option to withdraw and also have their data withdrawn, or to withdraw but state that they will allow their data to be used. If a focus group is being carried out, it will not be possible to withdraw one person's data following the intervention without removing the data for all the participants, because what one person says will affect the responses from others. It must be made clear on the participant information sheet that it will not be possible to withdraw data in this case. It is also necessary to make it as easy as possible for people to withdraw, bearing in mind that they might not feel comfortable telling the investigator directly that they no longer wish to participate. Options, such as posting a slip, will need to be included.

One should also guard against unrealistic assurances to participants about data being anonymous. It is essential that every effort is made to remove all identifying information relating to participants prior to dissemination. Information that could identify people is not limited to their names. It is sometimes possible with case studies that people may be identified. This needs to be made explicit in the participant information sheet. The words anonymous and confidential are often confused. These must be refereed to correctly on the participant information sheet.

It must be ensured that the documentation is inclusive. For example if the research involves people who cannot speak or write English, the documentation needs to be translated (a professional translator needs to be employed unless the investigator is fluent in Bengali). Consideration for people with special needs, for example, dyslexia, will need to be included and the provision for alternative formats of documentation should be made.

If research is related to other people, for example asking questions about family member's participants, consent or permission from them should also be taken, as applicable. The assumption should not be made that because participants are revealing information about family members (as opposed to others outside their family) that this will be all right. Even if research is carried out that does not ask participants about other people. Consideration should be given beforehand whether others are likely to be discussed. If so, it should be considered whether consent should be taken from them.

3.2. Confidentiality

Confidentiality refers to management of information that a subject (individual) has disclosed expecting that the information will not be divulged.***** It is the duty of the investigator to maintain appropriate confidentiality of research data. The investigator should handle the data in

such a way that an individual remains unidentified. ** The investigator should adopt following measures to maintain confidentiality:

- ✓ Code numbers for data
- ✓ Remove core sheets (containing names "and address of the subject)
- ✓ Omitting identifications
- ✓ Prevent unlimited access to data
- ✓ Train related manpower in confidentiality. Keep research records in locked cabinets. Provide security codes for computerized records.
- ✓ The investigator must establish safeguards of the confidentiality or research data. Subjects should be told of the limits to the investigators' ability to safeguard confidentiality and of the anticipated consequences of breaches of confidentiality.

  Degree of importance of confidentiality depends on the nature of research study. If the research study involves collection of data on sensitive issues, protections of confidentiality become prominent and essential.
- ✓ The investigators responsibility is to secure safeguards of the confidentiality
- ✓ Limitations of the investigator related to breach of confidentiality and anticipated consequences of breaches of confidentiality should be told to subjects.

* Confidentiality between investigator and subject is considered because disclosure of data may cause harm or distress.

** Foreseeable adverse social consequences must be discussed.

3.3. Inducement

Inducement means to encourage the participants to participate in the study

- ■ Participants may be paid for inconvenience and time spent.
- ■ They should be reimbursed for expenses incurred, In connection with their participation in research.
- ■ They may also receive free medical services. However, the payments should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment (undue inducement).

- All payments, reimbursements and medical services to be provided to research subjects should be mentioned in the research proposal and approved by an ethical review committee.

3.4. Compensation

It is the right of the participants included in a research study to have compensation from the investigator in case of injury, disability, caused by the participation in the study.

- Research participants who suffer physical injury as a result of their participation are entitled to such financial or other assistance as would compensate them equitably for any temporary or permanent impairment or disability.
- In the case of death, their dependants are entitled to compensation.

Compensation is necessary for the following conditions:

I. Accidental Injury:

- ✓ Death
- ✓ Permanent or Temporary disability
- ✓ Investigation, therapeutic intervention, directly related to the research study.

II. Equitable compensation:

- ✓ Significant physical injury from procedures performed solely for Research. Compensations not applicable if it is due to procedures for diagnosis or treatment of disease.
- ✓ Procedures & provision for compensation should be mentioned in the proposal and be reviewed by Ethical Review Committee.
- ✓ Ethical Review Committee should give guidelines, directions for compensation.
- ✓ Informed Consent Form should include details about compensation procedure / provision.

III. Obligation of the sponsor to pay:

Sponsors are advised to obtain adequate insurance against risk to cover compensation.

04. SCIENTIFIC MISCONDUCT

Beyond honest errors and errors caused through negligence are a third category of errors: those that involve deception: making up data or results (fabrication), changing or misreporting data or results (falsification), and using the ideas or words of another person without giving appropriate

credit (plagiarism)- all are against the values on which science is based. These acts of scientific misconduct not only undermine progress the values of scientific institutions. Anyone who engages in any of these practices is putting his or her scientific career at risk. Even infractions that may seem minor at the time can end up being severely punished.

The ethical transgressions discussed earlier - such as misallocation of credit or errors arising from negligence– are matters that generally remain internal to the scientific community. Usually they are dealt with locally through the mechanisms of peer review, administrative action, and the system of appointments and evaluations in the research environment. But misconduct in science is unlikely to remain internal to the scientific community. Its consequences are too extreme: it can harm individuals outside of science (as when falsified results become the basis of a medical treatment) and it attracts the attention of those who would seek to criticize science. As a result, Govt. agencies and the courts can all get involved.

Within the scientific community, the effects of misconduct - in terms of lost time, forfeited recognition to others, and feelings of personal betrayal - can be devastating. Individuals, institutions, and even entire research fields can suffer grievous setbacks from instances of fabrication, falsification, or plagiarism even if they are only tangentially associated with the case.

When individuals have been accused of scientific misconduct in the past, the institutions responsible for responding to those accusations have taken a number of different approaches. In general, the most successful responses are those that clearly separate a preliminary investigation to gather information from a subsequent adjudication to judge guilt or innocence and issue sanctions if necessary. During the adjudication stage, the individual accused of misconduct has the right to various due process protections, such as reviewing the evidence gathered during the investigation and cross-examining witness.

In addition to falsification, fabrication, and plagiarism, other ethical transgressions directly associated with research can cause serious harm to individuals and institutions. Examples include cover-ups of misconduct in science, and violations of due process in handling complaints of misconduct in science. Policymakers and scientists have not decided whether such actions should be considered misconduct in science and therefore subject to the same procedures and sanctions as falsification, fabrication, and plagiarism.

05. PREGNANT / NURSING WOMEN AND CHILDREN IN A RESEARCH

5.1 Pregnant / nursing women:

It is always best to avoid involvement of pregnant or nursing mother in a research except if any trial which gatherer new knowledge on pregnancy, fetus & lactation where non-pregnant or non-nursing women are not suitable participant. The research should be well designed in such a way that protect or advance the health of pregnant or nursing women or fetus or nursing infants and no more than minimal risk.

a. Justification of participation:

- It is mandatory to describe the opportunity and benefits to the women as a participant in a study e.g. Investigations, drugs, vaccines or therapeutic or preventive benefits. Example: Trials are-test the efficacy and safety of a drug for reducing perinatal transmission of HIV infection from mother to child; trials for detecting fetal abnormalities and for conditions associated with or aggravated by pregnancy etc. Deprivation from any opportunity and benefit is unethical.

- Women should not be encouraged to discontinue nursing without proper assessment where breast feeding is harmful to the infant and compensation of supplementary food should be considered.

b. Termination of pregnancy: In any time or as a research participant women who desire to undergo Medical Termination of Pregnancy (MTP) should be strictly fallow the Penal Code 1860 and Bangladesh Institute of Law and international Affairs, 1979.

c. Pre-natal diagnostic procedure: Research involved in prenatal diagnostic technique to detect foetal genetic disorders or any abnormalities should follow WHO guideline. (Genomic resource center, Gender & Genetics, Sex Selection & Discrimination, http://www.who.int/ genomics/ gender/en/index4.html)

5.2. Children:

Consideration should be taken before involve a children as study participant.

a. Involvement of children in a research as a participant should not be carried out equally well with adults.
b. Children participate in the research to obtain knowledge regarding their health needs.

c. Consent should be taken from the Parent or legal guardian (If, parents are not alive / unable to give concern) of each child before inclusion in the study.

d. Consent from each child should be taken to the extent of the child's intelligence and capabilities, such as in the case of mature minors from the age of seven years up to the age of 18 years.

e. Study should be well designed that ensure adequate medical and psychological support to the parent and children.

f. The parent or guardian is given the opportunity to observe the research as it proceeds, so as to be able to withdraw the child if they decide that it is in the child's best interest to do so. (Forum of Ethics Review Committees - Sri Lanka, 2007)

g. Any child at any moment want to withdraw / refused to participate from the study even their parent / guardian has been given consent should be respect unless there is no acceptable alternative medically recognized therapy.

h. Participation of children in a clinical evaluation of new drug trial is permitted only after phase III clinical trial in adult. On the basis of a therapeutic value of a drug in a primary disease of children, study can be carried out earlier.

i. Study design of intervention to the individual child participant for the benefit of diagnostic, preventive or therapeutic purpose should be justified in relation to anticipated risks involved in the study and anticipated benefits to society.

j. Intervention that applied to the individual child participant for the therapeutic benefit should be at least advantageous as any available alternative interventions.

k. The benefit & risk of the individual child participant should be intended before intervention. Otherwise benefit will be low when compared to the knowledge that is to be gained.

5.3 Vulnerable groups:

Effort may be made to ensure that individuals or communities invited for research be selected in such a way that the burdens and benefits of the research are equally distributed.

a. Racial equalities should be maintained on genetic research.

b. For the benefit of research economically or socially disadvantaged persons should not be used when there are person better off them.

c. Rights and welfare of mentally challenged and mentally differently able persons who are incapable of giving informed consent or those with behavioral disorders must be protected. Appropriate proxy

consent from the legal guardian should be taken after the person is well informed about the study, need for participation, risks and benefits involved and the privacy and confidentiality procedures. The entire consent process should be properly documented;

d. Involvement of participants such as prisoners, students, subordinates, employees, and service personnel etc. who have reduced autonomy as research participants, since the consent provided may be under duress or various other compelling reasons required adequate justification.

06. POST - TRIAL ACCESS

Helsinki Declaration of the World Medical Assembly (WMA), 2000 states that at the end of the trial every participant should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. This Declaration led to a lot of debate globally on account of lack of even basic drugs in most of the developing countries. The Declaration of the WMA in 2004 reaffirmed "its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review."

Therefore, whenever possible NREC should consider such an arrangement in the *a priori* agreement. Sometimes more than the benefit to the participant, the community may be given benefit in indirect way through improving their living conditions, establishing counseling centers, clinics or schools, and giving education on maintaining good health practices. For smaller scale or student projects post trial benefit to the participants may not be feasible but keeping in mind the post trial responsibility conscious efforts should be made by the guides and the institution to initiate steps to continue to support and give better care to the participants. (ICMR-2006)

07. INTERNATIONAL COLLABORATION / ASSISTANCE IN BIO-MEDICAL / HEALTH RESEARCH

Research in biomedical and health areas has gained greater momentum only by the second half of the 20th Century, especially since the 1960s, the scope of international co-operation and collaboration assumed such proportions as to have exploitative connotations with commercial and human dimensions. On the other hand, collaboration in medical research

suggests an interest in a humane and civil society, while on the other it could give the impression of experimentation on the population of one country by another. Different levels of development in terms of intellectual property rights etc; necessitate an ethical framework to guide such collaboration. The same concerns are applicable even when there is no formal collaboration between countries, but the research is undertaken with assistance from international organizations as sponsors (Governmental like National Institutes of Health, USA, non-Governmental like Bill & Melinda Gates Foundation, Ford Foundation or others like WHO, UNICEF, UNAIDS, etc.). (ICMR-2006)

Special Concerns

1. Given the magnitude and severity of the health problems in different countries, capacity building to address ethical issues that arise out of collaborative research must be promoted on a priority basis. Strategies should be implemented so that various countries and communities can practice meaningful self-determination in health development and can ensure the scientific and ethical conduct of research.

2. The collaborating investigators, institutions and countries can function as equal partners with sponsors even when in a vulnerable position by building appropriate safeguards. Community representatives should be involved early enough while designing the protocol and in a sustained manner during the development, implementation, monitoring and dissemination of results of research.

3. Careful consideration should be given to protect the dignity, safety and welfare of the participants when the social contexts of the proposed research can create foreseeable conditions for exploitation of the participants or increase their vulnerability to harm. The steps to be taken to overcome these should be described and approval taken from NREC.

4. Every adult participant in the research should voluntarily give informed consent and child her/his assent as may be applicable.

5. As different kinds of research (epidemiological studies, clinical trials, product development, behavioral and social science oriented research *etc*.) have their own particular scientific requirements and specific ethical challenges, the choice of study populations for each type of study should be justified in advance in scientific and ethical terms regardless of the place from where the study population is

selected. Generally, early clinical phases of research, particularly of drugs, vaccines and devices, should be conducted in communities that are less vulnerable to harm or exploitation. However, for valid scientific and public health reasons, if sufficient scientific and ethical safeguards are ensured it may be conducted in any phase after obtaining relevant regulatory clearances.

6. The nature, magnitude, and probability of all foreseeable harms resulting from participation in a collaborative research programme should be specified in the research protocol and explained to the participants as fully as can be reasonably done. Moreover, the modalities by which to address these, including provision for the best possible nationally available care to participants who experience adverse reactions to a vaccine or drug under study, compensation for injury related to the research, and referral for psychosocial and legal support if necessary, need to be described.

7. The research protocol should outline the benefits that persons / communities / countries participating in such research should experience as a result of their participation. Care should be taken so that these are not presented in a way that unduly influences freedom of choice in participation. The burden and the benefit should be equally borne by the collaborating countries.

8. Guidelines, rules, regulations and cultural sensitivities of all countries participating in collaborative research projects should be respected, especially by researchers in the host country and the sponsor country. These could be with reference to intellectual property rights, exchange of biological materials (human, animal, plant or microbial), data transfer, security issues, and issues of socially or politically sensitive nature. (ICMR-2006)

08. RESEARCHER'S RELATIONS WITH THE MEDIA AND PUBLICATION PRACTICES

Researchers have a responsibility to make sure that the public is accurately informed about results without raising false hopes or expectations. It should also not unnecessarily scare the people. Researchers should take care to avoid talking with journalists or reporters about preliminary findings as seemingly promising research that subsequently cannot be validated or could lead to misconcepts if reported prematurely. Or, the results of research may be reported in such a way that it would seem that the human application is round the corner, only to be told later by the researchers that considerable time has to pass before these findings can be translated into tools for human use. In such

circumstances, retractions most often do not appear in the media. Therefore, it is important to avoid premature reports and publicity stunts.

The best safeguard against inaccurate reporting is for the researcher to talk to media on condition that the reporter submit a full written, rather than oral version, of what will be reported, so that it enables the researcher to make necessary corrections, if needed, prior to publication. Investigator's publication plans should not threaten the privacy or confidentiality of participants, for example publication of pedigrees in the report on research in genetics can result in identification of study participants. It is recommended that a clear consent for publication be obtained besides the consent for participation in research or treatment and such a consent should preferably be obtained on two different occasions and not as a blanket one at the commencement of the study. Maintenance of confidentiality while publishing data should be taken care of. In case there is need for publication / presentation of photographs/ slides / videos of participant (s), prior consent to do so should be obtained. Identification features should be appropriately camouflaged. The same safeguard should be observed for video coverage.

With regard to authorship, the International Committee of Medical Journal Editors (ICJME) has laid down criteria based on credit and accountability. Only those who make substantial contribution to the article and take responsibility for the published matter can be co-authors. Plagiarism or falsification of data and authorship are important ethical issues in publications. The term 'misconduct in research' means fabrication, falsification, plagiarism, selective omission of data and claiming that some data are missing, ignoring outliers without declaring it, not reporting data on side effects/ adverse reactions in a clinical trial, publication of post-hoc analysis without declaring it, gift authorship, not citing others' work, not disclosing conflict of interest, redundant publication, and failure to adequately review existing research. The Commission on Research Integrity in US created by US Congress addresses the scientific, ethical, social and legal issues involving scientific misconduct in research. Consolidated standards of reporting trials (CONSORT) guidelines have been prescribed for publishing results of clinical research especially RCTs (Randomized Controlled Trials) and are available at http://www.consort- statement.org. (ICMR-2006)

09. GUIDELINES ON RESEARCH ETHICS AS PER NATIONAL HEALTH RESEARCH STRATEGIES:

- The National Research Ethics Committee (NREC) will set standards, advice the Departments and the Ministry of Health & Family Welfare on the management of research ethics for Bangladesh and arbitrate on matters of Ethics.

- The NREC will be responsible to review all clinical trials of both non-registered medicinal substances in Bangladesh and new indication of already registered medicinal substances.
- Research issues having religious or social sensitivity should be approved by NREC
- International collaborative research involving Bangladeshi population will have to get ethical approval by the NREC, while the administrative approval shall be given by the Government

Registration of Health Research as per National Health Research Strategy:

- Any health research to be conducted in Bangladesh has to be registered with the BMRC.
- BMRC has developed a Registration Form for registration of research studies. BMRC is developing electronic submission system for health research registration.
- There is a specific section in this system for Clinical Trial Registry.
- Within short period Clinical Trial Registry will be in operation in Bangladesh through the BMRC web site.
- The Clinical Trials Protocol should be reviewed and approved by the NREC.
- Clinical Trials should be registered in the Clinical Trial Registry in the BMRC.
- Clinical Trials be well monitored.
- Clinical Trials be conducted following ethical standard (Social or Scientific Value, Scientific Validity, Fair Subject Selection, Favorable Risk-Benefit Ratio, Independent Review, Informed Consent & Respect for Potential and Enrolled Subjects)

Monitoring of Clinical Trial

- The NREC conducts post-approval monitoring of Clinical Trial.
- It is mandatory to form Data Safety Monitoring Board (DSMB) for conducting Clinical Trial.
- Principal Investigator should report Serious Adverse Events (SAE) as well as Adverse Events (AE) to the NREC.
- Approval is given subject to several conditions.

SECTION – B

10. INTERVENTIONAL STUDIES

The importance of clinical studies has been increasing with the advances in science and technology and these studies designed to improve methods of preventing, diagnosing, and treating diseases, for better understanding of the etiology and pathophysiology of individual diseases, and to improve the quality of life of patients. Research on human participants is necessary to discover better medical and therapeutic modalities and it is contributed hugely to human good. However, such research on healthy participants and patients is associated with some degree of risk to the individual concerned. These guidelines have been framed to carry out the evaluation of drugs, vaccines, devices and other diagnostic materials on human participants including herbal remedies, in accordance with the basic ethical principles. These guidelines are important for the protection of research participants against any avoidable risk, guide the researchers in the preparation of research proposals/ protocols and facilitate ethical committees (ECs) to review and approve such studies and also to protect the researcher. For the clinical evaluation of proposed research intervention, the framework of guidelines is provided for the following areas:

1. Drug trials (including nutritional substances)
2. Vaccine trials
3. Surgical procedures / medical devices
4. Diagnostic agents - with special reference to use of radioactive materials and X-rays
5. Trials with herbal remedies

GENERAL PRINCIPLES

These guidelines follow the four basic principles of research involving human participants namely autonomy (respect for individual rights), beneficence (do good), non-maleficence (do no harm) and justice. A researcher is the key person who is responsible for the research trial and for protection of the rights, health and welfare of the participants included in the study. The researcher should have qualification and capability to pursue clinical research appropriately and should be aware of and meet all requirements of the study protocol as described under the General Principles and General Issues in these guidelines.

SPECIFIC PRINCIPLES

10. I DRUG TRIALS

A clinical trial is a systematic study of new drug(s) in human subject to generate data for discovering and / or verifying the clinical, pharmacological (including pharmacodynamic and pharmacokinetics), and / or adverse effects with the objective of determining the safety and/or efficacy of the new drugs. For new drugs, adequate evidence derived from animal studies must be available to ensure and toxicity prior to conducting a study in humans. It is designed to evaluate the safety and effectiveness of new drugs/ new formulations prospectively. A new drug may be defined as:

i. a new chemical entity (NCE);

ii. a drug which has been approved for a certain indication, by a certain route, in a certain dosage regimen, but which is now proposed to be used for another indication by another route or in another dosage regimen;

iii. a combination of two or more drugs which, although approved individually, are proposed to be combined for the first time in a fixed dose combination (FDC).

The proposed trial should be carried out only after approval of the Directorate General of Drug Administration (DGDA). All the guiding principles should be followed irrespective of whether the drug has been developed in this country or abroad or whether clinical trials have been carried out outside Bangladesh or not.

The difference between therapy and research should be maintained throughout the drug trials. A physician /investigator who run the new drug trial should ensure during consent that the patients have adequate understanding that the drug is experimental and its benefits for the condition under study are yet not proven.

10.1.1 Special considerations

i. It is extremely debatable to use placebo in drug trials and sham surgery in clinical trials. Each protocol using placebo needs very careful consideration before approval. Denial of the available treatment to control (placebo) group of patients is unethical.

ii. Trials of drugs without the approval of the DGDA and appropriate agencies should be dealt with according to the law of the land.

iii. On completion of the clinical trial, if the drug is found to be effective, the sponsoring agency should give the drug to the patient till its availability in the local market and after that at a reduced price for the participants wherever possible. A suitable *a priori* agreement should be done on post trial benefits.

iv. The criteria for termination of a trial must be defined *a priori* in the proposal of the trial and plan of interim analysis must be clearly presented. This is important that if the test drug is found more effective or less effective than the standard drug on interim analysis, the trial can be discontinued thereafter and better drug should be given to patient receiving less effective drug.

v. Issues of partner notification and discordant couples should be taken care of before initiating any HIV/ AIDS related trial.

vi. For new drug substances discovered in Bangladesh, clinical trials are required to be carried out in Bangladesh right from Phase I through Phase III and data should be submitted as required under regulations. Generally permission to carry out these trials are given in stages, considering the data found in earlier Phase(s).

vii. For new drug substances discovered in countries other than Bangladesh, Phase I data as required under regulations, from other country(ies) should be submitted along with the application. After Phase I data submission to the Licensing Authority, permission may be granted to conduct Phase II and Phase III trials concurrently with other global trials for that drug.

viii. In case of amendment or deviation in the protocol not only the approval of NREC may be obtained but also the Licensing Authority has to be notified of the same.

ix. Published and unpublished data regarding the drug concerned must be submitted along with the research proposal.

For accelerating drug development, which are indicated in life threatening/ serious diseases or specific diseases of relevance to Bangladesh – the toxicological and clinical data requirements shall be decided on a case by case basis. In such cases, particular studies may be abbreviated, deferred or omitted, as believed appropriate by the Licensing Authority and not by NRECs.

Common Principles of Good Clinical Practices (GCP) based on the international guidelines issued by World Health Organization (WHO) and International Committee on Harmonization (ICH) provide operative guidelines for ethical and scientific standards for the designing of a trial protocol including conduct, recording and

reporting procedures and should be strictly adhered to while carrying out a trial.

The clinical trials usually are of 3 types –

i. studies where intervention is clearly "demarcated research" such as phase I trial of a new compound;

ii. studies with a mix of standard medical practices and specific research elements, *e.g.* trials of two competing anti-nausea drugs following standard chemotherapy;

iii. studies involving research on therapeutic practices, such as the trial of two already approved anti-diabetic drugs.

10.1.2 Phases of Clinical Trials

All phases require approval from EC. The first three of the following four phases of clinical trials of drug require DGDA's clearance:

Phase I (Human Pharmacology) This is a first-in-human trial using a new chemical entity that is usually conducted in healthy volunteers to study acute toxicity and safety that is associated with the dose range of the drug. Because of drug side effects, the study should be conducted in well-equipped facilities in the hospital, and should not be conducted in children, the elderly and women with childbearing potential. Anesthesia or anticancer drugs should not be used in the healthy volunteers as a result of its high toxicity. Approximately, the number of the subjects should not exceed 30. Every subject should give a written informed consent before participating in the study. The study in this phase is usually an open study without any control group i.e., both subjects and investigators know the trial drug.

At least two participants should be administered each dose to establish the safe dose range with their intensity and nature. It is safer to start trial from the lowest dose, which can be increased to higher doses only after the safety of the lower doses is evidently established. Pharmacokinetics i.e. characterization of a drug's absorption, distribution, metabolism and excretion (ADME), should be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations considering patients with impaired elimination (renal or hepatic failure), and ethnic subgroups.

Investigator trained in clinical pharmacology should preferably carry out these studies. The duration of time lapsing between two trials in the same volunteer should be a minimum of 3 months and

be covered under some insurance scheme. Compensation should be given by the sponsors but no undue inducement is allowed.

Phase II (Therapeutic Exploratory Trials) – After the successful completion of phase I, an experimental drug is next tested to determine therapeutic effects, effective dose range and further evaluation of safety and pharmacokinetics in a limited number of patients of either sex in patients.

Phase II trials are typically conducted in a small (usually 20-25 patients), well-defined homogeneous group of participants, and generally limited to 3-4 centers. The dose used is lesser than the highest dose used in phase I. Anesthesia and anticancer drugs are allowed in this phase. An additional aim of this Phase II is evaluation of potential study endpoints, therapeutic regimens, concomitant medications and target populations e.g., age, gender, disease stage / degree. It is advisable to include a clinical pharmacologist as a co-investigator in such studies. Once the safety is confirmed, a phase III trial can then be conducted.

Phase III (Therapeutic Confirmatory Trials) – Phase III studies are conducted in patients with the target treatment using the new chemical entity being tested successfully in the phase II. The primary and secondary objectives are to evaluate the pharmacological effectiveness and to study a short-term toxicity, respectively. The number of the subjects in the phase II trials may considerably increase up to several thousands depending on sample size determination using a statistical method in conjunction with the existing preliminary data. Usually there is a comparison with standard drug and/or with a placebo if standard drug does not exist. In the phase III trials, control procedures are implemented beginning from subject selection, group randomization, treatment allocation, follow up, and evaluation. The trial in this phase is aimed to increase patient's survival or to improve patient's quality of life. Then, the trial design should be randomized, double blinded, i.e., both the investigators and the subjects do not know what drugs either investigational or comparator are given. When the drug gives the favorable results under the phase III trials, they are likely authorized for marketing.

Phase IV (Therapeutic Use Trials) – This phase is also called a post marketing surveillance study. The study is done after the drug has been registered, with the objectives being to study the therapeutic uses, any adverse effects, and toxicity of the drug in a larger number of patients who have been using the drug for a longer period of time, or to explore additional effectiveness for other indications other than the approved ones. Also, the study in this

phase can be done in other groups of population that have never been studied. Bioequivalence and bioavailability study also falls under this category.

10.1.3 Special Studies

Bioavailability / Bioequivalence studies - Bioequivalence studies should be carried out for all new drug substances intended for systemic absorption and if applicable with the available doses formulations which are approved elsewhere in the world. For drug not intended for systemic absorption, data on the extent of systemic absorption may be required. Effect of food on absorption following oral administration should also be evaluated. These studies are conducted most often in normal volunteers. Hence, all safeguards to protect participants must be in place, including ethical review of protocol, recruitment methods, compensation for participation, evidence of non-coercion and consent procedures. It is in such studies that volunteers often participate at short intervals and may participate at different centers within less than the prescribed period of three months between two studies. Mechanisms to prevent this must be developed at the study site.

10.1.4 Dissolution studies:

Dissolution is a process in which a solid substance solubilizes in a given solvent. In the pharmaceutical industry, drug dissolution testing is routinely used to provide critical in vitro drug release information for both quality control purposes and drug development. In vitro drug dissolution data generated from dissolution testing experiments can be related to in vivo pharmacokinetic data by means of in vitro-in vivo correlations. Dissolution and bioavailability data submitted in the new drug application must provide information that assures bioequivalence or establishes bioavailability and dosage correlations between the formulation(s) sought to be marketed and those used for clinical trials during clinical development of the product. Data regarding interaction of the new drug with drugs that are likely to be used concomitantly with it are required to be conducted and should be submitted from non-clinical studies and, if appropriate, from human studies.

10.1.5 Special Concerns

10.1.5.1 Multicenter Trials

A multicenter research trial is a clinical trial conducted at more than one medical center or clinic. Most large clinical trials, particularly Phase III trials, are conducted at several clinical research centers. The benefits of multicenter trials include a larger number of participants, different geographic locations, the possibility of inclusion of a wider range of population groups, and the ability to compare results among centers, all of which increase the generalizable of the study. Ideally, these trials should be initiated at the same time at all the centers.

i. All investigators should give a written acceptance of the protocol. The protocol may be modified to suit the local requirements, as well as should be appropriately approved by the ethics committee of the host institutes/country.

ii. In a meaningful multicenter trial, all study sites should be conducted in the same way and should follow standardized procedures and evaluation criteria. So, meetings should be arranged at the initial and intermediary stages of the trial to ensure consistent procedures at all centers.

iii. All research staff at the participating centers should be trained to familiarize them with the uniform procedures, data entry in the case record forms, ethics and GCP.

iv. For recruitment, evaluation/monitoring of laboratory procedures and conduct of trial, standardization of methods should be carried out.

v. If necessary, in the protocol there should be monitoring of adherence to protocol including measures to terminate the participation of some centers. For this purpose a central monitoring committee could be set up including ethics committee members.

vi. Specific role of coordinators and monitors should be defined.

vii. According to WHO's "Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards", centralized data management and analysis should be planned.

Viii. Drafting procedure for common final report and publication should be decided at the outset. No

individual centre should publish any data till appropriate authorities accept the combined report.

ix. If severe adverse reactions occur during the conduct of a double blind trial, the code of the administered drug could be broken.

x. It is advisable to establish communication between ECs reviewing multicenter studies in Bangladesh to discuss ethical concerns of the trial, preferably under the guidance of NREC. This is particularly important if any EC does not grant approval for a study at a site for ethical reasons.

10.1.5.2 Contraceptives

i. In case of contraceptives**,** all steps for clinical trials are applicable including informing participants clearly about the alternatives available. Basic health check to ensure that the subjects are healthy must be undertaken prior to the study.

ii. Where implant has been used as a contraceptive method for women, a proper follow up for removal of the implant should be done after the trial is over or the participant has withdrawn from the trial. If failures of contraceptives occur, the children who born should be followed up for any abnormalities.

10.1.5.3 Randomized Controlled Trial (RCT):

This is the most appropriate study design to reduce bias but ethical problems can arise when placebo is used in the control arm. Hence a proper justification should be provided for using the placebo. Standard therapy should be used in the control arm according to the Declaration of Helsinki. In some situations placebo can be used, for examples, self-limiting disease, and where no proven prophylactic, diagnostic or therapeutic method exists.

Superiority and Non-inferiority trials – Newer statistical analyses are applied recently in RCTs. When a trial is conducted to test if a new drug is superior to the existing one such a trial is termed superiority trial and when the trial is conducted to examine if the drug is as good as the existing one then it is called non-inferiority or active control equivalence trial (ACET).Sometimes clinically small difference in beneficial effect is expected. Previously in such

type of trial, an indeterminate result was found due to difference in clinical thought against statistical thinking. Then this concept arose. In superiority trials one of the arms can be placebo or active control but in equivalence trials use of placebo arm will be unethical as the drug's efficacy will have to be tested against a proven therapy.

To improve reporting of RCT with primary focus on 2 parallel groups that assess the possible superiority of one treatment compared with another, CONSORT (Consolidated Standards of Reporting Trials) Statement, including a checklist and a flow diagram, was developed in late 90s. As in medical literature, the reporting method of non-inferiority or ACET trials has been modified. CONSORT guidelines are now being extended to other trial designs too.

Monitoring and reporting adverse reactions or events:

In drug trial any adverse event or adverse drug reaction (AE/ ADR), expected and unexpected, should be specified in the concerned SOP. These reactions can be mild, moderate or severe and causality relationship should be examined. When an AE or unexpected ADR happens, it needs expedited review by the ethics committee. Unexpected AE/ ADRs and all SAE (serious adverse event) should be reported to the sponsor by the investigator within 24 hours and to the ethics committee that accorded approval to the study protocol within seven days. In the event of death the NREC should also be informed within 24 hours. During a clinical trial if any unexpected SAE as defined in the GCP (Good Clinical Practice) Guidelines occurs should be communicated promptly within 14 calendar days by the Sponsor to the Licensing Authority and to the Investigator(s) of other trial sites participating in the study, so that the regulatory authority can immediately stop the clinical trials of unapproved drugs or withdraw from market approved drugs based on report of Phase IV studies. All other serious unexpected reactions (ADRs) that are not fatal or life threatening must be filed as soon as possible but not later than 14 calendar days. At the end of the trial, all adverse events whether related to trial or not are to be listed, evaluated and discussed in detail in the final report.

The medical management of the adverse event is the responsibility of the investigator, and the protocol for adverse event management with allocation of responsibilities must be pre-defined in the protocol and submitted to the Ethics Committee. There must be a financial plan (including, if available, insurance) to manage adverse events and compensation for trial related injury. The Ethics Committee reviewing the protocol, must review these aspects also before giving approval.

10.2 VACCINE TRIALS

According to nature, vaccines can be prophylactic and therapeutic. When a patient suffering from a particular disease the therapeutic or curative vaccines may be given, while prophylactic vaccines are given to normal participants as well as pediatric group. The guidelines to conduct the clinical trial on investigational vaccines are similar to those governing a drug trial. The phases of these trials differ from drug trials as given below:

Phase I: In this phase the safety and biological effects including immunogenicity of a vaccine is determined during introduction of it to the human population (healthy volunteers). The individuals in these studies should be at the lowest risk of infection/disease possible. This phase includes study of dose and route of administration. Pharmacokinetic studies are generally not required for injectable characteristics of the immune response to the known or presumed action of vaccine. The class, subclass, and the function of specific antibody produced and the lag time for appearance and duration of adequate antibody titre is determined. Information about the induction of cell-mediated immunity, the cross reactive antibodies and/or interaction pre-existing antibodies which might affect immune system is also obtained.

Phase II: This phase range in a target group formed by a limited number of volunteers like, children, adults or those at risks of exposure to pathogens. This refers to the initial trials examining effectiveness (immunogenicity) and dose range as well as pharmacokinetics and safety issues. Early Phase II is usually an exploratory trial while the late Phase II is known as critical efficacy study

Phase III: This controlled study enrolled on a larger number of volunteers (in thousands) through multicenter which focuses on assessment of safety and effectiveness to prevent disease. These studies determine the protection offered by the vaccine and provide pivotal data for licensure. Efficacy in vaccine trials means reduction in incidence of the disease after vaccination compared to the incidence that occurred before vaccination. Effectiveness on the other hand provides information of protective rate deliberated on a given population which includes measurement of direct and indirect protection to a non - vaccinated person among the defined vaccinated population determined by vaccine coverage area, and correlation of vaccine strains with circulating strains.

Phase IV Studies: This phase happens after the vaccine has been licensed and introduced into use. This stage aims to detect rare adverse effects as well as to assess long term efficacy. The rarer or unexpected events may not be seen in smaller Phase II/III studies. To detect these events, these studies are done in the entire population or a subgroup or

heterogeneous group of people, over longer periods of time which are necessary to provide ongoing assessment of vaccine safety and effectiveness. This phase is also done for further research on age at vaccination, effect of simultaneous administration of other vaccines, efficacy and adverse events due to changes in vaccine strain, and interchangeability of vaccine.

Bridging studies in vaccine trials are conducted to support clinical comparability of efficacy, safety and immunogenicity of new formulation when there is change in vaccine composition with regard to adjuvant, preservative, or a change in manufacturing process, site or scale. These are performed either before or after product licensure. The rationale of bridging clinical studies is to demonstrate product equivalence to that used in earlier pre-clinical or clinical testing. When serologic bridging studies are to be done, only comparison of sera with historical control from an efficacy trial is warranted, and no clinical trial need be undertaken.

10.2.1 Combination Vaccines

The main goal in efficacy trial design of combination vaccines which are commonly used nowadays is to evaluate the efficacy of each antigenic component. When correlates of protection are validated for each component, immunogenicity end- points should be used. Prospective controlled trial is required when combination vaccines are not validated for each component. Further, non-inferiority trials should be conducted to demonstrate that the combination vaccine is not inferior in terms of immunogenicity or efficacy, to vaccines with individual components.

Vaccines Administered Simultaneously with the Combination Vaccines

When a new vaccine is administered simultaneously with already licensed vaccines that would be given to the same target population using the same (or overlapping) schedule, Phase III (Pre –licensure) studies should be obtained to support immunogenicity and safety data. With regard to immunogenicity, assessment should be performed to show that subjects still attain an acceptable immune response to both the combination vaccine and the other simultaneously administered vaccine. During such administration, the immunogenicity should be evaluated early in clinical development for all components to detect any possible immunological interference and such assessment would be valuable before proceeding to a large- scale trial of the investigational vaccine. These studies will evaluate safety and interference of the new combination vaccine with one type of simultaneously administered vaccine.

10.2.2 Special Concern

i. The participant should be informed about that some vaccines that contain active or live attenuated micro-organisms can possibly possess a small risk of producing that particular infection.

ii. In case of the participants in control groups or when subjected to ineffective vaccines run a risk of contracting the disease, free treatment for the disease should be given and where lifelong treatment is required then this should be insisted upon by NREC.

iii. For all the recombinant vaccines/ products the Guidelines issued by the National Institute of Health (NIH), Food and Drug Administration (FDA) and Guidelines issued by the authorities of Bangladesh should be strictly followed as the risks associated with these vaccines are not known.

iv. Post-trial access to the vaccine should be given first to the community from which the participants were drawn as well as to the control group. This should be done only if the vaccine is found to be safe and effective. But if the vaccine is for pediatric age group and by the time the study gets over the children in the control arm may cross the age when the vaccine is supposed to be protective. In such instances the control arm could be some other alternative vaccine for that pediatric age group although this does not restore clinical equipoise. EC may examine the feasibility and ethical aspects on a case-to-case basis.

v. For choosing vulnerable group like children, care should be taken to choose the particular age with regard to gender, ethnic background and health profile for testing vaccines for this age especially if they are from over-researched community.

vi. In RCTs if no effective vaccine exists as comparator then placebo can be used. The community should be involved to decide on the choice of comparator.

10.3 TRIALS WITH SURGICAL PROCEDURES, MEDICAL DEVICES

In the past two decades medical and health care technology has rapidly changed. Recently, considerable progress has been made in the conceptualization and designing of bio-equipments through a series of technological inventions which have revolutionized the preventive, diagnostic, rehabilitative, therapeutic (life-supporting or life sustaining devices) capabilities of medical sciences and biomedical technology. Several biomedical devices and critical care equipment have been imported and successfully installed in diagnostic and therapeutic services in the country. Similarly, various academic and research organizations as well as private entrepreneurs are taking active interest in the development and manufacture of medical devices. It is likely that new devices developed in the country may seek approval after appropriate clinical trials. Only through good manufacturing practices (GMP) can the end products reach the stage of large scale utilization by society.

Some low technology devices like thermometer and weighing instruments seek optional certification from Bangladesh Standard Testing Institute (BSTI) as a proof of quality, rather than as a pre-market approval. BSTI certifies and regulates few other low technology devices. But these procedures are not adequate enough to assure the quality of high technology medical devices. It appears that some imported high technology devices, approved or cleared by the country of origin or by the Federal Drug Administration (FDA) of the United States of America (USA), are permitted for marketing in the country. Regulatory mechanisms with the DGDA for certification, quality assurance and post market surveillance of both imported and indigenous medical devices appear inadequate. As the capacity of the country in this area is improving gradually, it is clear that the need for a regulatory mechanism/authority is increasing. In Bangladesh the concept of regulations governing investigations involving biomedical devices is relatively new. The attendant health risks through the errors caused by use of implantable devices require systematic and rigorous pre-clinical and clinical studies to evaluate their efficacy and safety besides the quality. For long term safety and/or performance every implant and installed diagnostic devices needs to be assessed through an appropriate mechanism. Implementation of these measures, i.e. evaluation, certification, post-market surveillance and regulatory action in the event of any inadequacy, is possible only through a well-conceived regulatory agency, which is supported by adequate legislative safeguards.

All countries which have their own medical device industry; also have policies and regulatory processes or mechanisms. Most of these countries (mainly USA, EU, Australia, Japan. China, South Korea, India and Brazil) are attempting to match the medical device regulations of different

countries with a view improve their export potentials. However, it should be borne in mind that not all the devices permitted for export by other countries have been approved for commercialization in their own countries. Therefore, there should a review of the existing certification procedures and regulatory mechanisms in other countries. The Directorate General of Drug Administration (DGDA) is taking steps to review the regulatory mechanisms.

10.3.1 Definitions of Device:

- "An instrument, apparatus, implement, machine, contrivance, implant, *in vitro*agent, or other similar or related article, including a component, part or accessory,

- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man, or

- intended to affect the structure or any function of the body of man, and

- which does not achieve any of its primary intended purposes / uses

- through chemical action within or on the body of man, or by being metabolized within the body."

Medical devices: A medical device is defined as an inert diagnostic or therapeutic article that does not achieve any of its principal intended purposes through chemical action, within or on the body.

Medicated devices: These devices are treated as drugs as they contain pharmacologically active substances. Medical devices include diagnostic test kits, crutches, electrodes, pacemakers, arterial grafts, intra-ocular lenses, orthopaedic pins and other orthopaedic accessories. Their purpose varies from being used primarily for specific affected parts of the body to being used as adjunct to primary therapies, for *eg*. lithotripsy with drug therapy for kidney stone. On the basis of risks involved, the devices could be classified as follows : -

a. Non critical devices- An investigational device that does not present significant risk to the patients eg. Thermometer, BP apparatus.

b. Critical devices - An investigational medical device that presents a potential serious risk to the health, safety or welfare of the participant for example, pace markers, implants, internal catheters.

For medical devices trails, all the general principles of clinical trials described for drug trials should be considered. Before pre market certification, safety evaluation and pre-market efficacy of devices for 1-3 years with data on adverse reactions should be obtained. The duration of the trial and extent of use may be decided in case-to-case basis by the

appropriate authorities. However, the following important factors that are unique to medical devices should be taken into consideration while evaluating the related research projects:

- Previous safety data of the medical device in animals should be obtained and likely risks posed by the device should be considered.
- Phase I trial is not necessary in medical and medicated devices trails as they are not used in healthy volunteers.
- Comparatively medical devices used within the body may have more risk than those used on or outside the body, for example, orthopedic pins vs. crutches.
- Medical devices not used regularly have less risk potential than those used regularly, for example, contact lens vs. intraocular lenses.
- Safe procedures to introduce a medical device in the patient should also be followed as the procedure itself may cause harm to the patient.
- Like drug trials, informed consent procedures should be followed. The patient information sheet should contain information on follow-up procedures to be adopted if the patient decides to withdraw from the trial.
- Study design of the intra body devices like implants can be very challenging and should have adequate protective safeguards. The study should be long enough to detect if there are any late onset ADRs.
- If in phase III full assessment of safety is not complete, the Phase III could extend to Phase IV.

10.4 DIAGNOSTIC AGENTS USE OF RADIO-ACTIVEMATERIALS AND X- RAYS

X-rays, gamma rays, beta rays, radioactive and radio opaque materials are often used for investigation and treatment of different diseases. In such cases doses of radiation must not exceed the radiation limit set by the regulatory authority Bangladesh Atomic Energy Commission (BAEC).

Special Concerns

- Data should be obtained using method that exposes the participant to least radiation.
- In case of death of a participant exposed to lethal radiation or radiological implant, necessary precaution as per radiological guideline must be taken to protect the relatives and neighbors.

- Research should be performed on patients undergoing the procedures for diagnostic or therapeutic purposes and safety measures should be taken for those as well as for others who may be exposed to radiation
- The protocol should make adequate requirements for detecting pregnancies to avoid risks of exposure to the embryo.
- Non-radioactive diagnostic agents are considered as drugs and the same guidelines that are used for drugs should be followed when using them.

10.5 TRADITIONAL AYURVEDA, UNANI (AU) REMEDIES AND MEDICINAL PLANTS

Ethical Issues in Clinical Trials with Herbal Products

Herbal and other traditional pharmacologic therapies are in widespread use throughout the world. Such widespread use suggests, but does not assure, that traditional medicines have a favorable risk-benefit ratio. Rather, traditional medicines may be regarded as a rich source of potentially attractive therapies. The actual benefits and risks remain to be evaluated by clinical trials supported and conducted according to the principles of modern clinical science.

All of the fundamental ethical principles of human participation in research apply equally to herbal remedies and research involving these compounds. Consent must be obtained, subject selection must be equitable, risks and benefits must be weighed and must be favorable to the potential participant, and experimental design must be sound.

Concerns that particularly apply to clinical trials with herbal products include:

- Product adulteration
- Interactions between herbal remedies and other entities
- Reproductive and organ toxicity data
- Prior dose finding

The uncertainty in these areas must be clearly disclosed to all concerned, particularly during the informed consent process.

In many regions of the world, strong belief that herbal medicines will be beneficial and safe may introduce bias, which can be minimized by careful attention to study design including appropriate control groups. Where possible, the community from whom the medicine originates should be consulted during the course of the research, and the results and benefits of the research should be shared with this community.

As in other types of research, a well trained, ethical investigator is the best assurance of patient safety in research. Therefore, skilled clinicians should be chosen as investigators to assure prompt recognition and appropriate treatment of any observed adverse event or worsening of a pre-existing condition.
Ethics committees must apply the same vigilant attitude towards herbal studies as they do towards conventional treatment protocols.

Nowadays, usage of traditional remedies has increased due to comparatively more costs of modern medicine healthcare and self medication and greater orientation of traditional remedies towards preventive health and also the desire of the aging population to stay young and healthy. However, media publicity together with the improved research technology tools and growth deciders like new Biotechnology developments for producing the evidence has thrown traditional knowledge to the status of a hidden treasure worth exploring. To establish the safety and efficacy of traditional remedies like other synthetic drugs with the same procedure is a difficult, as most of them are complex combinations leading to difficulty in assessment of their activity and risk/benefit ratio. This involves four sets of issues - chemical-manufacturing-control (CMC) issues, non-clinical issues, clinical issues, and ethical issues.

Besides Yoga and Naturopathy and Homeopathy, the recognized traditional systems in Bangladesh are *Ayurveda,* and Unani. The two unique features of herbal products used in the traditional Bangladeshi medical systems are that they are mostly used in compound forms and are multi-component mixtures including minerals in some of the formulations, and that important information is available regarding their former human use, granting safety and efficacy of these formulations. Therefore, a different approach is required which concerns two groups, namely, clinical investigators evaluating the benefits and risks of herbal products and the regulatory authorities.

For the herbal remedies and medicinal plants that are to be clinically evaluated for use in the Allopathic System and which may later be used in allopathic hospitals, the procedures laid down by the office of the Directorate General of Drug Administration for allopathic drugs should be followed. This does not pertain to guidelines issued for clinical evaluation of Ayurveda*, Unani* (AU) drugs or formulations by experts in those systems of medicine, which may be used later in their own hospitals and clinics. All the general principles of clinical trials described earlier pertain also to herbal remedies. However, when clinical trials of herbal drugs used in recognized Bangladeshi Systems of Medicine and Homeopathy are to be undertaken in Allopathic Hospitals, physicians from the concerned system as co-investigators/ collaborators/ members of the expert group is desirable

for designing and evaluating the study. as co-investigators/ collaborators/ members of the expert group is desirable for designing and evaluating the study.

10.5.1 Special Concerns

The AU drugs include herbal and herbo-mineral formulations. The herbal products can belong to one of the three categories:

1. From the ancient Ayurveda*, Unani* literature, lot of information about the use of a plant or its extract, metals, minerals and animal products have known or the plant may actually be regularly used by physicians of the traditional systems of medicine for a number of years and the substance is to be clinically evaluated for same indication for which it is being used or as has been described in the texts.

2. When the therapeutic effect not originally described in the texts of traditional systems, in case of an extract of a plant or a compound isolated from the plant and any compound formulation having plants, metals, minerals and animal products as ingredients has to be clinically evaluated or, the method of preparation is different, or it was not originally used for a certain indication by practitioners in that field, it has to be treated as a new substance or new chemical entity (NCE) and the same type of acute, sub acute and chronic toxicity data will have to be generated as required by the regulatory authority for synthetic products before it is cleared for clinical evaluation.

3. An extract or a compound isolated from a plant and any compound formulation having plants, metals, minerals and animal products as ingredients which has never been in use before and has not ever been mentioned in ancient literature, should be treated as a new drug, and therefore, should undergo all regulatory requirements before being evaluated clinically.

During incorporation with GMP rules for standardization, it is important that plants and AU remedies currently in use or mentioned in literature of recognized Traditional System of Medicine is prepared strictly in the same way as described in the literature. .It is a challenging task for modern scientists and drug controller to justify the beneficial effects of stored formulations, as traditional remedies have short life, increasing their stability and shelf life, and batch to batch variation.

It is important that plants and AU remedies currently in use or mentioned in literature of recognized Traditional System of

Medicine is prepared strictly in the same way as described in the literature while incorporating GMP norms for standardization. Since traditional remedies have short life, increasing their stability and shelf life, and controlling their batch to batch variation could be challenging tasks for modern scientists and drug controllers to justify the beneficial effects of stored formulations.

10.5.2 Classification of herbal medicines (WHO 2003):

Category 1: Indigenous herbal medicines:
This category of herbal medicines is historically used in a local community or region and is very well known through long usage by the local population in terms of its composition, treatment and dosage. Detailed information on this category of Traditional Medicine (TM), which also includes folk medicines, may or may not be available. It can be used freely by the local community or in the local region.

However, if the medicines in this category enter the market or go beyond the local community or region in the country, they have to meet the requirements of safety and efficacy laid down in the national regulations for herbal medicines.

Category 2: Herbal medicines in systems:
Medicines in this category have been used for a long time and are documented with their special theories and concepts, and accepted by the countries. For example, Ayurveda and Unani would fall into this category of TM.

Category 3: Modified herbal medicines:
These are herbal medicines as described above in categories 1 and 2, except that they have been modified in some way–either shape, or form including dose, dosage form, mode of administration, herbal medicinal ingredients, methods of preparation and medical indications. They have to meet the national regulatory requirements of safety and efficacy of herbal medicines.

Category 4: Imported products with a herbal medicine base:
This category covers all imported herbal medicines including raw materials and products. Imported herbal medicines must be registered and marketed in the countries of origin. The safety and efficacy data have to be submitted to the national authority of the importing country and need to meet the requirements of safety and efficacy of regulation of herbal medicines in the recipient country.

Category I –Phase 1 studies may not be necessary for formulations belonging to category 1. In Phase II dose ranging should be explored to find the effective dose as also maximum tolerated dose. To validate the statement with placebo or standard drug depending on the ethical requirements, RCTs would be the preferable methodology. The clinical trials would mostly fall in the non-inferiority group if literature is not available regarding the proven efficacy of the formulation. Superiority trial could be designed if the control arm is placebo or modern medicine, which is only less effective. If the outcome is encouraging, sometimes a pilot observational study to explore feasibility of conducting larger trials for validation can be designed.

The substance to be tested which is already in use in Bangladesh Systems of Medicine or has been described in their texts, the need for testing its toxicity in animals has been considerably reduced. Neither would any toxicity study be needed for Phase II trial. This is the unique reverse pharmacology approach for evaluating traditional formulations for traditional indication. If there are reports suggesting toxicity or when the herbal preparation is to be used for more than 3 months it would be necessary to undertake 4 - 6 weeks toxicity study in 2 species of animals in the circumstances described above or when a larger multicentric phase III trial is subsequently planned based on results of phase II study. Clinical trials with ASU preparations should be carried out only after these have been standardized and markers identified to ensure that the substances being evaluated are always the same. However, for phase I and phase II trials, for the formulations to be tried, Good manufacturing Practices (GMP) standards would not be required. But for Phase III GMP standards would be required for the formulations to be used in the trial as the number of participants would be larger and this will be followed by marketing approvals.

Category II and III: Like the other synthetic drugs, all the steps involved for regulatory approvals should be followed. However, for formulations falling under category two only limited toxicities as mentioned for category I would apply.

All formulations involving herbal component should satisfy following criteria as prescribed by WHO document "Operational Guidance: Information needed to support clinical trials of herbal products (2005)":

a) For Phase I / II studies –

Herbal Substance:

- plant description: genus, species (cultivar where appropriate); region(s) and country (ies) of origin; time of harvest; parts to be harvested
- plant processing: drying, mechanical disruption, solvent extraction (aqueous or organic solvents, others)
- analytical procedures
- specification
- storage conditions/shelf life.

Herbal Product:

- amount of active ingredient
- list of excipients
- type of product (tablet, capsule, etc.) and its method of manufacture
- analysis of recognized active ingredient(s) via chemical or biological parameters
- analysis of a considerable chemical constituent (analytical marker compound)
- analysis via chemical fingerprint (analytical markers)
- analysis for lack of contamination by pesticides, herbicides, heavy metals, synthetic drug adulterants, microbials, toxins, etc.
- dissolution studies
- storage conditions and stability during the length of the trial
- specification against which a certificate of analysis can be assessed before the clinical trial material is released.

b) For Phase III studies:

Performing generally the same procedures as for Phase I/II trials, but more extensively and with more strict control of error.

Herbal Substance:

- as above for Phase I/II trials.

In addition:

- statement that the plant is cultivated according to Good Agricultural Practices or harvested according to Good Wild crafting Practices
- reference batch.

Herbal Product:

- as above for Phase I/II trials

In addition:

- environmental impact statement.

This relevant information should be included in the protocol for evaluation of these products, because of the extensive use of traditional AU formulations both in animals and humans, which helps in analysis of the chemistry, manufacturing, and control of the product. The manufacture of the product should ideally be as per traditionally processed formulation to authorize the statement for efficacy as seen in traditional practice.

It is claimed that the extracts of herbal products and AU formulations provide a therapeutic advantage, as they are mixture of at least partially uncharacterized constituents and these unknown constituents may be additive or synergistic in action or may produce a balance to counteract adverse effects of any one constituent. This may thus provide more efficacy than would be provided by the known constituent alone. Thus, purification of the medicines down to known or otherwise single chemical constituents is not required as it may lead to loss of the advantage provided by the mixture.

Analysis of the active pharmaceutical ingredient(s) may be best approached by analysis of one or more active biomarker(s), analysis of a chemical constituent that constitutes a sizable percentage of the total ingredients, and a chemical fingerprint of the total ingredients for standardization and quality control. The latter two analyses would act as replacements for analysis of the unknown constituents that contribute to efficacy. In order to have the best standards by minimizing variation of content from batch to batch several analytical procedures may be needed to adequately quantify the constituents of herbal products or AU formulations.

10.5.3 Quality Control

For the maintenance of the quality control of the herbaland herbo-mineral formulation, Contaminating herbicides and pesticides levels as well as toxic contaminations must be particularly addressed. The presence of adulterants should also be ruled out.

For traditional ASU formulations extraction may be done as per classical method or by a special SOP prepared for it. Information on each individual plant species used as ingredient must be collected and authenticated and maintained as voucher specimens. The plant ingredient should be subjected to pharmacognosy and other relevant analysis in phytochemistry.

Formulations intended for administration in clinical trials should be prepared in bulk after standardization, and quality control. The stability and shelf life studies should also be carried out simultaneously for marketing purposes.

Regarding informed consent, inducements for participation, information to be provided to the participant, withdrawal from study and research involving children or persons with diminished autonomy, the recommendation should be made earlier. All apply to trials on plant drugs also. These trials have also got to be approved by the appropriate scientific and ethical committees of the concerned Institutes. However, it is preferable that such clinical trials be carried out with a competent *Ayurveda, Unani* physician as a co-investigator in such a clinical trial.

When a Folklore medicine / ethno medicine is ready for commercialization after it has been scientifically found to be effective, then the legitimate rights/share of the Tribe or Community from which the knowledge was gathered should be taken care of appropriately while applying for the Intellectual Property Rights and /Patents for the product.

11. PRINCIPLES OF EPIDEMIOLOGICAL STUDIES

11.1 INTRODUCTION

Epidemiology concern with the pattern of disease that occur in human populations & the factors influence these pattern. In the earlier years, epidemiology of infectious diseases was of great importance in Bangladesh, considering that these were very prevalent. Over the years, infections as a cause of diseases have diminished in importance as a result of various measures taken to control these. Improvement in economy and changes in life styles have contributed to the increase in numbers of non infectious diseases such as diabetes mellitus, ischaemic heart disease. Many studies in the western world have demonstrated that epidemiological studies can identify risk factors contributing to many diseases. This can lead to adoption of effective public health measures to prevent and reduce the incidence of these diseases.

Generally Epidemiological studies are in two categories – observational and non-observational. These studies are mainly based on cross-sectional, case-control or cohort approaches. Surveillance, programme evaluation and research are involved in Epidemiological studies. Ethics in epidemiological studies is multidimensional covering clinical medicine, public health and the social milieu. The code of ethics in epidemiological studies needs better understood in clinical research, that ensure the optimum importance between a clinical researcher and a patient. This aspect needs to be addressed in preparing a guideline for ethical review of scientific studies in Bangladesh.

Research in epidemiological aspects of health and disease may involve large numbers of study participants and may need to be conducted over a long period of time. In this, these studies differ from clinical trials. Mistakes or omissions, if not carefully checked for at the beginning, may create problem when these are detected later. To repeat the whole study will be wasteful and may not be possible. It is, therefore, essential that all important aspects such as technical, practical as well as ethical should be scrutinized carefully at the very beginning of the study.

11.2 DEFINITIONS

Observational Epidemiology: Predefined parameters in a defined population group over a specified period and frequency are recorded for finding the risks of exposure that affecting the health known as Observational studies. These are the following types:

a. Cross Sectional Studies (Surveys): Cross-sectional studies focus on comparing as well as describing a problem or situation at a point of time. It is primarily population based study. In this study sample may be an entire population or randomly selected from the representative

population based on census data & using questionnaires for measuring the prevalence of diseases & it's effect as well as to test hypotheses about the possible cause of disease or suspected risk factors. Informed consent is required from the participants who are directly involved only once in the defined period.

b. Case Control Studies: This usually compares the past history of exposure to risks among patients who have a specified condition/disease (cases) with the past history of exposure to this among persons who resemble the cases in such respects as age, sex socioeconomic status, geographic location, but who do not have the disease (controls). Case control studies can be done by following up available records, usually records in a hospital, but in the context of a country like ours it may require direct contact between research workers and study participants and informed consent to participate in the study is necessary. However, if it entails only a review of medical records, informed consent may not be required and indeed may very often not be feasible. But for such waiver of consent approval from NREC would be necessary.

c. Cohort Studies: These are longitudinal or prospective studies of a group of individuals with differing exposure levels to suspected risk factors. They are observed over a long period usually several years. The rate of occurrence of the condition of interest is measured and compared in relation to identified risk factors. It requires a study of large number of participants for a long time and involves asking questions, checking of records, routine medical examination and sometimes laboratory investigations. Individuals are being followed up as the cohort and it is essential to identify precisely every individual to be studied.

Experimental Epidemiology: In this study the investigators find out the effects of the intervention on health by altering one or more parameters under controlled conditions. Usually Experimental epidemiology done to test a preventive or therapeutic regimen or the efficacy of a diagnostic procedure by randomized controlled trials. Clinical evaluation of drugs /devices / products / vaccines etc is done under these epidemiological studies. Use of placebo as one of the arm of this trial that should be explained and informed consent taken from the participant is mandatory of this studies.

11.3 GENERAL PRINCIPLES

In principles of ethics it is always considered to respect the persons, duty to maximize possible benefits and minimize possible harm. It is also essential that all individuals in an epidemiological research are treated alike keeping in mind the rules of distributive justice. The welfare of the individual has to be balanced against the welfare of the community and society at large. The CIOMS / WHO Guidelines for Epidemiological Research assume that the individuals or populations being studied are

capable of giving informed consent understanding the implications of the study. With large segments of our population, given their level of education, the full understanding in the sense of industrialized countries may not be achievable. How the principle of "do no harm" is ensured under such circumstances without being paternalistic is a major issue that has to be taken into consideration in ethical guidelines. In cohort or survey techniques for incidence and prevalence of various diseases, a major issue that has to be considered is how much of intervention is justified and whether one is justified in withholding interventions. For example, if you are looking at longitudinal morbidity in a population group, should you give them health education that is well established with regard to preventive aspects, or should you leave them alone so that the natural evolution of the disease can be studied? Health education or other interventions including non-health interventions can be quite expensive. An alternate strategy that may be followed is to make curative therapy available to the population at their own request. This usually involves running a clinic, which is readily accessible to the population without any other intervention. However, it is generally considered unethical to withhold intervention or services.

11.4 SPECIFIC PRINCIPLES

I. **Informed Consent:** Individual included as participants in epidemiological studies, should be explained the purpose & general objectives of the study to the participant as the way that they can easily understand with ensuring the privacy. The role of investigator is crucial and he / she should remain vigilant and conscious of his / her obligations towards the participants / patients, all through the course of the studies.

II. In most epidemiological research it would be necessary to have the consent of the community to include the community members in the research. It could be the Union Parishad Chairman / School Head / Municipality Chief / Ward Commissioner etc, who are considered to be gate keepers of the society / community. After getting consent from the community, consent of the individual participants should also have to be there. One cannot coerce a participant if he / she denied to be a participant even after his community gives consent.

III. Inducement is not only unethical but also harmful as in vulnerable or dependent subjects inducement may strongly influence their consent. Researcher could pay for loss of wages / health related expenditure as a compensation.

IV. In epidemiological study researcher must explain all risk including risk of loss of privacy to the participant.

V. It is absolutely essential to maintaining **confidentiality** of the epidemiological data. In issues like national security, is essential to

carefully evaluation of some population based data from the starting of the study.

VI. During investigation it is important to prevent any social / cultural disturbance and should be made to **minimize harm** to the individuals and society at large.

VII. Research proposal should prepare in such a way to ensure that the benefits of the study are maximized for the individuals and the communities taking part. In some instances it may also be necessary to inform the concerned family members about the results, for instance, as in AIDS, STD etc.

VIII. In studies where there may be a conflict of interest like surveillance, outbreaks, epidemics, disasters and calamities, and epidemiological studies, the interest of the individuals involved in the study should be protected and may need relief and rehabilitation.

IX. Honesty and impartiality should be maintained at all stages of the study. Withholding of selective data and similar practices are unethical.

X. Benefits: The findings of prospective longitudinal studies should be released in timely manner to fellow researchers and policy makers and health care delivery authorities to take measures accordingly in prevention & control of program.

XI. Ethical Review Procedures: Ethical Committees should be independent and included at least one or two individuals with an understanding of the principles of epidemiology.

XII. Program evaluation and research: Ethical review would be required if program evaluation falls within the definition of research or serves as a component of a research project. The determination of whether an evolution study is research and therefore requires NREC review should be made on a case by case basis and should be guided by the definition of research.

XIII. Use of information for the purpose of research if it was originally collected for another purpose: Information originally collected for a purpose other than the current research purpose is considered secondary use of information. Secondary use of information has the potential to avoid duplication of primary data collection and the associated burdens on participation, An NREC must review the ethical acceptability of the research involving secondary use of information; including issues of privacy. The requirement for NREC review applies to information that may have been collected for a specific research purpose and is later proposed for a new research purpose.

It is not always possible to know what will happen to the participants as unexpected results or undesirable events can sometimes occur. Very often the benefits and risks of the research pertain not only to the individual participants, but also the community from which they are drawn. The benefits if any could be shared in a reasonable or workable manner.

11.5 Community Participation

A community can be defined as a group of people sharing the same location, beliefs, culture, ideals, goals, age, gender, profession, lifestyle, common interests, geographical locations or settings or disease. When research participants are drawn from a specific community, members of that community can be involved to discuss any concerns it may have regarding the research. In different ways such a dialogue can be facilitated. If an ethics committee does not have a member from the community, it may ask a local community representative to be the voice for all participants. On the other hand, community representatives can formally join together to form a group termed as Community Advisory Board, Community Working Group, or Community Advisory Group, which takes part in the research at all stages of the study. In international studies, particularly on issues involving communities, representation from this body ensures that the community's health needs and expectations are addressed, informed consent is appropriate, and access to research benefits is provided through research that is designed and implemented in the best interests of science and community.

12. TISSUE TRANSPLANTATION AND RELATED SUBJECTS

The medical advancements in science and technology related to transplantation have raised new ethical issues that need to be addressed. There is also a need for careful evaluation of these new methods and their outcomes through research. The inevitable necessity of standardized ethical guidelines for research on human subjects is universally recognized.

Tissue and organ transplant like other medical issues will make a rapid progress in this country and review of the guideline of ethical issues will be needed. The objective of the BMRC guideline is to promote ethical research.

12.1 Ethical Guidelines of Transplantation Research

Systematic control and strengthening research ethics committees all over the country would pave the way for achieving the goals in the coming years. This guideline mentions essential ethical principles, which should be considered in the research on tissue and organ transplantation.

12.1.1 Organ and tissue Transplantation

a. All transplantation research on tissues or organs should be done according to the Human tissue transplantation act Law-5, April-13, 1999, of Bangladesh.

b. Purpose of research in any Transplant should be scientific advancement and in accordance with goals of national health system and should not be for financial or commercial purposes.

c. For using the tissues or organs of foreigners in transplantation research, the approval of NREC required.

d. In view of the risk involved, the voluntary consent of the donor is absolutely essential. The donor should be informed of all possible risks in a manner easily understood by the participant before the consent is taken.

e. For using tissues and organs stored in the banks, the donor should mention his / her consent for this kind of use.

f. The system of obtaining consent for using the organs of deceased persons for research in Bangladesh already formulated by Human tissue transplantation act 1999. The consent of person before death or a donor card or the consent of his/her next to kin (decision maker) is necessary.

g. During the time of removal of tissues or organs from deceased person until the time of burying the deceased, observance of all customary and spiritual respects to cadaver and the removed tissues or organs is essential.

h. Research on living donors should be restricted to renewable tissues like bone marrow, liver. In the cases of absolute necessity under observance and approval of a ethical committee of the Institute and NREC, one can use pair organs whose removal will not greatly alter the physiologic functions, for research purposes e.g. Kidney. But removal of eye shall not be permitted in live donor as lost of binocular vision & disfigurement.

i. The donor should be lifetime insured (Life and Medical) and all of the related harms should be compensated by PI.

j. Surplus or waste tissues remained from diagnostic and therapeutic procedures or surgeries, by considering confidentiality and after approval of ethics committee, can be used for transplantation research, unless prior notification of owner's disagreement.

k. Financial incentives or special advantages should not be used for encourage persons for organ donation in the transplantation research with living donor. But only incidental expenses or work loss may be compensated.

l. The children, mentally retarded or mentally disabled persons, psychiatric patients and other special groups, who possibly have not competence for informed decision making, should not be tissue or organ donors in transplantation research.

m. The children mentally retarded or mentally disabled persons, psychiatric patients, should only be recipient of tissue or organ in transplantation research with direct therapeutic benefit for them.

n. Confidentiality of the donation shall be maintained on both sides. Recipient will not be informed the identity of donor and donor family also will not informed who receive the donor organ.

o. Under no circumstances should there be a conflict between scientific content of a study and the best interests of the patient. The experiment is be abandoned and the patient should receive the best treatment possible.

p. The transplant research team should have high technical expertise.

q. Adequate data management, tissue storage facilities, and surveillance procedures should be available in a centre before it is authorized to conduct research into transplantation.

r. At any time, a patient can refuse to take part as a participant for a research project, it should in no way interfere with his or her right to receive treatment of the best quality, which the team is capable of providing.

12.2 Guidelines on Stem Cell for Transplantation Research

a. Research related to human germ line genetic engineering or reproductive cloning is prohibited till the formulation of any Stem Cell Research Act by Government of Bangladesh.

b. Any in vitro culture of intact human embryo or any organized cellular structures that have the potential of developing into human, human organs and tissues, regardless of the method of its derivation beyond 6 days restricted to approval.

c. Transfer of human Blastocysts generated by any means including somatic cell nuclear transfer (SCNT) or parthenogenetic or androgenetic techniques into a human or nonhuman uterus restricted to approval.

d. Any research involving implantation of human embryo into uterus after in vitro manipulation, at any stage of development in humans or primates restricted to approval.

e. Creation of a human zygote by In vitro fertilization (IVF) or any other method with the specific aim of deriving a human embryonic stem cells cell line for therapeutic or research purpose may be performed with a approval of the BMRC and GOB.

f. The import of Biological materials for research and development should be regulated by GOB. Clinical trials using cells after major manipulation or those sponsored by multinationals involving stem cell products imported from abroad shall require prior approval of the BMRC and Health Ministry.

g. Animals in which any of human stem cells have been introduced at any stage of development should not be allowed to breed.

h. Studies on established fetal/adult stem cells, may be carried out with approval of BMRC and provided the cell line is registered with the GOB.

i. Once the cell line is established, it shall be registered with the BMRC and GOB.

j. Establishment of Umbilical Cord stem cell bank may be done with prior approval of GOB.

k. All clinical trials on stem cells shall be registered with GOB and BMRC.

l. No research on stem cell will be ethical if it involve direct or in direct unethical financial interest.

m. Stem cell research center should be established in the in the academic centers or universities with approval of GOB and BMRC.

12.3. Human fetal tissue Transplantation

Human fetal tissue could be used in transplantation research for a wide range of purposes. The use of fetal tissue will minimize the chance of rejection.

a. The transplantation research on tissues or organs of embryo or fetus should be approved by the "BMRC" in keeping with the national guidelines.

b. Such researches are only permitted in the public universities or research centre's those who have authorized standard research laboratory on this regards and under surveillance of the Ministry of Health and BMRC.

c. For using the organs and tissues of fetus in the transplantation research, scientific approval of the research and follow up, control and subsequent assessments by the research institute, BMRC and related authorities are necessary.

d. For prevention of misconduct in using fetal tissues, specialists who approve abortion should not be the member of the research group or the organization who subsequently uses the embryonic or fetal tissues. Any attempt of creation of human beings for transplantation purposes has been banned.

e. Financial relationship between the donor and the recipient in the research on transplantation of organs and tissues of embryo or fetus is forbidden.

f. Abortion of live fetus is restricted for research purpose.

g. Tissue for transplantation or research may be obtained from dead embryos or foetuses, their death resulting from legally induced or spontaneous abortion. Death of an intact embryo or foetus is defined as absence of respiration and heart beat.

h. Voluntary, informed, written consent will be obtained from the mother in two stages - first for the abortion, next for the donation of tissue from the foetus.

i. Termination of pregnancy should not be sought with a view to donate foetal tissue in return for possible financial or therapeutic benefits.

j. The mother's decision to donate foetal tissue is sufficient for the use of the tissue unless the father objects in writing. In cases of incest or rape, the father's objection carries no significance.

k. The mother will not dictate who shall receive the foetal tissue taken for transplantation.

l. Anonymity of donor and recipient will be maintained so that neither party is aware of the identity of the other.

m. Intact embryos or foetuses will not be kept alive artificially for the purpose of removing usable material.

n. Tissues from aborted foetus can be cultured and banked for use in research on transplantation. If such stored tissue is to be subsequently used for any purpose other than the original objective, a fresh sanction of informed consent will be obtained from the participant and approved by NERC.

12.4. Guideline on Xeno Transplantation

Paucity of organs from humans for transplantation into other humans has led to search for other sources such as animals.

a. The animal experiments for treating human should only be undertaken when there is accepted evidence of successful results.

b. Use of animal tissue or such trials in human patients will commence only on those patients when no other form of treatment is available and in the absence of the transplant, the patient is likely to suffer relentless deterioration in his/her health with fatal termination but permission from GOB would be required.

c. The animal trials should be carried out only at Public academic institutions having appropriate facilities needed for performing such researches and permission of the ethical committee of the institute and BMRC would be required.

13. HUMAN GENETIC AND GENOMIC RESEARCH

13.1 Areas of Concern

Highly sophisticated molecular biological tools, gene sequencing techniques, high throughput microarray generated information have led to the deciphering of the human genome and understanding diseases and traits linked to mutations which result in a host of dysfunctions related to not only autosomal and recessive disorders but **also** can determine genes that are abnormal or atypical in a variety of disorders. This has set the scene for rapid availability of **understanding the** knowledge on genetics related to public health, **regenerative organ transplantation therapy, infertility, malignancy, gene therapy**, general well being and can pinpoint defects and genetic traits in the individual and predict consequences on future progenies. Thus, human genetics and genomics are powerful tools in the biomedical field **and Funding from public and private resources has become available to rapidly facilitate research in this area. It is important to understand that there should be no limitation in the use of latest gene based technology in understanding genetic factors related to health which are beneficial** but also have the capacity for dangerous ethical consequences relating to security and potential risk to individuals and families.

Therefore, control and proper guidelines for human genetics and genomic research are of great importance to communities and populations globally. It is of even more importance for people living in regions where the capacity to understand the consequences of genetic research is limited due to lack of education. Thus all countries, especially populations living in the developing **and under developing** regions of the world need to follow strict guidelines on research on human genetics so as to control and carefully use and disseminate information generated such that it does not lead to misuse or commercial acquisition and thereby damage lives of individuals and populations.Based on the negative repercussions that such research generates a strict ethical guideline is needed universally and in the national context.

The requirement of careful monitoring and scrutiny of progress and advances in the field of genetics/genomics is needed for development and response to emerging ethical issues promptly and with extreme caution. Due to the very quick pace that developments are happening in the field all ethical guidelines related to this field needs to be constantly updated and guidelines modified effectively**. Therefore, emphases are given for developing ethical guidelines in areas where** genetic/genomic information can be most sensitive and include:

a. What controlling, monitoring and regulatory bodies/organizations should be there regarding various aspects of genetic research at the

institutional and national levels that should be responsible for formulating regulations, overseeing their implementations and recommending measures to be taken in case of failure to follow the regulations.

b. How mishandling of genetic information may pose physical and psychological risks to individuals and families and expose them to discrimination, stigmatization and other hazards in relation to their social and professional lives as well as to education-, employment- and insurance-related matters.

c. From whom and how consent for particular types of genetic research should be taken, and what information should be provided to the expected participants of the research on the use and dissemination of the research results, and how anonymity can be ensured about the genetic information gathered through the research.

d. How the questions of privacy and confidentiality should be addressed in relation to genetic research so that familial and societal harmony are not disturbed, and misunderstanding, separation and other psychological damages to individuals, families or society can be prevented.

e. How genetic counseling should be provided before or after, as applicable, to individuals undergoing genetic screening, testing or manipulation, and what treatment measures those individuals are entitled to in course of the research.

f. What sort of private, public or commercial utilization of genetic information and related patenting should be considered unethical or illegal (if a relevant act exists) and what procedural measures can prevent such activities.

g. How the intellectual property rights can be exercised regarding genetic research on Bangladeshi people, especially on the vulnerable populations.

h. What specific points of restriction and allowance should be considered in relation to genetic diagnostic procedures with human embryonic material and to corresponding research.

i. In genetic research, what sort and how much of information should be provided to the expecting parents regarding the prenatal diagnosis of sex or disorders of the embryo/fetus in preparing them for the possible consequences, and who should take the decision about the continuation of pregnancy.

j. What should be the sources/locations/procedures of collection,

storage, handover, use or disposal of genetic, embryos and genetic materials for research purposes.

k. What precautionary regulations should be in place for different procedures of gene manipulation, like in gene therapy, in order to restrict them to precautionary diagnostic and remedial measures for disorders rather than using them as trait-enhancing (eugenic) measures.

l. What guidelines should determine how a balanced approach may be taken in utilizing and expanding the huge potential of genetic research on one hand and not crossing the ethically sensitive limit of achievement on the other while using stem cell manipulation and other advanced technologies.

13.2 General Ethical Guideline

a. Existing genetics services in a nation should be available equally to everyone regardless of ability to pay and should be provided first to those whose need is greatest.

b. Genetic counseling should be non-directive.

c. All genetics services, including screening, counseling, and testing, should be voluntary, with the exception of screening newborns for conditions for which early and available treatment would benefit the newborn.

d. All clinically relevant information that may affect the health of an individual or fetus should be disclosed.

e. Confidentiality of genetic information should be maintained. When there is a high risk of serious harm to family members at genetic risk, the information should be used to avert this harm. If the individual refuses to tell her/his family, the professional may consider overriding confidentiality.

f. Individual privacy should be protected from institutional third parties, such as employers, insurers, schools, commercial entities, and government agencies.

g. Prenatal diagnosis should be performed only for reasons relevant to the health of the fetus and only to detect genetic conditions or fetal malformations.

h. Choices relevant to genetics services, including choices about counseling, screening, testing, contraception, assisted procreation where culturally accepted and abortion following prenatal diagnosis, where legal, should be available on a voluntary basis and should be respected.

i. Optimum support and education should be provided for children and families with genetic conditions.

j. Adopted children and others with biological relationships outside the family should be able to receive information about their biological relatives, under strict anonymity rules.

k. Research protocols should follow established procedures for review and informed consent.

l. Protocols for experimental human gene therapy should receive national review, with attention to the potential benefits or risks arising from various approaches to therapy.

m. All institutions and investigators, both public and private, carrying out research on human stem cells should be registered with the BMRC.

n. All new human pluripotent stem cell lines, irrespective of the source and methodology used, shall be created, and registered with BMRC detailing on its source, development, passage number, identity and movement.

o. All records pertaining to adult stem cell research must be maintained for at least 5 years and those for hES/iPS cell research for 10 years.

13.3 Basic Responsibilities of All Researchers

a. All researchers and equivalent persons shall conduct human genome/gene analysis research for such purposes as elucidating life phenomena, preventing diseases, improving diagnosis and treatment protocols, and promoting health.

b. All researchers and equivalent persons shall ensure the societal usefulness of their human genome/gene analysis research and shall pay attention to guaranteeing the human rights of individuals by prioritizing them over scientific or societal benefits.

c. All researchers and equivalent persons shall make it a basic practice to conduct human genome/gene analysis research only after obtaining the informed consent of donors or proxy consenters.

d. All researchers and equivalent persons shall not, in the absence of any justifiable reason, divulge personal information obtained in the course of their duties. This shall continue to apply after they resign their position.

e. All researchers and equivalent persons shall endeavor to protect personal information and shall also respond in good faith to

questions, complaints, etc. concerning the handling of personal information.

f. All researchers and equivalent persons shall, when any serious concerns arise in terms of guaranteeing the human rights of donors, etc., such as an unexpected divulgence of personal information, immediately report this to the director / head of their research institution and.

g. All researchers and equivalent persons shall conduct human genome/gene analysis research properly in compliance with these Guidelines and with respect for human dignity and human rights by, for instance, conducting research in accordance with a research protocol as authorized by the ethics review committee and approved by the director/head of their research institution.

h. All researchers and equivalent persons shall endeavor to guarantee the transparency of their research through, for instance, ensuring due process when conducting research, on-site investigations by outside experts, appropriate responses to inquiries from donors, etc. regarding the progress of research, and the release of research results into the public domain.

i. All researchers and equivalent persons shall, in consideration of the fact that the donation of human specimens is based on goodwill, make efforts to minimize the amount of human specimens donated from people by, for instance, properly preserving and utilizing specimens already provided.

j. No researchers and equivalent persons shall, when conducting human genome/gene analysis research, acquire personal information or human specimen by deception or other wrongful means.

13.4 Responsibilities of Director/Head of Research Institutions

a. Director/Head of research institutions, such as human specimen collecting institutions, that handle personal information shall designate a personal information custodian for the purpose of protecting personal information in human genome/gene analysis research.

Director/Head may, as required, also designate, upon specifying a chain of command, a co-custodian or an assistant who conducts actual operations under the supervision of a personal information custodian.

b. Director/Head of research institutions shall establish an ethics review committee as an advisory board to review the propriety of conducting human genome/gene analysis research etc. When, however, it is difficult to set up an ethics review committee for reasons such as the small size of a human specimen collecting institution, an ethics review committee established by a collaborative research institution, a public service corporation or an academic society may be substituted for an internal one.

c. Director/Head of research institutions shall keep track of the progress of human genome/gene analysis research by, for instance, receiving a research progress report on a regular basis, at least annually, and implementing an on-site investigation by qualified external persons on a regular basis, at least annually, and shall order the research altered or discontinued based on the ethics review committee submitting the opinion of alteration or discontinuation, or if necessary for any reason.

d. The regulatory bodies shall appreciate that stem cell research is a nascent field. While there have been tremendous advances in understanding the biology of stem cells, these are several elements of unpredictability in the translation of research in this area. It is of utmost importance that review of research in this field ensures highest degree of scientific rigor and resolution of ethical concerns. The members of the regulatory committee shall remain in constant touch with advances in this field.

e. Director/Head of research institutions shall deliver to a personal information custodian a copy of an approved research protocol, a copy of regular reports regarding research progress and a copy of on-site investigation results conducted by qualified external persons.

f. Each institution should maintain a registry of its investigators who are conducting stem cell research and ensure that all registered users are kept up to date with changes in guidelines and regulations regarding use of these cells. It shall also be the responsibility of the institution to ensure that most current standards are applied.

g. Director/Head of human specimen collecting institutions shall, in principle, anonymize a human specimen when providing it to an external institution, (When the human specimen collecting institution also conducts human genome/gene analysis research, its research division shall be considered to be an external institution).

h. Director/Head of human specimen collecting institutions shall, as required, ensure that donors and their families or blood relatives

will be able to receive genetic counseling by, for instance, establishing a pertinent genetic counseling system or explaining about genetic counseling and making referral to pertinent genetic counseling services.

i. The institutions carrying out stem cell research shall also establish suitable mechanisms for creating awareness and communicating scientific evidences to the public.

13.5 Duties of Principal Investigators

i. Principal investigators shall, prior to conducting human genome/gene analysis research, prepare a research protocol and seek approval from the director of his/her research institution before submission of research proposal to NREC for Ethical approval. Such a procedure must also be followed prior to altering a research protocol.

ii. Principal investigators shall, in preparing a research protocol, thoroughly take into account such factors as the necessity of the research and the research method intended to prevent disadvantage to donors and equivalent persons, in consideration of various impacts that donors and equivalent persons would be expected to experience as a result of the proposed human genome/gene analysis research.

iii. The investigators and the institutions where the stem cell research is being conducted bear the ultimate responsibility of ensuring that research activities are in accordance with laid down standards and integrity. In particular, scientists whose research involves hES cells should work closely with monitoring/regulatory bodies, demonstrate respect for autonomy and privacy of those who donate gametes, blastocysts, and be sensitive to public concerns about research that involves human embryos. Sponsors shall also take note of their responsibilities and liabilities under various statutes and regulations governing research and development in the area in-force or to be introduced in the country in near future.

iv. Principal investigators shall oversee research conductors so that they will properly conduct human genome/gene analysis research by, for instance, having all research conductors observe matters described in an approved research protocol.

v. The physician/scientist engaged in stem cell research and therapy shall ensure that no hype or unrealistic expectations is created in the minds of subjects or public at large regarding stem cell therapy. They must inform the parent and the family. The bare facts both what is known and what is not known about the status of stem cell research for the given indication and the alternatives available for

the same. Their responsibility is to generate robust scientific evidence through controlled trials which may be applied for the benefit of the patients.

vi. The basic scientists engaged in stem cell research from human sources shall be vigilant to safeguard human rights and human dignity of those from where samples have been obtained. The biological material should be treated with utmost respect and care in all experiments. The use of human embryos shall be restricted.

vii. Principal investigators shall, with regard to the progress of human genome/gene analysis research, report to the Director/Head of their research institution & NREC in writing on a regular basis, at least annually.

viii. Principal investigator shall, in principle, conduct human genome/gene analysis research by using anonymized human specimens or genetic information. When a donor, proxy consenter or equivalent person agrees and, at the same time, a research protocol authorized by the ethics review committee and approved by the director/head of a research institution allows not to anonymize human specimens or genetic information, anonymization is not required.

ix. Principal investigators shall not, in principle, provide an unanonymized human specimen or genetic information to an external institution. When a donor, proxy consenter or equivalent person agrees to provision without anonymization and, at the same time,a research protocol authorized by the ethics review committee and approved by the director/head of a research institution allows not anonymizing human specimens or genetic information, it is permitted to provide unanonymized human specimens or genetic information to an external institution.

x. Principal investigators shall, in contracting out a part of work in human genome/gene analysis research, in principle, anonymize human specimens or genetic information to be provided to the contractor concerned. When a donor, proxy consenter or equivalent person agrees and, at the same time, a research protocol authorized by the ethics review committee and approved by the director/head of a research institution allows not to anonymize human specimens or genetic information, anonymization is not required.

xi. Principal investigators shall, both on a regular basis and in response to a request from parties including donors, explain clearly or release into the public domain the progress and results of human genome/gene analysis research. This shall not, however, apply to a part that is essential for the protection of human rights of a donor

or equivalent person and/or intellectual property rights of researchers.

xii. Principal Investigator shall be understood that while no bar is placed in carrying out experiments which may lead to benefit to humanity, but this should not take them down on the slippery road to prohibited areas of research.

xiii. Once the cell line is established, it shall be registered with the BMRC

13.6 Matters to be included

Matters to be included in explanatory documents for donors and proxy consenters, etc. shall, in general, be as follows, but adjustments may be made according to the details of the research:

- That the donation of human specimens is voluntary.
- That any person who has received a request for human specimen donation will not be treated in a disadvantageous manner as a result of not agreeing to donate a human specimen.
- That a donor or proxy consenter, etc. may revoke, in writing, the informed consent they gave, at any time without suffering any disadvantage (including, where necessary, the methods for receiving requests for revocation).
- That, where consent has been revoked by a donor or proxy consenter, etc., the human specimens and research results related to the said revocation will be disposed of, unless, for instance, they have been anonymized in an unlinkable fashion.
- The reasons for selection as a donor.
- The significance, objectives and method of research (the targeted disorder, analytical methods and so forth; where future additions and/or alterations are anticipated, a description to that effect; in the case of a single-gene disorder or the like, the necessity of the research, measures for preventing disadvantage and other items worthy of special mention), the period of research.
- When personal information is used jointly with other institutions in collaborative research: (i) the fact that it is collaborative, (ii) the items of the personal information used jointly, (iii) the scope of the joint users, (iv) the purpose for which the personal information is used by them, and (v) the names of the persons responsible for the management of the personal information.

- In the case of long-term, ongoing research, the research institution's point of view regarding the organization and systems necessary for conducting the ongoing research.
- Where obtaining the informed consent of donors is difficult, the importance of the research and the reasons why the research cannot be realized without the donation of human specimens from donors.
- The predicted research results and any predicted risks and/or disadvantages to a donor, etc. (including any disadvantages in social life, such as social discrimination).
- That a donor or proxy consenter, etc. may, upon request, obtain or inspect documents on the research protocol and research method to the extent that doing so does not impede the protection of personal information of other donors, etc. or the securing of research originality.
- Whether a donated human specimen or the genetic information derived there from will be anonymized in a linkable or unlikable fashion and the specific method of anonymization; when anonymization is not possible, a description to this effect and the reasons for this.
- Whether or not a human specimen or the genetic information derived there from can be provided to other institutions; and if so, that the ethics review committee would review the handling of personal information, the names of the receiving institutions, and that the purposes of use at the receiving institutions are appropriate.
- The anonymization method, etc. when part of the research is entrusted.
- Matters regarding the disclosure of genetic information (if not disclosed, the reasons there for).
- Matters regarding the disclosure of personal information (including where and how requests for disclosure are received, the method for confirming that a person is a donor or proxy consenter, etc., and if charges are incurred for disclosure, a description to this effect).
- That research outcomes might generate intellectual property rights, such as patent rights, in the future; the names of any envisaged organizations to which such intellectual property rights, such as patent rights, would belong, were they to be generated.

- That genetic information derived from human specimens might, upon anonymization, be publicly announced in an academic society, etc.
- The methods of preserving and using the human specimens.
- The method of preservation, use or disposal of human specimens after the completion of research (including the possibility of using them in other research and the details of the predicted research).
- When human specimens might be provided to a human cell, gene or tissue bank for division and distribution as general research resources, the academic significance of the bank concerned, the name of the organization operating the bank, the method of anonymization for the human specimens being provided, and the name of the responsible person at the bank.
- Information related to the use of genetic counseling (for instance, that genetic counseling is available in the case of single-gene disorders or the like).
- The method of raising research funds.
- That the donation of human specimens is without compensation.
- Information regarding the address and other details of contact points for inquiries (for instance, the correction of personal information and the revocation of consent) and complaints, etc.

13.7 Human Genome/ Gene analysis, Genetic screening and diagnosis

Genomic research is an upcoming field which is fast emerging after the results of human genome project were made publicly accessible. It involves the study of genes (ANNEXURE –A). Advances in technology such as microarray, RT-PCR, flow cytometry etc and ample funding opportunities, both national and international, increase in commercial interest, more public awareness on personalized medicine, and media coverage have increased genetic research as well as whole genome research. These developments have raised many ethical issues associated with genetic research those are needed to be addressed.

13.7.1 Prenatal Diagnosis

Screening for genetic defects in a fetus or embryo during pregnancy has evolved significantly over the last decade. It may involve investigations carried out in the mother or the fetus. Prenatal diagnosis refers to tests carried out in the embryo or fetal tissue before it is born to detect certain genetic features or defects. In contrast, prenatal screening is testing for diseases or conditions in a fetus and carried out in mother or on fetal biological material for suspected genetic conditions through standard protocols.

Pre-implantation genetic diagnosis (PGD or PIGD) is genetic profiling of embryos or oocytes prior to implantation or fertilization.PGD thus is an adjunct to assisted reproductive technology and in vitro fertilization (IVF) to obtain oocytes or embryos for evaluation.PGD is considered in a similar fashion to prenatal diagnosis.

The role of prenatal diagnosis is needed or managing the remaining weeks of the pregnancy, determining the outcome of the pregnancy, planning for possible complications with the birth process and in the newborn infant, deciding whether to continue the pregnancy and finding conditions that may affect future pregnancies.

There are a variety of non-invasive and invasive techniques available for prenatal diagnosis such as ultrasonography, amniocentesis, chorionic villus sampling, genetic analyses of fetal blood cells in maternal blood and biochemical analyses of maternal serum. Methods employed for analysis of fetal and placental tissues include pathological examination of the fetus or fetal parts and the placenta, radiography, microbiologic culture, biochemical analysis, karyotyping, fluorescence in situ hybridization (FISH), DNA probes etc.

As with all medical interventions associated with human reproduction, PGD raises strong, often conflicting opinions of social acceptability, particularly due to its eugenic implications. For example, in Germany the use of PGD had been prohibited by an Embryo Protection Act, though this prohibition was partly relaxed later. In other countries PGD is permitted in law but its operation is controlled by the state.

PGD can potentially be used to select embryos without a genetic defect, to have increased chances of successful pregnancy, to match a sibling in HLA type in order to be a donor, to have less cancer predisposition, and for sex selection.

Sex selection is indicated only in X linked disorders where male are the sufferers. However, due to prevailing inclination for male child in many societies, prenatal sex determination other than strong medical indication should not be allowed.

Several genetic disorders can be detected in utero but do not have satisfactory treatment or cures. Presently, the detection and elimination of genetic disorders generally relies on a combination of prenatal diagnosis plus abortion of an affected fetus. Many individuals, regardless of their views regarding abortion, consider prenatal diagnosis plus abortion a less than optimal solution to the problem of genetic disease.

Even if abortion (or rejection of pre-embryos) is not used to avoid disease, many ethical questions remain about the use of genetic technologies to modify the genes of a fetus or pre-embryo. Genetic manipulation introduces larger questions about the potential effects of genetic technologies on human relationships, questions that also exist with abortion or rejection of pre-embryos.

There is inherent difficulty in providing ethical guidelines for use of a technology which is still in its rudimentary stages or yet to come. There is little direct empirical evidence to predict how genetic technology will be used; complicating attempts to formulate ethical guidelines for its use. Ethical guidelines should include these aspects. (ICMR, 2006, India)

Guidelines for Prenatal Diagnosis

1. Equitable distribution of genetics services, including prenatal diagnosis, is owed first to those with the greatest medical need, regardless of ability to pay, or any other considerations (justice).
2. Prenatal diagnosis should be voluntary in nature. The prospective parents should decide whether a genetic disorder warrants prenatal diagnosis or termination of a pregnancy with an affected fetus (autonomy).
3. If prenatal diagnosis is medically indicated, it should be available regardless of a couple's stated views on abortion. Prenatal diagnosis may, in some cases, be used to prepare for the birth of a child with a disorder (autonomy). Prenatal diagnosis for adult-onset disorders may require special counseling, so as to avoid testing of children who may be carried to term.
4. Prenatal diagnosis is done only to give parents and physicians information about the health of the fetus. The use of prenatal diagnosis for gender selection, apart from a situation with risk for sex- linked disorders, is not acceptable (non-maleficence). Prenatal diagnosis for paternity testing, except in cases of rape or incest, is generally unacceptable, but should be considered on a case-by- case basis.
5. Prenatal diagnosis solely for relief of maternal anxiety, in the absence of medical indications, should have lower priority in allocation of resources than prenatal diagnosis with medical indications (justice).
6. Counseling should precede prenatal diagnosis (non-maleficence).

7. Physicians should disclose all clinically relevant findings to the woman or couple, including the full range of variability in the manifestations of the condition under discussion (autonomy).
8. The woman's and/or couple's choices in a pregnancy with an affected fetus should be respected and protected, within the framework of the family and of the laws, culture and social structure of the country. The couple, not the health professional, should make the choice (autonomy). (WHO, 2003, ICMR, 2006, India)

The following points should be noted and reflected in guidelines:

a. Prenatal sex determination will not be allowed.

b. Termination of pregnancy for a genetic cause has to be restricted by strict medical supervision.

c. BMRC should be aware for any uncertain future developments and research applications in these fields.

d. Genetic manipulation to modify the genes of a fetus or pre-embryo will not be allowed.

13.8 GENE THERAPY

The term "gene therapy", when it is used subsequently, will mean somatic cell gene therapy only. BMRC would not be expected to receive, and should not approve, research proposals for the introduction of DNA and RNA into germ (reproductive) cells or embryos. "Gene therapy" will also refer to research protocols with either therapeutic or non-therapeutic aims. Therapeutic research is conducted with the intent of providing a direct benefit to research participants, while non-therapeutic research is conducted with the intent to derive knowledge and not to be of direct benefit to research participants (More on Gene therapy ANNEXURE-B).

A research proposal must be evaluated based on medical, scientific, ethical and safety aspects. The proposal must be first approved by the concern institutional biosafety committee before submitting to NREC of BMRC. The following also need to be taken into account when protocols for gene therapy are being considered by BMRC:

a. The balance of potential risks and benefits associated with the gene therapy experiment. Diseases for which gene therapy is being considered should be those which impose a severe burden on affected individuals and for which there is no treatment or only inadequate treatment. There is accumulating evidence that gene therapy is relatively safe for humans, but the choice of diseases for

clinical trials or research remains critical. There should be good reason to believe that clinical outcomes will be improved.

b. The objectives and rationale of the proposed gene therapy or research should be clear, based on a sound understanding of the biological system being studied and where possible and appropriate, based on prior studies in animals.

c. The structure and characteristics of the DNA or RNA, and of the vector (carrier of the DNA or RNA), to be used for gene transfer must be known.

d. It should be possible to measure the effects of treatment and research.

e. Procedures should be in place which ensures the long-term follow-up of those studied or treated.

f. How consent to participation is obtained, and on what information it is to be based should be carefully considered.

13.8.1 Basic Requirement of a proposal for gene therapy

When reviewing a proposal for gene therapy, or introduction of DNA or RNA into humans for research purposes, BMRC should also be satisfied that:

(a) The research team has the necessary knowledge of, and experience in, molecular biology and the disease being treated.

(b) The research team has appropriate facilities in order to carry out the research.

(c) Research on Gene therapy will be restricted to public academic Institution.

(d) The purity of the material to be administered and the methods of handling it during its preparation and distribution are in accordance with current guidelines.

(e) Experiments in vitro and/or in animal models have demonstrated that the inserted DNA or RNA:

(i) will not enter the germ cells;
(ii) is likely to have the intended effect in humans;
(iii) is unlikely to cause undesirable side effects in humans.

(f) The potential risks have been assessed, taking into consideration the patient, the patient's family, the health professionals involved in treatment and its evaluation and the community.

In seeking to satisfy itself and on the technical aspects of a proposal for gene therapy or related technology, and to ensure that all requirements have been met, the BMRC may need to consult with the clinical trials, drug trials and bio safety committees of the institution. (NHMRC, Australia)

13.8.2 Supervision of gene therapy

Expert supervisory body

Continuing supervision of gene therapy is necessary. No existing body is constituted for this task. Therefore it is recommended that a new, expert supervisory body be established. An example of such a body is the British Human Fertilization and Embryo Authority.

The supervisory body should be of sufficient standing to command the confidence of existing Research Ethics Committees and of the public, the professions and Parliament. It should have a responsibility for:

i. advising on the content of proposals including the details of protocols for therapeutic research in somatic cell gene modification;

ii. advising on the design and conduct of the research;

iii. advising on the facilities and service arrangements necessary for the proper conduct of the research;

iv. advising on the arrangements necessary for the long term surveillance and follow-up of treated patients;

v. receiving proposals from clinicians who wish to conduct gene therapy in individual patients and making an assessment of:

   a. the clinical status of the patient;

   b. the scientific quality of the proposal, with particular regard to the technical competence and scientific requirements for achieving therapy effectively and safely;

   c. whether the clinical course of the particular disorder is known sufficiently well
   ■ for sound information, counseling and advice to be given to the patient (or those acting on behalf of the patient)
   ■ for the outcomes of therapy to be assessable;

   d. the potential benefits and risks for the patient of what is proposed;

e. the ethical acceptability of the proposal; and

f. the informed consent documents.

In the light of this assessment the expert supervisory body should make a recommendation on whether the proposal should be approved, and if so on what, if any, conditions.

The supervisory body should also have a responsibility for:

vi. acting in co-ordination with existing Research Ethics Committees;

vii. acting as a repository of up-to-date information on research in gene therapy internationally;

viii. setting up and maintaining a confidential register of patients who have been the subjects of gene therapy;

ix. oversight and monitoring of the research; and

x. providing advice to Appropriate authority, on scientific and medical developments which bear on the safety and efficacy of human gene modification.

It is recommended that any proposal for gene therapy be approved by this body as well as by NREC.

13.9 Stem Cell Research

Human embryonic stem cell (HESC) research offers much hope for alleviating the human suffering brought on by the ravages of disease and injury. HESCs are characterized by their capacity for self-renewal and their ability to differentiate into all types of cells of the body. The main goal of HESC research is to identify the mechanisms that govern cell differentiation and to turn HESCs into specific cell types that can be used for treating debilitating and life-threatening diseases and injuries.

Scientists recently succeeded in converting adult human skin cells into cells that appear to have the properties of HESCs by activating four genes in the adult cells. The reprogrammed cells - "induced pluripotent stem cells" (iPSCs) - could ultimately eliminate the need for HESCs. However, at present, the consensus in the scientific community is that both HESC and iPSC research should be pursued, as we do not yet know whether iPSCs have the same potential as HESCs or whether it is safe to transplant them into humans. Thus, the controversies around HESC research will continue, at least in the near-term.

While the principal source of the controversy surrounding HESC research lies in competing views about the value of human embryonic life, the scope of ethical issues in HESC research is broader than the question of the ethics of destroying human embryos. It also encompasses questions about, among other things, whether researchers who use but do not derive

HESCs are complicit in the destruction of embryos, whether there is a moral distinction between creating embryos for research purposes and creating them for reproductive ends, the permissibility of cloning human embryos to harvest HESCs, and the ethics of creating human/non-human chimeras.

13.**9.1 Guidelines for Human Pluripotent Stem Cell Research**

The types of research that conform to the Guidelines include:

- **Research to derive or study human embryonic stem (ES) cell lines or other cell lines of a pluripotent nature from human embryos provided that:**

The embryos used, whether fresh or frozen were originally created for reproductive purposes and are no longer required for such purposes.

There was free and informed consent from the persons for whom the embryos were originally created for reproductive purposes. Where third party donor gametes were used to create the embryo, the third party gamete donor(s) must have given at the time of donation free and informed consent to the unrestricted research use of any embryos created, when these embryos are no longer required for reproductive purposes.

The ova and the sperm from which the embryos were not created, nor the embryos themselves, were obtained through commercial transactions, i.e., were acquired by payment of money in excess of costs actually incurred or in exchange for healthcare services.

- **Research to derive or study human embryonic germ cell (EG) lines or other cell lines of a pluripotent nature from human fetal tissue or amniotic fluid, provided that:**

The proposed research does not compromise the pregnant woman's decision on whether to continue her pregnancy. To ensure that such compromise does not occur, the stem cell researcher shall provide BMRC with satisfactory evidence that the pregnant woman's decision to discontinue the pregnancy was made prior to any request made to her to participate in the research.

There was free and informed consent from the pregnant woman for the use of her fetal tissue in research.

- **Research to derive and study human stem cell lines of a pluripotent nature from the umbilical cord and placenta provided that:**

There was free and informed consent from the both parents of the newborn. If there is disagreement between the parents, the umbilical cord and placenta cannot be used for research.

- **Research to derive, induce or study human stem cell lines of a pluripotent nature from human somatic tissues, provided that:**

When the tissue is from a legally competent person, there was free and informed consent from the prospective research participant.

When the tissue is from a legally incompetent person (the tissue has been obtained from a surgical, diagnostic or other legitimate practice) there was appropriate legally competent third party has authorized its availability for research.

When the tissue is from a cadaver, there is a legally appropriate advance directive that appropriately specifies the use of tissue for stem cell research, or there is authorization from an appropriate legally competent third party.

- **Research involving the grafting of human ES cells, EG cells, induced pluripotent stem (iPS) cells, or other human cells that are likely to be pluripotent into non-human animals, from birth to adulthood, provided that:**

The research is designed to reconstitute a specific tissue or organ to derive a pre-clinical model or to demonstrate that the cells are pluripotent (e.g., teratoma formation).

These non-human animals grafted with human stem cells will not be used for reproductive purposes.

There is overwhelming evidence from pre-clinical models for safety and efficacy. The research is carried out in well-designed clinical trials.

There is free and informed consent from the prospective research participants. (CIHR,2010,Canada).

13.9.2 Research that restricted with the Guidelines

The types of research that do not conform to the Guidelines include:

- Research involving the creation of human embryos specifically to derive stem cell lines or other cell lines of a pluripotent nature.

- Research involving somatic cell nuclear transfer into human oocytes (cloning) or involving stimulation of an unfertilized egg to produce a human embryo (parthenogenesis) for the purposes of developing human embryonic stem cell lines or other cell lines of a pluripotent nature.

- Research involving the directed donation of stem cell lines or, other human cells or cell lines of a pluripotent nature to particular individuals, unless the research involves autologous donation.

- Research in which human or non-human ES cells, EG cells, iPS cells, or other cells that are likely to be pluripotent are combined with a human embryo.

- Research in which human or non-human ES cells, EG cells, iPS cells, or other cells that are likely to be pluripotent are grafted to a human fetus.

- Research in which human ES cells, EG cells, iPS cells, or other cells that are likely to be pluripotent are combined with a non-human embryo.

- Research in which human ES cells, EG cells, iPS cells, or other cells that are likely to be pluripotent are grafted to a non-human fetus. (CIHR, 2010, Canada)

- Any in-vitro culture of intact human embryo, or any organized cellular structures that have the potential of developing into human organs and tissues, regardless of the method of its derivation, beyond 6 days.

- Clinical trials using cells after major manipulation or those sponsored by multinationals involving stem cell products imported from abroad.

BMRC also follow guidelines of "Guidelines for the Conduct of Human Embryonic Stem Cell Research" by ISSCR, 2006, "Guidelines for Stem Cell Research" ICMR, 2012 and NEGHR, Philippine wherever required in respect to consider religious, social and cultural norms, values as well as if the law permits.

13.10 BIO-BANK

A biobank is a form of biorepository devoted for storing human biological samples include embryonic stem cells, neonatal tissues (Wharton's Jelly), iPS cell lines, adult stem cell lines, sperm, ova etc. from large number of individuals intended for future use by multiple researchers for multiple purposes. Multiple biobank exist in the developed countries and some developing countries. As future research on genomics, personalized medicine, cancer etc. will heavily depend on biorepository, it has invoked research and medical ethical questions as well as national issues.

Types of biobank:

1. **Tissue banks** harvest and store human tissue from living, cadaver and biomedical (pathological) samples.
2. A **virtual biobank** is a virtual repository which provides data extracted from and characterizing samples stored at an existing biobank.
3. **Population banks** store biomaterial as well as associated characteristics such as lifestyle, clinical, and environmental data.

The biorepository activities involve three components:

1. C**ollection** of tissue samples;
2. The **repository** storage and data management; and
3. The **recipient** investigators, type of research and its outcome. (ICMR, 2006, India)

13.10.1 Repository Collections

The steps involve the initial process of collecting, processing, freezing, "anonymizing", and storing tissue with its corresponding clinical information in a database. As tissue banking concerns research at a later time, the ethical issues pertain to consent requirements for the banking and further uses of tissue and DNA samples, their control and ownership, and the benefit sharing to the individual or community. Permission must be obtained for shipping samples abroad.

The sample collector must obtain informed consent of the donor for DNA banking or for cell-line transformation and banking. The process of seeking informed consent for purposes of banking must clearly be stated in addition to possible risks and benefits, the conditions under which samples from the Repository shall be provided to other researchers, how long and in what condition the

samples shall be preserved in the Repository and what will be the costs to individual researchers in obtaining samples from the Repository. The sample collector must also clearly inform every donor that he reserves the right to order destruction of his sample from the Repository at any time.

To prevent any exploitation and protect the rights of participants, the three main requirements at collection level are:

1. Individual informed consent,
2. Approval of the 'Institutional Review Board' and
3. the 'Repository Ethics Committee' **(which may be formed by the BMRC)**

Human biological samples: These include whole or part of an organs, tissues, cells (somatic and gonadal), body fluids or samples like serum, buffy coat, DNA, hair, nails, excreta, sweat, buccal scrapings *etc.*

Unidentified Specimens: Identifiable personal information was not collected or, if collected, was not maintained and cannot be retrieved by the repository.

Identified Specimens: These specimens are linked to personal information in such a way that the person from whom the material was obtained could be identified by name, patient number, or clear pedigree location (*i.e.*, his or her relationship to a family member whose identity is known).

13.10.2 The use of research samples

General Principles

An Ethics Committee exclusive to the Repository formed by the BMRC should play an important role in looking at the issues related to informed consent, privacy and confidentiality, risk-benefit analysis, benefit sharing, maintain linkages with other biobank and repositories while adhering to the basic principles of bioethics *viz.* Autonomy, Justice, Beneficence and Non-maleficence.

The samples supplied to the investigators are:

Unidentified Samples: Sometimes termed "anonymous," these samples are supplied by repositories to investigators from a collection of unidentified human biological specimens.

Unlinked Samples: Sometimes termed "anonymized," these samples lack identifiers or codes that can link a particular sample to an identified specimen or a particular human being.

Coded Samples: Sometimes termed "linked" or "identifiable," these samples are supplied by repositories to investigators from identified specimens with a code rather than with personally identifying information such as a name or other identifying number.

Identified Samples: These samples are supplied by repositories from identified specimens with a personal identifier (such as a name of person/patient number) that would allow the researcher to link the biological information derived from the research directly to the individual from whom the material was obtained. (ICMR, 2006, India)

- **Guidelines for using repository samples:**

a) Primary use:

By primary use it is meant that the biological material will be used for the intended purpose as described in the protocol submitted for approval from Ethics Committee. Ownership of the sample lies with the individual, family or community as the case may be. Local Ethics Committee should consider following points for approving primary use:

i. consent should be in written form, given voluntarily by the donor who has the capacity to do so. The use of the samples shall be reserved for the defined purpose only;

ii. participants have the right to withdraw at any time. This does not apply to anonymized samples;

iii. if sample is inadequate or contaminated re-contact is necessary for fresh and specific consent. This should be incorporated in the prior consent form;

iv. while obtaining data/samples from vulnerable subgroups with reduced autonomy, Ethics Committee should ensure that informed consent be obtained from legally authorized representatives in the presence of impartial witness. The risks and benefits should be adequately explained;

v. when samples have to be obtained for specific research from participants belonging to specified communities, permission of the group leader/local leader/authorities must also be obtained. However individual consent should never be compromised even if permission of the gatekeepers/village panchayat.

vi. group consent of the population/community should be obtained through its culturally appropriate authorities

before sampling starts, particularly so for group specific research like genetic research;

vii. samples obtained for archival purposes in a prospective study. (ICMR, 2006, India)

b) Secondary Use:

Every request for secondary use shall be examined by the NREC/IRB to ensure that:

i. the proposed use does not transgress the original consent given for the earlier study and the validity of the objectives of the new study;
ii. provisions for ensuring anonymity of the samples for secondary use are stated;
iii. after anonymizing sample, results are not communicated to the donor;
iv. for postmortem uses of samples the permission of the next of kin, legally authorized representative should be obtained; and
v. waiver of consent is given whenever the donor is not traceable or the sample is anonymized. (ICMR, 2006, India)

c) Other Use:

1. Any researcher who intends to use samples from a Repository must submit a Statement of Research Intent, which must be approved by the Ethics Committee of the Repository, which shall be responsible for determining whether the intended research is consistent with the informed consent provided by the donor, and, where applicable, of the group.
2. Unless scientifically essential, the Repository must not provide to an individual researcher any information linked to the samples. When linked information is to be provided, only the minimal information as required for the intended research shall be provided.
3. If any commercial use is made of the samples in the Repository, appropriate written benefit-sharing agreements, consistent with the policies stated earlier, must be jointly signed by the donor, sample collector and Repository in-charge. It is also desirable that community consultations are held prior to collection of samples to be stored in a Repository, and group consent is obtained before individual consent.
4. There should be appropriate Material Transfer Agreements with the Repository for depositing samples as well as for

taking them out with clear reasons. Third parties must be allowed to take samples only after approval from Repository ethics committee.

5. The identity of the Repository from which samples were obtained must be revealed in all reports, patents or copyrights arising out of these samples.
6. Due intellectual property rights should be given while granting access to samples, through a contractual agreement.
7. For any publication resulting out of research from samples taken from repository, appropriate acknowledgement should be given to the original contributor of samples, sponsors of research, repository, donors and participants. (ICMR, 2006, India)

13.10.3 Biobank ethical issues:

The key event which arises in biobanking is when a researcher wants to collect a human specimen for research. When this happens, some issues which arise include the following: right to privacy for research participants, ownership of the specimen and its derived data, the extent to which the donor can share in the return of the research results, and the extent to which a donor is able to consent to be in a research study.

- **Governance**

There is no internationally-accepted set of governance guidelines which are designed to work with biobank. Biobanks typically try to adapt to the broader recommendations of guidelines which are internationally accepted for human subject research, and use changing guidelines as they become accepted. Biobanks need ethical oversight from an independent reviewer and the governance process is intended to be public. Institutional review boards typically enforce standards set by their own institutes following government regulations.

- **Informed consent**

Because donating a specimen involves consideration of many issues, different people will have different levels of understanding of what they are doing when they donate a specimen. Since it is difficult to explain every issue to everyone, problems of giving informed consent arise when researchers take samples. Researchers support biobanking despite risk to participants because the benefit is high, it pays respect to people's wishes to involve themselves in research, current practices and culture support this kind of research, and consensus is that the risk of participation is low.

- **Privacy for research participants**

There is broad consensus that when a person donates a specimen for research then that person has a right to privacy thereafter. To this end, researchers balance the need for specimens to be anonymous or de-identified from protected health information with the need to have access to data about the specimen so that researchers can use the sample without knowing the identity of the donor

- **Ownership of specimens**

When a person donates a specimen to a researcher it is not easy to describe what the participant is donating because ownership of the specimen represents more rights than physical control over the specimen.

The specimens themselves have commercial value, and research products made from specimens can also. Fundamental research benefits all sectors, including government, non-profit, and commercial, and these sectors will not benefit equally. Specimens may be subject to biological patenting or research results from specimen experimentation may lead to the development of products which some entity will own. The extent to which a specimen donor should be able to restrict the way their specimen is used is a matter of debate.

- **Return of results**

There is broad consensus that participants in clinical research have a right to know the results of a study in which they participated so that they can check the extent to which their participation delivered beneficial results to their community.

- **Incidental finding**

Participant shell let know if there are any incidental finding that is beneficial for the participant.

- **System of disposal of material.**

- **Donor discrimination**

Biobanks should prevent donor communities from facing discrimination as a result of participating in a biobank project.

- **Commercialization**

Different aspects of biobank serve public, private, commercial, and noncommercial interests. Set guidelines to fairly balance public, private, commercial, and noncommercial interests. Who owns biological specimens and data derived there from? When biobank

and related projects are publicly funded, the result will benefit private industry. To what extent is this outcome satisfactory?

Some additional points:

Apart from the guidelines outlined in this document, BMRC should form specific committees with relevant experts and specified terms of references (TORs) in dealing with issues not detailed in this document or those arising from its content from their socio-cultural medical, and legal perspectives.

When constructing the informed consent forms, every effort must be made to minimize the effects of general and health-related illiteracy of the common people of Bangladesh on t heir understanding of what would be done on them and with the research materials or information derived from them.

Education both professional and public has to be taken "as the key to ethical genetics service" (Review of ethical issues in medical genetics 2003).

It any research proposal requires periodic review to decide whether the research is being conducted properly and whether it should be discontinued, the proposal should include provision for periodic review.

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ANNEXURE - A

Genes which code for a protein, enzyme, or a transporter in a particular individual, and to find out if there is any mutation, single nucleotide polymorphism, or copy number variations, RNAi, introns and exons etc which may determine the susceptibility of the individual to a disease or the response to drugs.

Single Nucleotide Polymorphism (SNP)

SNP genotyping is the measurement of genetic variations of single nucleotide polymorphisms (SNPs) between members of a species. It is a form of genotyping, which is the measurement of more general genetic variation. SNPs are one of the most common types of genetic variation. A SNP is a single base pair mutation at a specific locus, usually consisting of two alleles (where the rare allele frequency is >1%). SNPs are found to be involved in the etiology of many human diseases like cancer, infectious diseases (AIDS, leprosy, hepatitis, etc.) autoimmune, neuropsychiatric, Sickle–cell anemia, ß Thalassemia and Cystic fibrosis and are becoming of particular interest in pharmacogenetics. SNPs are usually biallelic and thus easily assayed. A single SNP may cause a Mendelian disease. For complex diseases, SNPs do not usually function individually; rather, they work in coordination with other SNPs to manifest a disease condition as has been seen in Osteoporosis.
In studies on human genetic polymorphisms, such as single nucleotide polymorphisms (SNPs), little immediate benefit is expected for the individuals contributing the test samples. Such lack of immediate benefits should be noted in the informed consent form obtained prior to sample collection.

Mutation

In genetics, a mutation is a change of the nucleotide sequence of the genome of an organism, virus, or extra chromosomal genetic element. Mutations result from unrepaired damage to DNA or to RNA genomes (typically caused by radiation or chemical mutagens), from errors in the process of replication, or from the insertion or deletion of segments of DNA by mobile genetic elements. Mutations may or may not produce discernible changes in the observable characteristics (phenotype) of an organism. Mutations play a part in both normal and abnormal biological processes, including evolution, cancer, and the development of the immune system.

There are a number of diseases caused by mutation in human genome e.g. Sickle-cell disease, Hemophilia, Cystic fibrosis, Down syndrome, Duchenne muscular dystrophy etc.

Although mutations that change in protein sequences can be harmful to an organism; on occasions, the effect may be positive in a given environment. In this case, the mutation may enable the mutant organism to withstand particular environmental stresses better than wild-type organisms, or reproduce more

quickly. In these cases a mutation will tend to become more common in a population through natural selection.

For example, a specific 32 base pair deletion in human CCR5 (CCR5-Δ32) confers HIV resistance to homozygotes and delays AIDS onset in heterozygotes. The CCR5 mutation is more common in those of European descent. One possible explanation of the etiology of the relatively high frequency of CCR5-Δ32 in the European population is that it conferred resistance to the bubonic plague in mid-14th century Europe. People with this mutation were more likely to survive infection; thus its frequency in the population increased. This theory could explain why this mutation is not found in southern Africa, which remained untouched by bubonic plague. A newer theory suggests that the selective pressure on the CCR5 Delta 32 mutation was caused by smallpox instead of the bubonic plague.

Ribonucleic Acid Interference (RNAi)

RNA interference (RNAi) also called post transcriptional gene silencing (PTGS), is a biological process in which RNA molecules inhibit gene expression, typically by causing the destruction of specific mRNA molecules. Two types of small ribonucleic acid (RNA) molecules – microRNA (miRNA) and small interfering RNA (siRNA) – are central to RNA interference. RNAs are the direct products of genes, and these small RNAs can bind to other specific messenger RNA (mRNA) molecules and either increase or decrease their activity, for example by preventing an mRNA from producing a protein. RNA interference has an important role in defending cells against parasitic nucleotide sequences – viruses and transposons – but also in directing development as well as gene expression in general.

siRNA and miRNA has many applications in biomedical research such as for treatment of HIV, viral hepatitis, cardiovascular and cerebrovascular diseases, metabolic disease, neurodegenerative disorders (Alzheimers disease, Parkinson's disease, Huntington's disease) and cancer (Pancreatic and colonic carcinoma, Lymphoblastic leukemia etc).

Genetic Screening

Genetic screening implies search in population of individuals who have, or are susceptible to have a serious genetic disease; or who, though not at risk themselves, are carriers and thus at risk of having children with the particular genetic disease. It is essential that screening must be purposive. Also, besides validation of screening tests, it shall also be ensured that a suitable intervention is possible. Rarely, screening may be permissible to allay anxiety, but it should not be forgotten that response of different individuals might vary; therefore, the need may be carefully evaluated by the health care provider. Depending on nature of the genetic defect that is identified and its pattern of inheritance, siblings and other blood relations as well as existing and future offspring may be affected. This raises ethical questions that differ significantly, from the normal rules and standards applied to handling of personal medical records.

Genetic Disease Diagnosis

Laboratory advances in molecular genetics have resulted in numerous clinical applications for DNA analysis. Genetic tests can contribute a great deal of information to clinical diagnosis. These genetic tests including PCR, fluorescence detection, real-time PCR, and automated sequencing have been used in different diagnostic tests. The general principles of informed consent, confidentiality and other criteria used for any investigation in genetics should be followed. Since the knowledge in this field is new, and relatively complicated, a DNA test must be preceded and followed by appropriate genetic counseling.

- **Pre-morbid diagnosis in children (clarification of each term is required):** Parents are advised not to get the diagnosis done especially in cases like Huntington's disease etc. for which there is no available intervention till the child reaches the age of proper "consent".

- **Pre-morbid diagnosis in adults (clarification of each term is required)**: It may be carried out with informed consent. However, appropriate genetic counseling must be provided and documented before offering such services.

- **DNA diagnosis in forensics:** The laboratories carrying out DNA diagnosis in forensics should follow the guidelines evolved by National Accreditation Board for Laboratories functioning under the Department of Science and Technology.

- **Late-onset Neurological Conditions (untreatable) diagnostic testing (clarification of each term is required):** For example in Huntington disease, where there are clinical symptoms, the diagnosis is confirmed according to the number of triplet repeats in the IT15 gene increased over the usual number. Relevant issues are consent and discussion of result disclosure to other family members.

- **Pre-symptomatic Testing (clarification of each term is required):** The genetic diagnosis of Huntington disease in a family member can then enable unaffected family members to be tested to determine if they have the mutation. If the mutation is present (a positive result) the person will develop the condition if they live long enough. Testing can provide certainty regarding their risk and enable life planning. However both positive and negative results can impact on family dynamics. Again, informed consent is essential, as are the issues of 'whom to tell' and 'when to tell'.

- **Familial Cancers (breast, ovarian, colorectal and prostate cancers and melanoma) Diagnostic Testing (mutation searching):** Where there is a strong family history of some specific cancers, genetic testing may confirm that the onset of cancer involves inherited susceptibility. For these conditions, the test involves searching for the family specific mutation in the genes that have been identified as associated with the condition. A negative result on a mutation search only means that a genetic basis has not been confirmed. A positive result however

means that asymptomatic blood relatives can have the genetic test that would look for the specific mutation. Specific issues include consent and family communication and dynamics.

- **Karyotyping:** Karyotyping is used as a tool for the etiological diagnosis of patients with mental retardation (MR) and birth defects. A precise diagnosis may lead to prevention or even an earlier detection of some pathogenic signs (e.g. obesity in Prader–Willi patients, Wilms tumor in Wilms tumor, aniridia, genitourinary anomalies mental retardation (WAGR) syndrome) or may enable improved medical care for the individual (e.g. echocardiogram if a gene implicated in congenital heart disease is involved). Moreover, a diagnosis often is essential for genetic counseling and reproductive choices of the individual and his/her family.

The consequences of DNA testing for conditions for which no treatment is available or for conditions manifesting late in life e.g. breast cancer, Alzheimer's disease etc. should be seriously considered before embarking on such studies. Information so derived should not disclose the identity of the individuals.

ANNEXURE – B

Gene therapy is the use of DNA as a pharmaceutical agent to treat disease. It derives its name from the idea that DNA can be used to supplement or alter genes within an individual's cells as a therapy to treat disease. The most common form of gene therapy involves using DNA that encodes a functional, therapeutic gene to replace a mutated gene. Other forms involve directly correcting a mutation, or using DNA that encodes a therapeutic protein drug (rather than a natural human gene) to provide treatment. In gene therapy, DNA that encodes a therapeutic protein is packaged within a "vector", which is used to get the DNA inside cells within the body. Once inside, the DNA becomes expressed by the cell machinery, resulting in the production of therapeutic protein, which in turn treats the patient's disease.

Types of gene therapy:

Gene therapy may be classified into the two following types:

1) **Germ line gene therapy**

2) **Somatic gene therapy**

1) Germ line gene therapy

In germ line gene therapy, germ cells (sperm or eggs), are modified by the introduction of functional genes, which are integrated into their genomes. Germ cells will combine to form a zygote which will divide to produce all the other cells in an organism and therefore if a germ cell is genetically modified then all the cells in the organism will contain the modified gene. This would allow the therapy to be heritable and passed on to later generations. Although this should, in

theory, be highly effective in counteracting genetic disorders and hereditary diseases, some jurisdictions, including Australia, Canada, Germany, Israel, Switzerland, and the Netherlands prohibit this for application in human beings, at least for the present, for technical and ethical reasons, including insufficient knowledge about possible risks to future generations and higher risk than somatic gene therapy (e.g. using non-integrative vectors). The USA has no federal legislation specifically addressing human germ-line or somatic genetic modification (beyond the usual FDA testing regulations for therapies in general).

2) Somatic gene therapy

(NHMRC, Australia) Somatic cell gene therapy involves the introduction of DNA (deoxyribonucleic acid) or RNA (ribonucleic acid) into the somatic (non-reproductive) cells of humans, or the introduction into humans of cells whose genetic material has been modified, in order to provide an alternative form of treatment to improve the health of individuals. It involves the use of a gene carrier or 'vector' (often a defective virus) to carry a gene into cells with a view to integration of the gene into chromosomal DNA and its long term expression. However, additional novel and varied strategies for introducing or modifying gene expression in humans have been devised which make the boundary between gene therapy and other treatment strategies hazy. Consider immunization with a virus expressing a particular protein, or immunization with naked DNA, to treat or prevent a chronic viral infection such as HIV, or as part of cancer treatment. These methodologies overlap with the traditional concept of gene therapy in that DNA is introduced into somatic cells, but could also be thought of as modifications to standard immunization strategies in which DNA, rather than protein, is used to generate the immune response. Sometimes there may be uncertainty about whether a proposed research project should be considered to fall under the heading of 'gene therapy'. Where there is doubt as to whether a research proposal falls into the category of gene therapy, researchers should seek guidance from the BMRC.

DNA or RNA can also be introduced into somatic cells to mark their distribution and fate. Although no therapeutic benefit is expected, such studies are important for understanding the underlying basis for diseases or as first steps in the development of some somatic cell gene therapies for serious diseases. There may be other justifiable therapeutic or non-therapeutic reasons for introducing DNA or RNA into human somatic cells. While the introduction of DNA or RNA into somatic cells is ethically acceptable, the introduction of DNA or RNA into germ (reproductive) cells or embryos is ethically unacceptable, since there is insufficient knowledge about the possible consequences including hazards and effects on future generations.

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