What to do today (Feb 2, 2023)?

Part III.4.4 Efficacy Assessment

- The analysis goal should be to answer the primary and secondary questions; the methods should be chosen following the primary/secondary variables along with baseline information.

- Statisticians need to
  - understand the statistical procedure(s): the requirements/assumptions, comparisons with alternative approaches
  - if a statistical software package is used, know well the defaults, underlying assumptions, and the outputs structure of the particular function/procedure
  - be able to interpret the analysis results using the language that the other team members understand

Part III.4.4 Efficacy Assessment

A. Types of Analyses: according to different features of analysis,

- Estimation; Hypothesis Testing
- One-Sample, Two-Sample, Multi-Sample Problems; Regression Analyses
- Categorical Data Analyses; Survival Analyses; Longitudinal Analyses; High-Dimensional Data Analyses ... ...
- Parametric Analyses; Nonparametric Analyses; Semiparametric Analyses; ...
- Meta-Analysis of Multiple Studies; Analysis Following Interim Reviews; ...

Part III.4.4 Efficacy Assessment

B. Analysis Challenges: for example

- *Competing Events* (those that preclude the assessment of the primary response variable)
  e.g. competing risks in survival analysis with the primary response of a cause-specific mortality: informative censoring
- *Composite Outcomes* (combinations of clinical and other outcomes as a composite response variable)
  e.g. components not be consistent in indicating intervention effect; or one dominates the composite

Part III.4.4 Efficacy Assessment

B. Analysis Challenges: for example (cont'd)

- *Surrogate Responses* (substites for what are harder to measure)
  e.g. biomarker as a surrogate for the clinical progression
- *Covariate Adjustments*
  e.g. measurement errors; surrogate covariates
- *Incomplete Data Analysis*
  e.g. censored survival times; drop-outs
- ... ...

Example for Clinical Trial: ACTG359

Part A. the primary study and its extension

- Gulick, et al (2000). "Randomized Study of Saquinavir with Ritonavir or Nelfinavir Together with Delavirdine, Adefovir or Both in HIV-Infected Adults with Virologic Failure on Indinavir: AIDS Clinical Trials Group (ACTG) Study 359," *The Journalof Infectious Diseases*, 182: 1375-84.

- Gulick, et al (2002). "Durability of Response to Treatment for Antiretroviral-experienced Subjects: 48 Week Results from AIDS Clinical Trials Group (ACTG) Study 359," *The Journal of Infectious Diseases*, 186: 626-33.

Example for Clinical Trial: ACTG359

Part B. statistical research projects motivated by ACTG359

- *the repeated confidence bands (RCB) approach*
  Hu and Lagakos (1999a,b); Zhao, Hu and Lagakos (2009)

- *in longitudinal data analyses*
  Hu and Lagakos (2007); Hu, Lagakos and Lockhart (2009a,b)

Example for Clinical Trial: ACTG359

ACTG 359: a prospective, randomized, 2×3 factorial, partly blinded, multicenter study of the AIDS Clinical Trial Group

- **Background:** Recorded in late 1990s, successful standard treatments (protease inhibitor-containing regimens) but $\geq 20\%$ HIV-infected adults with virologic failure
- **Goal:** To find "salvage" therapy regimens
- **Study Enrollment:** Opened in Sep 1997 and closed to accrual in Oct 1998; recruited were 277 subjects, *indinavir* experienced patients with HIV-RNA $\geq 2,000$ copies/mL

ACTG359's Early Stage

- Study team was formed in Sep 1996
- Many conference calls, meetings in person and email exchanges about **how** to achieve the goal:
  - what specific regimens to compare?
  - what endpoints to consider?
  - what follow-up procedure to take?
  - how to determine the study size?
  - how to conduct interim reviews?

  ... ...
- One of the many problems to solve:
  my sample size calculation, > 80/arm; budget, < 50/arm ???

2×3 Factorial Design*:

Arm	1st PI	2nd PI	NNRTI	ntRTI
A	saquinavir	ritonavir	delavirdine	adefovir placebo
B	saquinavir	ritonavir	delavirdine placebo	adefovir
C	saquinavir	ritonavir	delavirdine	adefovir
D	saquinavir	nelfinavir	delavirdine	adefovir placebo
E	saquinavir	nelfinavir	delavirdine placebo	adefovir
F	saquinavir	nelfinavir	delavirdine	adefovir

∗*pooling arms over other factors to compare each factor's levels*

The Team's Efforts to Make ACTG359 "A Gold Mine" ...

- Primary comparison:
  proportion of week 16 HIV-RNA below detection (i.e., $\leq$ 500 *copies/mL)*
- Secondary comparisons:
  HIV-RNA magnitude, CD4 count, safety
- Study extension:
  to study the durability of treatments by 24-week extension
- Various substudies

Protocol of ACTG359 ... ...

Statistical Monitoring in Clinical Trials

Repeated Confidence Bands:

- Hu, X.J. and Lagakos, S.W. (1999). "Interim Analyses Using Repeated Confidence Bands," *Biometrika*, 86: 517-29.
- Hu, X.J. and Lagakos, S.W. (1999). "Interim Analyses for the Mean Function of a Stochastic Process, with application to AIDS Clinical Trials," *Statistics in Medicine*, 18: 2287-99.
- Zhao, L., Hu, X.J. and Lagakos, S.W. (2009). "Statistical monitoring of clinical trials with multivariate response and/or multiple arms: a flexible approach", *Biostatistics*, 10: 310-23.

Repeated Confidence Bands (RCB): Motivation

ACTG359 at the design stage ...

- Lack confidence in the treatment efficacy:
  demanding safety and efficacy monitoring
- Lack information about desired outcomes:
  not to pre-specify a stopping rule – to use Jennison-Turnbull RCI approach?
- Lack knowledge about clinically meaningful metric (i.e., HIV-RNA changes over time):
  how about extending RCI to RCB?

Repeated Confidence Bands (RCB): Definition

- Target function $\mu(s), s \in [0, S]$ (eg, mean of HIV-RNA over time)
- Interim reviews scheduled at times $T_k : k = 1, \ldots, K$

RCB – natural extension of RCI

$\{B_k : k = 1, \ldots, K\}$ forms RCB for $\mu(\cdot)$ with level $1 - \alpha$ if

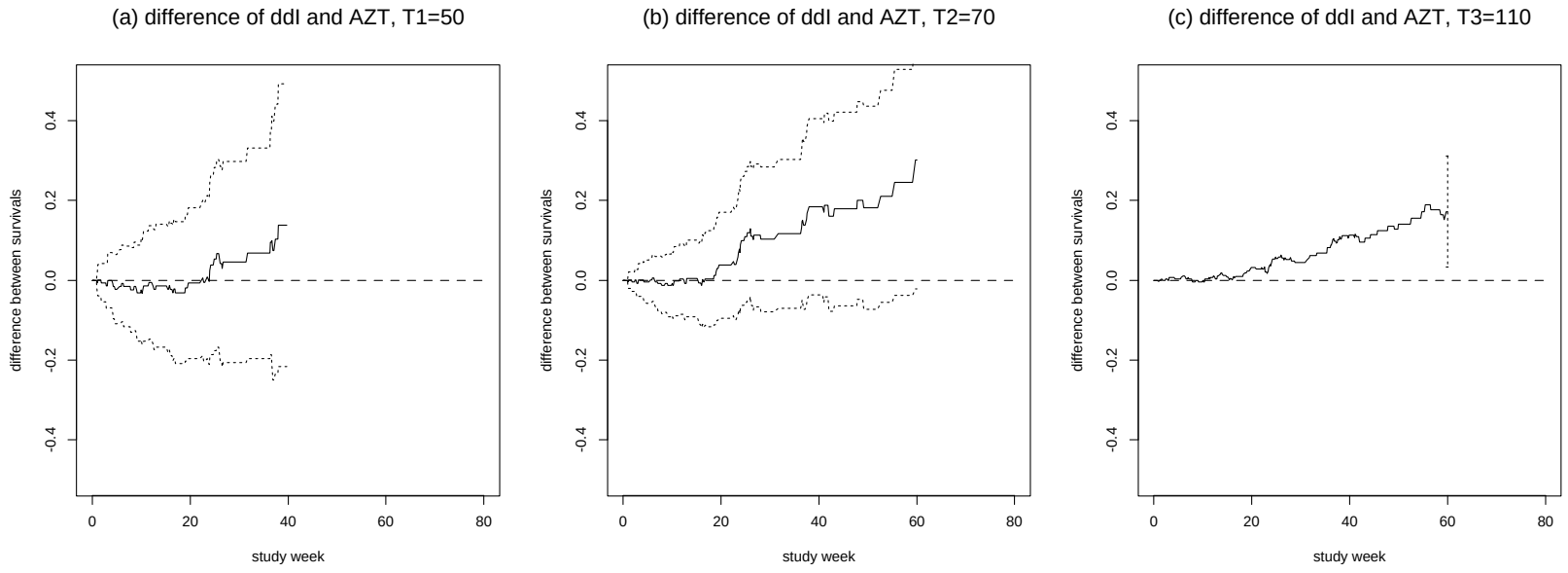
$$\mathrm{P}\big\{\mu(\cdot) \in B_k, 1 \leq k \leq K\big\} \geq 1 - \alpha,$$

where B_k depends only on the data collected up to T_k.

RCB: Notion of Varying Targeted Domain

- Concern of RCB's inefficiency: eg, Marvin's comment
- Steve's brilliant idea: *RCB with adaptive domains*
- Implementation and justification:
  - target changed from "$\mu(s) : s \in [0, S]$" to "$\mu(s) : s \in \mathcal{E}_k$" at the kth review
  - applying the idea of Lan-DeMets spending function to achieve the nominal confidence level: overall and at each review
- Usefulness:
  - incorporating staggered entry for long-term/slow-accrual trials
  - improving efficiency on the mainly interested in situations with target becoming clearer as the trial progressing

RCB Illustration by ACTG 116/117 Data for ddI vs AZT on Survival: Consistent with the Original and Revealing a Trend



Multivariate RCB

- Motivation:
  - study with multiple arms, or multivariate response
  - desire to make joint inferences
- Natural extension of RCB
- Additional gains: *varying target as the trial proceeds*
  - with terminated arms
  - with more focused primary goal
- Our plan to apply it in a new HIV study ... ...

STAT 854. Biometrics: Methods in Biomedical Studies

What have we studied?

- **Part I – Introduction**
- **Part II - Epidemiologic Concepts and Designs**
- **Part III - Clinical Trials**

What to study next?

Part I. Introduction
Part II. Epidemiologic Concepts and Designs
Part III. Clinical Trials

Part IV. Modern Biostatistical (Analytic Epidemiologic) Approaches

- **Part IV.1 Incomplete Data Analysis**
  - **IV.1.1 Introduction**
  - **IV.1.2 Models and Methods for Missing Data**
  - **IV.1.3 Coarsened Data Analysis**
  - **IV.1.4 Measurement Errors**
  - **IV.1.5 Truncation**
- **Part IV.2 Other Important Topics**
  - **IV.2.1 Measures of Risks**
  - **IV.2.2 Measurement Error Revisit**
  - **IV.2.3 Confounding and Its Control**
  - **IV.2.4 Causation vs Association**
  - **What other topics that interest you?**

Part IV. Modern Biostatistical (Analytic Epidemiologic) Approaches

Part IV.1 Incomplete Data Analysis
(*supplementary*; Ref: Tsiatis, 2006 *"Semiparametric Theory and Missing Data"*)

- **Part IV.1.1 Introduction**
  Incomplete data are prevalent in practice:
  - Many studies set out in advance to collect data following a "nice" plan but do not work out quite as intended, especially when the studies involve human beings.
  - Many studies even begin with the knowledge that the desired information is not affordable.

Part IV.1.1 Introduction: Some examples of incomplete data

- Nonresponse in sampling survey

e.g. We send out questionnaries to a sample of randomly chosen individuals: some may provide only a partial answer or no answer to some questions, or, many not return the questionnaire at all.

- Dropout or noncompliance in clinical trial

e.g. In a randomized clinical trial, subjects are enrolled and then randomly assigned to one of the treatment arms: some subjects may "drop out" of the study – failing to show up for any clinic visit after a certain point, and some others may miss clinic visits occasionally or quit taking their assigned treatment.

Part IV.1.1 Introduction: Some examples of incomplete data

- Surrogate measurements

e.g. In some studies, the response of interest or some important covariate may be very expensive to obtain, such as the daily average percentage fat intake of a subject. A cheaper measurement (surrogate) is to have subjects recall the food they ate in the past 24 hurs.

- Observations on biomarkers

e.g. In AIDS studies, the time to AIDS since HIV infection has become not desirable endpoint for it takes long to collect enough information on it. Many recent AIDS studies use biomarkers, such as CD4 counts and HIV RNA as study responses. Efforts should be made to establish the association of time to AIDS with the biomarkers.

Original Objective: making an inference about some aspect (parameter, finite/infinite dimensional) of the distribution of the "full data" (i.e., the data that would have been observed if there is no data incompleteness)

Inherent Problem: when data are incomplete, depending on how and why they are missing, our ability to make an inference may be compromised. Moreover, not accounting for incomplete data properly when analyzing the data can lead to severe biases.

Most software packages, by default, delete records for which data are incomplete and conduct the "complete-case analysis". e.g. Cook et al (2011)

Serious attempts since 1980s to address the problem ... ...

What to study next?

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