# Ethics Principles for Clinical Research

Yupaporn Wattanagoon
Department of Clinical Tropical Medicine
Faculty of Tropical Medicine
Mahidol University

# Ethics

- A set of principles of right conduct.
- The rules or standards governing the conduct of a person or the members of a profession: medical ethics.

# Ethics

- The philosophical study of the moral value of human conduct and of the rules and principles that ought to govern it
- A social, religious, or civil code of behavior considered correct, esp. that of a particular group, profession, or individual
- The moral fitness of a decision, course of action, etc.

# Hippocratic Oath

*Primum non nocere*

Above all, do no harm.

# Hippocratic Oath

"I will follow that system of regimen which, according to my ability and judgment, I consider for the benefit of my patients and abstain from whatever is deleterious and mischievous."

Hippocrates, 400 BC

# Medical Ethics

The International Code of Medical Ethics

“A physician shall act in the patient's best interest when providing medical care.”

WMA
“The health of my patient will be my first consideration”

DoH 2013

# Clinical Research

- Clinical studies: Drugs, vaccines, devices
- Epidemiological studies
- Socio-behavioral studies

# The Aim of Biomedical Research

- The primary purpose of medical research involving human subjects is to
  - *understand the causes, development and effects of diseases and*
  - *Improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments).*

# The Requirements for Biomedical Research

Even the best proven interventions must be evaluated continually through research for their

- safety,
- effectiveness,
- efficiency,
- accessibility and
- quality.

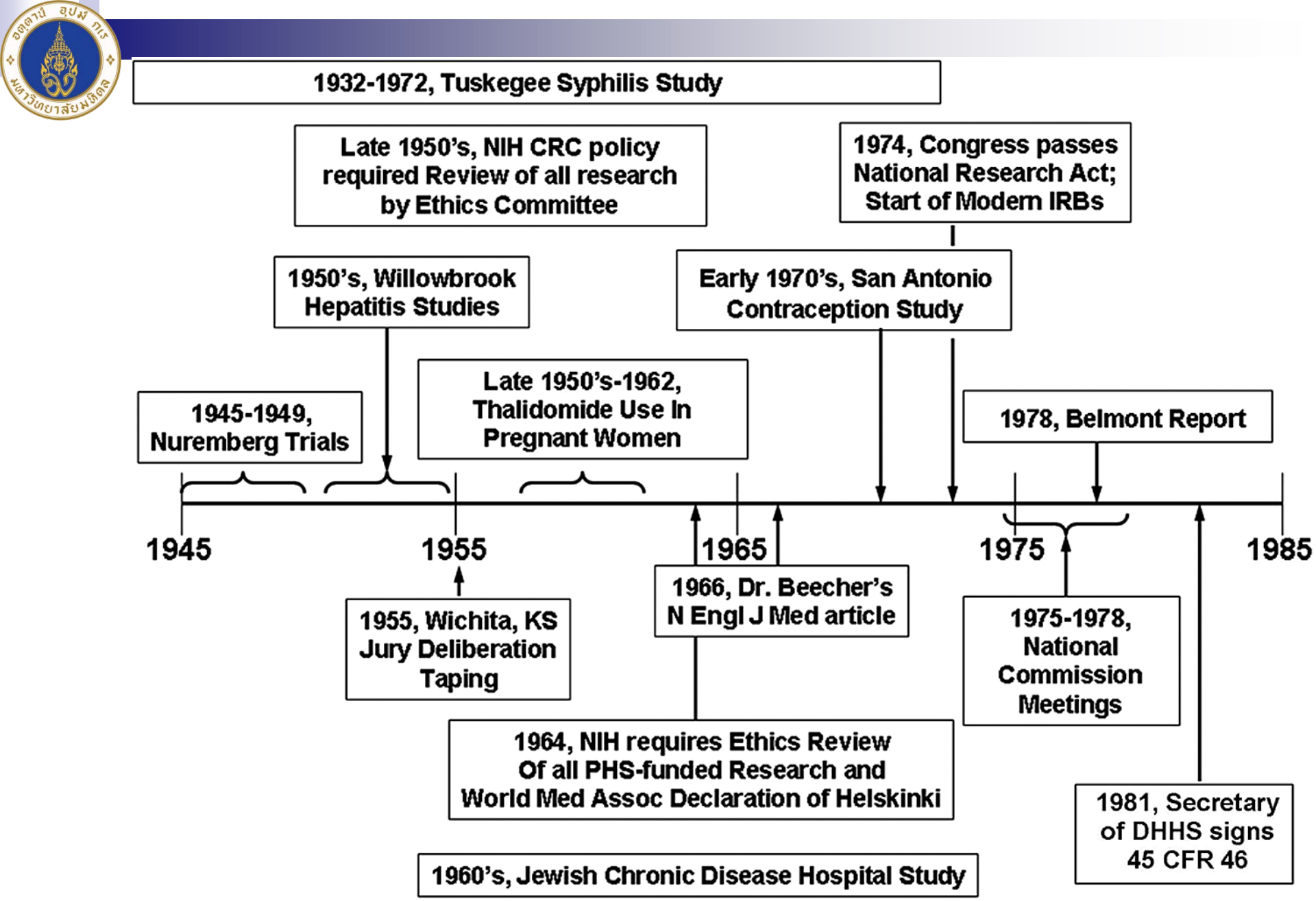
# Distinction between Medical Practice and Research

- Practice: interventions designed solely to enhance the well being of an individual patient or client.
  - *Purpose – provide diagnosis, preventive treatment or therapy*

- Research: intended to test a hypothesis,
  - *permit conclusions to be drawn,*
  - *contribute to generalizable knowledge*

# Why are we concerned with Ethics?


Powell's Mission Impossible
TIME
HOW MEDICAL TESTING HAS TURNED MILLIONS OF US INTO ...
HUMAN GUINEA PIGS




Todd WR, Respiratory Care 2008;53(10): 1325-9

# Nuremberg War Crimes

Nazi doctors' trials for
medical experiments
conducted among
civilians and Allied forces
under the custody of
the German Reich
**without subjects' consent**

Committed murders,
brutalities cruelties,
tortures, atrocities and
other inhuman acts

# Nazi Medical Experiments

- High altitude experiments
- Freezing experiments
- Gas Experiments
- Sea water experiment
- Sulfanilamide experiments
- Bone, nerve, muscle transplantation
- Sterilization of subjects

# Nazi Medical Experiments

- Malaria experiments
- Epidemic jaundice experiment
- Spotted fever
- Poison
- Incendiary bomb experiments

Tribunal condemned experiments and established "Nuremberg Code"

# Nuremberg Code 1947

- Voluntary and informed consent
- Require prior animal experiment
- Anticipated scientific findings
- Only conducted by qualified scientists
- Avoid physical and mental suffering
- No death or disabling injury

# Declaration of Helsinki (DoH)

## World Medical Association (WMA)

## DoH 1: 1964

18th WMA General Assembly, Tokyo, Japan, October 1975

- The interests of the subject should always be placed above the interests of society.
- Every subject should get the best known treatment.

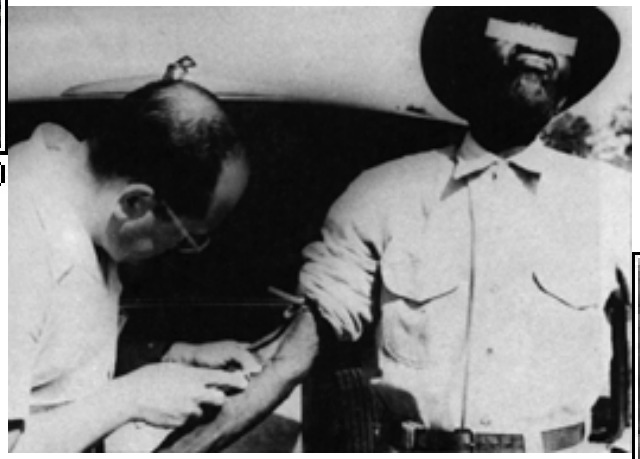
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

## DoH 10: 2013

# Tuskegee Syphilis Experiment

(Courtesy National Archives)

1932-1972




The study lasted nearly 40 years
(Courtesy National Archives)

# Tuskegee Syphilis Experiment

- US Public Health Service study on natural history of syphilis  from 1932-1972
- Studied illiterate 399 black sharecroppers from Alabama
- To study how syphilis affected blacks as opposed to whites
- Data to come from autopsies of these men
- Informed that they were being treated with ‘bad blood’ and were given token doses of medicine

## Macon County Health Department

**ALABAMA STATE BOARD OF HEALTH AND U.S. PUBLICH HEALTH SERVICE COOPERATING WITH TUSKEGEE INSTITUTE**

Dear Sir:

Some time ago you were given a thorough examination and since that time we hope you have gotten a great deal of treatment for bad blood. You will now be given your last chance to get a second examination. This examination is a very special one and after it is finished you will be given a special treatment if it is believed you are in a condition to stand it.If you want this special examination and treatment you must meet the nurse at.....on..... at_____ M. She will bring you to the Tuskegee Institute Hospital for this free treatment. We will be very busy when these examinations and treatments are being given, and will have lots of people to wait on. You will remember that you had to wait for some time when you had your last good examination, and we wish to let you know that because we expect to be so busy it may be necessary for you to remain in the hospital over one night. If this is necessary you will be furnished your meals and a bed, as well the examination and treatment without cost.

- **REMEMBER THIS IS YOUR LAST CHANCE FOR SPECIAL FREE TREATMENT. BE SURE TO MEET THE NURSE.**

Macon County Health Department

This letter is reproduced from an educational website at the University of Illinois's Poynter Center for the Study of Ethics and American Institutions

# Tuskegee Syphilis Experiment

- PHS kept men from receiving treatment even after the discovery of penicillin in 1940

"We trusted them because of what we thought they could do for us, for our physical condition . . . We were just going along with the nurse. I thought [the doctors] was doing me good."

(Jones, 1981)

# Tuskegee Syphilis Experiment

- Exposed by the media in 1972
- Congressional investigation
- Clinton apologized in 1997

# Lessons from Tuskegee

- Need for Informed consent
- Difference between treatment and research
- Need for review of research by IRB

# Roles of IRB

- safeguard the rights, safety, and well-being of all trial subjects.
- Special attention to trials that may include vulnerable subjects

The IRB/IEC should obtain the following documents:

- *trial protocol(s)/amendment(s)*
- *written informed consent form(s) and consent form updates*
- *subject recruitment procedures (e.g. advertisements), written information provided to subjects*
- *Investigator's Brochure (IB), available safety information*
- *information about payments and compensation available to subjects*
- *the investigator's current curriculum vitae and/or other documentation evidencing qualifications*
- *any other documents that the IRB/IEC may need to fulfill its responsibilities*

ICH-GCP

# Roles of IRB

- The IRB/IEC should review and approve all trial documents within a reasonable time.
- The IRB/IEC should consider the qualifications of the investigator(s).
- The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects.
- The IRB/IEC must have at least 5 members and one member with non-scientific background, who collectively have the qualifications and experience to review all aspects of the trial.
- The IRB/IEC should establish Standard Operating Procedures (SOPs) and follow those procedures.
- The IRB/IEC should retain all relevant records for a period of at least 3 years after completion of the trial.

ICH-GCP

# Investigator's Responsibility

- 4.1 Investigator's Qualifications and Agreements
- 4.2 Adequate Resources
- 4.3 Medical Care of Trial Subjects
- 4.4 Communication with IRB/IEC
- 4.5 Compliance with Protocol
- 4.6 Investigational Product(s)
- 4.7 Randomization Procedures and Unblinding
- 4.8 Informed Consent of Trial Subjects
- 4.9 Records and Reports
- 4.10 Progress Reports
- 4.11 Safety Reporting
- 4.12 Premature Termination or Suspension of a Trial
- 4.13 Final Report(s) by Investigator Upon completion of the trial

# Principles of Bioethics

# Basic Principles of Ethics

- Autonomy / Respect for Persons
- Beneficence / Non-maleficence
- Justice

The Belmont Report, 1979
US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

# 1. Respect for Persons (Autonomy)

- Autonomy – capacity to deliberate about personal goals and action
  - *Requires giving weight to a person's opinions and choices and refraining from obstructing their action unless they are detrimental to others*
  - *Respect for freedom of action*
  - *Respect for different cultural values*
  - *Requires giving protection to those with diminished autonomy*

# Autonomy in Research

- Voluntary participation
  - *No undue inducement*
  - *Voluntary termination*
  - *Legally authorized representative*
- Adequate information to make informed consent
  - *Full disclosure of risks and benefits*
  - *Continuing disclosure*
- Comprehension
  - *Culturally appropriate consent*

# 2. Beneficence/Non-maleficence

- **Risk :** possibility that harm may occur
- **Benefit :** something that aids or promotes well-being

# 2. Beneficence/Non-maleficence

- **Ethical obligation:**
  - *to maximise possible benefits*
  - *to minimise possible harms and wrongs.*

    *the risks of research should be reasonable in the light of the expected benefits, that the research design be sound, and that the investigators be competent both to conduct the research and to assure the well-being of the research subjects.*

## *Non-maleficence:* Do no harm

holds a central position in the tradition of medical ethics, and ***guards against avoidable harm*** to research subjects

- *not to injure one person despite benefits that may accrue to others in research*

# Types of Benefits

- Micro orientation
- Macro orientation
  Society

- Individual benefit
- Community benefits
- Social benefits

❑ recognizes longer term benefits and risks that result from improvement of knowledge and development of new procedures.

# Benefit Assessment

## Potential Benefits

- Physical benefits
  - *Improvement of disease*
- Psychological benefits
  - *Comfort from suffering*
  - *Feeling of helping others in the future?*
- Economic benefits
  - *Financial benefits related to research participation?*
- Benefit to science/society
  - *Generalisable knowledge*
  - *Effective interventions in the future*
  - *Change in practice standards: decreasing morbidity and mortality*

# Risk Assessment

## Risk – possibility that harm may occur

- Physical risks
  - *Bodily harm*
  - *Simple inconvenience*
- Psychological risks
  - *Emotional suffering*
  - *Breach of confidentiality*
- Social risks
  - *Unemployment or social discrimination*
- Economic risks
  - *Financial costs related to participation*

# Assessment of Risk In Research

- Types of risks in research
  - ***Minimum risk:*** *risks encountered in everyday life*
  - ***More than minimum risk*** *but with direct benefit to the subject*
  - ***More than minimum risk*** *without direct benefits to the subject but benefits society*
  - ***More than minimum risk*** *but no perceived benefits*

# 3. Justice

- **Fair distribution**
  - *Subject selection: Study Population*
  - *Distributive Justice: equitable distribution of both the burdens and the benefits*
- **What is deserved:**
  - *giving a person the benefit one is entitled to.*
- **Equal treatment:**
  - *Different treatment requires justification (contraindication, underlying diseases/co-morbidity etc.)*

# Injustice

- Unjust social patterns
  - *Social class*
  - *Racial, ethnic bias*
  - *Gender and sexual bias*
  - *Cultural bias*
  - *Developed vs. developing countries*

*Consider social justice in subject selection and distribution of risks and benefits*

# Justice Questions In Health Research

- Recruitment of charity ward patients while benefits of health care enjoyed by private patients
- Nazi use of war prisoners perceived as grave injustice
- Tuskegee patients deprived of treatment when it was already available
- Recruitment of vulnerable population because they are available, easier to manipulate and not because they manifest any condition related to the study

# Considerations To Justify Research

- Brutal or inhuman treatment of human subjects is *never morally justified*.
- Risks *should be reduced* to levels necessary to achieve research objectives and alternative procedures should be considered.
- Significant risk *should be justified*.
- Use of vulnerable subjects *should be justified*.
- Risks and benefits *should be explained* in the consent form.

# Application of Ethics Principles

- Autonomy / Respect for Persons
  - *Informed consent*
- Beneficence / Non-maleficence
  - *Risk-Benefit Assessment*
- Justice
  - *Selection of subjects*

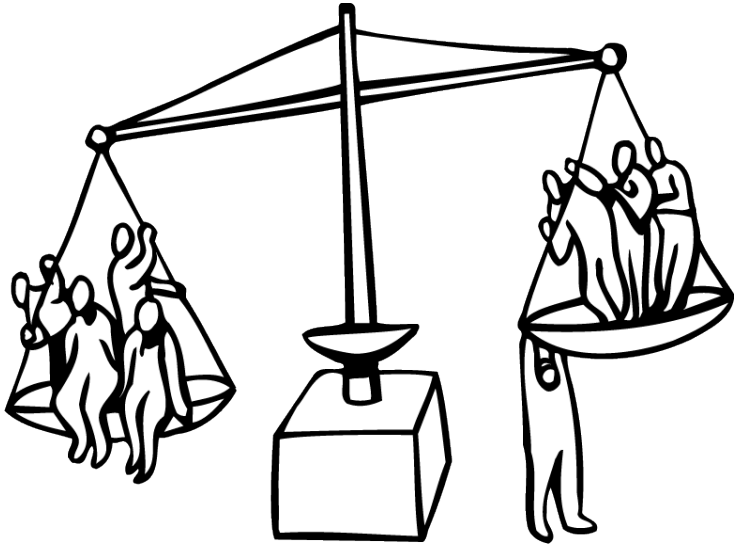
The Belmont Report, 1979
US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

# Justice: Subject Selection

- **Social justice**
  - *Identifying a participation criteria based on ability of a class to bear burdens and appropriateness of further burdens on a group*
  - *Order of preference in subject selection (adults before children, etc.)*
- **Individual justice**
  - *Not to offer beneficial research only to some patients researchers favor*
  - *Select only 'undesirable persons' for risky research*

# Beneficence / Non-maleficence

## Risk : Benefit Assessment



Benefits should outweigh risks

# Autonomy / Respect for Persons

## Informed Consent (IC)

- *Regarded as part of the project proposal*
  - Simple language
  - Use of medical terminology/jargon should be avoided
  - A copy should be offered to the subject
  - By signing, the staff member confirms that consent was given freely
- *Statement (information sheet):*
  - Describe the study and the nature of subject's involvement in it
  - Given to or read to each prospective subject
- *Certificate of consent:*
  - attesting the subject's consent

# Critical Features of IC

To protect the ***rights*** of the study participants

- Informed consent can only be granted when *individuals know what they are agreeing to do*
- The ability to *give and withdraw it freely.*
- The consent process is very important and it is essential that *everyone involved in a research project understands it.*
- The consent form is an instrument for the researcher to *communicate necessary information to a respondent.*

# Inducement to Participate

- Financial or other inducements to participate in studies should be avoided, although it is reasonable to compensate for costs incurred

- Compensation is *not* used as a way of recruiting study subjects to meet sample sizes, or as a way of keeping them in the study

- Compensation should not be interpreted or used as an incentive for participating in the study

- Any compensation should be only to defray extra costs or loss of benefits, and must be reasonably related in amount to these types of expense

# Ethical Principles Applied to Epidemiology (I)

## Informed Consent

- *Individual consent*

❑ Subjects understand purpose/nature of the study, risks and benefits, what needs to be done when participating in the study

❑ Justify with the ethical review body how the study would be ethical in its absence.

- *Community agreement*

❑ The refusal of individuals to participate in a study has to be respected.

# Ethical Principles Applied to Epidemiology (II)

## *Maximising Benefit*

- Communication of study results
- Impossibility of communicating study results
- Release of study results
- Health care for the community under study
- Training local health personnel

# Ethical Principles Applied to Epidemiology (III)

## *Minimizing harm*

- Causing harm and doing wrong
- Preventing harm to groups
- Harmful publicity
- Respect for social mores
- Sensitivity to different cultures

# Epidemiological Research

- Research data bases
  - *Who owns them?*
  - *Who has access to them?*
  - *Who may use them?*
- Need to protect privacy and confidentiality of data to prevent stigmatization and other types of harm
- Need to anonymize data

# Ethical Obligations in Social Science Research

To pursue a study that has potential benefit to humans

- To ensure that the design of the study is appropriate to its objectives (so that individuals are not subjected to unnecessary or unproductive research)

- Results are disseminated

# Essential Elements in Social Science Research

- To protect the individual's physical and mental integrity
- To respect the moral and cultural values and religious and philosophical convictions and other fundamental rights
- To pursue the highest attainable level of health care

# Unlike Biomedical Research (I)

- The potential risks to the research subject are *not* usually physiological

- Researchers need to be aware of the dangers of exposing the subject to potential *psychological* or *social harm* or *inconvenience*

# Unlike Biomedical Research (II)

- It is carried out to ultimately benefit many individuals

- There is *rarely* a direct benefit for individual respondents

- There is the opportunity for them to offer valuable information in a way that may contribute to improving many people's lives.

# Common Research Methodologies

- Types
  - *Quantitative - generalizable*
  - *Qualitative – in depth*
- Methods
  - *Interviews*
  - *Focus group discussion*
  - *Survey*
  - *Participatory/observation*

# Determination of Significant Risk

- Sensitive nature of the topic
  - *May cause stigmatization – loss of reputation*
- Type of social interaction
  - *Intervention may cause psychological stress or harm – Milgram study*
- Financial implications
  - *Loss of job or profession*
- Legal implications
  - *Drug addiction, prostitution, abortion as criminal activities*

# Confidentiality Protection

- Allow researchers to conduct important difficult research on some on important societal problems
  - *Drug abuse*
  - *High risk sexual behaviors*
  - *Violence*
  - *Diseases associated with stigma – STD, HIV-AIDS*

# Confidentiality Protection

- Recognize confidentiality issues in
  - *Initial study design*
  - *Identification, recruitment and consent processes for the study population*
  - *Security, analysis and final disposition of data*
  - *Publication or dissemination of data and results*

# Minimizing Risk

- Avoid disclosing identifiable data
  - *Use of surrogate subjects*
  - *Adequate physical structures*

- Protecting confidentiality of data – key element in minimizing risk

# Other Guidelines

**CIOMS:** Council for International Organizations of Medical Sciences

- *CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects 2002*
- *CIOMS International Ethical Guidelines for Epidemiological Studies 2009*

**National Law:** National Health Act
Child Protection Act

**Thai Medical Council Act:** Research Ethics

Don't fear pressure

for pressure is what turns rough stones into

diamonds

# Thank you for your attention!!!!!!