

# 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 these improvements in health care were produced by conducting research in human subjects



# What is Research ?

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

- 



# 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

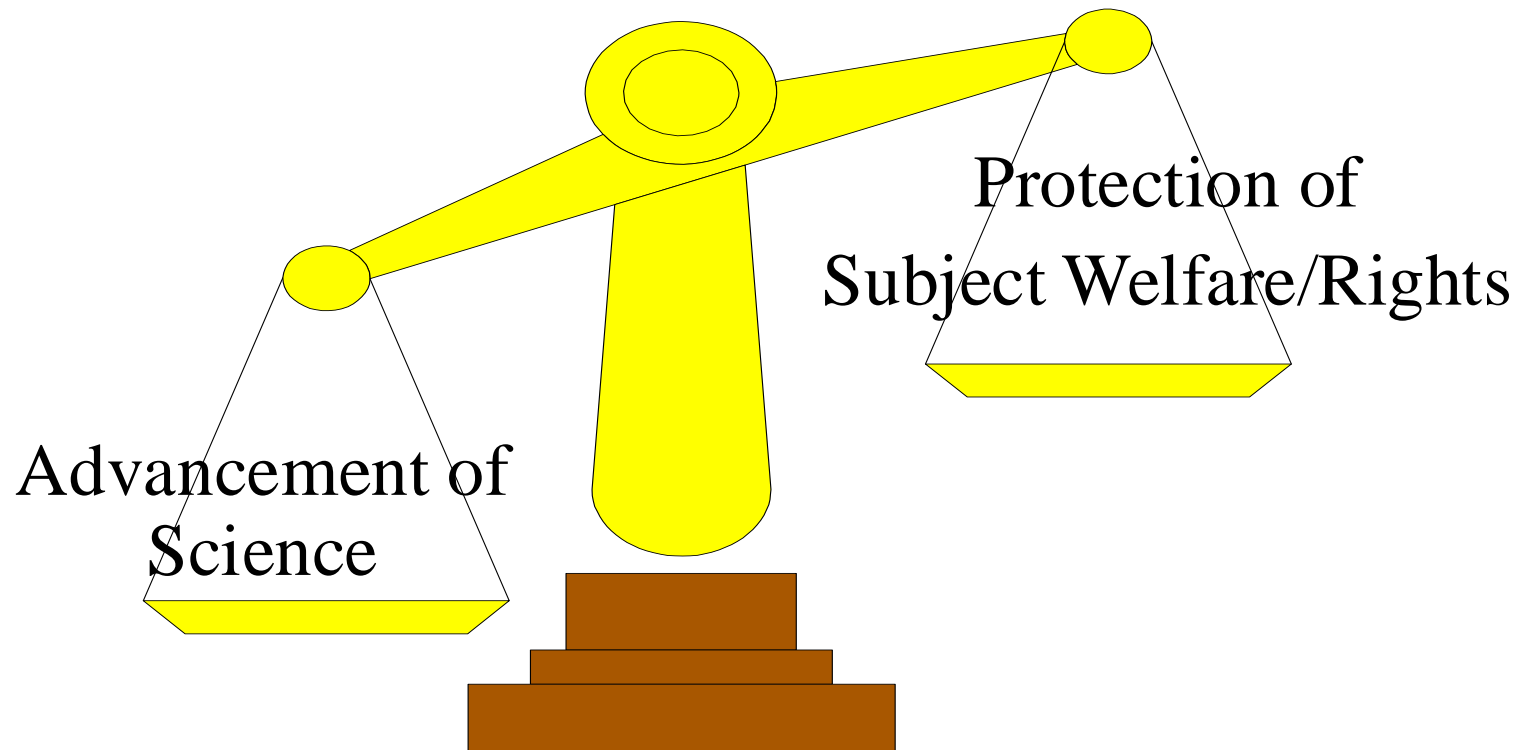


# Research Subjects

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



# Balancing Two Goals



# History of Research Ethics

- Before 19<sup>th</sup> century
  - Small scale, involving few individuals, therapeutic in intent
- 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 20<sup>th</sup> 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
- High Altitude Experiments
- Hypothermia Experiments
- Malaria Experiments
- Typhus experiments



World War II



# 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

SPECIAL ARTICLE  
ETHICS AND CLINICAL RESEARCH\*

HENRY K. BEECHER, M.D.†

EDITOR

**H**UMAN experimentation since World War II has created some difficult problems with the increasing employment of patients as experimental subjects when it must be apparent that they would not have been available if they had been truly aware of the man that would be made of them. Evidence is at hand that many of the patients in the examples to follow never had the risk satisfactorily explained to them, and it seems obvious that further benefits have not known that they were the subjects of an experiment although some consciousness have been suffered as a direct result of experiments described here. There is a belief prevalent in some sophisticated circles that attitudes in these matters would "blow progress." But, according to Pope Pius XII: "... science is not the highest value to which all other values of values... should be subordinated."

I am aware that there are troubling changes. They have grown out of troubling questions. They can be documented, as I propose to do, by examples from leading medical schools, university hospitals, private hospitals, governmental military departments (the Army, the Navy and the Air Force), governmental institutes (the National Institutes of Health), Veterans Administration hospitals and industry. The basis for the changes is broad:

I should like to affirm that American medicine is sound, and most progress in it usually obtained. There is, however, a reason for concern in certain areas, and I believe the type of activities to be mentioned will do great harm in medicine unless more controlled. It will certainly be charged that any mention of these matters does a disservice to medicine, but not one so great, I believe, as a restriction of the practices to be cited.

\*From the Anatomical Laboratory of the Harvard Medical School at the Massachusetts General Hospital.

†Chief, Professor of Research in Anesthesiology, Harvard Medical School.

At the Brook-Little Conference on "Problems and Responsibilities of Clinical Research" I commented that "what seems to be the lack of ethical control in experimentation are by no means few, but are often, very few, indeed." I thought it was obvious that I was by "accident" referring to the fact that examples could only be found in all companies which have in one way or other in one significant way, joining the great procession, that we are witness, here, this day.

Experimentation in man takes place in several areas: in self-experimentation, in patient volunteers and normal subjects in therapy, and in the different areas of experimentation as a patient's need for his health. So far as that, at least in theory, of patients in general. The present study is limited to the last category.

REASONS FOR URGENCY OF STUDY

Ethical issues are increasing not only in number but in variety — for example, in the recently added problems arising in transplantation of organs.

There are a number of reasons why serious attention to this general problem is urgent. Of immediate importance is the expansion and continuing increase in available funds, as shown below.

MEDICAL RESEARCH ON HUMAN BEINGS: FIVE YEAR AGGREGATED COSTS (APPROXIMATE) IN MILLIONS OF DOLLARS		
1961	1,300,000	1,300,000
1962	1,500,000	1,500,000
1963	1,800,000	1,800,000
1964	2,200,000	2,200,000
1965	2,800,000	2,800,000

\*National Institutes of Health figures based upon decade averages, including funds for construction, funds supplied by its John Hay Van Hook Institute of Health.

†Approximate, compiled by Dr. David C. Cooke, of Massachusetts General Hospital.

Since World War II the annual expenditure for research in large part is spent in the Massachusetts General Hospital has increased a remarkable 77-100%. At the National Institutes of Health, the increase has been a gigantic 654-655. This "national" rate of increase is more 20 times that of the Massachusetts General Hospital. These data, such as they are, illustrate our opportunities and increasingly expanded responsibilities.

Taking into account the sound and increasing emphasis of recent years that experimentation in man must provide general application of new procedures in therapy, plus the great mass of money available, there is reason to fear that these requirements and these resources may be greater than the supply of responsible investigators. All this heightens the problems under discussion.

Medical schools and university hospitals are increasingly dominated by investigators. Every young man knows that he will never be promoted to a

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



And at the same time !



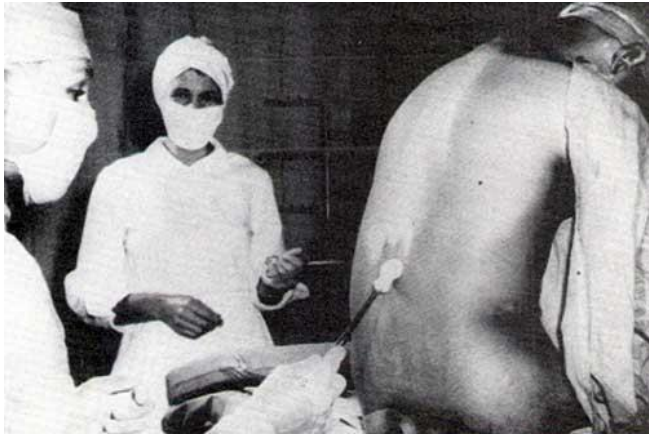


# Tuskegee Syphilis Study (1932 - 1972)

- 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

الفائدة

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

*The  
Washington  
Post*

- 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 not 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



**THE REPUBLIC OF SUDAN  
FEDERAL MINISTRY OF HEALTH  
DIRECTORATE OF RESEARCH**

## Guidelines for Ethical Conduct of Research Involving Human Subjects

Second Edition

2017



# Putting Principles into Practice



# “What Makes Clinical Research Ethical ?”

## Guidelines for Research Ethics

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

القيم الاجتماعية والعلمية  
الصلاحية العلمية  
العدل في اختيار الأشخاص محل البحث  
تغليب المنافع على المخاطر  
الموافقة المستنيرة  
احترام الأشخاص محل البحث  
المراجعة المستقلة  
منظور المجتمع



# 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



S. Harris



### 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

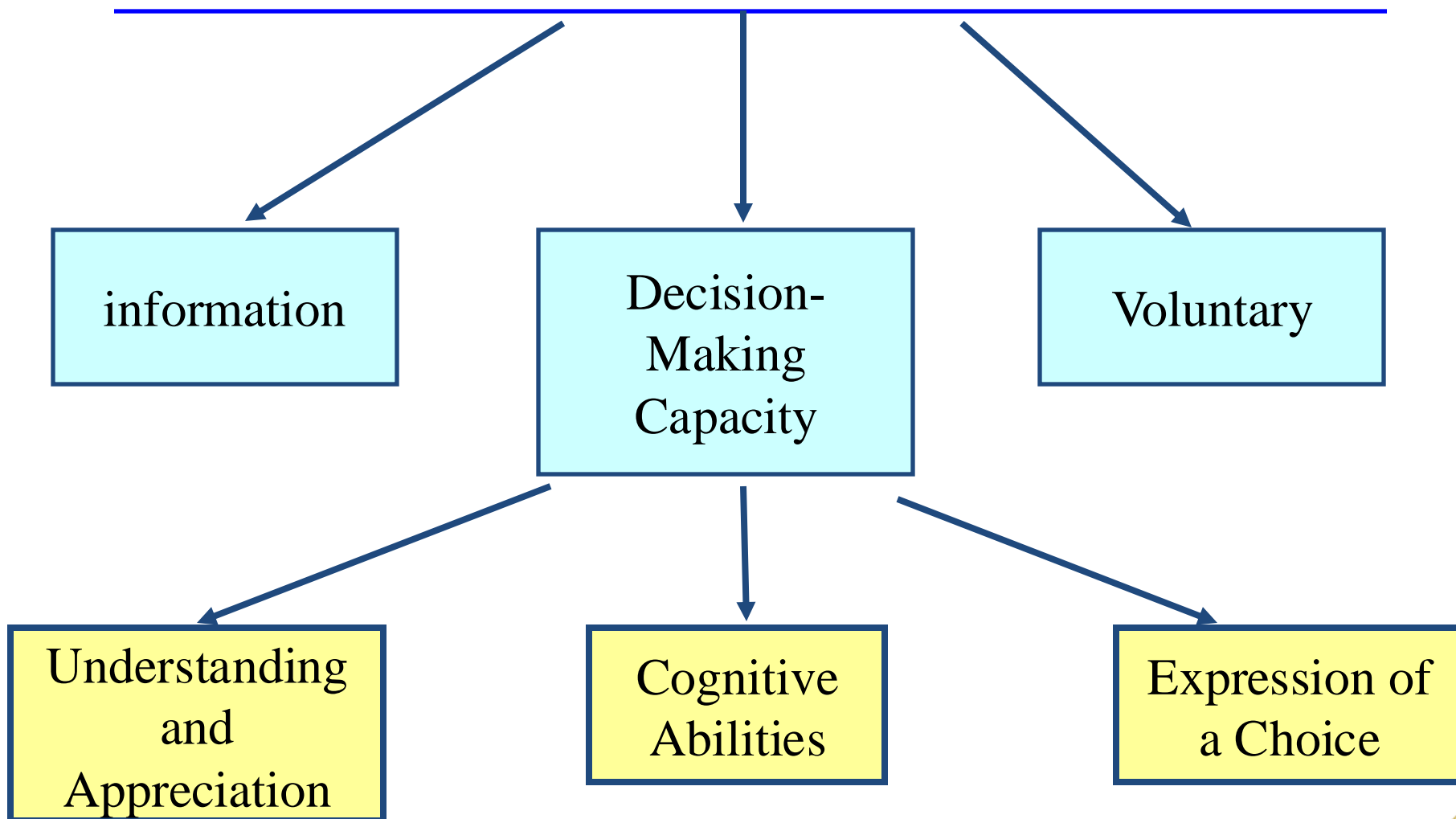


# 5. Informed Consent

- 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 minimize 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**



# Acknowledgment

The Middle East Research Ethics Training  
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<http://www.mereti-network.net/>



THANK YOU

