ETHICS IN RESEARCH

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Ethics in human research

Human research *is research conducted with or about people, or their data or tissues, with the sole intention to do well. It involves significant risks and it is possible for things to go wrong. Despite the best of intentions and care in planning and practice, sometimes things go away. Now and then mishaps may arise because of technical errors or an ethical insensitivity, neglect or disregard. So, there are* ***different ethical principles*** *for medical research involving human subjects, including research on identifiable human material and data:*

1. ***THE NUREMBERG CODE (Established in 1948)***
2. ***THE DECLARATION OF HELSINKI (Established in 1964)***
3. ***THE BELMONT REPORT (Established in 1979)***
4. ***COMMON RULE***

THE NUREMBERG CODE

A well-known chapter in the history of research with human subjects opened on December 9, 1946, when an American military tribunal opened criminal proceedings against 23 leading German physicians and administrators for their willing participation in war crimes and crimes against humanity. As a direct result of the trial, the Nuremberg Code was established in 1948 and are as follows:

1) The voluntary consent of the human subject is absolutely essential.

2) The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

***3) The experiment should be so designed and based on the results of animal experimentation** and a knowledge of the natural history of the disease or other problem under study, that the anticipated results will justify the performance of the experiment.*

4) The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

Contd.....

5) No experiment should be conducted, where there is an a priori reason to believe that death or disabling injury will occur; *except, perhaps, in those experiments where the experimental physicians also serve as subjects.*

6) The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7) Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8) The experiment should be conducted only by scientifically qualified persons. *The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.*

9) During the course of the experiment, the human subject should be at liberty to bring the experiment to an end, *if he has reached the physical or mental state, where continuation of the experiment seemed to him to be impossible.*

10) During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, *if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgement required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.*

THE DECLARATION OF HELSINKI

*In **1964**, the World Medical Association established recommendations guiding medical doctors in biomedical research involving human subjects. It was revised in 1975, 1983, 1989, and 1996, and is the basis for Good Clinical Practices used today. Issues addressed in the **Declaration of Helsinki** include:*

- ***Research with humans should be based on the results from laboratory and animal experimentation.***
- ***Research protocols should be reviewed by an independent committee prior to initiation.***
- ***Informed consent from research participants is necessary.***
- ***Research should be conducted by medically/scientifically qualified individuals.***
- ***Risks should not exceed benefits***

THE BELMONT REPORT

The Belmont Report was published in 1979, with attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. The Report is a statement of the basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects.

The Belmont Report established three basic ethical principles – respect for persons, beneficence, and justice –which are the cornerstones for the regulations involving human subjects.

The three basic ethical principles and their corresponding applications according to the report are:

Principles		*Applications*	
1. Respect for persons	*Individuals should be treated as autonomous agents*	***1. Informed consent***	*Subjects, to the degree that they are capable, must be given the opportunity to choose what shall or shall not happen to them.*
	Persons with diminished autonomy are entitled to protection		*The consent process must include three elements:* *i) information* *ii) comprehension* *iii) voluntariness*
2. Beneficence	*Human subject should not be harmed*	***2. Assessment of risks and benefits***	*The nature and scope of risks and benefits must be assessed in a systematic manner.*
	Research should maximize possible benefits and minimize possible harms		
3. Justice	*The benefits and risks of the research must be distributed fairly*	***3. Selection of subjects***	*There must be fair procedures and outcomes in the selection of research subjects*

COMMON RULE

This is a set of regulations that have been adopted by many research agencies in the United States and elsewhere. The main elements of the Common Rule include:

- ***Requirements for assuring compliance by research institutions***
- ***Requirements for researchers obtaining and documenting informed consent***
- ***Requirements for Institutional Review Board (IRB) or Ethical Committee (EC) membership, function, operations, review of research, and record keeping***
- ***Additional protection for certain vulnerable research subjects–pregnant women, prisoners, and children.***

Ethical Committee (EC)
[ICMR Ethical Guidelines_2017]

Composition of an EC:

- *ECs should be multi-disciplinary and multi-sectoral.*
- *There should be adequate representation of age and gender.*
- *Preferably 50% of the members should be non-affiliated or from outside the institution.*
- *The number of members in an EC should preferably be between seven and 15 and a minimum of five members should be present to meet the quorum requirements.*
- *The EC should have a balance between medical and non-medical members/technical and non-technical members, depending upon the needs of the institution.* ***Members of EC*** *are as follows:*

  1. Chairperson/Vice Chairperson; 2. Member Secretary/Alternate Member Secretary; ***3. Basic Medical Scientist(s) (preferably one pharmacologist); 4. Clinician(s); 5. Legal expert/s; 6. Social scientist/philosopher/ethicist/ theologian; 7. Lay person(s) from the community.***

Lay Person(s) or Layman's Role Ethical Committee

A layperson or layman [Laity means "common people" (Greek: laik'l,)] is a person who is not an expert in a given field of knowledge.

Qualifications:

1) *Literate person from the public or community.*
2) *Has not pursued a medical science/ health related career in the last 5 years.*
3) *May be a representative of the community from which the participants are to be drawn.*
4) *Is aware of the local language, cultural and moral values of the community.*

[Desirable: Involved in social and community welfare activities.]

Functions:

- *Ethical review of the proposal, International Classification of Diseases (ICD) along with translation(s);*
- *Evaluate benefits and risks from the participant's perspective and opine whether benefits justify the risks;*
- *Serve as a patient/participant/ community representative and bring in ethical and societal concerns;*
- *Assess on societal aspects if any.*

Laboratory Animal Ethics: The Three "R"

The guiding principles for ethical treatment of animals in testing and experimentation were first introduced by Russell and Burch in 1959 and are known as ***the three Rs****:*

- ***Replacement***
- ***Reduction***
- ***Refinement***

1. Replacement

1. ***Replace higher model organisms with lower ones, for example, use non-sentient beings (sentience can be described as the ability to be conscious, perceive pain or suffering and experience subjectivity).***

2. ***Where possible, adopt in vitro or in silico alternatives such as:***
    a) ***Cellular fractions, whole cells, tissues or organs in culture, animal products***
    b) ***Mechanical or computer modelling that can simulate human biology or predict pharmacological properties of drugs***
    c) ***Artificial animals (dummies) and audio-visual aids to teach dissection and anatomy and to demonstrate protocols***
    d) ***Micro-dosing and clinical testing in humans***
    e) ***An interesting alternative to the use of animals to teach and practice surgeries in medical schools is the advent of the human-patient simulators that have a realistic human anatomy and physiology and can be programmed to bleed, breathe, convulse, and so on like humans.***

2. Reduction

1. *Design experiments properly and calculate the number of animals needed*
2. *Plan studies where animals can be used as their own controls*
3. *Share animals between experiments or research labs (same batch of controls or different organs from same animal for various purposes)*
4. *Collaboration with statisticians to get the best possible results with the lowest number of animals*
5. *Perform thorough literature searches and consult experienced researchers to avoid repeating experiments already performed*
6. *Encourage publishing of negative data to prevent unnecessary repetition of experiment*
7. *Plan sensible breeding strategies for animals to avoid an excess in supply that may not be used for experiments*

3. Refinement

1. Refine experiments and protocols to minimize pain and distress in animals
2. Refer to standard guidelines and regulations and determine appropriate end-points and termination criteria for experiments
3. Acquire and provide proper training for careful handling of animals
4. Learn to identify pain and distress signals in animals
5. Understand their normal as well as abnormal physiology and behaviour
6. Use appropriate analgesics, anesthetics, and/or anti-inflammatory drugs for animals under testing
7. Use non-invasive experimental procedures as much as possible
8. Pay special attention to animals during post-surgical care
9. Identify alternatives to the commonly used pain and disease-inducing reagents (such as Freund's adjuvant, toxins, allergens or infectious agents) and to procedures (like foot pad injections, toe clipping, retro-orbital blood collection, ascites production or tumor induction)
10. J. Consult animal technicians and veterinarians if in doubt about any procedure or technique used or about the health and response of animals

Euthanasia

Euthanasia can be defined as the act or practice of killing or permitting the death of hopelessly sick or injured individuals (such as persons or domestic animals) in a relatively painless way for reasons of mercy. The word comes from the Greek euthanatos, which means "easy death."

Voluntary euthanasia *is that which is requested by the subject or agreed to by him when proposed by others. This includes cases of: (1) asking for help with dying; (2) refusing burdensome medical treatment; (3) simply deciding to die.*

Involuntary euthanasia *is where the agreement of the subject could be obtained but is not. Here, the person wants to live but is killed anyway. This is usually murder but not always. Consider the following examples:*
A soldier has their stomach blown open by a shell burst. They are in great pain and screaming in agony. They beg the army doctor to save their life. The doctor knows that they will die in ten minutes whatever happens. As he has no painkilling drugs with him he decides to spare the soldier further pain and shoots them dead.

Nonvoluntary euthanasia *is where the agreement of the subject cannot be obtained because he is unconscious or otherwise unable to express his agreement verbally or rationally. This includes cases where: (1) the person is in a coma; (2) the person is mentally retarded to a very severe extent; (3) the person is severely brain damaged.*

Active (positive or direct) euthanasia *is where death is produced deliberately and actively by positive means.*

Passive (negative or indirect) euthanasia *is where death is deliberately produced by withholding or withdrawing the ordinary means of nutrition or treatment of the subject's condition.*

Active euthanasia *refers to euthanasia as a result of someone performing an act such as injection of a lethal drug, whereas* ***passive euthanasia*** *means euthanasia resulting from the omission of an act.*