Research Ethics

History of Human Research

- 1700- 1800s
  - Louis Pasteur did human studies to find a rabies vaccine, some died of rabies/ smallpox, yet no one thought of consent
  - Edward Jenner inoculated an 8-year-old with a milkmaid's cowpox lesion without consent
- Pre-World War II
  - US soldiers were given 100 gold coins to sleep in mosquito infested tents and 100 more if they got yellow fever
- World War II
  - Many medications/ chemicals/ poisons were tested in war and on captured soldiers
  - Unit 731 – Japanese did brutal experiments on Chinese

1946 Nuremberg Code of Ethics

- Stipulated 10 requirements for ethical research
  - Voluntary consent
  - Experiment will yield fruitful results
  - Previous research justifies its conduct
  - No unnecessary physical/ mental suffering
  - No reason to expect death
  - Risk never exceeds humanitarian importance
  - Prior arrangements to protect subjects
  - Conducted only by scientifically qualified persons
  - Subject can withdraw at any time
  - Researcher can terminate study if too high of a risk

1964 Declaration of Helsinki

- Stipulated 18 basic principles (8 new ones) for ethical research, such as
  - Well-being of subject takes precedence over science and society
  - Duty of physician to protect life
  - Subject must volunteer and be informed
  - Assess risks vs benefits and give greater weight to lessen risks

Bias

Risk of Bias

- Characteristics of a study that can introduce systematic errors in the magnitude or direction of the results

Types of Bias

- Selection Bias
  - Systematic difference in baseline characteristics between two groups … when selecting the groups for a study
  - E.g. participants have difference ages, health status … 1 group is kids, 1 is adults
- Performance Bias
  - Systematic difference in treatment (aside from the intervention)
  - E.g. patients who know they are control group will go on other treatment
- Attrition Bias
  - Systematic difference in loss to follow up/ study withdrawal between the two groups
    - Participants who are lost due to adverse treatment etc. must be accounted for and not just ignored
- Detection Bias
  - Systematic difference in how outcomes are determined between two groups
  - E.g. the researcher being aware of which group is intervention, and which is control … he should be double blind
- Reporting Bias
  - Systematic difference in reported and unreported outcomes
  - E.g. only reporting positive results
- Funding Bias
  - Systematic difference in the direction of results or effect sizes
  - E.g. industry sponsored studies may report only for favourable results
- Biased Follow Up Time
  - Prevalent user bias
    - Exposure starts before follow up
    - e.g. Including only current users of a treatment in a study can make the treatment look safer or more effective because early risks and those who discontinued are excluded.
  - Immortal time bias
    - Follow up starts before exposure
    - E.g. Classifying patients as exposed only after they survive a certain period creates a span of “immortal” time that falsely inflates survival in the exposed group.

Randomised Controlled Trial

- Analytic, experimental
- Patients are screened to meet inclusion criteria and then invited to participate … they are then randomly assigned to either the treatment group or the placebo group
- Advantages
    - Controls for systematic, unsystematic and unknown bias
    - Rigorous evaluation of a single variable in a precisely defined group of subjects
    - Prospective design
    - Evaluates a pre-defined hypothesis
    - Can establish causality, treatment efficacy
- Disadvantages
    - Limited applicability
    - Limited generalisability
        - Lack of representation of population groups in the trial
    - Expensive, time consuming
    - Sometimes unethical
    - The study population is not truly representative of a population
- Sources of Bias
    - Selection of study population
    - Randomisation
    - Deviation from intervention
    - Missing outcome data
    - Measurement
    - Selective reporting

Cohort Study

- Analytic, observational study of two or more groups (no randomisation) over time … comparing exposed and unexposed groups and what proportion of people from each group got sick, stayed healthy
- May require "person years exposure" (be aware, common sense)
    - 2 people taking med for 6 months is *same* as 3 people taking med for 4 months
- Determination of exposure of interest results from
    - Preference
        - Smoking cigarettes
    - Circumstance
        - Disease, living near a toxic waste site
- Followed up over time, a number of years
- Advantages
    - Establishes a sequence of events, following people over time
    - Exposure precedes outcome
    - Reduces bias in measuring predictor variables
        - Recall or measurement bias
    - Reduces survivor bias
        - Because it includes undiagnosed, misdiagnosed, dead
    - Can study multiple outcomes
    - Can study outcomes over time
    - Measures incidence, relative risk
- Disadvantages
    - Cant control for unknown confounding variables
    - There may be systematic differences between groups
    - Large sample size required especially for rare or long term outcomes
    - Lengthy
    - Expensive
    - Not feasible for rare outcomes