Introduction to Research Ethics

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Objectives

By the end of the session the participants will be able to

1. Define why research ethics ?
2. Recognize how research ethics guidelines have evolved.
3. Identify what makes research ethical

Why research Ethics?

- Research has produced significant achievements, including the development of many new drugs, devices and techniques.

- Many of the these improvement in health care was produced by conduction if research in human subjects

What is Research ?

- A systematic investigation designed to develop or contribute to generalizable knowledge

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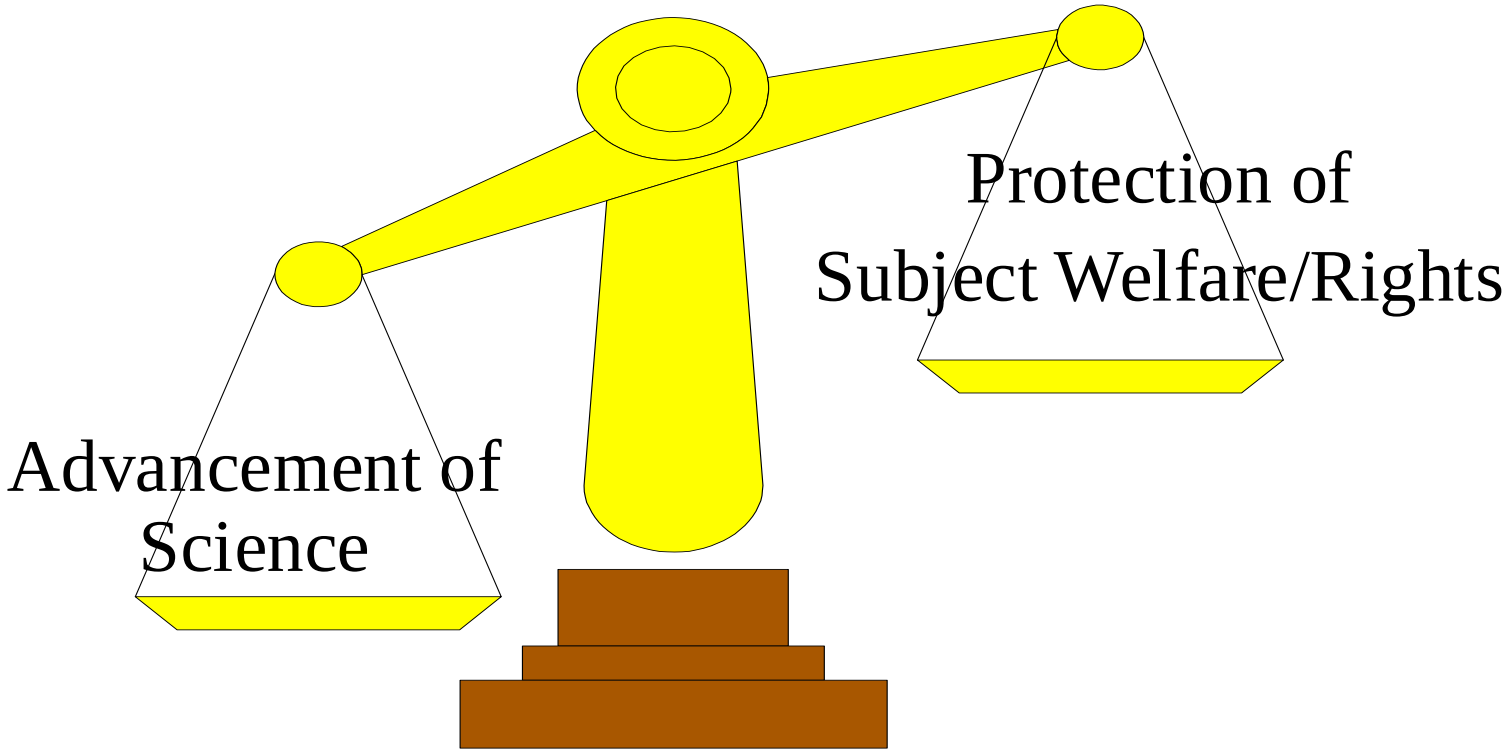
Non Research Examples

- **Case Study:**
  - Single case study example usually subjective and does not suggest generalizability
- **Quality Assurance Surveys:**
  - Program evaluation purposes, with no generalization, usually do not constitute human subject research and usually do not require research ethics committee review

Research Subjects

- Means to obtaining research based knowledge.
  - Respect for dignity safety and autonomy is important

Balancing Two Goals



History of Research Ethics

- Before 19th century
  - Small scale, involving few individuals, therputic in intend

- Edward Jenner (1749-1823) first tested smallpox vaccines on his son and on neighborhood children.
- Johann Jorg (1779-1856) swallowed 17 drugs in various doses to record their properties.

History of Research Ethics

- Moses Maimonides (1135 – 1204) instructed colleagues always to treat patients as ends in themselves, not merely as means for learning new truths.

- Claude Bernard (1865) wrote in his “An Introduction to the Study of Experimental Medicine”::

  “[The first principle of medical morality] “consists in never performing on man an experiment which might be harmful to him to any extent, even though the result might be highly advantageous to science.”

- Louis Pasteur (1822-1895), "agonized over treating humans, even though he was confident of the results obtained through animal trials. He finally did so only when he was convinced the death of the child, the first test subject, "appeared inevitable.”

History of Research Ethics

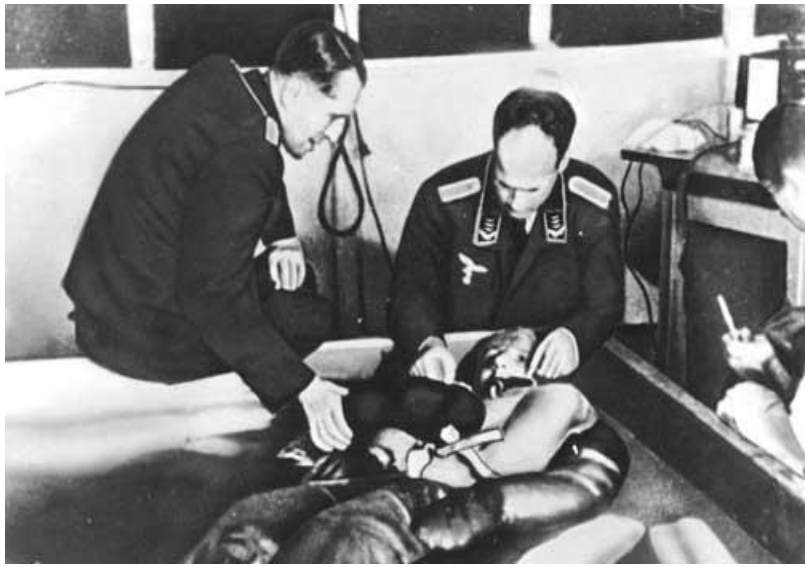
- Beginning of 20th century
  - Larger scale clinical trials
  - collect systematic data
  - groups of individuals
  - vulnerable groups

- Prisoners
- Orphans
- Mentally ill

No Formal Codes of Research Ethics

NEW ERA IN RESEARCH ETHICS

- **NAZI WAR EXPERIMENTS**
- Medical experiments conducted by the German physicians on concentration camp prisoners



World War II

- High Altitude Experiments
- Hypothermia Experiments
- Malaria Experiments
- Typhus experiments

Nuremburg Nazi Doctors' Trial (1947)

Nazi doctors and scientists put on trial for the murder of concentration camp inmates who were used as research subjects

15 of 23 guilty, 7 hanged, 5 life sentences

Nuremberg Code (1947)

First Codification of Research Guidelines

Human Rights + Welfare of Subjects

10 codes

Article 1

The first and longest principle

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

Articles (2-8, 10)

- Scientific value
- Favorable risk/benefit ratio
- Suffering by subjects should be avoided

Article (9)

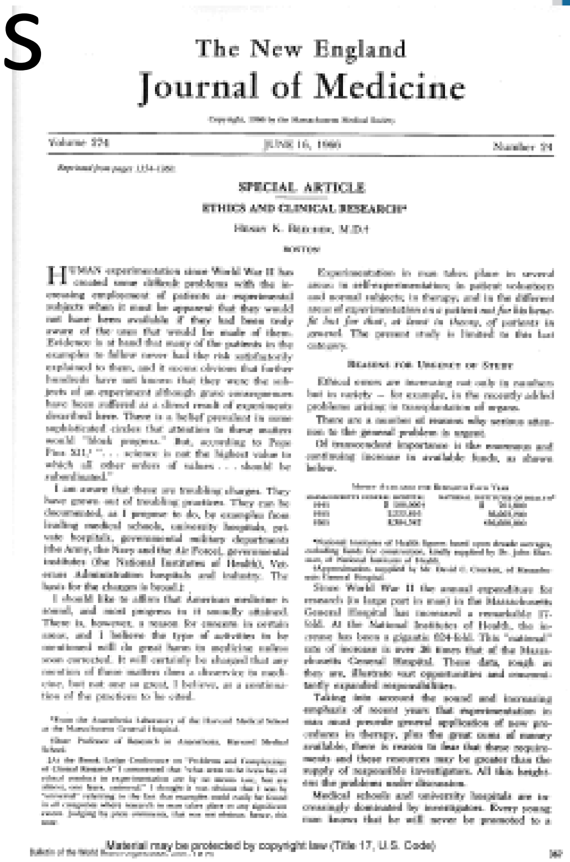
Subjects have the right to withdraw at any time

Declaration of Helsinki (1964)

- World Medical Association - 1953
- Interprets Nuremberg Code for research that involves patients who are receiving medical care
- Some risks justified by “potential therapeutic or diagnostic value for the patient”.
- In case of legal incompetence, informed consent should be obtained from the legal guardian
- Review of research by an independent review committee
- It is revised in 1975, 1983, 1996, 2000, 2008 and 2013.

Research Abuses

- 1966, Henry Beecher: Published 22 examples of abuses
- Withholding antibiotics from patients with rheumatic fever
- Purposely infecting institutionalized children with hepatitis
- Injecting live cancer cells into nursing home patients



The New England Journal of Medicine

Volume 274 JUNE 16, 1966 Number 24

SPECIAL ARTICLE

ETHICS AND CLINICAL RESEARCH*

BOSTON

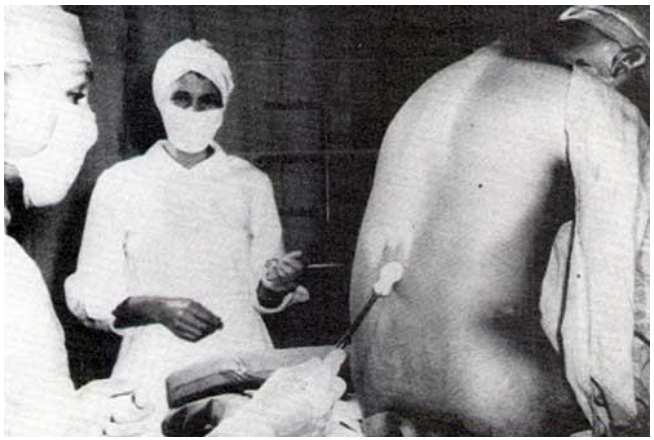
Abuses and exploitations of humans in research continued despite having ethics codes

And at the same time !

Tuskegee Syphilis Study (1932 - 1972)

- Tuskegee, Alabama- Macon county
  - High prevalence of syphilis
  - Although treatment existed, blacks in the rural southern town were not receiving treatment
  - Lack of funds/Lack of doctors
- Study natural course of syphilis
  - Enrolled 400 black males infected with syphilis
  - Not an experiment but rather a “study in nature”

Tuskegee Syphilis Study (1932 - 1972)



- 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
- 1972 press reports caused the U.S. Gov’t to stop the study

Response to Ethical Lapses

- U.S. National Research Act (1974)
  - National Regulations – force of law
  - Independent review of research by Institutional Review Boards (IRBs)

Review could not be left to discretion of investigators

- Belmont Report (1979)
  - Statement of ethical principles
  - Respect , Beneficence, Justice

Research Ethics Principles

إحترام الأشخاص	Respect
الفائده	Beneficence
العدل	Justice

Respect – Autonomy

- **Elements of autonomy include:**
- Decision making capacity
  - the ability to understand information
  - the ability to appreciate information
  - the cognitive ability to process information and come to a decision
- Voluntariness: be free from
  - Coercive influences
  - Undue inducement

Beneficence

- **General rules governing research that go along with expressions of beneficent actions include:**
- Do no harm (non-maleficence)
- Minimization of harms
- Maximization of benefits
- A favorable risk-benefit ratio

Justice

The principle of justice in the sense of “fairness in distribution” requires:

- research is designed so that its burdens and benefits are shared equitably among groups of populations
- fairness in the selection of research subjects, e.g., one should not select subjects based on their easy availability or their compromised position (e.g., individuals in a mental institutions)

Headlines

May, 2006

The Washington Post

Panel Faults Pfizer in '96 Clinical Trial In Nigeria: Unapproved Drug Tested on Children

Feb, 2005

SciDev Net

Cameroon suspends trial AIDS drug after protests

Feb, 2009

CNN

Growth of clinical trial outsourcing raises issues

Trovan Case in Nigeria

- Epidemic outbreak of bacterial meningitis in Nigeria
- Pfizer conducted trial of Trovan in children
- Pfizer accused of conducting trial without
  - Approval from relevant local regulatory authorities
  - Ethical approval/Informed consent lacking
- Did Pfizer researchers take advantage of
  - The absence of a functional ethics committee.
  - The desperation of the affected poor, illiterate people.
  - The emergency situation that facilitated recruitment of participants.

Trovan Case in Nigeria

- Pfizer's experiment was "an illegal trial of an unregistered drug," the Nigerian panel concluded, and a "clear case of exploitation of the ignorant”.

CIOMS 1993,2002,2016

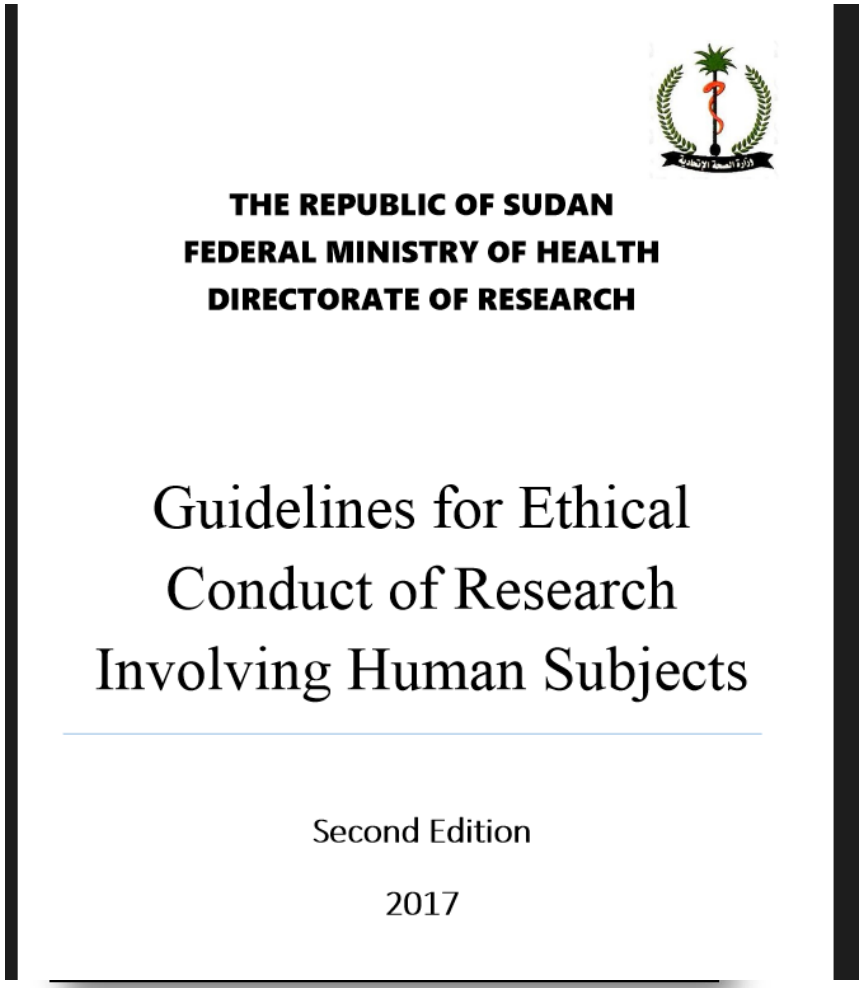
- Council for International Organizations of Medical Sciences: International Ethical Guidelines for Biomedical Research Involving Human Subjects
- Apply Helsinki to the conduct of International Clinical Trials

Guidelines that Govern Human Subjects Research in Sudan

- Soon after the CIOMs and WHO had established their guideline the Federal Ministry of Health (FMOH) issued a Decree (Ministerial Decree no 11 / 2002) to form a National Health Research Ethical Committee (NHREC) responsible of protection of human subjects included in research..

Guidelines that Govern Human Subjects Research in Sudan

- It was no until 2008 that the NHREC issued a document “National Guidelines for Human Subject Protection” as a guideline to be followed for research involving human subjects
- This was further reviewed and amended in 2017 through a grant from the EDCTP



Putting Principles into Practice

“What Makes Clinical Research Ethical ?”
Guidelines for Research Ethics

- **Value - Social and Scientific** — القيم الاجتماعية والعلمية
- **Scientific Validity** — الصلاحية العلمية
- **Fair Subject Selection** — العدل فى اختيار الأشخاص محل البحث
- **Favorable Risk-Benefit Ratio** — تغليب المنافع على المخاطر
- **Informed Consent** — الموافقة المستنيرة
- **Respect for Enrolled Subjects** — احترام الأشخاص محل البحث
- **Independent Review** — المراجعة المستقلة
- **Community Perspective** — منظور المجتمع

Tanslated by Prof. Dr. Wafaa E. Abdel-Aal
National Research Centre, Cairo, Egypt

1. Value
Social and Scientific

To be ethical clinical research must lead to improvements in health or advancement in generalizable knowledge

- Clinical trials, especially in developing countries, should address problems that are relevant to the community.

- If research lacks value, it is unethical because it exposes subjects unnecessarily to potential harms without a compensating societal benefit and it wastes time and resources.

2. Scientific Validity

Research must be conducted with an appropriate methodology to ensure that the results will answer the original research questions

- **Invalid research:**
  - underpowered studies
  - studies with inappropriate endpoints or statistical tests
  - studies that cannot enroll sufficient subjects


THANK YOU FOR NOT DOING RESEARCH THAT HAS ALREADY BEEN DONE

3. Equitable Selection of Subjects

- Selection of subjects is equitable
- Convenient (vulnerable) groups should not be targeted.
- CIOMS #13
  - Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests.
  - More formally, they may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests

3. Equitable Selection of Subjects

- Avoid choosing groups based solely on easy availability or compromised position.
- Not involving groups unlikely to benefit from the subsequent applications of the research.
- Ensuring that the benefits and risks of research are distributed fairly among all groups in society

4. Favorable Risk-Benefit Ratio

- Risks are identified
- Risks are minimized
- Potential benefits enhanced
- Risks are reasonable to potential benefits to subject and society

Favorable Risk-Benefit Analysis

RISK OF HARMS

Participants

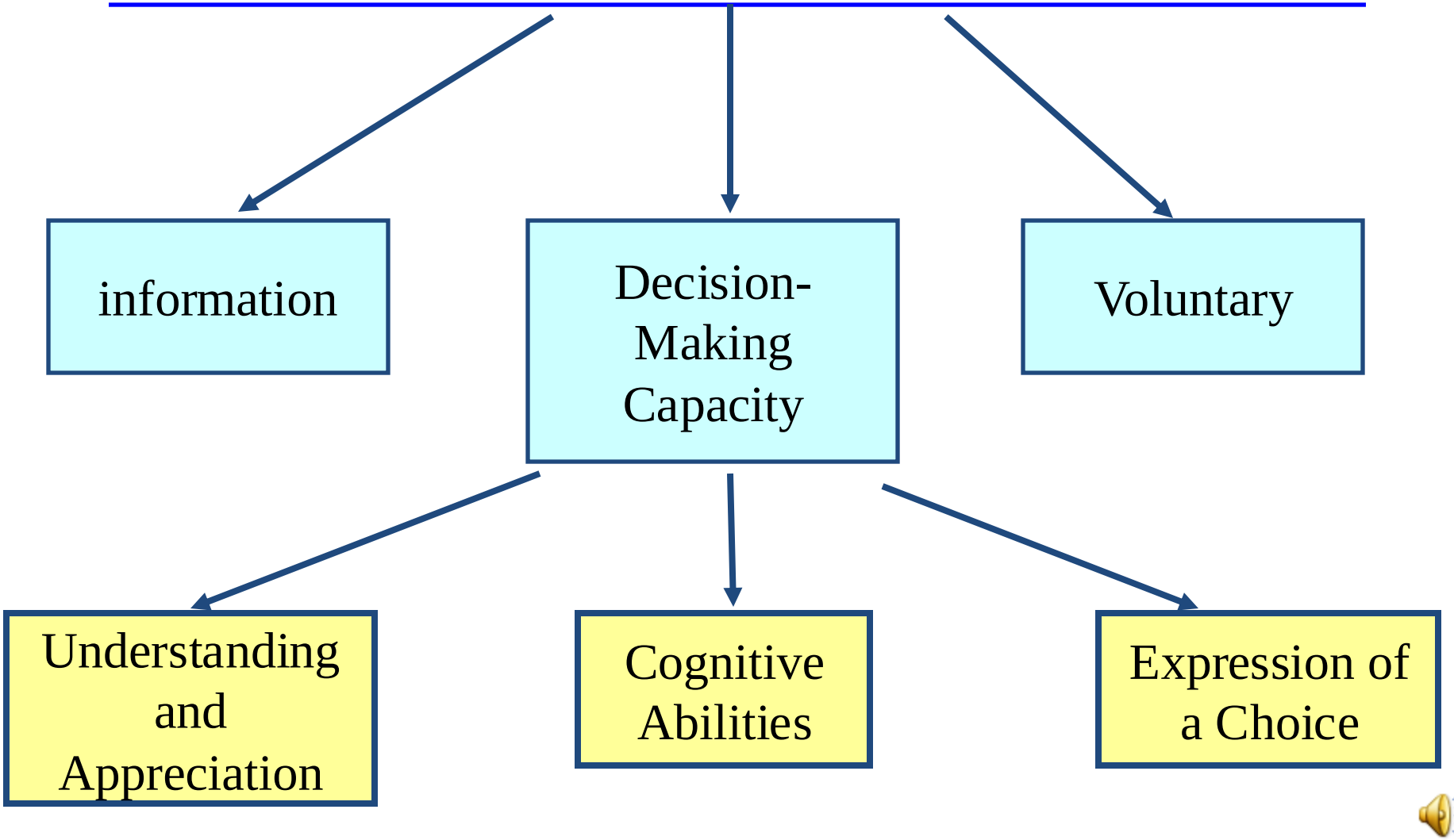
POTENTIAL BENEFITS

Participants + Society

5. Informed Consent

- Informed consent ensures that individuals themselves decide:
  - whether to enroll in research and
  - whether research fits with their own values, interests, and goals.
- Research on individuals who cannot decide requires surrogate consent
  - children and mentally impaired

The CIOMS Guidelines have defined informed consent as consent given by a competent individual who:



6. Respect for Enrolled Subjects

- The ethical requirements of research do not end with a signed consent document.
- Respecting enrolled subjects includes:
  - Permitting withdrawal
  - Protecting privacy& confidentiality
  - Informing of new risks & benefits
  - Informing of results of clinical research
  - Maintaining welfare of subjects (e.g. treatment of the adverse effect)

7. Independent Review

- Investigators have multiple legitimate interests,
  - the enhancement of the health of society,
  - advancement of their careers,
  - and protection of the rights and welfare of human subjects.

- These multiple interests can lead to potential conflicts of interests that can promote the use of questionable scientific design and research conduct that puts human subjects at risk.

- Independent review of the research helps minimizes these conflicts.

- To be independent, members of RECs or IRBs must be free from academic, political, and social influences that can affect their decisions.

8. Community Enrolment

- To be ethical research must be responsive to the needs of the community
- Should involve the community in which it occurs.
  - planning, conducting and overseeing the research.
- There should be assurances that the results will be integrated into the health system

"What Makes Clinical Research Ethical ?"
Guidelines for Research Ethics

- **Social and Scientific Values**
- **Scientific Validity**
- **Fair Subject Selection**
- **Favorable Risk-Benefit Ratio**
- **Informed Consent**
- **Respect for Enrolled Subjects**
- **Independent Review**
- **Community Perspective**

Emanuel et al. JAMA. 2000, vol 238, No. 20

Acknowledgment

The Middle East Research Ethics Training Initiative (MERETI)

http://www.mereti-network.net/

Thank You