Human Subject Protection: **Conducting Research among Vulnerable Subjects**

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The evolution of clinical research ethics

Born in scandal

The Nazi Doctors' Experiments

- High altitude experiments
- Cold water experiments

The Nuremberg Trial

- United States vs. Karl Brandt et al.
- 15 of 23 defendants found guilty
- 7 sentenced to death

The "Dock" of defendant physicians at the "Doctor's Trial," November 1946
(UPI/Bettmann Newsphotos)

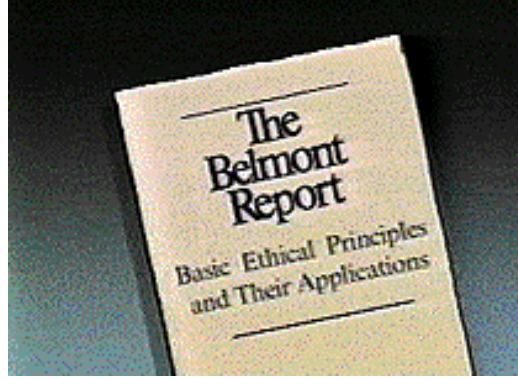
The Nuremberg Code (key points)

- **Informed consent of volunteers must be obtained without coercion in any form.**
- Human experiments should be based upon prior animal experimentation.
- Anticipated scientific results should justify the experiment.
- Only qualified scientists should conduct medical research.
- Physical and mental suffering and injury should be avoided.
- There should be no expectation of death or disabling injury from the experiment

The Tuskegee Syphilis Study

- 1932-Macon County, Alabama
- US Public Health Service (PHS)-now CDC
- The study of untreated disease
- 200 to 300 syphilitic black males
- “government doctors” were examining “bad blood”
- 1943-penicillin available, but not given to study subjects
- 1972-Jean Heller-New York Times

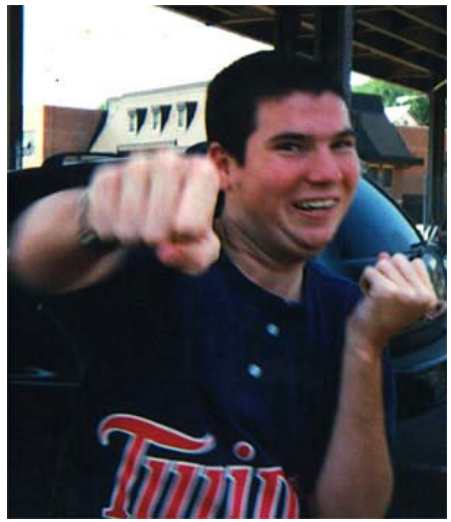
Definition: Practice vs. Research



- Practice: interventions that are designed solely to enhance the well-being of an individual patient and that have a reasonable expectation of success.
- Research: an activity designed to test an **hypothesis**, permit conclusions to be drawn, and thereby to develop or contribute to **generalizable knowledge**

More recent tragedies...

- 1996-Hoiyan (Nicole) Wan-U Rochester
- 1999-Jesse Gelsinger-U Penn
- 2001-Ellen Roche-John Hopkins U



More history in http://www.sskrplaw.com/bioethics/

Human Guinea Pigs

"83% of Americans believe it essential or very important that new drugs be tested in humans; only 24% are very confident that patients in clinical trials are not treated as guinea pigs." (Anita Kuntz, Time magazine April 22, 2002.)

IRB Related Law in Taiwan

- 醫療法第78條第三項規定：人體試驗計畫醫療機構應提經有關醫療科技人員、法律專家及社會工作人員會同審查通過;計畫變更時亦同。
- 醫療機構人體試驗委員會組織及作業基準
  - 衛署醫字第092202507函公告(Nov. 12, 2003)

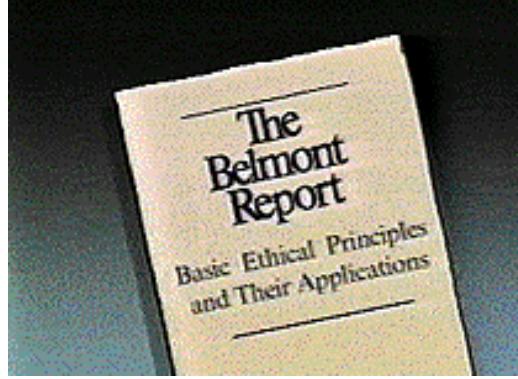
The primary roles of IRB

- Subjects are lacking of medical knowledge.
- As an independent committee to evaluate the benefit and judge risk of clinical research for subjects.
- Medical ethic and human subject protection.

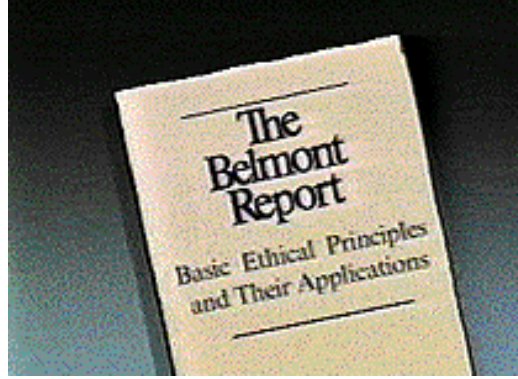
Documents of ethical principles

- Nuremberg Code, 1949
- The Declaration of Helsinki, 1964, 1975, 1983, 1989, 1996, 2000
- **The Belmont Report, 1979**

Basic Ethical Principles



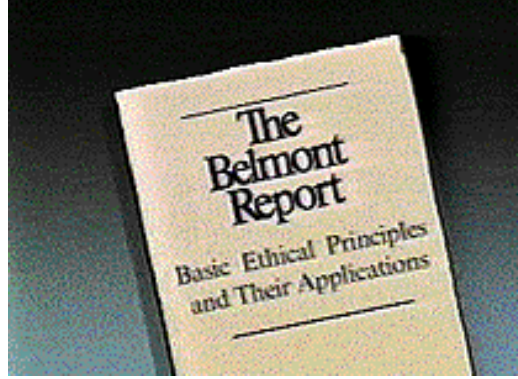
- Respect for persons: informed consent
- Beneficence: risk/benefit assessment
- Justice: subject selection



Applications of ethical principles

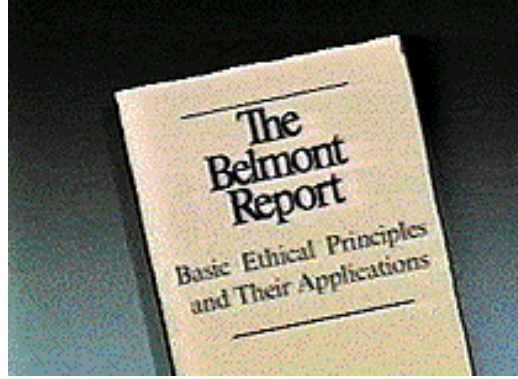
- Informed consent (respect for persons)
- Assessment of risks and benefits (Beneficence)
- Selection of subjects (Justice)

Respect for persons

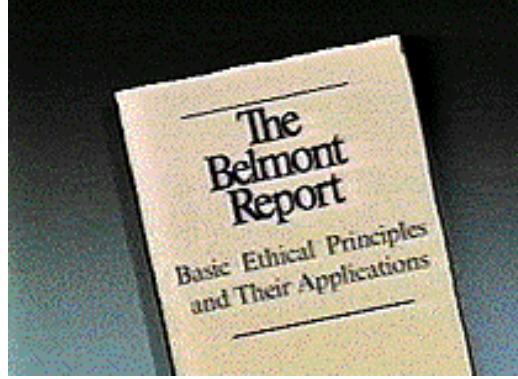


- Individuals should be treated as autonomous agents (autonomy)
- Persons with diminished autonomy are entitled to protection.

Beneficence



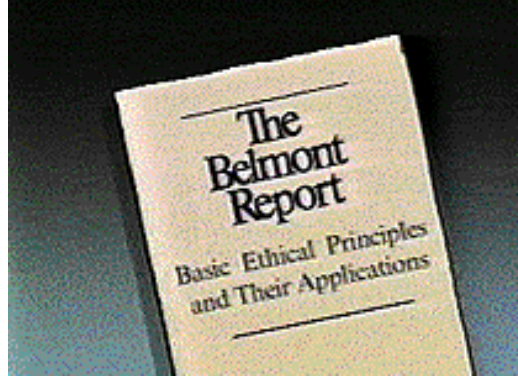
- Do no harm
- Maximize possible benefits and minimize possible harms



Justice

- Fairness in distribution
- An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly

Vulnerable subjects



- Those groups that may contain some individuals who have limited autonomy: institutionalized, low socioeconomic, elderly, terminally ill, student, employees groups.
- Children, mentally incapacitated, individuals with dementia and other cognitive disorders, prisoners
- Pregnant women.

Vulnerable subjects

- Cognitive or communicative vulnerability
- Institutional vulnerability
- Deferential vulnerability
- Medical vulnerability
- Economic vulnerability
- Social vulnerability

IRB's responsibility

- An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. **Special attention should be paid to trials that may include vulnerable subjects**. (ICH E6 GCP)

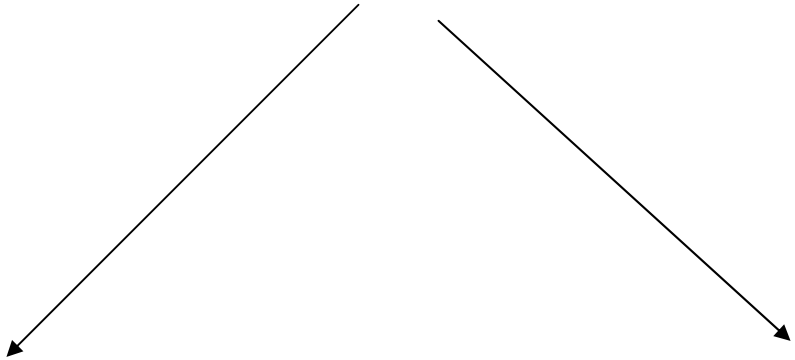
人體試驗委員會應確保受試者之權利，安全以及福祉受到保護，且對於易受傷害受試者之臨床試驗，應特別留意

藥品優良臨床試驗準則　第四條

Vulnerable subjects – practical issues

- Additional safeguards?
- Special attention?
- But how?

Elements of Autonomy



Capacity

Voluntariness

Freedom from the control or influence of others.

From David Forster

Vulnerable Subjects
(Have Actual or Potential Limitations on Autonomy)

- Lack of Capacity
  - Children
  - Mentally Disabled
  - Temporary
  - Fluctuating
- Limits on Voluntariness
  - Fatal or Incurable Disease
  - Emergency Situations
  - Hierarchical Social Structure
  - Economically Disadvantaged
  - Educationally Disadvantaged
  - Marginalized Social Groups

From David Forster

Improving of autonomy

- Decision-making capacity
- Education
- Obtain assent
- Permission from surrogate decision
- Individual participant

Excluding women of childbearing

- FDA (1977)
  - Thalidomide: nausea-deformity of limbs
  - Diethylstilberstrol: miscarriage- daughter vagina cancer
  - Equitable subject selection: excluded women from all researches is unethical
  - Adequate birth control: adolescent?
  - “Acceptable way?: approval sexual activity
  - Don’t use the word “requirement”!

ICF Consent Processing

- Reproductive/fetal risk: teratologic, mutagenic
- Mandatory pregnancy-related exclusion
- Pregnancy prevention advice
- Pregnancy testing

Research in public school

- No more than minimal risk
- More than minimal risk with prospect of direct benefit
- More than minimal risk and no prospect of benefit with generalizable knowledge about children's disorder of condition: consent from both parents

Civil Law (Taiwan)

- 第 12 條
  - Adult: age ≧ 20
- 第 13 條
  - Age ＜7: incompetent
  - Age ≧ 7 and ＜20: limited competency
  - Married, age ＜20: competent

- Minimal risk?
  - Probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
- Waiver of parental permission
  - Inconvenience, expense and not a part of curriculum
  - Passive consent and parental notification

4 Research Categories

I. Research **not involving greater than minimal risk** (46.404)	III. Research involving **greater than minimal risk** and **no prospect of direct benefit** to individual subjects, but likely to yield **generalizable knowledge** about the subject's disorder or condition (46.406)
II. Research involving **greater than minimal risk** but presenting the **prospect of direct benefit** to the individual subjects (46.405)	IV. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (46.407)

IRB Review Guidelines

Risk \ Benefit	**Prospect of Direct Benefit**	**No Prospect of Direct Benefit**
Minimal risk	• Parental permission • Child's assent	• Parental permission • Child's assent
Minor increase over minimal risk	• Risk/benefit ratio • Parental permission • Child's assent	• Knowledge • Subject's experience • Parental permission • Child's assent
More than a minor increase over minimal risk	• Risk/benefit ratio • Parental permission • Child's assent	Not authorize to IRB

Exemption parent consent?

- Visual vocabulary
- Conflict with friends
- Recording playground conversations
- Educational records
- No child left behind act (2001)

Risk/benefit: 188 IRB Chairman

JAMA 2004; 291:476-482

To age eleven	Minimal risk	Minor increase	>Minor increase
venipuncture(10mL)	152 (81%)	32 (17%)	2 (1%)
MRI (no sedation)	90 (48%)	66 (35%)	17 (9%)
Sexual behavior investigation	83 (44%)	55 (29%)	36 (19%)
Skin test	43 (23%)	81 (43%)	51 (27%)
Pharmacokinetics (mortality: 1/10000)	13 (7%)	56 (30%)	111 (59%)
Lumbar puncture (health conscious children)	4 (2%)	30 (16%)	147 (78%)

Protections for decision impaired subjects

- Capacity assessment
- Enhancing comprehension
- Surrogate consent
- Discussion and appearance of patient/consumer representative
- family members
- Advocacy group members
- Closed friends
- scientific/clinical expertise

Special protection for prisoners as a research subject

- Nuremberg 1946: Stateville, Illinois, US for malaria research involved 400 prisoners for 2 years (Andrew Ivy defended: obtain consent, base on animal experiments and directed by qualified persons, acceptable?).
- Phase I and cosmetic testing: ill or died was not insignificant.
- 1972: 40-year long Tuskegee syphilis study
- 1976 end of research in federal prisons

Special considerations for prisoner subject

- Definition: institution, detained in other facilities, house arrest, pending trail or sentencing
- Composition of IRB
- Newly incarcerated individual must be withdrawn
- No more than minimal risk, inconvenience
- Direct benefit

College students

- Convenient, easy to recruit, relatively inexpensive
- Exchange for extra credit, payment, recommendation letter
- Extra opportunities
- Confidentiality: identifying information (medical information, self-esteem, depression, drug abuse, sexual behavior and so forth).

Conclusions

Excluding vulnerable subjects

- Unjustly exclude from the benefits of research
- Limited financial incentives to avoid undue influence may unfairly provide those in greatest need with the least compensation
- Mistrust or resentment toward researchers

Protective Mechanisms: Risk/Benefit

- Review of research by an IRB
- Informed consent of subjects
- Institutional assurances of compliance

Points to consider

- Research?
- Vulnerable subject?
- Special protection
  - Minimal risk? (confidentiality, criminal liability)
  - Rights and welfare of subjects affected?
  - IRB composition: expertise, surrogate
  - Confidentiality
  - Inform consent processing

Informed Consent Process

- Three components
  - Information
  - Comprehension
  - Voluntariness

Thank You for Attention