Ethics of Research Involving Human Subjects
DISCLAIMER

The following information are the personal views of the presenter and do not necessarily represent the views or opinions of the Ministry of Health nor the Medical Research & Ethics Committee.
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What is Ethics?

Research Ethics is about norms, values, right and wrong, good and bad, and what ought and ought not to be done in the context of research.

Ethics of Research Involving Human Subjects is all of the above but with emphasis on the dignity, safety and well-being of the human subject.
Definitions

Research

A **systematic** investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

Human Subjects

A **living** individual about whom an investigator conducting research obtains (a) data through intervention or interaction with the individual or (b) identifiable private information.
Who is responsible for research ethics?

- Should investigators be responsible for research ethics?

Two events salient and influential of subsequent development in research ethics

1. Nazi experiments on POW & Nuremberg Trial (1946); similar experiments by Japanese physicians (Unit 731)
2. Tuskegee Syphilis study
Nazis experiment & Nuremberg Trial

- Hypothermia experiments: A prisoner is submerged in cold tank; goal of to determine how long German pilots would survive after parachuting into the cold north sea.

- High altitude experiments: Prisoners put into low-pressure tanks with little oxygen; goal to test how long pilots would survive after being ejected.
Prisoners of war & citizens of occupied countries as subjects

- Experimental surgeries without anesthesia
- Effectiveness of weapons – conventional, biological, chemical
- Course of untreated diseases
- Subjects incinerated after studies
Tuskegee Syphilis Study

- Study in Tuskegee, Alabama between 1932 and 1972 to determine the natural history of untreated latent syphilis.
- Over 400 black men with syphilis and about 200 men without syphilis, who served as the controls, were the subjects.

**Ethical issues:**
- Inadequate disclosure of information
- Subjects believed they were getting free treatment
- Told that spinal taps was therapy
- US Gov’t actively prevented men from receiving penicillin
- In 1972 press reports caused the U.S. Gov’t to stop the study
Chronology of Regulation of Research Involving Human Subjects

- Nuremburg Code, 1947 (CODE)
- Declaration of Helsinki, 1964 (GUIDELINES)
- U.S. National Research Act, 1974 (LAW)
- Belmont Report, 1979 (REPORT)
- ICH-GCP, 1996 (SOP)

US Code of Federal Regulations (LAW)

- *Title 45 CFR Part 46*: Addresses the protection of human subjects of biomedical research
- *Title 21 CFR 50*: FDA policy on protection of human subjects for research on FDA regulated product
- *Title 21 CFR 56*: FDA requirement for IRB review
Nuremberg Trial 1947: Nazi doctors and scientists put on trial for the murder of concentration camp inmates who were used as research subjects. During the trial fundamental ethical principles for human subject research were codified into the Nuremberg Code that sets forth ten articles:

• Article 1: “The voluntary consent of the human subject is absolutely essential.”
• Article 9: “Subjects have the right to withdraw at any time”
• Articles (2-8, 10): Scientific value; Favorable risk/benefit ratio; Suffering by subjects be avoided

The Nuremberg Code became the first codification of research guidelines to protect human subjects; BUT without the force of law
“the most widely accepted guidance worldwide on medical research involving human subjects.” Christie. BMJ 2000

World Medical Association (est. 1946), in response to the Nuremberg Code, develop this guideline for research ethics; adopted at its 18th General Assembly in Helsinki in 1964

Has gone thru’ 7 revisions since, latest October 2013 Brazil

Extend Nuremberg code to include:

- Research combined with medical care
- Incompetent subjects and Vulnerable subjects
- Review by an independent review committee
- International research (research in developing countries)

However, like all other guidelines, they lack the force of law
Tuskegee was a watershed event.

- As a result of the Tuskegee study, protection for human subjects was strictly regulated in the US.
- U.S. National Research Act (1974): a national regulation with force of law behind it; require independent IRB review (no more investigators’ discretion)
- National Commission established to report on how human subjects of Biomedical Research could be better protected. Issued the Belmont Report (1979)
ICH-GCP

- A document produced in 1996 at the International Conference for the Harmonization (ICH) of technical requirements for registration of pharmaceuticals for human use

- An international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials involving the participation of human subjects
Three ethical principles for clinical research

*The Belmont Report 1979* introduced 3 fundamental ethical principles that is now widely accepted:

1. Respect for person
2. Beneficence and non-malfeasance
3. Justice
1. Respect for Person

2 ethical convictions:
1. Individuals must be treated as autonomous agents
2. Persons with diminished autonomy must be protected

“An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation.”

Commission

“Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated” Commission
2. Beneficence and non-malfeasance

In research, beneficence is understood in a stronger sense, as an obligation.

Two general complementary rules (*Commission*):

1. Do not harm
2. Maximize possible benefits and minimize possible harms.

“In research .... one should not injure one person regardless of the benefits that might come to others”  
*Claude Bernard*
3. Justice

All individuals must be treated fairly.

In research, concern is with **distributive justice**, i.e. distribution of benefits or burdens

“Research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research” *Commission*
Seven requirements for Ethical research

1. Societal/Scientific value
2. Scientific validity
3. Fair subject selection
4. Favorable risk-benefit ratio
5. Respect for subjects
6. Informed consent
7. Independent review
1. Social or Scientific Value

Each study must have social or scientific significance. The treatment or hypotheses being tested should improve health and well being or increase knowledge about the research area.

Basic reason why Value is ethically important:

Human subjects should not be exposed to unnecessary harm or placed at risk of potential harm without some possible social or scientific benefit from the research.
2. Scientific Validity

Clinical research should be well designed not only to ensure its scientific quality but also its ethical propriety.

Two reasons why Validity is ethically important:

1. **Avoidance of exploitation.**

   "Scientifically unsound research on human subjects is ipso facto unethical in that it may expose subjects to risks or inconvenience to no purpose."  *CIOMS 2002*

2. **Accuracy of outcomes / findings**

   Scientifically valid design ensures research outcomes are accurate and reproducible.
3. Fair subject selection

Fair subject selection means that vulnerable individuals or “convenient” sample are not unfairly targeted for risky research; and the rich and socially powerful are not favored for potentially beneficial research. Subjects should not be selected that can cause biased or inaccurate outcomes.

Fair selection of subject for research entails:

1. Decisions about who will be included through the development of specific inclusion and exclusion criteria
2. Strategy for recruiting subjects, such as which communities and individuals to be approached
3. Fair subject selection

Important vulnerable \((\textit{NOT to be unfairly targeted})\) or underrepresented \((\textit{NOT to be unfairly excluded})\) groups:

1. Children
2. Women
3. Emergency patients
4. Populations of developing countries
5. Minority populations
6. Institutionalized populations (\textit{vulnerable only})
7. Members of a group with a hierarchical structure, e.g., students, employees, subordinates, armed forces, prisoners ICH GCP 1.61 (\textit{vulnerable only})
8. Fetus and embryo (\textit{Vulnerable only})
4. Favorable risk benefit ratio

There is always an element of risk in Clinical research. The assessment of risks and benefits is therefore arguably the most important responsibility of an IRB/IEC.

Clinical research can be justified only if, consistent with the scientific aims of the study and the relevant standards of clinical practice, and:

1. Risks to individual subjects are minimized
2. Benefits to individual subjects are enhanced
3. Benefits to individual subjects and society are proportionate to or outweigh the risks
5. Respect for research subjects

Individuals must continue to be treated with respect from the time they are enrolled, throughout their participation and even after their participation ends.

Respecting subjects means doing the following:

1. Protect subject’s confidentiality & privacy
2. Provide opportunity to withdraw early, without penalty
3. Monitor subject’s well-being. Have procedures to manage:
   - Adverse reactions, emergencies, change in clinical status
   - Pregnancy: discontinuation? Monitor till outcome
5. Respect for research subjects (cont)

4. Inform subject of new information, and re-consent if necessary

5. Inform subject of study results, in recognition of contribution to research

6. Compensate subject for research injury
6. Informed Consent

ICH-GCP 4.8

- Should be revised when new information becomes available relevant to subject’s consent
- Text should not coerce or induce participation or continued participation
- Should not contain statements that cause subject to waive any legal rights, or appears to release investigator, institution or sponsor from liability of negligence
6. Informed Consent

ICH-GCP 4.8

- Language used should be as non-technical as practical and should be understandable to the subject.
- Should provide subject with ample time and opportunity to enquire about details of study and to make decision.
- Informed consent form must be signed and dated by subject before participation.
6. Informed Consent

MREC Guidelines on Research Involving Minors

- Assent of Minors is required in research involving subjects of age 7 to <18 yrs
- Assent must be respected in most situations
- Agreement of parents or legal guardians is required before assent of minor is obtained
- Assent information sheet must be in a language easily understood by the relevant age group
6. Informed Consent

MREC SOP on Waiver of Informed Consent

- Waiver of informed consent is to be regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee (CIOMS, 2002)
- Must satisfy one or more of the following criteria:
  - Involves no more than minimal risk
  - Study designed to investigate, evaluate or examine public service programmes
Medical records and biological specimens taken in the course of clinical care may be used for research without the consent of the patients/subjects only if

- the research poses minimal risk,
- the rights of interests of the patients will not be violated,
- their privacy and confidentiality or anonymity are assured, and
- the research is designed to answer an important question and will be impractical if the requirement of informed consent is to be imposed.

Refusal or reluctance of individuals to agree to participate is not evidence of impracticability sufficient to warrant waiving informed consent. (CIOMS, 2002)
Study involving the collection or use of existing data, documents, records, pathological specimens, or diagnostics if these sources are publicly available, or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. (Mercer University, 2006)
6. Informed Consent

ICH-GCP

21 essential elements must be stated in patient information sheet

Malaysian GCP

22 essential elements must be stated in patient information sheet
7. Independent Review

A fundamental requirement for ethical research for 2 reasons:

1. Independent review by unaffiliated individuals minimize the impact of conflicts of interest (of investigators, sponsors, institutions).

2. Independent review is important for social accountability; assures the public that human subjects who enroll in trials will be treated ethically.
7. Independent Review

ICH GCP 1.31 Institutional Review Board (IRB) or Independent Ethics Committee (IEC)

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.
7. Independent Review

**ICH GCP 1996**

2.6 A trial should be conducted in compliance with the protocol that has received prior IRB/IEC approval/favourable opinion.

The IRB/IEC should consist of a reasonable number of members who collectively have the qualifications and experience to review and evaluate the science, medical aspects and ethics of the proposed trial.
7. Independent Review

ICH GCP 3.3 Procedures should include the following:

- Initial and continuing review (frequency) of trials
- Expedited review
- Specify no subject to be included in trials until IRB/IEC issues written approval
- No deviations / changes of protocol should be initiated without prior written IRB/IEC approval EXCEPT to eliminate immediate hazards to subjects or involving only logistical or administrative aspects.
ICH GCP 3.3 Procedures

Specify investigator should promptly report to IRB/IEC:

- deviations from or changes to protocol to eliminate immediate hazards to trial subjects
- changes increasing the risk to subjects
- adverse drug reactions
- new information

• (www.nih.gov.my/mrec)
Case Study

Edward Jenner had a theory that if he could inject someone with cowpox germs, the person can be protected against smallpox infection.

On May 1796, he extracted some liquid from a cowpox patient and then some liquid from the sores of a patient with mild smallpox.

Jenner asked a local farmer if he could inoculate the farmer’s son James against smallpox. He explained to the farmer that if his theory was correct, James would never contract smallpox. The farmer agreed.

Jenner made two small cuts on James's left arm. He then poured the cowpox liquid into the open wounds which he bandaged. James went down with cowpox but was not very ill. Six weeks later when James had recovered, Jenner infected him with the smallpox liquid. To Jenner's relief James did not catch smallpox. His experiment had worked.

Is this study compliant with the 3 ethical principles and 7 requirements of research involving human subjects?
Thank You

MREC
Protecting Human Research Subjects