Ethical Considerations in Clinical Research—An Overview

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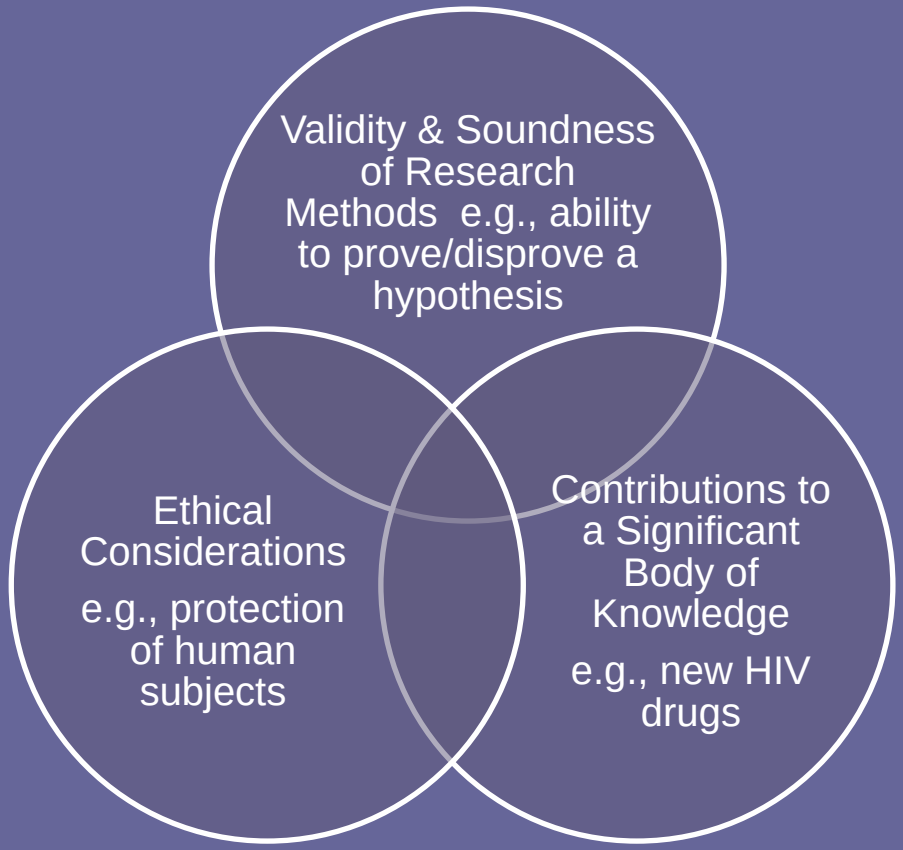
Learning Objectives

- ***Describe*** the evolution of ethics in clinical research
- ***Review*** medical ethics principles & definitions
- ***Discuss*** how such principles apply in clinical research
- ***Review*** strategies to help avoid ethical problems
- ***Know*** your resources & how to find additional information

Definition and Classifications of Medical Ethics

- Definition: “A system of moral principles, governing conduct…of persons in a profession…”
- Sub-Classes:
  - Clinical
  - ***Research -Focus of today!***
  - Education

Essential Features of Research



History & Evolution of Research Ethics

- Over 100 years ago, there were no laws governing the development of medications & medical devices.
- Likewise, there were no ethics guidelines for researchers ***and participants*** in such research.
- Almost anyone could be asked ***or made*** to participate in clinical research.
- Many “participants” were injured

Tuskegee Study

"Beginning in the 1930s, 399 men signed up with the *U.S. Public Health Service* for free medical care. The service was conducting a study on the effects of syphilis on the human body. The men were never told they had syphilis. and were denied access to treatment, even for years after penicillin came into use in 1947. By the time the study was exposed in 1972,

* 28 men had died of syphilis

*100 others were dead of related complications

*At least 40 wives had been infected and 19 children had contracted the disease at birth."

http://www.tuskegee.edu/global/Story.asp?s=1211670

McGill University Study

1957-60

- Ewan Cameron (McGill U. in Montreal) administered psychedelic drugs to 52 unsuspecting patients in order to carry out brainwashing experiments for the CIA.
- Experiments disclosed publicly for the first time in 1977 in the *New York Times*.
- Not until 1988 that the survivors received settlement.

Codes & Declarations

- **Nazis**

  The need for regulation and codes of behavior emerged from revelations of the research atrocities committed by the Nazis.

- **Nuremberg Code**

  This 1947 code for biomedical research was the first to focus on the importance of informed consent.

- **Helsinki Declaration**

  This 1964 declaration provided guidance in such areas as the use of animals for research purposes.

More Codes and Laws

- **The American Sociological Association (ASA)** adopted a formal code of ethics in 1969.

- **The National Research Act (1974)**
  - Passed by Congress for the purpose of protecting human subjects participating in experiments.

- **American Psychological Association (1982)**
  - *The Ethical Principles in the Conduct of Human Research with Human Participants*

- Of course, while it's essential to have codes, the responsibility for ethical research ultimately lies with the individual researcher(s).

Medical Ethics Principles & Concepts

- ***Autonomy***--The right of the subject to freely participate or not, provided they meet the inclusion criteria.
- ***Beneficence--*** Subjects should be **told the truth** about risks and benefits of their participation.
  - Informed Consent--Subjects should be **informed** about the risks and benefits.
- ***Non-maleficence-*** Will the research harm the subject?
- ***Justice*** **-** Will all subjects be treated fairly

Other Ethical Factors in ***Clinical Research***

- **No Pressure nor Coercion -** Never any pressuring of participants.
- **Safety -** Safety of participants essential.
- **Credit -** Every researcher must receive precise, appropriate credit.
- **Communicate -** One should try to make results known to participants and stop if interim results warrant. (See Low-Tidal Volume Case)
- **Improper Research Process or Use of Results**
  One should be conscious of possible bad uses of research.

Institutional Review Board (IRB)

- Main Purpose: To protect human subjects in research conducted within an organization.
- In order to be eligible for public funding (grants) academic health centers and other institutions such as hospitals and Bd's of Ed. conducting research are required to have an IRB.
- IRB ensure that research meets set criteria.

IRB Focus

- **About the Investigator(s)**
  - Who is the primary investigator, and who is supervising the study?
  - Do all study personnel have appropriate training.

- **About Research Participants**
  - What are general characteristics of participants (e.g. age, sex etc.)?
  - Any special characteristics of participants (e.g. children, alcoholics, mentally retarded, pre-exisiting illnesses, etc.)?
  - Any other institutions/individuals cooperating/cosponsoring the study?
  - How will subjects be selected for, or excluded from, participation in this study?

The Major IRB Concern

- **Risks**
  - Any immediate risks to the subjects, including possibly causing them embarrassment, inconvenience, or discomfort?
  - Are there any long-range risks to the subjects?
  - If there are risks, what is the necessity for them, and how will subjects be compensated for facing such risks?
  - What is being done to minimize Risks (see Methocholine Challenge & Lower VT Cases)

Informed Consent Document

- A ***gateway*** document ***& process*** to participation in human subject research.
- Must be first approved by the researchers and the **Institutional Review Board (IRB).**
- Signed by the Subject/Participant or their surrogate and witnessed.
- Must be administered by study personnel been approved to do so by the IRB.
- Signed copy must be kept on record.

Informed Consent—Cont.

- Explain the study and offer to answer questions.
- Participation is always voluntary.
- What is the time commitment?
  e.g. 45 minutes to complete the survey
- Any benefits for the participant to be expected?
  Realistically, there are often few *direct* benefits.
- Any potential risks, and how have these been managed?
- Confidentiality & Anonymity

Waiver of Informed Consent

- Must be Approved in Advance by the IRB.
- Research must meet one of more criteria.
  - Retrospective research using existing data (e.g., chart review).
  - Survey Research-Sending out a survey - ***Administrative Burden Example***

Challenges in Informed Consent

- Difficult for certain ***Special Populations*** to give voluntary consent.
  - Children
  - Mentally challenged
  - Critically ill—ICU patients/subjects
  - Terminally ill patients/subjects
  - Prisoners
  - Students
  - Military

Other Ethical Concerns in Clinical Research

- ***Procedural Integrity*** - Did the Researchers Follow the Approved Protocol?
- ***Data Integrity*** - Did they falsify data
- ***Plagiarism*** - Did the researchers try to pass another's work off as their own?

Scientific Rigor—Covid 19

- Spector-Bagdady K; Higgins PDR; Lok AS **Clin Infect Dis. 2020**
- **COVID-19 Clinical Trial Oversight at a Major Academic Medical Center: Approach of the Michigan Medicine COVID-19 Clinical Trial Committees.**
- Findings:
  - Clinicians - eager to offer the best care in the absence of guiding data - ***have provided patients with COVID-19 diverse clinical interventions.***
  - This usage has led to perceptions of efficacy of some interventions that, while receiving media coverage, ***lack robust evidence.***
  - Moving forward, ***randomized controlled clinical trials (RCTs) are necessary*** to ensure that clinicians can treat patients effectively during this outbreak and the next. To do so, academic medical centers must address two key research issues:
    - (1) how to effectively and efficiently determine ***which trials have the best chance of benefiting current and future patients***, and
    - (2) how to establish a ***transparent and ethical process for subject recruitment while maintaining research integrity*** and without overburdening patients or staff.

Case 1 – Informed Consent

- You observe a physician researcher attempting to obtain informed consent for an experimental therapy from a patient in moderate to severe respiratory distress.
- **Suggested Action:** Tactfully suggest that consent be obtained from a surrogate or Medical POA. If that fails, consider escalating it to the compliance hotline or directly to the IRB.

Case 2 – Consent of Critically Ill

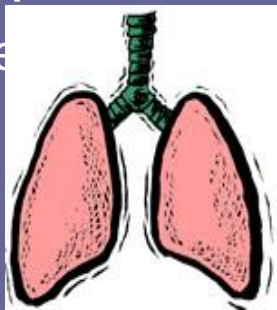
- A research protocols calls for obtaining informed consent on the trials of a new drug to help clear thick secretions on Covid 19 + patients.
- **Challenge:** Obtaining informed consent on a sedated and critically ill patient .
- **Suggested Action:** Attempt to gain consent from a surrogate or have surrogate appointed by the courts.

Case 3: Interim Results & Cross-over Provision!

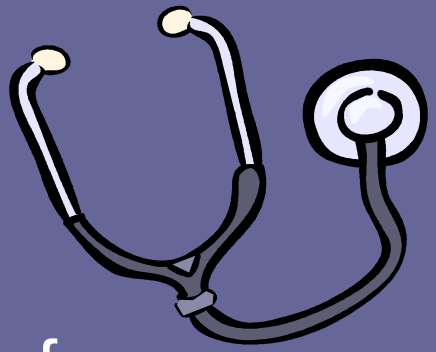
- A study is comparing the safety and efficacy of traditional (control group) vital volumes of 8-10 mls/kg IBW, in mechanically ventilated patients, versus lower tidal volumes 4-6 mls / kg (experimental group). Interim results result show a much lower mortality rate in the low- tidal volume group. What is the appropriate action.
- **Suggested action**: Ensure that there is a cross-over provision, which permits those in the group with higher risk, receive the treatment which is safer. Then, ensure that the protocol has a provision for obtaining, analyzing and responding to interim results

Case 3 (Cont.) Lower Tidal Volume Ventilation

- Mattay, MA, et al, *NEJM*, 342 (18) 1301-1308 (2000)
  - Findings: Ventilation with Lower Tidal Volumes (6 mls/kg) as compared with Traditional Tidal Volumes results in less acute lung injury and acute respiratory distress syndrome.
- Multi-center, randomized trial.
  - Control Group: VT = 12 mls/ kg
  - Experimental Group: VT = 6 mls/kg
- Trial stopped: After 861 subjects enrolled, interim statistical analysis revealed large "between group" differences
- 28 Day Mortality: Controls=39.8% vs Exp. 31.0%: P Value = 0.007 (7 in 1000 likelihood that this was due to chance



Case 4 – Rescue Protocol



- A research protocol to test the efficacy of an experimental bronchodilator, calls for the administration of methocholine, to first cause bronchial constriction (methocholine challenge), then the administration of the experimental agent to relieve the constriction. What provisions could help minimize the risk to subjects?
- Suggested Action: A rescue protocol which includes the use of a “code cart” and trained personnel, and the testing of such rescue procedures.

Case 5 — Coercion

- The researcher and faculty member wants to test a new skin treatment and asks his students to participate. Some students are reluctant because of a variety of reasons (e.g., modesty) but agree to for fear of reprisal.
- **Suggested Action:** Research done by faculty which employs their students is strongly discouraged and is not permitted in many cases. Revise the protocol to recruit subjects who are not associated with the university.

Case 6—Coercion Continued

- The protocol described in the preceding case (Case 5) has been revised to recruit subjects who are students from an inner-city clinic outside of the university. They will be offered $2,000 for their participation, plus free health care
- Suggested action: Depending upon the specifics, these subjects still might be considered vulnerable to coercion, due to their socio-economic status and the relatively high level of remuneration. At very least, the compensation for participation should be substantially reduced and consideration given to targeting a different population.

Case 7 – Parental Consent, Assent and Consent

- A protocol is drafted to determine the effectiveness of a program to educate grammar school children on asthma management. The participants will be administered a validated asthma knowledge questionnaire before and after the program and changes in their knowledge will be recorded and analyzed.
- **Suggested Action:** Unless their legal guardian or parent will also be participating, many of these children will be too young to consent on their own behalf. So, their parent or legal guardian will need to give consent to permit the participation of their child.

Case 8 – Data Confidentiality

- A research protocol is being prepared to obtain tissue samples from cancer patients ***for future use.*** The biopsy procedures for obtaining the tissue are proper and the informed consent document is clear and accurate about the risks involved. The data will be kept on a departmental computer used by a limited number of faculty within the department, including a few not involved in this project.
- **Suggested Action:** Revise the protocol to ensure that the procedures pertaining to a *tissue repository* are followed and ensure that the data is kept in a pass-word protected and secure computer accessible only by study personnel.

Case 9 – Adverse Events

- An approved protocol is being implemented to test the safety and efficacy of a new cardiac medication. Since beginning the study, two of the four subjects recruited have become acutely ill with an abnormal heart rhythm; one of who required admission in the ICU.
- **Suggested Action:** Though possibly unrelated to the study medication, these cases should be reported to the IRB as Adverse Events (AE's) and additional recruitment should be stopped. Consideration should be given to ceasing the experimental medication until additional clarity can be gained

Case 10 – The IRB as a Resource

- You are a novice researcher beginning to prepare a protocol for a research project in which you are involved. You have many unanswered questions related to procedures and subject recruitment logistics.
- **Suggested Action:** Consult with the principal investigator for the project and then contact the IRB on any remaining questions.

Take Home Messages- Avoiding Ethical Problems

- Identify Practical Resources
  - More experienced researchers.
  - IRB
- Avail yourself of these existing resources.
- Participate in all available research and ethics training within your organizations.
- If it does not feel right, it may not be.
- Exercise common sense and good judgment.
- Don’t let your ego get in the way.
- If you have questions…or need add’l info…***Ask***!

Selected References

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- American Association for Respiratory Care**, *AARC Statement of Ethics and Professional Conduct*,** Revised: Dec. 2007
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