Week 5

Ethics, smethics.

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Today.

- A short history of unethical research.
- The IRB.
- Ethics training.

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Short History

… of inappropriate research actions and responses.

[Photo from Tuskegee Syphilis Experiment]

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Inappropriate Research Actions

- Nazi War Crimes (1939)
  - German physicians and administrators for their willing participation in war crimes and crimes against humanity. Horrifying procedures were conducted for research purposes on thousands of concentration camp prisoners without their informed consent.

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Inappropriate Research Actions cont.

- Syphilis Study in Tuskegee, GA (1932-1972)
  - US Public Health Service Research Project
  - 600 low-income African-American males, 400 of whom were infected with syphilis.
  - Monitored for 40 years, but never told about their disease.
  - Penicillin available in the 1950s, but participants denied treatment.
  - In some cases, when participants were diagnosed as having syphilis by other phyisicians, researchers intervened to prevent treatment.
  - Many participants died of syphilis during the study.
  - The study was stopped in 1973 by the US Dept. of Health, Education, and Welfare only after its existence was publicized and became a political embarrassment.

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1953

James Watson and Francis Crick discover the structure of DNA, for which they eventually would share the Nobel Prize in 1962. They secretly obtained key x-ray diffraction data from Rosalind Franklin without her permission. She was not awarded a Nobel Prize because she died in 1953 from ovarian cancer (at age 37), and the prize is not awarded posthumously.

1956-1980

Saul Krugman, Joan Giles and other researchers conduct hepatitis experiments on mentally disabled children at The Willowbrook State School. They intentionally infected subjects with the disease and observed its natural progression. The experiments were approved by the New York Department of Health.

1950s-1963

The CIA begins a mind control research program, which includes administering LSD to unwitting subjects.

Recent Example

Biotechnology

China's CRISPR twins: A time line of news

It's been three months since news broke that twin girls had been genetically modified using CRISPR. There's a lot to catch up on.

Feb 22, 2019

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Response to Research Abuses

- Nazi Atrocities
  - Drew attention to lack of international standard on research with human participants.
  - Let to formulation of the Nuremberg Code (1948).
- The National Research Act (1974)
  - Passed in response to syphilis study.
  - Codified requirements that human participants in research must be protected.
  - Set the stage for the Belmont Report (1974).

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Nuremberg Code

1. The **voluntary consent** of the human subject is absolutely essential.
2. The experiment should be such as to **yield fruitful results** for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to **avoid all unnecessary physical and mental suffering and injury**.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment..
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by **scientifically qualified persons**. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

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The Belmont Report

- Three basic ethical principles:
  - **Respect for Persons**
    - Individual autonomy
    - Protection of individuals with reduced autonomy
  - **Beneficence**
    - Maximize benefits and minimize harms
  - **Justice**
    - Equitable distribution of research costs and benefits

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Respect for Persons

- Treat individuals as autonomous persons; allow individuals to choose for themselves.
- Can withdraw from study if wanted.
- Persons with limited autonomy (children, individuals with disabilities, prisoners, etc.) need additional protections, even too the point of excising them from activities that may harm them. Extent of protection depends upon risk of harm and likelihood of benefit.

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Beneficence

- The IRB determines whether risks to subjects is reasonable in relation to anticipated benefits.
- Obligations of beneficence affect both researcher and society
  - Researchers required to give forethought to maximization of benefits and reduction of risk involved in proposed research.
  - Society should recognize longer term benefits and risk that may improve knowledge.

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Justice

- Treat people fairly.
- Do not exploit those readily available or malleable.
- Fair distribution based on problem/issue under investigation.

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Respect for Persons - Applied

- **Informed Consent Process** (serious discussions starting around 1972).
  - ***Information*** - Does the consent form provide all the information necessary for the individual to make a reasoned decision?
  - ***Comprehension*** - Is the consent form crafted in language understandable to the potential participant?
  - ***Voluntariness*** - Doe the consent form clearly indicate that participation in the research is voluntary?
  - What additional protections can be in place to protect those with limited autonomy?

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Beneficence - Applied

- **Assessment of Risks and Benefits**
  - **Risk** refers to the probability of harm; when considering risk one should consider both the *probability* and the *severity* of the envisioned harm; **benefit** refers to something promotion health, well-being, or welfare.
  - What are the risks of harm to the participants (consider physical, psychological, emotional, social, profession, and economic harms)? Are the risks justified? Can they be minimized?
  - Can the research design be improved to minimize risk and maximize benefit? (Researcher competence)
  - What are the benefits (to the participant; to society)?

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Justice - Applied

- **Selection of Subjects**
  - Is potential subject pool appropriate for proposed research?
  - Is it appropriate to involve vulnerable populations (e.g., economically disadvantaged; those with limited cognitive capacity) in the research or are they enrolled for convenience or because they are easily manipulated as a result of their situation?
  - Are recruitment procedures fair and impartial?
  - Are the inclusion and exclusion criteria fair and appropriate?

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Activity (Discussion #1)

- Go to: https://bioethicsresearch.org/resources/case-studies/ or
- Select one case.
- Read case and answer questions.

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Internal Review Board (IRB)

IRB Decision Tree

BENEFICENCE
Risk/Benefit Analysis
Experimental Design
Qualifications of PI

JUSTICE
Subject selection
Inclusion/exclusion criteria
Recruitment

RESPECT FOR PERSONS
Informed consent
"Surrogate" consent
Assent

Confidentiality or anonymity
Protection of subjects
(especially vulnerable)

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What is the IRB?

- Reviews all research activities involving use of human subjects excluding invasion of the body and animals.
- Serves as University resource to assure ethical treatment of human subjects and compliance with federal and university policies.

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Definitions

Update to Common Rule (45 CFR 46) on Jan. 2019.

- **Research** - systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.
- **Human subjects** - is defined as a living individual about whom an investigator conducting research:
  - Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; OR
  - Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.
    - Identifiable private information is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.
    - An identifiable biospecimen is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

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Routes

- Exempt Status:
  - Certain types of research may qualify for exemption according to federal regulations contained in 45CFR46. Once the IRB-SBS determines that a study is exempt, **informed consent is not required**. Exemptions are valid from date of IRB review until a date determined by the IRB. (NEP; minimal risk interviews, observations, surveys; archival data)
- Expedited Status
  - Federal rules (45CFR46.110) permit expedited review for certain types of research involving **no more than minimal risk** and for minor changes in approved research. The IRB-SBS chair or designee may determine that a project is eligible for expedited review using criteria outlined in the IRB-SBS Standard Operating Procedures. Expedited studies are reviewed by the chair or by one or more experienced reviewers designated by the chair.
- Full Board Review

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Steps in the Process: Your Actions

- Solid, defensible research design
- Complete on-line investigator training (CITI)
- Complete appropriate protocols and forms
- Submit proposal through Cayuse IRB.
- If changes, submit "modification". If completed, fill out "full report" form.

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Steps in the Process: Board Actions

- Chair/staff determines status — exempt, expedited, full board review
- Protocol, if full board, assigned to primary and secondary reviewers.
- Reviewers present results of their analysis to full board.
- Decision rendered.

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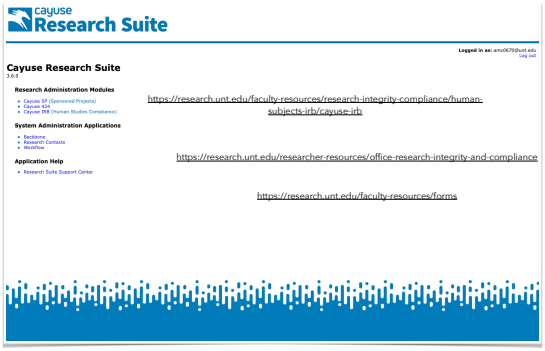

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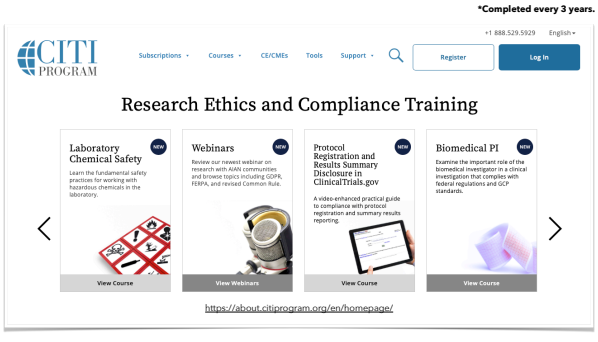

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Activity (Discussion #2)

- Consider your research topic of interest?
  - Without presenting the design of the study, what might be some ethical issues you might have to consider when planning your study?
  - How does the informed consent process look like?
  - What are the benefits and risk involved?
  - How do you expect to recruit participants?
  - What criteria are you considering for inclusion or exclusion from your study?
  - How will you ensure confidentiality or anonymity?
  - What happens with the data at the end of your study?

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Further Research Misconduct

- **Fabrication**: making up data or results and recording and reporting them.
- **Falsification**: manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.
- **Plagiarism**: the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.

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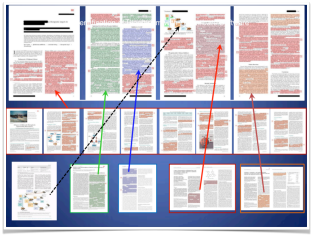
Plagiarism

- Several tools for non-originality detection: WCopyFind, iThenticate.



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Falsification.

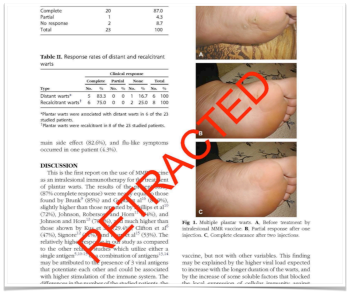
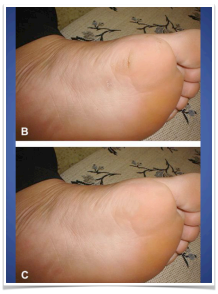


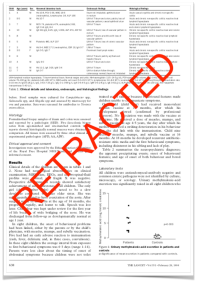
Table II. Response rates of distant and recalcitrant warts

Type	Clinical response: Complete		Partial		None		Total	
	No.	%	No.	%	No.	%	No.	%
Distant warts*	2	33.3	0	0	1	16.7	6	100
Recalcitrant warts†	6	75.0	0	0	2	25.0	8	100

*Plantar warts were associated with distant warts in 6 of the 23 studied patients.
†Plantar warts were recalcitrant in 8 of the 23 studied patients.



Fabrication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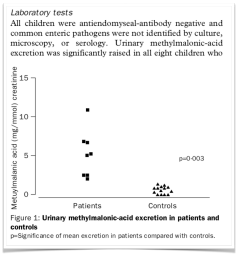
Laboratory tests

All children were antiendomyseal-antibody negative and common enteric pathogens were not identified by culture, microscopy, or serology. Urinary methylmalonic-acid excretion was significantly raised in all eight children who

Figure 1: **Urinary methylmalonic-acid excretion in patients and controls**

p=Significance of mean excretion in patients compared with controls.

DePauw (2012)

- Falsifying or fabricating research data
- Using another's ideas without obtaining permission or giving due credit (e.g., plagiarism)
- Ignoring or circumventing human-subject requirements or animal-use guidelines
- Ignoring potential conflicts of interest and not disclosing involvement with firms whose products are based on one's research
- Participating in relationships with students, research subjects, or clients that may be interpreted as questionable
- Using unauthorized and confidential information in one's research
- Failing to present data that contradict one's previous research
- Overlooking others' use of flawed data or questionable interpretation of data
- Changing the design, methodology, or results of a study in response to pressure from a funding source
- Publishing the same data or results in two or more publications
- Inappropriately assigning authorship credit
- Withholding details of methodology or results in papers or proposals
- Using inadequate or inappropriate research designs
- Dropping observations or data points from analyses based on a "gut feeling" that they were inaccurate

Protect yourself.

- Keep meticulous records.
- Record everything; retain everything.
- Label thoughtfully and consistently.
- Print, sign, date and have your data and notes witnessed.
- Maintain a "chain of custody".
- Prepare as if you might need to defend yourself in a court of law.

Resources

- Pg. 54-62 of Kowalski et al. (2018): Ethical decision-making process.
- Pg. 89-90 of Creswell & Creswell (2019): Table 4.1 *Ethical Issues*

Conclusion

- Adherence to ethical guidelines is absolutely necessary for research.
- Important to consider as designing research study.
- Be systematic in one's approach will be beneficial to conducting ethical research.
- Important unknown ethical considerations for biomedical and tech research.