Principles and Ethics of Clinical Research

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Goals of clinical research

• New therapies
• Improving outcomes
• Reducing toxicities/side effects
History of clinical research

- Herophilos (335-280 BC)
- Avicenna (980-1037)
- Edward Jenner (1749-1823)
- Walter Reed (1851-1902)
Herophilos (335-280 BC)

- Began to use scientific inquiry in medicine.
- Used dissection
- Recognized brain as center of nervous system
- Described difference between arteries and veins
- Described changes in the pulse with disease states
Avicenna (980-1037)

• Introduced experimentation into medicine and the idea of a clinical trial.
Ibn Sina

- TB
- Diabetes
The Canon of Medicine
Avacenna

1. The drug must be free from any extraneous accidental quality.
2. It must be used on a simple, not a composite, disease.
3. The drug must be tested with two contrary types of diseases, because sometimes a drug cures one disease by its essential qualities and another by its accidental ones.
4. The quality of the drug must correspond to the strength of the disease. For example, there are some drugs whose heat is less than the coldness of certain diseases, so that they would have no effect on them.
5. The time of action must be observed, so that essence and accident are not confused.
6. The effect of the drug must be seen to occur constantly or in many cases, for if this did not happen, it was an accidental effect.
7. The experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man.
Stuff we still think about

• The effect of the drug must be seen to occur constantly or in many cases, for if this did not happen, it was an accidental effect.

• The experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man."
Edward Jenner (1749-1823)

- “Don’t think, try.” William Harvey
Smallpox

- In late 1700’s about 20% of people died of smallpox.
Observation

- Milkmaids didn’t get smallpox.

Julien Dupre
They got cowpox.
Experiment

• Jenner inoculated 17 people with the pus from cowpox blisters including James Phipps with blister pus from Sarah Nelms after she got cowpox from Blossom the cow.
Clinical trials as of 1800

• Make an observation and develop a hypothesis.

• Try your idea on a person.
Walter Reed (1851-1902)

- Army Doctor, born in Virginia.
Research in Cuba on Yellow Fever

- Was yellow fever transmitted by fomites or a live vector?
The undersigned, Antonio Benino, being more than twenty-five years of age, native of Caracas, in the province of Coro, the son of Manuel Benino and Josefina Castro, here states by these presents, being in the enjoyment and exercises of his own free will, that he consents to submit himself to experiments for the purpose of determining the methods of transmission of yellow fever, made upon his person by the Commission appointed for this purpose by the Secretary of War of the United States, and that he gives his consent to undergo the said experiments for the reasons and under the conditions below stated.

The undersigned understands perfectly well that in case of the development of yellow fever in him, that he endangers his life to a certain extent but it being entirely impossible for him to avoid the infection during his stay in this camp, he prefers to take the chance of contracting it intentionally in the belief that he will receive from the said Commission the greatest care and the most skillful medical service.

It is understood that at the completion of these experiments, within two months from this date, the undersigned will receive the sum of $100 in American gold and that in case of his contracting yellow fever at any time during his residence in this camp, he will receive in addition to that sum a further sum of $100 in American gold, upon his recovery and that in case of his death because of this disease, the Commission will transmit the said sum (two hundred American dollars) to the person whom the undersigned shall designate at his convenience.

The undersigned binds himself not to leave the bounds of this camp during the period of the experiments and will forfeit all right to the benefits named in this contract if he breaks this agreement.

And to bind himself he signs this paper in duplicate, in the Experimental Camp, near Casasola, Cuba, on the 30th day of November, nineteen hundred.

On the part of the Commission: Walter Reed
Mej. & Surg., U.S.A.

Antonio Benino
Reed’s informed consent

- each volunteer explicitly consented to participate, and balanced the certainty of contracting yellow fever in the general population against the risks of developing an experimental case, followed by expert and timely medical care. The volunteers agreed to remain at Camp Lazear for the duration of the experiments, and as a reward for participation would receive $100 "in American gold," with an additional hundred-dollar supplement for contracting yellow fever.
Coincidence?

Reed and his daughter
Blossom, 1901
Lowlights and Progress
Food Drug and Cosmetics Act  1938

• Requires that drugs be shown to be safe before marketing. This leads to the need for human trials.
Nuremberg Code  1947

• Informed consent required for experiments.
• Experiments must be scientifically necessary and conducted by qualified personnel.
• Human trials should be preceded by animal studies and surveys of a disease's natural history.
• Benefit to science must be weighed against risks and suffering of experimental subjects.
Declaration of Helsinki 1964

• Clinical research should be **based on animal and laboratory experiments**.
• Clinical research should be conducted and supervised only by **qualified** medical workers.
• Clinical research should be preceded by a **careful assessment of risks and benefits** to the patient.
• Human beings should be **fully informed** and must freely consent to the research.
• **Responsibility** for the human subject must always rest with a medically qualified person, and never with the subject.
• Results of experiments that do not comply with ethical guidelines should not be accepted for **publication**.
• Special care must be taken with informed consent of minors.
• Also mentions consideration of the welfare of animal subjects and the environment.
Beecher article 1966

• Cited 22 examples of unethical human research
• Suggested that publishers should exercise judgement about whether researchers obtained informed consent and properly weighed the risks and gains, before deciding to publish results
Belmont Report 1979

- **Principal of Respect**: recognizes the *autonomy* of humans and requires clear informed consent.
- **Principal of Beneficence**: Research must be shown to be beneficial and reflect the Hippocratic idea of do no harm.
- **Principle of Justice**: The benefits to some must be balanced against the risks to subjects.
Belmont report

• Principles of ethical research involving human subjects

• Respect for persons
  • Autonomy
  • Protection

• Beneficence
  • Do not harm
  • Maximize benefits while minimizing possible harm

• Justice
  • Exploitation of vulnerable populations
  • Public funding and intended treatment population
How do we find new drugs?
Idea

Identify Target

Find Drug

Test in Cells and Animals

This takes a long time
How do we start testing it in people?
Phase I trial

• Is it safe to give to people?

• What is the correct dose?
Phase II Clinical Trial

• Does it work?
Phase III Clinical Trial

- Does it work better than what is currently being used?
If a drug works in animal models and in the lab why do we still need to test it in people?
Remember Avicenna

The effect of the drug must be seen to occur constantly or in many cases, for if this did not happen, it was an accidental effect.

The experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man."
Goals of clinical research

New therapies
Improving outcomes
Reducing toxicities/side effects
Why do clinical research?
Do clinical trials really make a difference?

• Benefit to future patients.

• Benefit to Current Patients.
Female Breast Cancer Mortality, California, 1973-1996

Rate per 100,000

Rates are age-adjusted to the 1970 US population. Prepared by the California Department of Health Services, Cancer Surveillance Section.
5 Year Event-Free Survival
Acute Lymphoblastic Leukemia

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Challenges for the future.

• How do we protect patient’s privacy?

• How can we go through drugs more rapidly?

• Can we divide diseases into smaller groups?