2024 Summer Institute In Statistics for Clinical & Epidemiological Research

Module 3:

Design, Conduct, and Analysis of Randomized Clinical Trials with Time to Event Primary Endpoints

Lecture 13:

Overview of RCT Design

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Clinical Trials

- Experimentation in human volunteers
- Investigates a new treatment/preventive agent
  - Safety:
    - Are there adverse effects that clearly outweigh any potential benefit?
  - Efficacy:
    - Can the treatment alter the disease process in a beneficial way?
  - Effectiveness:
    - Would adoption of the treatment as a standard affect morbidity / mortality in the population?

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Regulatory Environment: Drugs

- Wiley Act (1906)
  - Labeling
- Food, Drug, and Cosmetics Act of 1938
  - Safety
- Kefauver – Harris Amendment (1962)
  - Efficacy / effectiveness
    - " [If] there is a lack of substantial evidence that the drug will have the effect ... shall issue an order refusing to approve the application. "
    - "...The term 'substantial evidence' means evidence consisting of **adequate and well-controlled investigations, including clinical investigations**, by experts qualified by scientific training"
- FDA Amendments Act (2007)
  - Registration of RCTs, Pediatrics, Risk Evaluation and Mitigation Strategies (REMS)

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Regulatory Environment: Medical Devices

- Medical Devices Regulation Act of 1976
  - Class I: General controls for lowest risk
  - Class II: Special controls for medium risk - 510(k)
  - Class III: Pre marketing approval (PMA) for highest risk
    - "…**valid scientific evidence** for the purpose of determining the safety or effectiveness of a particular device … adequate to support a determination that there is reasonable assurance that the device is safe and effective for its conditions of use…"
    - "Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, **from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness**…"
- Safe Medical Devices Act of 1990
  - Tightened requirements for Class 3 devices

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Clinical Trial Design

- Finding an approach that best addresses the often competing goals: Science, Ethics, Efficiency
  - Basic scientists: focus on mechanisms
  - Clinical scientists: focus on overall patient health
  - Ethical: focus on patients on trial, future patients
  - Economic: focus on profits and/or costs
  - Governmental: focus on safety of public: treatment safety, efficacy, marketing claims
  - Statistical: focus on questions answered precisely
  - Operational: focus on feasibility of mounting trial

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Statistical Planning

- Satisfy collaborators as much as possible
- Discriminate between relevant scientific hypotheses
  - Scientific and statistical credibility
- Protect economic interests of sponsor
  - Efficient designs
  - Economically important estimates
- Protect interests of patients on trial
  - Stop if unsafe or unethical
  - Stop when credible decision can be made
- Promote rapid discovery of new beneficial treatments

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Statistics and Science

- Statistics is about science
  - Science in the broadest sense of the word
- Science is about proving things to people
  - Science is necessarily adversarial
    - Competing hypotheses to explain the real world
  - Proof relies on willingness of the audience to believe it
  - Science is a process of successive studies
- Game theory: Accounting for conflicts of interest
  - Financial
  - Academic / scientific

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Science vs Statistics

- Recognizing the difference between
  - The parameter space
    - What is the true scientific relationship?
  - The sample space
    - What data will you / did you gather?

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"Parameter" vs "Sample" Relationships

- The true scientific relationship ("parameter space")
  - Summary measures of the effect in population
    - Means, medians, geometric means, proportions…
- Scientific "sample space" scales:
  - Estimates attempting to assess scientific importance
    - Point estimate is a statistic estimating a "parameter"
    - Interval estimates
      - CI describes the values in the "parameter space" that are consistent with the data observed (the "sample space")
- Purely statistical "sample space" scales
  - The precision with which you know the true effect
    - Power, P values, posterior probabilities

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The Problem of Clinical Trial Design

Happy families are all alike; every unhappy family is unhappy in its own way.

Leo Tolstoy, *Anna Karenina, 1873-77*

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The Problem of Clinical Trial Design

Unbiased clinical trials are all alike; every biased clinical trial is biased in its own way.

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Statistical Sampling Plan

- Ethical and efficiency concerns are addressed through sequential sampling
- During the conduct of the study, data are analyzed at periodic intervals and reviewed by the DMC
- Using interim estimates of treatment effect
  - Decide whether to continue the trial
  - If continuing, decide on any modifications to
    - scientific / statistical hypotheses and/or
    - sampling scheme

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Demystification

- All we are doing is statistics
  - Planning a study
  - Gathering data
  - Analyzing it

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Sequential Studies

- All we are doing is statistics
  - Planning a study
    - Added dimension of considering time required
  - Gathering data
    - Sequential sampling allows early termination
  - Analyzing it
    - The same old inferential techniques
    - The same old statistics
    - But new sampling distribution

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Overall Goal

- "Drug discovery"
  - More generally
    - a therapy or preventive strategy
    - for some disease
    - in some population of patients
- A series of experiments to establish
  - Safety of investigations / dose
  - Safety of therapy
  - Measures of efficacy
    - Treatment, population, and outcomes
  - Confirmation of efficacy
  - Confirmation of effectiveness

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Phases of Investigation

- Series of studies support adoption of new treatment
- Preclinical
  - Epidemiology incl risk factors
  - Basic science: Physiologic mechanisms
  - Animal experiments: Toxicology
- Clinical
  - Phase I: Initial safety / dose finding
  - Phase II: Preliminary efficacy / further safety
  - Phase III: Confirmatory efficacy / effectiveness
- Approval of indication
  - (Phase IV: Post-marketing surveillance, REMS)

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Treatment "Indication"

- Disease
  - Putative cause vs signs / symptoms
    - May involve method of diagnosis, response to therapies
- Population
  - Restrict by risk of AEs or actual prior experience
- Treatment or treatment strategy
  - Formulation, administration, dose, frequency, duration, ancillary therapies
- Outcome
  - Clinical vs surrogate; timeframe; method of measurement

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Scientific Method

- Planned experiment includes protocol specified in advance, including
  - Overall goal
  - Specific aims
  - Materials: Patients, treatments
  - Methods: Administration, monitoring, outcomes
  - Methods: Statistical analysis plan
    - Sampling plan
    - Statistical models for analysis
    - Planned interpretation of spectrum of results

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Specific Aim

- One of a series of studies used to support adoption of a new standard of treatment
  - Phase I: Initial safety / dose finding
  - Phase II: Preliminary efficacy / further safety
  - Phase III:
    - Therapeutics: Establish effectiveness
    - Prevention: Establish efficacy
  - Phase IV:
    - Therapeutics: Post-marketing surveillance
    - Prevention: Effectiveness

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Screening Studies

- Before we embark on an expensive, large scale Phase 3 confirmatory study, we will need
  - Preliminary evidence of safety concerns
  - Preliminary evidence of efficacy
  - Estimates of the hypothesized treatment effect that is
    - clinically important to detect, and
    - plausible in the target population

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Refine Scientific Hypotheses

- Target population
  - Inclusion, exclusion, important subgroups
- Intervention
  - Dose, administration (intention to treat)
- Measurement of outcome(s)
  - Efficacy / effectiveness, toxicity
  - Primary, secondary, supportive, exploratory
- Criteria for scientific credibility
  - Superiority, approx equivalence, noninferiority, etc.
- Statistical hypotheses in terms of some summary measure of outcome distribution
  - Mean, geometric mean, median, odds, hazard, etc.

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Statistical Design

- Comparison groups
  - Multiple treatments, doses, controls
- Randomization
  - Ratios, stratification, blocking
- Blinding
  - Double, single, or only adjudicators
- Statistical analysis model
  - Measure of treatment effect, covariate adjustment
  - Criteria for statistical evidence: Frequentist, Bayesian
- Sampling scheme
  - Sample size, stopping rules
- Plans for inference
  - Statistical control of multiplicity

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Statistical Analysis Models

- We focus on time to event endpoints
- We discuss Cox proportional hazards regression as the most common analysis for time to first event
  - We contrast the operating characteristics of PH regression with respect to precision and adjustment for covariates with
    - Linear regression
    - Poisson regression
    - Logistic regression
- For recurrent events we consider the choices of
  - Poisson regression, negative binomial regression, Anderson-Gill

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Next Lecture

- **Screening Trials**
- Precision of inference
- Randomization and Blinding
- Statistical analysis model and covariate adjustment
- Sample size formulas: Accrual and length of follow-up
- Sequential sampling
- Plans for inference
- Statistical control of multiplicity

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