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 0:

Course Overview

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Abstract

- A great many clinical trials investigate the potential effects of a treatment on the incidence of some clinical (or subclinical) event. Statistical analysis often focuses on time to event(s).
- The analysis of data measuring time to event is often complicated by incomplete observations: Some subjects did not have an observed event at the time of data analysis.
- Statistical methods developed for use in the setting of “right censored data”, include parametric and semiparametric regression models, as well as nonparametric methods.
- Problems that arise in clinical trial settings interact with the statistical behavior of the analysis methods in such a way as to warrant special attention.

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Science and Statistics

- **Statistics is about science**
  - (Science in the broadest sense of the word)
- Science is about proving things to people
  - (The validity of any proof rests solely on the willingness of the audience to believe it)
- In RCT, we are trying to prove the effect of some treatment to
  - Scientists (both basic scientists and clinical scientists)
  - Regulators
  - Clinicians
  - Patients
- **Question for this course:**
  - What do we need to consider as we strive to meet the burden of proof with RCT using time to event primary endpoints?

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What is Science?

- **Clinical / scientific issues are most important in RCT design**
  - Need to know current knowledge as well as immediate goals
  - Define appropriate subjects, comparators, procedures, outcomes
  - Maintain scientific rigor: randomization and blinding when possible
- **We consider two different aspects of "Science"**
  - Scientific knowledge about some area of investigation
    - Our clinical trials will need to be relevant
  - Scientific method and rigor in learning new things
    - We will need designs that minimize erroneous conclusions

For the interested: "The Scientist Game" (www.RCT-design.com/ScientistGame/index.asp)

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What is Role of Statistics?

- Statistical expertise is crucial when addressing clinical and scientific issues
  - Interpreting results of prior studies
  - Understanding of conditional probabilities
  - Anticipating confounding and other biases
  - Looking ahead for statistical limitations that might preclude certain designs
- Once clinical and scientific issues mostly resolved, statistician's role is to maximize and quantify RCT precision
  - Randomization and blocking strategies
  - Defining probability models and summaries of effect
  - Statistical analysis models
  - Estimating sample size requirements
  - Inferential estimates of effects
  - Quantifying precision of inference (frequentist and/or Bayesian)

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A Logical Disconnect Statisticians Need to Avoid

"Because the light is so much
better here under the street light."

- A drunk looking for keys lost down the street

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A Caver's Guide to Research

- Wandering in the dark
- A multitude of passages
  - Most are deadends
- Ideal companions
  - Willing to explore deadends
- Worst companions
  - Come back and tell you they went somewhere
- Most important rules
  - Recognize when you are back at the entrance

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General Philosophy

"Everything should be as simple as possible,
but no simpler."

- A. Einstein (paraphrased)

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Course Outline

- Clinical settings using incidence of events as outcome of treatment
- The various alternative approaches available for analysis
- Special focus on proportional hazards regression
- Statistical clinical trial design, including group sequential
- Adaptive designs that transcend group sequential

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RCT Settings Using Time to Event Outcomes

- Overall goal: Drug discovery
- Estimands
  - Clinical
  - RCT
  - ICH E9 (R1)
- 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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Statistical Analysis of Time to Event Outcomes

- Distribution-free methods
  - Kaplan-Meier
  - Aalen-Johansen
  - Two sample tests
    - Restricted means, quantiles, survival prob at time t
    - Weighted log rank tests
    - U statistics ("Win ratio")
- Parametric regression
  - Exponential, Weibull, accelerated failure time models
  - Negative binomial, Poisson for recurrent events
- Semi parametric regression
  - Cox proportional hazards
  - Anderson-Gill for recurrent events

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Proportional Hazards Regression

- Estimating equations
- Statistical information
- Impact of covariate adjustment

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General Clinical Trial Design

- Randomization
  - Randomization ratio, blocking, stratification
- Covariate adjustment
- Sequential sampling
- Precision
  - Number of events
  - Number of subjects
- Controlling for multiplicity
- Sensitivity for MNAR

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Adaptive Clinical Trial Design

- General Methods
- Adaptive sample size re-estimation (SSRE)
- Inference following adaptive design

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