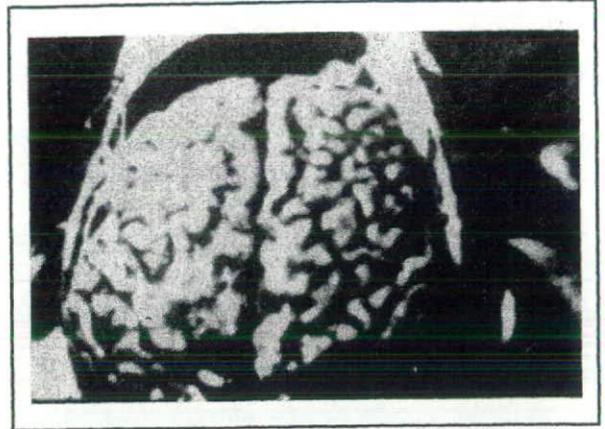


吉村健一	腫瘍学における統計学	講義録腫瘍学		174-177	2008
吉村健一	臨床腫瘍医が必要とする生物統計学の基本用語.	Cancer Treatment Navigator.		52-53	2008
笹栗俊之、他	福岡県における研究倫理審査委員会の実態調査 -IRB メンバー教育システムの構築を目指して	臨床評価	36(2)	393-419	2008
笹栗俊之	福岡臨床研究倫理審査委員会ネットワーク(RecNet Fukuoka)の活動について..	薬理(印刷中).			印刷中
佐藤 雄一郎	「人体」と「ヒト組織」と:議論のあり方についての管見」	HAB Newsletter	15(2)	3-4	
佐藤 雄一郎	「ブレインバンクをめぐる倫理的・法的社会的問題	精神の医学 20(1)予			印刷中

## IV. 付録

付録 1. PRIM&R セミナー資料  
倫理審査委員教育用スライド(IRB 101)  
(研究分担者: 山上須賀、他)





**Nuremberg Medical Trial**

- Use of prisoners for research is a universally accepted practice
  - malaria studies at Stateville Penitentiary



- "I hereby accept all risks connected with the experiment ... and I hereby absolve from liability the University of Chicago ... the State of Illinois ... the warden of the state penitentiary. I hereby certify that this offer is made voluntarily and without compulsion. I shall be entitled to remuneration amounting to [xx] dollars."

## Nuremberg Medical Trial

- Sentences returned August 19, 1947
  - 7 defendants sentenced to death
  - 9 received prison terms (up to 20 years)
- Nuremberg Code

## Nuremberg Medical Trial

- "there are no universal standards existing which govern experimentation on human beings ..."

## Nuremberg Medical Trial

- Sentences returned August 19, 1947
  - 7 defendants sentenced to death
    - Brandt (Reich Commissioner for Health), Gebhardt (Surgeon General of SS, Head German Red Cross), Hoven (Chief Physician, Buchenwald), Sievers (Director, Reich Research Council) and others
  - 9 received prison terms (up to 20 years)
- Nuremberg Code



## The Nuremberg Code

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

- "The Nuremberg Code was conceived in reference to Nazi atrocities and was written for the specific purpose of preventing brutal excesses from being committed or excused in the name of science. The code ... is in our opinion not necessarily pertinent to or adequate for the conduct of medical research in the United States"

Joseph Gardella, MD  
Dean, Harvard Medical School

- Brooklyn Jewish Chronic Disease Hospital (1963)
  - live cancer cells injected into 22 elderly indigent patients without their consent
  - performed without knowledge or consent of hospital's research committee

#### Declaration of Helsinki (18th World Medical Assembly 1964)

- I.9. "... each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He should be informed that he is at liberty to abstain from participation in the study, and he is free to withdraw his consent to participation at any time ..."

- "A physician has no right to withhold from a prospective volunteer any fact which he knows may influence the decision. It is the volunteer's decision to make. ... Deliberate nondisclosure of the material fact is no different from deliberate misrepresentation of such a fact. ..."

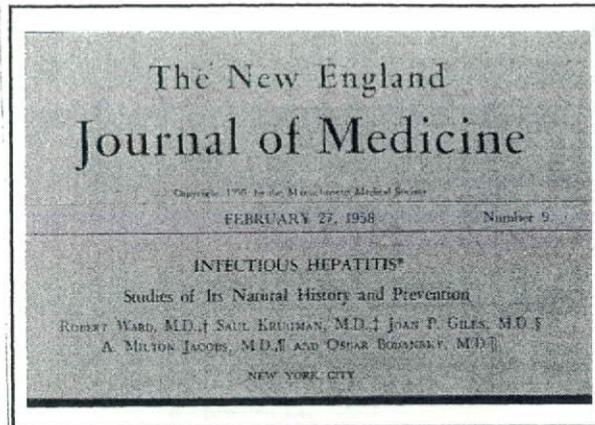
Board of Regents of the State University of New York 1966

#### Declaration of Helsinki (18th World Medical Assembly 1964)

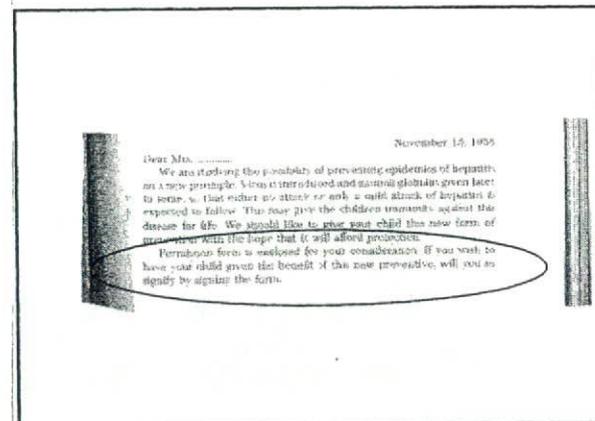
- Two categories of research
  - Non-therapeutic Research
  - Clinical Research Combined with Professional Care (Therapeutic Research)
- necessity for subject consent only absolute with non-therapeutic research
- physicians required to obtain consent from patient/subjects only when "consistent with patient psychology"

- NIH Livingston Committee (1964)
  - Recognized risks of ethically questionable research, but did not recommend NIH oversight
- National Advisory Health Council (1966)
  - "... PHS support of clinical research and investigation involving human beings should be provided only if the judgment of the investigator is subject to prior review by his institutional associates to assure an independent determination of the protection of the rights and welfare of the individual or individuals involved..."

- Henry Beecher (NEJM 1966)
  - twenty-two examples of potentially serious ethical violations in experiments found in recent issues of medical journals
  - research had not taken place "in a remote corner, but [in] . . . leading medical schools, university hospitals, top governmental military departments, governmental institutes and industry."



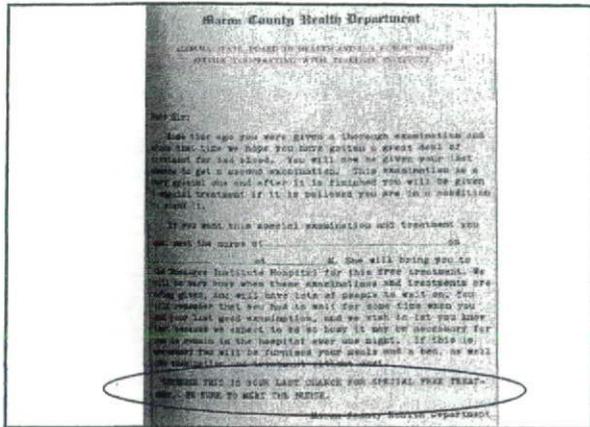
- Penicillin, sulfonamides withheld in patients with streptococcal disease
- Thymectomy and skin grafts
- Adverse circulatory responses to intra-abdominal stimuli
- Dose dependent toxicity of chloramphenicol
- Cyclopropane and cardiac arrhythmias
- Effect of ingested and IV ammonia on patients with liver disease
- Vesicourethrography in normal newborns



- "... the more reliable safeguard is provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator."

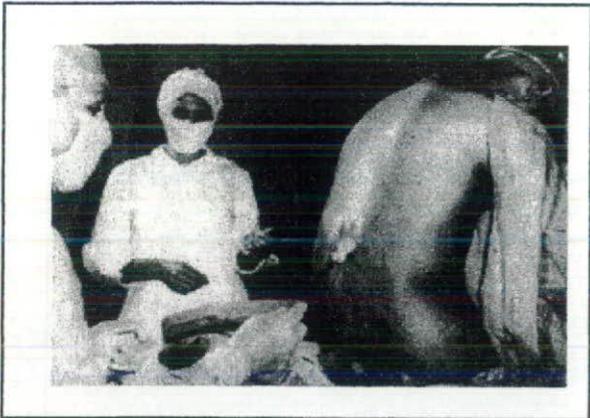
### PHS Syphilis Study

- Started in 1932, sponsored by US PHS
  - purpose of the research was to study natural history of syphilis
  - 400 black men with syphilis from rural south



### PHS Syphilis Study

- as late as 1969 CDC reviewed data and concluded study should continue
- "disease had appeared in a way that was natural and inevitable and that the study would be of immense benefit to future patients"



### PHS Syphilis Study

- "Syphilis Patients Died Untreated.

"For 40 years, the U.S. Public Health Service has conducted a study in which human guinea pigs, not given proper treatment, have died of syphilis and its side effects ... The study was conducted to determine from autopsies what the disease does to the human body."

Jean Heller  
Washington Evening Star  
July 25, 1972



### PHS Syphilis Study

- Ad Hoc Panel Conclusions
  - PHS study was "ethically unjustified" and should be stopped immediately and remaining subjects be given necessary medical care

## PHS Syphilis Study

- Ad Hoc Panel Conclusions
  - neither DHEW nor any other agency in the government had adequate policies for oversight of human subjects research



Primitive spelling bees

## National Research Act (1974)

- established National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
  - Recommend regulations to protect the rights and welfare of human subjects of research
  - Develop principles to govern the ethical conduct of research

## Belmont Report (1979)

- three basic ethical principles that should govern human subject research:
  - respect for persons
  - beneficence
  - justice

## National Commission

- "investigators should not have the sole responsibility for determining whether research involving human subjects fulfills ethical standards. Others who are independent of the research must share in this responsibility"

## Respect For Persons

- "Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection" (National Commission)

## Respect For Persons

- Individuals should be treated as autonomous agents
  - An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation
  - To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others

## Beneficence

- "Beneficence is understood ... as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do no harm, and (2) maximize possible benefits and minimize possible harms" (National Commission)

## Respect For Persons

- Informed Consent
  - Information
    - Reasonable person vs reasonable volunteer
  - Comprehension
  - Voluntariness

## Beneficence

- Favorable risk-benefit relationship

## Respect For Persons

- Persons with diminished autonomy are entitled to protection
  - "Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them ... The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit."





## Risk-benefit relationship

- Clinical equipoise
  - there must "exist . . . an honest, professional disagreement among expert clinicians about the preferred treatment"
  - if the clinician personally prefers one arm over the other, randomization is still ethically sound when there are other responsible and competent clinicians who disagree



## Justice

- Justice requires that we treat persons fairly and we give each person what he is owed.
- "An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly." (National Commission)
  - The principle requires that both benefits and burdens be distributed fairly.

## Risk-benefit relationship

- Risks and benefits must balance
  - Comparing arms of the research
  - Comparing participation in the research and standard care

## "What makes research ethical?"

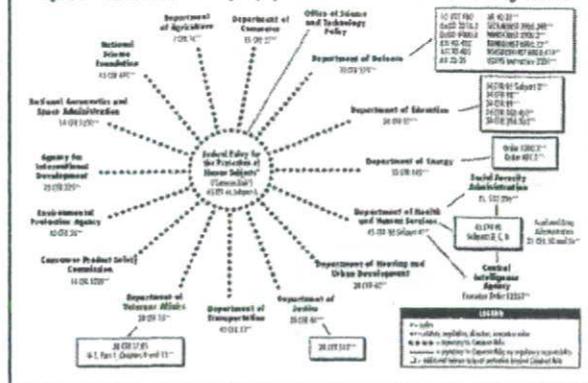
- value
  - enhancements of health or knowledge must be derived from the research
- scientific validity
  - the research must be methodologically rigorous
- fair subject selection
- favorable risk-benefit ratio
  - risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks

## “What makes research ethical?”

- independent review
  - unaffiliated individuals must review the research and approve, amend, or terminate it
- informed consent
  - individuals should be informed about the research and provide their voluntary consent
- respect for enrolled subjects
  - subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored

Emanuel JAMA. 2000;283:2701-2711.

Figure C-1. Common Rule and Agency-Specific Human Research Protection Regulations



50,000 B.C.: Gals Eisenberg invents the first and last silent mammography machine.

## Assurance

- Agreement between Federal Government and the institution that:
  - All research activities will be guided by the ethical principles of the Belmont Report
  - Research will comply with Common Rule
  - All research will require written informed consent\*
  - All research will be reviewed by an IRB\*

## Federal Regulations

- 45 CFR 46 Subpart A (Basic Policy for Protection of Human Research Subjects)
  - final regulations issued in 1981
- 21 CFR 50 (Informed Consent)
- 21 CFR 56 (IRBs)
  
- Common Rule

## What is an IRB?

- IRB is a body constituted to assure compliance with 45 CFR 46 (Federal Policy for the Protection of Human Subjects)

## IRB Responsibilities

- Risks to subjects are minimized
- Risks to subjects are reasonable in relation to anticipated benefits to subjects, and the importance of the knowledge that may be expected to result
- Selection of subjects is equitable
- Informed consent obtained and documented
- Adequate provision for monitoring data
- Adequate provisions to protect privacy of subjects

## What does the IRB do?

- "Protect human subjects"?
  - Facilitates conduct of ethical research
- Protects the institution
- Protects the investigator

## What is human subject research?

- Research means a systematic investigation ... designed to develop or contribute to generalizable knowledge.
- A human subject is a living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

## OIG Report (1998)

- IRBs face major changes in the research environment
- IRBs review too much, too quickly, with too little expertise
- IRBs face conflicts which threaten their independence
- IRBs and their institutions provide little training for investigators and their board members

## Therapy vs Research

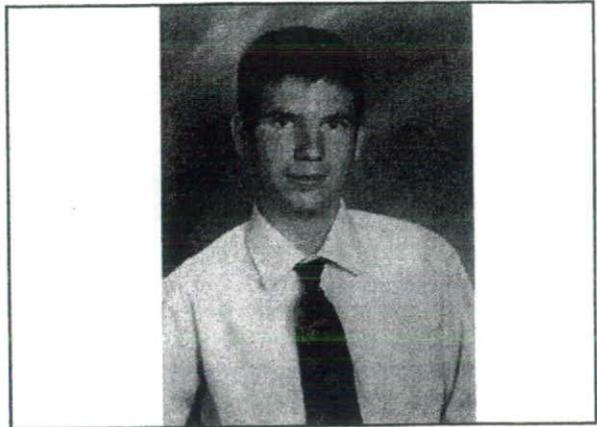
- IRB does not regulate the practice of medicine
- Innovative therapeutic practices, even if unproven, which are performed in the course of rendering treatment are not research.
- However, if there is an intent to develop or contribute to generalizable knowledge (eg, intent to publish) then that activity should be classified as research

Rush Presbyterian (October 1998)



### Report puts hospital's human research on hold

**By David H. Freedman**  
 Rush Presbyterian Medical Center's human research program is on hold after the U.S. Office of Inspector General (OIG) issued a report last week that criticized the center's research ethics board and its procedures. The report, which is the first of its kind to focus on a hospital's research ethics board, says the board is "not independent" and "not representative" of the community. The OIG also found that the board's procedures are "not transparent" and "not consistent" with federal regulations. The report also criticized the center's research ethics board for not having a clear role and for not being able to enforce its decisions. The OIG says that the center's research ethics board is "not independent" and "not representative" of the community. The OIG also found that the board's procedures are "not transparent" and "not consistent" with federal regulations. The report also criticized the center's research ethics board for not having a clear role and for not being able to enforce its decisions.



- Consent form did not mention previous deaths in monkeys
- Consent form did not mention previous adverse events in patients
- AEs not reported to FDA
- Dose increased without FDA notification or approval
- Eligibility criteria altered



- Genovo (which owned the patent on the adenovirus vector) provided 20% of the annual research budget for IHGT
- Wilson was founder and 30% shareholder in Genovo
- Genovo had exclusive rights to develop Wilson's research into commercial products
- Penn held 5% equity in Genovo



Wellington held out some beads and other trinkets, but the islanders had seen their finest lawyers — kinks of whom were chanting, "Sue him! Sue him!"

- Penn, IHGT, Wilson, Genovo settle with Gelsinger family for undisclosed amount
- Penn settles with DOJ for \$500,000
- Restrictions placed on Wilson's human subjects research for 5 years

### OIG Report (2000)

- Minimal progress in recasting Federal requirements to grant IRBs more flexibility
- No education requirements have been enacted
- No progress in insulating IRBs from conflicts that can compromise their effectiveness and independence
- Minimal progress in moderating workload pressures

THE NATION'S NEWSPAPER

# USA TODAY

Monday, July 10, 2000

## Clinical trials halted

Feds: Cancer study endangered patients

By Edward T. Pounds  
USA TODAY

WASHINGTON — In a continuing crackdown on mishandled medical experiments, federal health officials have shut down all government-sponsored clinical trials involving human subjects at the University of Oklahoma College of Medicine in Tulsa. They acted, officials say, after concluding that a cancer study there endangered patients' safety.

A federal watchdog agency issued the suspension June 29 in a letter.

**More trials**

The number of clinical trials per new drug has risen sharply.

1977-1980	30
1981-1984	30
1985-1988	36
1989-1992	50
1993-1995	68

Source: Drug and Therapeutics Administration, U.S. Food and Drug Administration

By Thom Powers, USA TODAY

THE SUN

Friday, July 20, 2001

HOWARD COUNTY

Washington, Maryland 20894

# U.S. halts Hopkins research

**Clinical Trials Fide**

Most researchers in the United States are not required to register their trials with the FDA.

**Patrols Safety Risk**

Officials say they discovered a number of safety risks in the study.

**More on this**

U.S. halts Hopkins research



## PHS Syphilis Study

- "The United States government did something that was wrong - deeply, profoundly, morally wrong. It was an outrage to our commitment to integrity and equality for all our citizens ...

"What was done cannot be undone. But we can end the silence. We can stop turning our heads away. We can look at you in the eye and finally say, on behalf of the American people: what the United States government did was shameful.

"And I am sorry."

President Bill Clinton  
May 16, 1997



Superman in his later years

## Federal Regulations and Policy

### Additional Protections

- Subpart B Fetuses, pregnant women neonates
- Subpart C Prisoners
- Subpart D Children
- Mentally incapacitated ( never formalized with subpart)

## Applying Federal Regulations and Guidelines

### A Shared Responsibility

## Food and Drug Administration

### Authority

- Federal Food, Drug and Cosmetic Act

### FDA regulates products based on interstate commerce and intended use/marketing

### Regulations

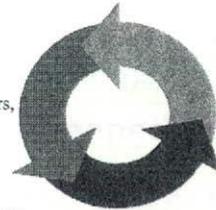
- IRB 21 CFR 56
- Informed Consent 21 CFR 50
- Investigational Drugs 21 CFR 312, 314, 320
- Investigational Devices 21 CFR 812, 813
- Conflict of Interest 21 CFR 54

### No Subpart B or C



## Human Subjects Protection is a Shared Responsibility

IRB  
Chair, members,  
staff



Investigator  
PI, Co-Investigators,  
Staff

Institution  
Institutional officials, leadership

Sponsors  
Regulators

## Other Regulations, Policies and Guidelines

- Veteran's Affairs 38 CFR Part 16
- State/Local Regulations
  - medical records, autopsy, genetics
- Federal agency policy
  - inclusion of women and minorities
- Institutional policy
- ICH (Good Clinical Practice)
- JCAHO
- The Family Educational Rights and Privacy Act (FERPA) (20 U.S.C. § 1232g; 3 Institutional policy)
- International policies and ethic codes
- Other funding agencies (USAID)

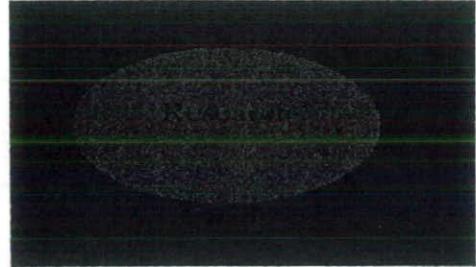


How do you know what constitutes research with human subjects?

### Is this research with human subjects?

- I'm only looking at records that are linked to an code, but no actual name. They are my patients.
- I'm just doing an innovative procedure in the cath lab.
- I am doing a questionnaire for my masters thesis.
- Do I need IRB approval to interview individuals to write my book?
- I'm just getting a small sample of tissue from the OR.
- This is a quality improvement initiative to consider the cost of recommending specific antibiotics but I want to publish it.
- The state wants to investigate an outbreak of E.Coli and needs to use our records.

### Is It "Research"?



### HHS Definition of research

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

45 CFR 46.102 (d)

### Definitions of "Human Subject"

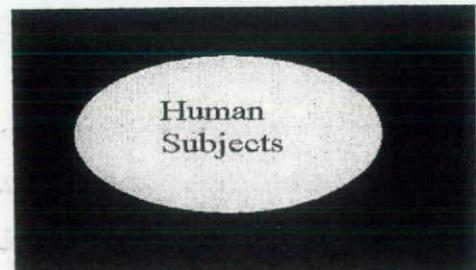
HHS: A living individual about whom an investigator... conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

FDA: Recipient of test article or control

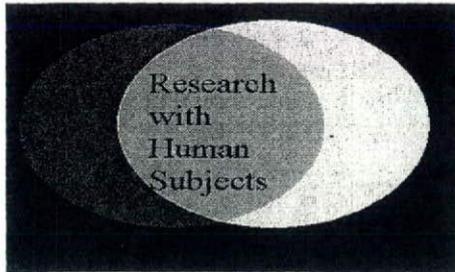
### FDA = Clinical Investigations of FDA Regulated Products

- A Clinical Investigation means any experiment in which a drug (or biologic or significant risk device) is administered or dispensed to or used involving one or more human subjects

### Are "Human Subjects" Involved?



## Is It "Research With Human Subjects"?



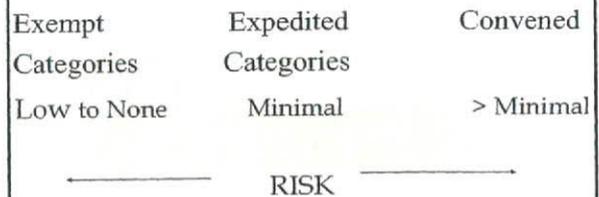
"I am confused, it seems like there are many different types of IRB review, some quicker than others. How is this decision made? What are the types of review?"

## Institutional Policies Define Research

- Pilot Studies
- Case reports
- Quality Improvement
- Interviews about systems versus personal opinions
- Samples without identifiers
- What and when is use of registry data research

## Review Continuum

Categories of Research determine route of review



## Two Helpful OHRP Guidance Documents

Guidance on Research Involving Coded Private Information or Biological Specimens – August 10, 2004

Engagement in Research (Jan 26, 1999)  
Revised Draft ( December 8, 2006)



"I think my research is exempt, so that means I do nothing, right?"