Human experimentation and related ethical issues

DEFINITION;

- Conduction of medical experiments on human beings
- Set of scientific activities the primary purpose of which is to develop or contribute to generalizable knowledge about the chemical, physiological or psychological processes involved in human functioning
- Called ‘human experimentation’ because uses humans as subjects
- Therapeutic research versus nontherapeutic research

TYPES

1. Therapeutic	**Subject is ill**	Condition is likely to improve
2. Research	Subject is healthy	Medicines +procedures well accepted May have neg/positive
3. Innovative	Subject can be healthy/not	Not accepted May have neg/positive

Ethics in medical research

- Nuremberg code (1947)
- Declaration of Helsinki (1964)
- ICMR guidelines on human research (2006)
- Drugs and cosmetic rules (1945)
- Autoexperimentation

Policy to regulate research practices

Nuremberg code

- Developed by Allies after WW2
- Standards against which to judge Nazis
- Silent regarding informed consent if incompetent

Declaration of Helsinki (1964)

- Beyond Nuremberg code
- Differentiates clinical versus nonclinical research
- Proxy consent
- Primary emphasis on medical/clinical

Nuremberg code (1947)

- World war II (1939-1945)
- Nazi Physicians
- Held in NUREMBERG, GERMANY (~ NUREMBERG TRIALS)
- Cruel experiments (eg: starvation, infection with bacteria -antibiotics)

- US Judges in 1947 developed a code Outlined the basic principles to be followed if experimentation was to be conducted in future

1. Voluntary consent-essential
2. Fruitful results
3. Results - justify the performance of the trial
4. Avoid all unnecessary physical and mental suffering
5. No experiment-death causing(even with consent) - exception when physician himself is a subject
6. Risk<benefit
7. Adequate facilities to prevent injury in subjects
8. Only by scientifically qualified persons
9. During the experiment to have liberty to end
10. The physician should end if possibility of injury

http://www.cirp.org/library/ethics/nuremberg/

Declaration of Helsinki (1964)

- 18 th WMA general assembly
- Held at Helsinki,Finland
- In June 1964 (75,83,89,96,2000,02,04)
- Note: aimed at physicians > other research personnel
- Underrepresented population should also be included

- Privacy and confidentiality
- Duty of the care of physician
- Welfare of animals used in experimentation
- Environment –no harm

ICMR guidelines on human research 2006

3 main guidelines:

1. PURPOSE: increase knowledge
2. CONDUCT: dignity and well being of the subjects
3. EVALUATION: at all stages

Principles

1. Essentiality: absolutely essential > other alternatives
2. Voluntariness, informed consent: subject is well informed, can abstain whenever needed
3. Non-exploitation -> remuneration
4. Privacy and confidentiality
5. Precaution and risk minimisation
6. Professional competence
7. Accountability and transparency: no manipulation
8. Maximization of public interest: beneficial to humankind
9. Institutional arrangements: no discomfort to the subjects
10. Public domain: results are made known publically
11. Totality of responsibility of the researcher
12. Compliance: duty of everyone involved, all these guidelines are adhered, both in letter and spirit

- Respect for self determination and dignity of all subjects in research
- Need for free and informed consent
- Importance of protecting subject confidentiality
- Equity in the selection of subjects and distribution of risk
- Right of subjects to withdraw participation at any time without penalty

Major issues

- Research as moral imperative?
- Informed consent
- Who should be a research subject?
- Paying research subjects

Research as moral imperative?

- Usually utilitarian: improve treatment and techniques
- Benefited from previous research; must continue
  - Deontological
- Indispensable to progress
  - Health as a public good
  - Science is an instrument of progress

- **Informed consent**
  - Principle of respect
  - Autonomy
  - Competence
  - Coercion?
  - Who can consent?

- **Who should be a research subject?**
  - Volunteers in scientific community
  - Only what researcher would do him/herself
  - Economically and socially disadvantaged, children, prisoners

- **Paying research subjects**
  - Pay for their costs
  - No undue inducement
    - Set payment low so no coercion
    - Reflect the nature of the risk: how assess this?
      - When is too much risk?
    - What about patients?
    - fMRI studies?
    - Differs among labs and sets up competition

    Some argue that it is paternalistic

Pillars of Protection for Human Subjects in Research

- Consent
- Peer Review
- Research Integrity
- Duty to protect subjects
- Carry out studies per protocol
- Communicate with subjects
- Report findings honestly
- Conflict of Interest

The Common Rule

- 1986 the “Common Rule” proposed and then codified in 1991
- First time after more than 25 years in the making a comprehensive regulatory framework existed that formally governed all human subjects research conducted by the federal government or in facilitates receiving federal funds
- Defines requirements for informed consent
- Codifies special requirements for vulnerable populations
  - Pregnant women, fetuses, IVF
  - Prisoners
  - Children
- Requires institutional assurance of compliance

- Due to the growing public concern for adequate protection of human subjects in research, there are today many federal, state and institutional policies, procedures and regulations.
- On July 12, 1974, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.
- The guidelines established by this commission after nearly four years of deliberation, clearly defined the basic ethical principles that should underlie the conduct of all biomedical research on human subjects.
- These guidelines, referred to, as “The Belmont Report”

These guidelines stress three ethical principles:

1. Respect for persons (autonomy of the individual and individuals with diminished autonomy are entitled to protection).
2. Beneficence (the obligation to do no harm and to maximize possible benefits).
3. Justice (fairness).

Today, there are Institutional Review Boards (IRB), which are responsible for the review and approval of all research involving human subjects and are guided by the ethical principles as set forth in the "Belmont Report".

Animal Research and Bioethical Issues

- The ethical assessments related to the use of animals in research are wide-ranging.
- It is generally thought that it may be necessary to use laboratory animals in some cases in order to create improvements for people, animals or the environment.
- At the same time, the general opinion is that animals have a moral status, and that our treatment of them should be subject to ethical considerations.

Such views are reflected in the following positions:

(i) Animals have an intrinsic value which must be respected.

(ii) Animals are sentient creatures with the capacity to feel pain, and the interests of animals must therefore be taken into consideration.

(iii) Our treatment of animals, including the use of animals in research, is an expression of our attitudes and influences us as moral actors.

- The guidelines reflect all these positions, and stipulate principles and considerations that can be used as tools when balancing between harm and benefit.
- The three Rs **(Replace, Reduce, Refine)** are established principles that are also enshrined in legislation.
- These principles can establish absolute limits for experiments on animals, even when there are great benefits.
- These principles also state what can reasonably be considered harm and benefit, and the principles thus facilitate good assessments.
- Assessments of harm and benefit associated with experiments on animals are particularly demanding, because experiments may result in researchers intentionally causing actual harm to animals, while the future benefits are often uncertain.

- The guidelines are dynamic and must be reviewed in line with technological developments and the appearance of new ethical issues.
- New gene technology methods create new opportunities for the use of genetically modified animals in research, which is a growing trend.
- Genetically modifying laboratory animals, i.e. changing the genetic material of laboratory animals using gene technology, gives rise to a special responsibility in that this method entails a double intervention:
  - first, intervention in the animal's genetic material and
  - second, use of the animal as a research object.
- This practice has the potential to change our view of humans and our attitudes towards generating or eliminating genetic characteristics in ourselves.

Guidelines

1. **Respect for animals' dignity**
   Researchers must have respect for animals' worth, regardless of their utility value, and for animals' interests as living, sentient creatures. Researchers must be respectful when choosing their topic and methods, and when disseminating their research. Researchers must provide care that is adapted to the needs of each laboratory animal.
2. **Responsibility for considering options (*Replace*)**
   Researchers are responsible for studying whether there are alternatives to experiments on animals. Alternative options must be prioritised if the same knowledge can be acquired without using laboratory animals. If no good options are available, researchers should consider whether the research can be postponed until alternative methods have been developed. When justifying experiments on animals, researchers therefore must be able to account for the absence of options and the need to acquire knowledge immediately.

3. The principle of proportionality: responsibility for considering and balancing suffering and benefit

Researchers must consider the risk that laboratory animals experience pain and other suffering and assess them in relation to the value of the research for animals, people or the environment.

Researchers are responsible for considering whether the experiment may result in improvements for animals, people or the environment.

The possible benefits of the study must be considered, substantiated and specified in both the short and the long term. The responsibility also entails an obligation to consider the scientific quality of the experiments and whether the experiments will have relevant scientific benefits.

4. Responsibility for considering reducing the number of animals (*Reduce*)

Researchers are responsible for considering whether it is possible to reduce the number of animals the experiment plans to use and must only include the number necessary to maintain the scientific quality of the experiments and the relevance of the results.

This means, among other things, that researchers must conduct literature studies, consider alternative experiment designs and perform design calculations before beginning experiments.

5. Responsibility for minimising the risk of suffering and improving animal welfare (*Refine*)

Researchers are responsible for assessing the expected effect on laboratory animals. Researchers must minimise the risk of suffering and provide good animal welfare. Suffering includes pain, hunger, thirst, malnutrition, abnormal cold or heat, fear, stress, injury, illness and restrictions on the ability to behave normally/naturally.

6. Responsibility for maintaining biological diversity

Researchers are responsible for ensuring that the use of laboratory animals does not endanger biological diversity. This means that researchers must consider the consequences to the stock and to the ecosystem as a whole.

7. Responsibility when intervening in a habitat

Researchers are responsible for reducing disruption and any impact on the natural behaviour of individual animals, including those that are not direct subjects of research, as well as of populations and their surroundings.

8. Responsibility for openness and sharing of data and material

Researchers are responsible for ensuring that there is transparency about research findings and facilitating the sharing of data and material from experiments on animals. Such transparency and sharing are important in order to avoid unnecessary repetition of experiments.

In general, the negative results of experiments on animals should be public knowledge. Disclosing negative results may give other researchers information about which experiments are not worth pursuing, shine a light on unfortunate research design, and help reduce the use of animals in research.

9. Requirement of expertise on animals

Researchers and other parties who handle live animals must have adequately updated and documented expertise on animals. This includes specific knowledge about the biology of the animal species in question, and a willingness and ability to take care of animals properly.

10. Requirement of due care

There are national laws and rules and international conventions and agreements regarding the use of laboratory animals, and both researchers and research managers must comply with these. Any person who plans to use animals in experiments must familiarise themselves with the current rules.

Some **factors** used in guidelines to assess whether or not animals should be used in experiments, include:

- Aim of the experiment
- Realistic potential to achieve goals
- Species of animal
- Possible pain
- Duration of discomfort or distress
- Duration of experiment (interms of lifespan)
- Number of animals
- Quality of animal care
- Available alternatives to the experiment
- Credibility of the researchers

- Research with *humans* is necessary to medical progress, but we have set strict limits on the extent to which humans can be exposed to risk and harm in research
- Cline and Sanchez claim that animals in research are treated "humanely and with dignity.."
- the reality is that the level of protection afforded to research animals is far, far less than that afforded to human participants in research.
- Most animals involved in research are killed at the termination of the experiment, are kept in conditions not conducive to their welfare, and are otherwise harmed in myriad and significant ways, for example through the infliction of physical injuries, infectious diseases, cancers, or psychological distress.

- While nonhuman animals cannot provide consent to research participation, we have reasoned in the case of humans that an inability to consent entitles an individual to greater protection and not lesser protection.
- What justifies our differential treatment of humans and nonhuman animals in research?

- The claim that "animal research is necessary to medical progress" assumes a strong causal connection between the two
- What data have available cast doubt upon the robustness of this connection.
- Despite strong claims about the historical benefits of animal research from the scientific community, the accuracy of animal models in predicting human responses has not been evaluated sufficiently, and the lack of certain kinds of data make this evaluation especially challenging.

- Animal studies also frequently appear to be poorly designed.
- The predictive value of animal research might increase if study design improved.
- This does not mean that animal research has never produced any or even many important medical benefits, but these claims require empirical validation, not simply repeated assertion.
- Moral obligations to animals

Intrinsic and extrinsic ethical factors for ethical use of animals

Intrinsic Ethical Factors	Extrinsic Ethical Factors
- Pain - Self-awareness - Conscious of others - Ability to plan for the future - Value of being alive	- Human Necessity / Desire - Human sensitivity to animal suffering - Brutality in Humans - Effect on other animals - Religious status of animals - What is natural

Alternatives to Animal Testing

1- Cell cultures

- Almost every type of human and animal cell can be grown in the laboratory.
- Scientists have even managed to coax cells to grow into 3D structures, such as miniature human organs, which can provide a more realistic way to test new therapies.
- Human cells have been used to create innovative little devices called ‘organs-on-chips’. These can be used instead of animals to study biological and disease processes, as well as drug metabolism.
- Devices have already been produced that accurately mimic the lung, heart, kidney and gut. The ultimate goal is to use these chips to create a whole ‘human-on-a-chip’.
- Cell cultures have been central to key developments in areas such as cancers, sepsis, kidney disease and AIDS, and are routinely used in chemical safety testing, vaccine production and drug development.

2- Human tissues

- Both healthy and diseased tissues donated from human volunteers can provide a more relevant way of studying human biology and disease than animal testing.
- Human tissue can be donated from surgery (e.g. biopsies, cosmetic surgery and transplants). For example, skin and eye models made from reconstituted human skin and other tissues have been developed and are used to replace the cruel rabbit irritation tests.
- Human tissue can also be used after a person has died (e.g. post-mortems). Post-mortem brain tissue has provided important leads to understanding brain regeneration and the effects of Multiple Sclerosis and Parkinson's disease.

3- Computer models

- With the growing sophistication of computers, the ability to ‘model’ or replicate aspects of the human body is ever more possible.
- Computer models of the heart, lungs, kidneys, skin, digestive and musculoskeletal systems already exist. They can be used to conduct virtual experiments based on existing information and mathematical data.

4- Volunteer studies

- Rapid advances in technology have allowed for the development of sophisticated scanning machines and recording techniques that can be used to safely study human volunteers.
- An innovative technique called microdosing can also be used in volunteers to measure how very small doses of potential new drugs behave in the human body. These microdoses are radio-labelled, injected into human volunteers and measured (usually in blood samples) using a very sensitive measuring device called an accelerator mass spectrometer.
- Less high-tech studies for nutrition, drug addiction and pain can also be carried out on consenting humans in the interest of advancing medical science.

Alternatives are better

- Crude skin allergy tests in guinea pigs only predict human reactions 72% of the time. But a combination of chemistry and cell-based alternative methods has been shown to accurately predict human reactions90% of the time.
- The notorious Draize skin irritation test in rabbits can only predict human skin reactions 60% of the time. But using reconstituted human skin is up to 86% accurate.
- The standard test on pregnant rats to find out if chemicals or drugs may harm the developing baby can only detect 60% of dangerous substances. But a cell-based alternative (EST) has 100% accuracy at detecting very toxic chemicals.
- The cruel and unreliable shellfish toxin testing on live mice has now been fully replaced with a far superior analytical chemistry method that is better at protecting humans.
- Cell-culture based tests have considerably reduced the use of rodents in the initial screening of potential new medicines, while speeding up the process so that 10–20 times the number of compounds can be screened in the same period.