Ethics in Research

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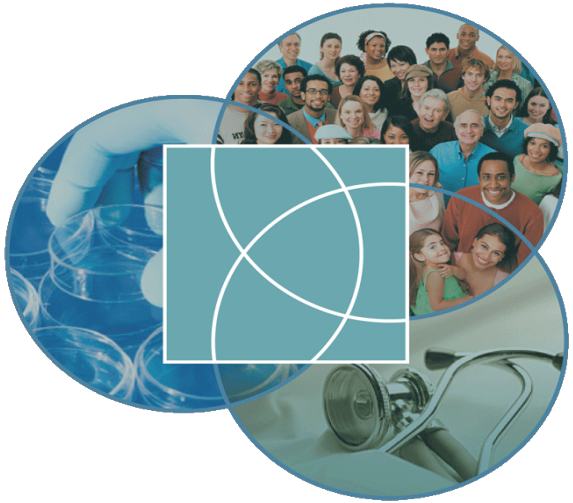
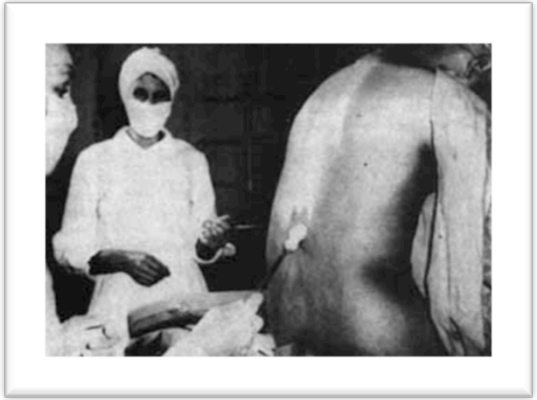


Ethics in Research

- Ethical concerns for all research
- Special ethical concerns in trials
- Case studies

Case: Tuskegee Syphilis Study

- Prospective cohort study funded by the US Public Health Service (1932 to 1972)
- 600 poor, illiterate, black men
  - 399 with syphilis; 201 without syphilis
  - Followed for 40 years for tertiary syphilis
- Never informed of condition, no consent
- Never treated



Ethical Principles Violated in Tuskegee

- Beneficence (likely benefit should outweigh risk)
- Respect for autonomy (voluntary consent and freedom to withdraw)
- Truth-telling (tell participants the truth)
- Justice (equal access to benefits and risks of research)

Human Subjects Protection

- Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects
- World Health Organization – ICH-GCP
  - International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice (GCP)

Case: Clinical Trial of TGN1412

- Novel antibody that activates T cells
- Developed to treat leukemia and rheumatoid arthritis
- Promising in animal studies

Case: Clinical Trial of TGN1412

- In a Phase I trial, 6 healthy young volunteers were randomized to the drug, 2 to placebo
- Active infusion was 1/500th dose given to monkeys
- All 6 had immediate cytokine storm, life-threatening organ damage, and required intensive care
- 5 hospitalized for a month, 1 for 3 months

Goodyear, BMJ 2006

Ethical Dilemma Illustrated in TGN1412

- Study participants are put at risk
- Society (other people or patients) benefit

Institutional Review Board

- Oversight by NIH Office of Human Research Protections based on Federal regulations
- Delegated authority to Universities and others
- Become familiar with your local IRB rules, regulations and processes

US Federal and Local Regulations

- UCSF - Committee on Human Research
  - http://www.research.ucsf.edu/chr/
- NIH - Office for Human Research Protection
  - http://ohrp.osophs.dhhs.gov/polasur.html
- Code of Federal Regulations Title 45, Part 46
  - http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm

What Studies Need IRB Approval?

Experimental Clinical Practice	Quality Improvement; Learning Healthcare System	Research
Aims to improve health for one patient	Based on evidence, aims to improve healthcare for patients in a system	Aims to obtain generalizable knowledge and improve care for a population of patients
Does not need IRB approval	Generally does not need IRB approval	Needs IRB approval

Case: Facebook

- During one week in January 2012, Facebook altered comments, videos, pictures and web links posted by friends on the social networks of 689,000 users
- Randomly reduced either positive or negative emotional content

Kramer, PNAS, 2014

Case: Facebook

- Findings
  - When positive content was reduced, users posted less positive, more negative material
  - When negative content was reduced, members posted more positive, less negative materials
- Made thousands of people more happy or sad!
- Participants not informed of study

Purpose of Informed Consent

- Describe risks, benefits and burdens
- Respect values and choices of participants
- Deter research with unacceptable risk
- Ensure participants freely choose to enroll
- Ensure participants know they can withdraw

Problems with Informed Consent

- Often difficult to understand
  - Median length ~ 6 pages (27 pages for HIV trials)
- Many participants still have misconceptions
  - Believe study provides optimal clinical care
  - Minimize study risks
  - Believe they need to participate to get clinical care

Suggestions to Improve Informed Consent

- Make sure language is readable for people with limited education
- Ensure that the informed consent form conveys key information by testing in a group of people like the study participants
- Train staff
- Take time

Case: Diabetes Study in Havasupai Indians

- 200 blood samples collected from tribe members
- Consent form stated that blood samples could be used to study "behavioral/medical" disorders
- Later shared with other investigators to study
  - Genetic basis of schizophrenia
  - Degree of inbreeding
  - Tribe ancestors migrated across Bering Strait

Mello, NEJM, 2010

Future Use of Genetic Material

- Specific consent – studies of diabetes only
- Tiered consent – participants choose
  - ❑ Refuse consent for future studies unless asked
  - ❑ Consent for diabetes only
  - ❑ Consent for a broader range of disease outcomes
  - ❑ General consent for any research
- General consent

Mello, NEJM, 2010

Alternatives to Informed Consent

- Permission from parent or guardian
- Waiver of consent if approved by IRB
  - For minimal risk studies
  - For studies of emergency interventions where consent isn't possible
- Deferred - enter study without consent; consent later
- Prospective – consent before eligible

Case: Breach of Confidentiality

Dr. Bernard Lo, MD

I am writing to inform you that a portable computer hard drive used by an employee of the Birmingham VA Medical Center is missing. This portable hard drive was used to back-up information related to research projects with which the employee was involved. A file on the portable hard drive included information from the Unique Physician Identification Number Directory, which includes demographic information and identifiers, such date of birth, state license number, business address, and Social Security Number. This file was obtained by VA from the Centers for Medicare and Medicaid Services (CMS) to conduct research on veterans' health care.

Harms if Confidentiality Breached

- Psychosocial risk
  - Sensitive or stigmatizing topics
  - Sense of violation
- Economic risk
- Legal risk if illegal activities
- Loss of public trust in research

How to Protect Confidentiality

- Train staff
- Limit access to data
- Use only coded or de-identified data
- Encrypt all identified data

Ethical Concern for Research in Low-Resource Areas

- Informed consent may be difficult due to language and culture
- Host country may lack IRB resources
- Optimal therapy may not be feasible
- Patients in low-resource area may not be able to afford drugs proven effective

Prevention of Vertical Transmission of HIV

- Trials in the US showed that treatment of HIV+ pregnant women and their newborn with IV zidovudine reduced infection of the newborn by 50-65%
- Multiple trials in low-resource areas studied cheaper oral regimens compared to placebo
- In some trials, participants were not give standard of care treatment for HIV infection
- Many trials funded by the US CDC or NIH

TDF2 Trial
Pre-exposure Prophylaxis (PrEP) for HIV

- 1219 HIV- heterosexual men and women from Botswana
- Randomized to one pill per day containing tenofovir and emtricitabine (Truvada) or placebo
- Outcome – new HIV infection
- Funded by US CDC and NIH; drugs provided by Gilead
- 62% reduction in risk of HIV infection in treated group

Summary

- Ethical research important to maintain trust of patients, participants and the public
- Some concerns covered by regulatory authorities, but requires personal responsibility
- Discuss with local ethics officials and colleagues