1. Scientific Setting

1.1 Introduction and motivation

(i) Historical perspective
(ii) Why study clinical trials
(iii) Context for Clinical trials (a classification of study types)
(iv) Clinical trials: definition
(v) Course overview
(i) Historical perspective (Meinert, 1986)

- *Ambroise Pare (1510-1590):* Battlefield injuries were treated with boiling oil. Pare ran out of oil and used a mixture of egg yolk, oil of roses, and turpentine. The next morning those treated with the mixture were better.

- *James Lind (1747):* In one of the first experiments using a concurrent control; James Lind took 12 patients with scurvy and treated them with 6 different treatments (2 per group): a quart of cider per day, two spoons of vinegar three times a day, a half-pint of seawater per day (the two worst patients were assigned to this group), two oranges and one lemon per day, or a concoction of herbs mixed by a hospital surgeon. Those receiving the citrus were fit for duty after 6 days.
• **Haygarth 1799**: Perkin’s tractors used to stroke the body of an ailing person. Haygarth used sham tractors (made of wood) and found 4/5 patients reported pain relief.

• **Gull and Sutton (1865)**: Shows that patients with rheumatic fever improved using placebo treatment with mint water.

• **Fisher and MacKenzie (1923)**: Develops the idea of randomization while working in agricultural experiments. Amberson (1931) used randomized treatment assignment in a study of sanocrysin treatment for tuberculosis.

• **Medical Research Council of the UK (1931)**: Appoints “Therapeutic Trials Committee” to advise and assist in arranging proper clinical trials of new therapeutics.
Multi-site clinical trials: Emerged in late 1930’s and early 1940’s. One of the first was a trial to evaluate patulin for treatment of the common cold (published in 1944). Other examples of early multi-site trials include:

▶ Streptomycin treatment for pulmonary tuberculosis (published in 1948).
▶ VA trials of various chemotherapeutic agents for tuberculosis.
▶ Polio vaccine trials (started in autumn 1953) involved tens of thousands of volunteers.
▶ The NCI was established in 1937 and led to establishment of the NIH; the institutes support the largest number of trials.
<table>
<thead>
<tr>
<th>Year</th>
<th>Clinical Trials</th>
<th>Regulations</th>
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<tbody>
<tr>
<td>1906</td>
<td>Pure Food and Drug Act</td>
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<td>1912</td>
<td>Sherley Amendment</td>
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<td>1923</td>
<td>First randomization (Fisher and MacKenzie)</td>
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<tr>
<td>1931</td>
<td>First randomization in a clinical trial (Amberson, et.al)</td>
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<td>Committee on clinical trials by the Medical Research Council (MRC) in the UK</td>
<td>Formation of the FDA</td>
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<td>1937</td>
<td>Formation of the NCI and first research grant from the NIH</td>
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<td>1938</td>
<td>US Federal Food, Drug and Cosmetics Act</td>
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<td>1944</td>
<td>Publication of first multicenter trial (Patulin Clinical Trial Committee)</td>
<td>FDA distinguishes prescription and OTC drugs</td>
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<tr>
<td>1963</td>
<td>Publication of <em>Statistical Methods in Clinical and Preventive Medicine</em> (Hill)</td>
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<tr>
<td>1966</td>
<td>Mandated creation of IRB’s for studies funded by US Public Health Service</td>
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<tr>
<td>1977</td>
<td>FDA: “General Considerations for Clinical Evaluation of Drugs”</td>
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<td>1988</td>
<td>FDA: “Guidelines for the Format and Content of the Clinical and Statistical Content of an Application”</td>
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<td>1990</td>
<td>EC Commission: ”Good Clinical Practice for trials on Medicinal Production for the <em>European Community</em> ”</td>
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Key legislation related to FDA regulation:

- Pure Food and Drug (Wiley) Act (1906)
  - Requires *labeling* of foods and drugs
- Food, Drug, and Cosmetics Act (1938)
  - FDA has authority to oversee the *safety* of food, drugs, and cosmetics.
- Kefauver Harris Amendment (1962)
  - Requires manufacturers to provide substantial evidence of effectiveness and safety of drugs.
    “The term ‘substantial evidence’ means evidence consisting of adequate and well-controlled investigations, including clinical investigators, by experts qualified by scientific training.
- FDA Amendments Act (2007)
  - Registration of RCTs, Pediatrics, Risk Evaluation and Mitigation Strategies (REMS).
Two important resources:

- **International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines (www.ICH.org).**
  - A joint effort by regulatory authorities of Europe, Japan, and the United States (FDA)
    - Part 8: General Considerations for Clinical Trials
    - Part 9: Statistical Principles for Clinical Trials
    - Part 10: Choice of a Control Group and Related Issues in Clinical Trials

- **Consort guidelines (www.consort-statement.org)**
  - Consort statement: evidence-based minimum set of recommendations for reporting the results of clinical trials.
  - (22-item checklist and flow diagram).
(ii) Why study clinical trials?

- Clinical trials form the core of evidence-based medicine. Evidence-based medicine is a stated cornerstone of our main-stream health care system.
- The results from clinical trials must inform clinical practice. The statistical design is concerned with generalizability and reproducibility.
- Clinical trials involve human experimentation, and must therefore be approached carefully.
- Clinical trials infrastructure and methods are actively evolving. 20-years ago IRB’s would approve vague clinical trials that did not even have a maximal sample size. Clinical research is subject to increasing public scrutiny.
• Knowledge of clinical trials and relate methods is important for most public health professionals.

  Virtually all biostatisticians are involved in clinical trials (design and/or analysis).

  Clinical trial design is a multi-disciplinary endeavor that requires collaboration between clinician-scientists, statisticians, informaticians, research coordinators, study managers, and those who care for subjects.
Example

“Medicine at the Crossroads: Part 6 Random Cuts”
(PBS / BBC video, 1993)
(iii) Context: types of studies

- Common objectives of studies in the health sciences include:
  - Identifying individuals at risk for developing disease.
  - Identifying potential causes for disease.
  - Evaluating treatments for the disease.
  - Evaluating prevention measures.
  - Understanding basic science of disease biology.
  - The type of study follows from the objective and clinical setting.
Example: Smoking and lung cancer

How would you study this?
A classification of study types

- Descriptive
- Analytic-Observational:
  - Case-control study
  - Cohort study
- Analytic-Experimental:
  - Clinical trial
Analytic-observation studies

- Case-control study:
  - **Participants**: People with disease (cases); people without disease (controls).
  - **Comparison**: Compare exposure to risk factors in cases and controls.
  - **Advantages**: Good for rare diseases (and common exposures); relative quick.
  - **Disadvantages**: Time sequence between exposure and disease initiation is not always apparent; confounding.

- Cohort study:
  - **Participants**: Exposed individuals; unexposed individuals.
  - **Comparison**: Compare disease incidence in exposed and unexposed groups.
  - **Advantages**: Good for rare exposures (and common diseases); prospective design gives correct time sequence (exposure precedes outcome) and reduces chance for confounding.
  - **Disadvantages**: Potential for imbalances make it difficult to infer causality.
Analytic-experimental studies

- Experimental study:
  - **Participants**: Sample from relevant study population; intervention (exposure, treatment) is assigned as part of the study.
  - **Comparison**: Outcome compared across intervention groups.
  - **Advantages**: Best design for studying causality; exposure occurs before outcome; chance of confounding is minimized.
  - **Disadvantages**: Not always ethical or practical.
  - **Note**: An experimental study is a cohort study in which the exposure is assigned by investigators. This is an essential (defining) distinction.
Schematic representation of the research process

Research Process

Underlying Population

$\mu$ denotes unknown center

Inference about $\mu$

Sample summary measure: $\bar{X}$
Schematic representation: Analytic-observational studies

Underlying Population A

\[ \mu_A \]

Sample A

Statistics A

\[ \bar{X}_A \]

Inferential Question:

\[ \mu_A = \mu_B \]

Underlying Population B

\[ \mu_B \]

Sample B

Statistics B

\[ \bar{X}_B \]
Schematic representation: Analytic-experimental studies

Underlying Population:

$\mu_A$ : Hypothetical mean, treatment A
$\mu_B$ : Hypothetical mean, treatment B

Inferential Question:

$\mu_A = \mu_B$

Sample

Statistics:

$X_A$
$X_B$

Treatment A

Treatment B
(iv) Clinical trials: Definition

- A clinical trial is:
  - A planned experiment which involves patients that is designed to elucidate the most appropriate treatment of future patients. (Pocock, 1983)
  - A planned experiment designed to assess the efficacy of a treatment in man by comparing the outcomes in a group of patients treated with those observed in a comparable group of patients receiving a control treatment, where patients in both groups are enrolled, treated, and followed over the same time period. (Meinert, 1986)
  - A prospective study comparing the effect and value of intervention(s) against a control in human beings. (FFD)
  - An experiment testing medical treatments on human subjects (Piantadosi, 1997).

- I tend to take a broad view:
  - A clinical trial is any intervention study involving humans.

- The focus in this course is on medical intervention studies.
Clinical trials: Types of questions

- Types of questions that can be evaluated in clinical trials:
  - Therapeutic intervention studies:
    - Safety: Are treatment-related toxicities at a suitably low level?
    - Efficacy: Does the treatment offer beneficial effects on the disease process.
    - Effectiveness: Does the treatment offer benefits when used as part of standard routine practice.
  - Some examples of non-therapeutic intervention studies:
    - Behavioral interventions: Examples: Smoking cessation; diabetes prevention.
    - Prevention studies: Examples: Women’s Health Initiative (HRT for prevention of cardiovascular disease); lung cancer screening trial.
    - Community intervention studies: Interventions on schools to promote healthy lifestyles.
Clinical trials: Types of questions

Clinical trials have been used to

- Determine if a new treatment is beneficial.
- Determine if a new treatment has more benefits than a standard treatment.
- Determine if a new treatment is equivalent to a standard treatment.
- Determine if an old treatment is harmful.
- NOTE: A clinical trial cannot be used to determine if a new (untried) substance is harmful.
Clinical trials as experiments

- Clinical trials are approached with “trepidation” because they involve experimentation on human volunteers.
- As scientific experiments clinical trials must:
  ▶ Answer a scientifically meaningful questions.
    Must discriminate between viable hypotheses
  ▶ Provide results that inform (convince) medical practice.
    Use valid materials and methods
    Use valid measurement of the experimental outcome
    Provide a valid quantification of uncertainty in the experiment.
Clinical trials as experiments

As experiments on humans clinical trials must:

▶ Be ethically justifiable for the individuals entering the trial:
  As much as possible, minimize harm and maximize benefit for individuals in the trial.
  Avoid giving individual participants harmful treatments.
  Avoid giving individual participants inferior treatments.

▶ Maintain the ethical responsiveness to all likely future recipients of the therapy under evaluation:
  Identify (and approve) new beneficial therapies.
  Avoid approving ineffective or harmful treatments.
  Avoid unnecessary delays in the evaluation process.
(v) Course Overview:

1. Scientific Setting
   1.1 Introduction and overview
   1.2 The study question
   1.3 Case Study

2. From scientific setting to statistical design
   2.1 Refining the scientific questions to statistical hypotheses
   2.2 From statistical hypotheses to scientific decisions
   2.3 Case study

3. Fixed-sample clinical trial design
   3.1 On choosing the sample size
   3.2 Frequentist evaluation of a fixed-sample trial
   3.3 Bayesian evaluation of a fixed-sample trial
   3.4 Case study
4. Trial monitoring and adaptation
   4.1 Elements of trial monitoring
   4.2 Interim analyses: group sequential trial design
   4.3 Group sequential design families
   4.4 Frequentist evaluation of sequential trials
   4.5 Adaptation during trial conduct
   4.6 Case study

5. Development of a study protocol