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 1:

Overall Goal: Drug Discovery

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RCT Settings Using Time to Event Outcomes

- **Overall goal: Drug discovery**
- Estimands
  - Clinical
  - RCT
  - ICH E9 (R1) strategies for intercurrent events
- Why an “event”? Why ”time to event”?
- Why incomplete observations: Informative vs noninformative?
  - Administrative censoring
  - Competing risks
  - Intercurrent events and protopathic events
  - Loss to follow-up
- How to define “tends to be”?
  - Choice of summary measure

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Overall Goal: "Drug Discovery"

- More generally
  - a therapy / preventive strategy or diagnostic / prognostic procedure
  - for some disease
  - in some population of patients
  - to achieve some desired outcome

- A ***sequential***, ***adaptive*** series of experiments to establish
  - Safety of investigations / dose (phase 1)
  - Safety of therapy (phase 2)
  - Measures of efficacy (phase 2)
    - Treatment, population, and outcomes
  - Confirmation of efficacy (phase 3)
  - Confirmation of effectiveness (phase 3, post-marketing)

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The Enemy

"Let's start at the very beginning, a very good place to start…"

- Maria von Trapp
(as quoted by Rodgers and Hammerstein)

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First

- Where do we want to be?
  - Describe some innovative experiment?
  - Find a use for some proprietary drug / biologic / device?
    - "Obtain a significant p value"
  - Find a new treatment that improves health of some individuals
    - "Efficacy"
  - Find a new treatment that improves health of the population
    - "Effectiveness"

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What Do We Want from Health Care?

- Prevention of disease
- Diagnosis of conditions
- Prognosis from disease
- Treatment of disease

- Who, what, when, where, why, how?

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Who Might We Want to be Treated?

- **Who** do we mean by "we"?
- Personalized medicine vs (sub)populations
  - Fixed effects
    - Demographics
    - Behaviors
    - Environmental exposures
    - Genetics
    - Disease
  - Random effects

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What is Treatment?

- **What** do we mean by "treatment"?
  - Drug(s), device(s), behaviors vs sequence vs combination
  - Formulation(s)
  - Dose vs dosing strategy (reductions, escalations)
- **Where / how** do we mean by "treatment"?
  - Administration (oral, topical, IV, IM, water supply)
- **When** do we mean by "treatment"?
  - Starting, stopping, frequency
  - Drug holidays
- **Why** do we want "treatment"?
  - Clinical measurement
  - Timeframe

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Estimands in RCT

- Estimands
  - **Disease**: criteria for diagnosis
  - **Population**: demographics, concomitant medical conditions
  - **Treatment regimen**: formulation, administration, dose, frequency, duration, modifications, prophylaxis, rescue
  - **Outcome**: severity, time
- Selection of estimands
  - **Basic science**: Not unless ethical
  - **Clinical relevance**: The true goal of public health
  - **Regulatory criteria**: Efficacy, safety, effectiveness vs comparator
  - **Scientific rigor**: Unbiased (randomization), burden of proof
  - **Statistical definition**: Summary measures

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Scientific Method

- We will use well-designed experiments to investigate candidate treatments
- Randomization is the key method whereby we find the causal effects of the intervention
  - "Causal" at the time of first application of the intervention
  - Ensuing treatments are potential mediators of effect
- We must do "per-randomization" analyses to ensure control of unmeasured confounding
  - Every randomized subject must have an outcome
  - *Any* missing data means that the analysis will not truly be according to randomization

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Clinical Science: Treatment "Indication"

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

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Safety (Short and Long Term)

- Multiple levels of concern
- Safety of conducting RCTs
  - Phase I dose finding studies
- Safety in the ideal population
  - Phase II or phase III efficacy studies
- Safety in the general population
  - Phase III effectiveness studies
  - Vulnerable populations
  - Concomitant renal, liver disease
  - Expansion of indication to patients with little benefit
  - Changes in behavior associated with adoption
  - Rare but serious adverse events

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Efficacy

- An efficacious treatment has demonstrated an ability to beneficially modify
  - An endpoint thought to be an indicator of good clinical outcome
  - In some subset of patients
  - Under some conditions that are at least marginally relevant
- **A Moving Target**: Definition of efficacy can vary widely according to choice of endpoint and magnitude of importance
  - Basic science
    - Does treatment have any effect on the pathway
  - Clinical science
    - Does treatment have a sufficiently large effect on a clinically relevant endpoint

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Effectiveness

- An effective treatment will, upon adoption, improve the average health of the population
- **A Moving Target**: A treatment can be both efficacious and ineffective depending on factors of clinical trials
  - Target population
  - Control treatment
  - Intervention
  - Measurement of outcome(s)
  - Summary measure of outcome distribution
- N.B.: Effectiveness is a very hard thing to demonstrate in a RCT, but there are gradations

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Ultimate Goal

- Medical science in general, and the FDA in particular, are rightly concerned with the process by which new treatments are adopted
- Randomized clinical trials are the mainstay of this process
- Obviously, effectiveness is our eventual goal
  - There are many ways to get there, however
    - Study safety, efficacy separately
    - Study bottom-line "effectiveness"
- Sometimes scientific / clinical judgment holds sway
  - Can results of RCT be safely generalized to other settings?

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Regulatory Agencies

- Considers treatment risks / benefits
  - Safety
  - Efficacy
- Considers public health
  - Effectiveness
- Ultimately a governmental setting
  - Approval of introduction of drugs, biologics, devices, diagnostics
  - Oversight of marketing claims
  - Responding to political (economic) pressures

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Carrying Coals to Newcastle

- 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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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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Body of Evidence

- Ultimately, regulatory approval will be based on
  - Current scientific knowledge and beliefs
  - Historical studies, both observational and RCT
  - Preclinical evidence: *in vitro* and animal studies
  - Preliminary studies: Phase 1, 2
  - Registrational confirmatory trials
- Strength of evidence
  - Rigorous evidence from adequate and well-controlled RCT(s)
  - Scientific and clinical judgment generalizing those results to
    - Related diseases and more general populations
    - Variations in treatment strategies
    - Impact on long term outcomes

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Scientific Judgment in Burden of Proof

- We cannot answer every question with a RCT
- We always have to take some leap of faith
  - But we should try to keep it to a hop
- Science is adversarial
  - When have we demonstrated safety, efficacy, effectiveness to meet reasonable doubt?

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Scientific Method

- The key tools for a well conducted RCT are all part of the scientific method
  - Interventional experiment
    - Ensures proper definition of indication
  - Well defined study protocol
    - Avoids multiple comparisons
  - Randomized assignment
    - Ensures comparability of treatment arms (on average)
  - Unbiased ascertainment of results

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Points Meriting Repeated Emphasis

- Randomization is our friend…
  - If we randomize, we do not (on average) need to worry about differences between the treatment groups with respect to factors present at time of randomization
  - Any difference in outcomes can be attributed to treatment
  - Again, recognize that treatment can lead to differential use of other ancillary treatments, however
- But like all friends, we must treat it with respect.
  - We must analyze our data in groups defined at the time of randomization
  - Discarding or missing data on randomized subjects may lead to bias
  - It certainly leads to diminished scientific credibility

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Comment on "Intent to Treat"

- I view this term problematic
  - Originally, it was coined to describe the estimand associated with a "by-randomization" analysis when the target population is everyone who would ultimately be started on an effective therapy
  - The term is widely abused
- "By-randomization" is the true goal
  - The RCT may not be considering an intention to treat, e.g.,
    - Randomized withdrawal among tolerators
    - Randomized withdrawal among responders
    - Restricted eligibility criteria
    - Restricted ancillary therapies
    - etc.

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Next Lecture

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