Evolution of the Ethics and Regulation of Research Involving Humans: Trials, Tribulations & Tragedies

November 18, 2015

Presented by:
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Associate Vice Chancellor of Academic Affairs
Institutional Official
About Schulman IRB

- Established in 1983
- Superior audit history with FDA—five consecutive audits with no findings
- 21 CFR Part 11 compliant electronic systems
- Compliant with FDA, OHRP and Health Canada requirements
- Full Board meetings five days a week
- Dedicated daily expedited review of qualifying minimal risk protocols
About Schulman IRB

- Review outcome provided within **one business day** of new study review
- **One business day** turnaround for complete new site submissions
- Dedicated streamlined processes tailored to **Phase I** timelines
- **Expert oncology Board members** experienced in all phases of oncology research
- Customized services for **institutions**
- **Experienced primary points of contact** for sponsors, CROs, institutions and sites
Clinical Quality Assurance (CQA) and Human Research Protection (HRP) consulting services provided by Provision Research Compliance Services

Provision is a joint venture between Schulman IRB and Falcon Consulting Group
The industry’s choice for central and local IRB services.

Get Started
Begin the initial review process.

Forms
Download the latest forms for your study.

Contact Us
Request more info & send feedback.
Ernest Prentice, PhD
Associate Vice Chancellor for Academic Affairs
Institutional Official of the Human Research Protection Program
University of Nebraska Medical Center

- Institutional Official for UNMC Human Research Protection Program and Animal Care and Use Program
- Previously served as Executive Chair and Co-Chair of UNMC IRB as well as Chair of UNMC IACUC
- Consults with universities, hospitals and law firms on research ethics and regulatory issues
- PRIM&R faculty, frequent speaker at research conferences and regular contributor to research ethics literature
- Chaired HHS Secretary’s Advisory Committee on Human Research Protection (SACHRP) 2003-2007
- Awarded OHRP medallion for Outstanding Achievement in Human Subject Protections
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Basic Premise

Research ethics and IRBs did not evolve naturally. It took a series of forceful, and often painful, events to drive change.
“To understand what is happening today or what will happen in the future, I look back”

Oliver Wendell Holmes
Outline

- Crimes, Trials And A New Code (1945-47)
- Willowbrook Hepatitis Study (1956-72)
- The Thalidomide Tragedy (1962)
- Declaration of Helsinki (1964)
- Henry Beecher’s “Catalyst” (1966)
- Tuskegee Syphilis Study (1932-72)
- The Belmont Report (1979)
- Huge Regulatory Change (1981)
1945-1947
Crimes, Trials and a New Code
THE WAR IN EUROPE IS ENDED!
NAZIS SIGN SURRENDER TERMS;
V-E WILL BE PROCLAIMED TODAY;
LAST FIGHTING IN CZECH POCKET

GAINS ON OKINAWA
Island-Wide Advance Is
Made as U. S. Troops
Use Flame-Throwers
7 MORE SHIPS SUNK

Pulitzer Awards
For 1944 Revealed

GERMANY SURRENDERS: NEW YORKERS MASSED UNDER SYMBOL OF LIBERTY

GERMANS CAPITULATE UNCONDITIONALLY
American, Russian and French Generals
Accept Surrender in Reims Schoolhouse
Used as Eisenhower’s Headquarters

REICH CHIEF OF STAFF ASKS FOR MERCY
“The defendants in this case are charged with murders, tortures and other atrocities committed in the name of medical science...for the most part [the victims] ...are nameless dead.

“The...distorted concepts which brought about these savageries are not dead. They must not become a spreading cancer...for the reason so well-stated by Justice Jackson in this courtroom a year ago...

*General Telford Taylor*
May 15, 1941

Dear Mr. Reich Leader,

“The experiments will be conducted at the airforce ground-level testing station for high altitude research…the experiments during which…the test persons may die…cannot be conducted with monkeys…since monkeys react… differently…”

Sincerely,

Dr. Sigmund Rascher
The Nuremberg Code

- Voluntary consent
- Yield fruitful results otherwise unobtainable
- Based on animal experiments
- Avoid physical and mental suffering
- Not done if injury expected
- Risk less than importance of problem
- Protect subject from injury
- Conducted by qualified people
- Termination by subject
- Termination by investigator

Nuremberg Military Tribunal
Control Council Law No. 10 (1947)
1956

Situational Ethics!
Willowbrook State School

Staten Island (1956-1963)

Subjects:
• Institutionalized children

Intervention:
• Deliberate infection with hepatitis A

Recruitment:
• Coercive recruitment through restricted admission
• Rationalization of risk and ethics

Introducing Jerry Rivers...
INFECTIONOUS HEPATITIS*

Studies of Its Natural History and Prevention

ROBERT WARD, M.D.,† SAUL KRUGMAN, M.D.,‡ JOAN P. GILES, M.D.,§
A. MILTON JACOBS, M.D.,∥ AND OSCAR BODANSKY, M.D.∥

NEW YORK CITY
1962

Tragedy Awakens Congress and the FDA Takes Action!
Marketed in Germany as a safe, mild sedative for pregnant women until tragedy strikes!
The FDA Heroine
1962: Kefauver – Harris Amendments

Drug amendments of 1962 were enacted in response to Thalidomide related birth defects

- IND submission to FDA for human studies – *Now Required*
- Ethical scientific pre-review – *Not Required*
- Informed Consent of Human Subjects – *Loosely Required*
- Preclinical testing using animals – *Now Required*

*28 FR 179 (Jan. 8, 1963)*
1964

A New Code is Issued by the WMA!
Declaration of Helsinki
Basic Principles
World Medical Association, 1964

• Research based on animal experiments
• Conducted only by qualified persons
• Importance of research proportionate to risk
• Risks-benefits assessed beforehand
• Effects of drugs on personality considered

1966

Complacency Altered!
Beecher’s “Catalyst”

- 22 examples of unethical research
- Highly funded investigators
- Prestigious institutions
- Declaration of Helsinki violated
- Indictment of moral complacency

“...unethical or questionably ethical procedures are not uncommon”

*NEJM, Vol. 274 (24), 1354-60, 1966*
Another Wake-Up Call for the Federal Government!
Tuskegee
1932-1972

The infamous study that was not supposed to die until the last of its subjects did.
“Remember this is your last chance for special free treatment.”

“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.”
Published Papers

1936-1964

UNTREATED SYPHILIS IN THE MALE NEGRO

A COMPARATIVE STUDY OF TREATED AND UNTREATED CASES.

Read before the annual meeting of the American Medical Association, Section on Dermatology and Syphilology, Kansas City, Mo., May 11-12, 1965.

R. A. YONDERLEHR, Assistant Surgeon General,
TALIAFERO CLARK, Medical Director (Retired),
O. C. WENDER, Surgeon, and J. R. HELLER, Jr., Assistant Surgeon, United States
Public Health Service

The Tuskegee Study of
Untreated Syphilis

The 30th Year of Observation

DONALD H. ROCKWELL, MD; ANNE ROOF YOSS, MD;
AND M. BRITTAIN MOORE, JR., MD, ATLANTA

UNTREATED SYPHILIS IN THE MALE NEGRO

BACKGROUND AND CURRENT STATUS OF PATIENTS IN THE
TUSKEGGEE STUDY

STANLEY H. SCHUMAN, M.D.,* SIDNEY OLANSKY, M.D.,**
EUNICE RIVERS, R.N.,*** C. A. SMITH, M.D.,****
AND DOROTHY S. RAMBO, R.N.*****

From the Venereal Disease Program, Division of Special Health Services, U.S. Public Health Service,
Washington, D. C.

UNTREATED SYPHILIS IN THE MALE NEGRO

Twenty-Two Years of Serologic Observation in a Selected Syphilis Study Group

SIDNEY OLANSKY, M.D., DUHON, N. C.
AD HARRIS
JOHN C. CUTLER, M.D.
AND
ELEANOR Y. PRICE, CHAMBLEE, GA.

Since 1932 there has been carried on a
untreated syphilis

Twenty Years of Followup Experience
In a Long-Range Medical Study

By EUNICE RIVERS, R.N., STANLEY H. SCHUMAN, M.D., LLOYD SIMPSON
and SIDNEY OLANSKY, M.D.

O ONE OF the longest continued medical
surveys ever conducted is the study of un-
treated syphilis in the male Negro. This study
At Tuskegee, each of the 600 patients initially
was given a complete physical examination, in-
xcluding chest X-rays and electrocardiograms.
This certificate is awarded to

In grateful recognition of 25 years
of active participation in the
Tuskegee medical research study.

Awarded 1958

Surgeon General
Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER
The Associated Press

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were induced to serve as guinea pigs, have gone without medical treatment for the disease and a few have died of it. Doctors in the service say they are now rendering whatever other medical services they can give to the survivors have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants.
The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Charge:

“Conduct a comprehensive investigation...to identify the basic ethical principles which should underlie the conduct of...research involving human subjects...”

Public Law 93-348
July 1974
1981

Huge Regulatory Change!
The New Regulations

The Belmont Report

Effective July 27, 1981

Justice Respect Beneficence

45 CFR 46  21 CFR 50, 56
Criteria for IRB Approval

- The risks to the subjects are minimized (B)
- The risk-benefit relationship of the research is acceptable (B)
- The selection of subjects is equitable (J)
- An appropriate study monitoring plan is in place (B)
- The process of informed consent is appropriate (R)
- Obtainment of informed consent will be appropriately documented (R)
- Privacy of subjects and confidentiality of data are appropriately protected (B)
- Appropriate additional protections are in place for vulnerable subjects (R, B)

45 CFR 46.111; 21 CFR 56.111
Beneficence (B), Justice (J), Respect for Persons (R)
Outline (cont’d)

• Cold War Guinea Pigs Revealed (1994)
• A Death in Rochester (1996)
• The Federal Crackdown Begins in Chicago (1998)
• The First “Gene Therapy” Death (1999)
• Tragedy at Hopkins (2001)
• All’s quiet on the IRB front (2003-2010)
• Tuskegee all over again in Guatemala (2010)
• The Advanced Notice of Proposed Rule-Making (2011)
1994
Cold War Guinea Pigs Revealed
The ACHRE Charge

- Investigate past human radiation experiments (1944-1974)
- Examine current research practices and protections
- Formulate recommendations for improvement

January 15, 1994
“...current rules protecting human subjects and the practices of individual scientists are a significant improvement over those of earlier decades. But we did find evidence of some serious problems in the conduct and oversight of human research today.”

*October, 1995*
1996

A Death in Rochester
Rochester Death Halts MIT-Funded Study

By Dan McGuire

A University of Rochester research project funded by an MIT grant has been suspended following the death of a student participant in the study.

The student’s family plans to file a $100 million lawsuit, according to Reuters. MIT has not been named as a defendant.

Rochester sophomore Hsiyuan (Nina) Wan, 19, died on the morning of March 31 apparently due to a fatal dose of the anesthetic lidocaine.

The drug was being administered as part of testing for a pollution research project. Wan had been taken to the emergency room at Rochester University’s Strong Memorial Hospital on March 29 after suffering cardiac arrest.

“This is a tragic loss. I am devastated by the news,” said the study’s principal investigator, MIT Professor William G. Dally, director for the Center for Environmental Health Sciences. “I want to express my profound condolences to the family of Ms. Wan,” he said. Dally also serves on the MIT Committee on the Use of Humans as Experimental Subjects.

The Wan family’s lawyer, Salvatore Aspromonte, said that the family was going to sue the doctors and the hospital. “Anyone else beyond that is just speculative,” he said. He was unaware that MIT was involved in the research.

Lung tests cited in death.

Wan was one of 200 participants involved in the Rochester branch of the research study, which was funded by the National Institute of Environ
1998

The Federal Crackdown Begins in Chicago
Report puts hospital's human research on hold

By Janice Milius

The research at St. Luke's Medical Center in Chicago, one of the nation's most prominent hospitals, is under scrutiny after a recent complaint by a patient. The hospital has been accused of failing to properly inform patients about the risks and benefits of clinical trials, and of obtaining consent in an unethical manner.

The hospital, like many others, relies on federal funding for many of its research projects. The federal government has strict regulations in place to protect patients and ensure ethical research practices. However, some critics argue that these regulations are too lenient and that more needs to be done to protect vulnerable patients.

The Illinois Attorney General's office has launched an investigation into the hospital's research practices, and the federal Office for Human Research Protections (OHRP) is also looking into the matter. OHRP is a federal agency that oversees research involving human subjects.

The hospital has denied any wrongdoing and has said it is cooperating fully with the investigations. However, the situation has raised concerns among both patients and researchers about the safety and ethics of clinical trials.

Experts have called for greater transparency and accountability in the research process. They argue that patients have a right to know about the potential risks and benefits of participating in clinical trials and that researchers have a responsibility to protect their patients.

The hospital has defended its research practices, saying that it follows all federal regulations and meets the highest ethical standards. However, the ongoing investigations suggest that more needs to be done to ensure that patients are fully informed and that their rights are respected.

In the meantime, patients are being advised to be cautious when participating in clinical trials and to carefully review any consent forms before signing them.
1999

The First “Gene Therapy” Death
Informed Consent?

Then...

“I don’t know what they used us for. I ain’t never understood the study”

Survivor of Tuskegee Syphilis Study, 1932-1972

and Now...

“It looked safe. It was presented as safe. I encouraged my son to do this. But, I wasn’t given all the information...and some of the information I was given was not true. I have come to the painful conclusion that I was fairly naïve to have trusted the investigators.”

Paul Gelsinger, father of 18 year old Jesse Gelsinger who died in a gene therapy study trial September, 1999 at the University of Pennsylvania
2001

Tragedy at Hopkins
The New York Times

Johns Hopkins Admits Fault in Fatal Experiment

by GINA KOLATA
Published July 17, 2001

BALTIMORE, July 16 — Johns Hopkins University said today that it accepted full responsibility for the recent death of a volunteer in an experiment. In a report on its investigation into the death, the university said the researcher who conducted the experiment and the ethics committee that approved it had failed to take adequate precautions to protect research subjects.

"Regardless of the fact that we are unlikely ever to know precisely how or why this happened, Hopkins takes full responsibility for what did happen," said Dr. Edward B. Miller, the dean and chief executive of Johns H Medicine.
Powell’s Mission Impossible

HOW MEDICAL TESTING HAS TURNED MILLIONS OF US INTO...

HUMAN GUINEA PIGS
2010

Expose’ of the Guatemalan Syphilis Study
Guatemalan Syphilis Study
U.S. PHS Grant RG65
1946-1948

Use of prostitutes to infect prison inmates:

“This group, lowest in the social scale of local prostitutes and most frequently infected with syphilis and gonorrhea were to be permitted, after discovery of presence of acute gonorrhea or infectious syphilis, to continue going to the prison and were to be paid by us for offering their service to any inmate who desired to utilize her at no cost to himself.”

—John C. Cutler

Presentation by Susan Reverby
President Barack Obama calls Guatemalan President Alvaro Colom “to express his deep regret.”

Colom calls it “crimes against humanity.”

Presentation by Susan Reverby
“It is clear that many of the actions undertaken within the Guatemala experiments were morally wrong. The Commission further concludes that the individuals who approved, conducted, facilitated, and funded these experiments are morally culpable to various degrees for these wrongs... We should be ever vigilant to ensure that such reprehensible exploitation of our fellow human beings is never repeated.”
2011

The ANPRM: Fiction or Reality?
Rule Changes Proposed for Research on Humans

By Andrew Pollack

Published July 24, 2011
2015

The NPRM: Moving Closer to Reality
Department of Homeland Security:

Executive Summary

Purpose of the Regulatory Action

Summarize the Major Provisions of the Proposed Regulatory Action

The proposed rulemaking includes

- Revised guidance for the protection of human subjects
- Clarification of the scope of the rule
- Amendments to the regulations

Proposed Rule

1. Revisions to the regulations
2. Additional requirements for research involving human subjects

More Provisions To Modernize the Common Rule

- Further clarification of the scope of the rule
- Revisions to the regulations
- Additional requirements for research involving human subjects

Federal Register / Vol. 80, No. 179 / Tuesday, September 8, 2015 / Proposed Rules

September 8, 2015
The Bottom Line

• The rights and welfare of human subjects take precedence over the interests of the investigator, institution, and sponsor(s) no matter where or when the research is conducted.

• This demands an unconditional commitment to sound research ethics and scientific integrity.

• We must learn from the past.
2015 and Beyond

“What experience and history teach us is this - - that people and governments never have learned anything from history or acted on principles derived from it.”

G.W.F. Hegel
Philosophy of History (1832)
The End
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