Utilizing Seamless Adaptive Designs and Considering Multiplicity Adjustment for NASH Clinical Trials

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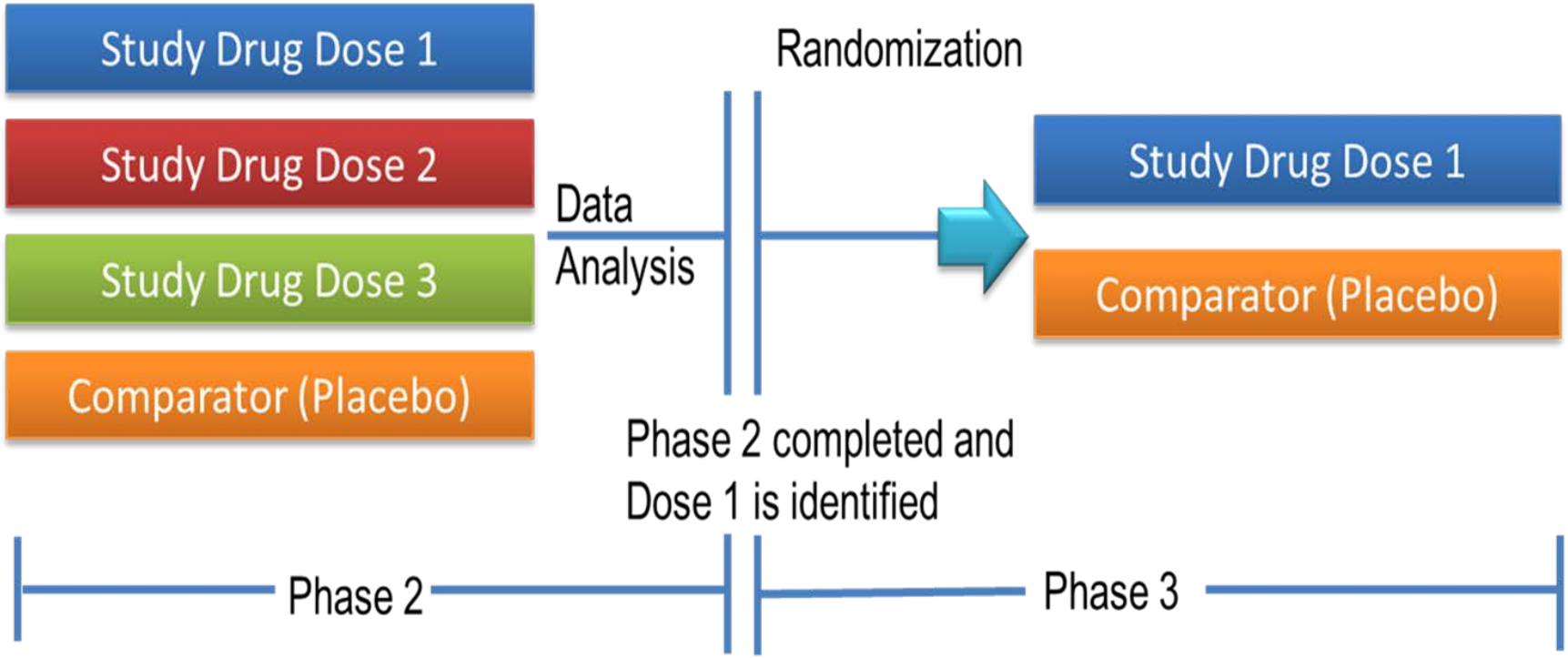
Clinical Trial Phases—Objectives

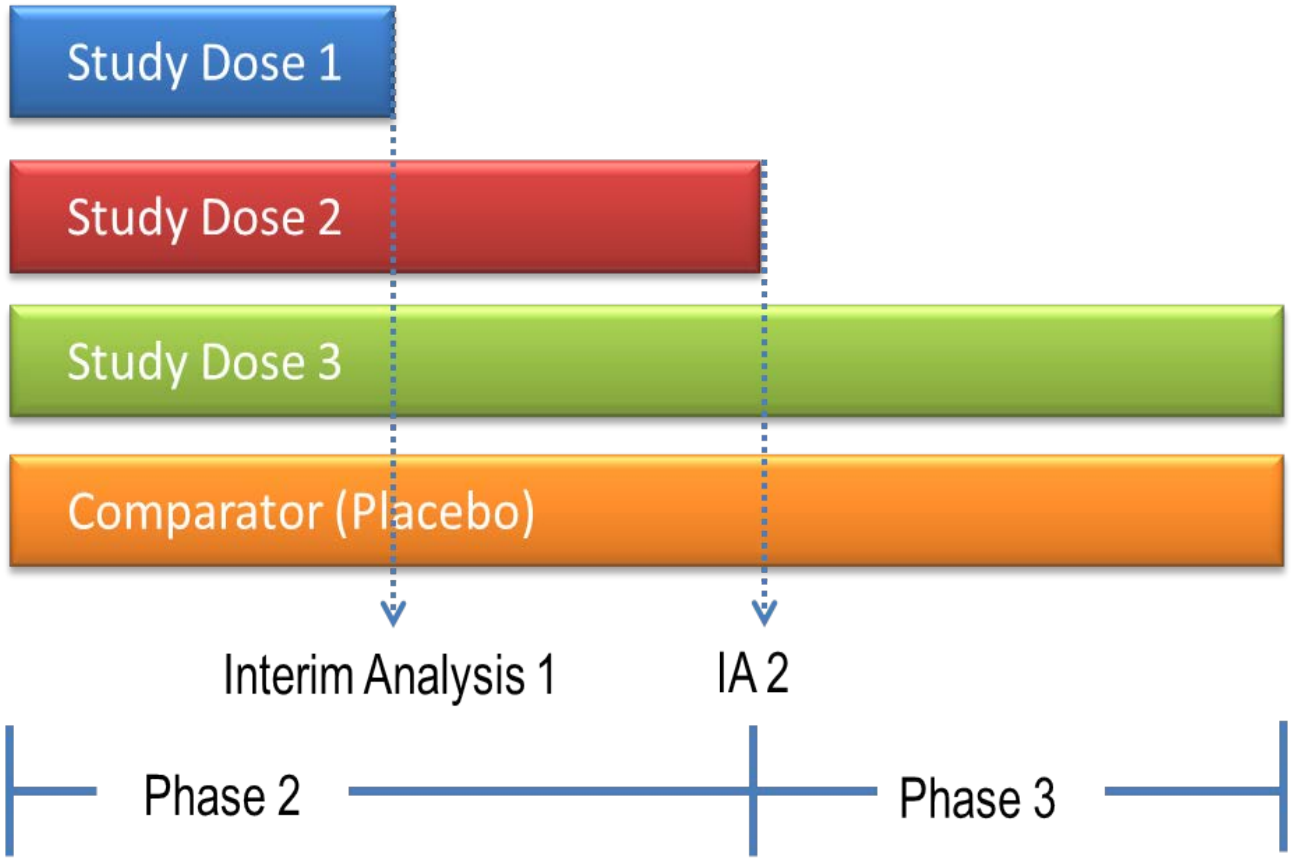
- **Phase 1:** To test a new drug (or treatment), evaluate its safety, determine a safe dosage range, and identify side effects.
- **Phase 2:** To identify suitable dose(s) and further evaluate the safety of the study drug.
- **Phase 3:** To confirm the study drug's effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug to be used safely.
- **Phase 4:** To gather information on the drug's effect in various populations, including verifying and describing the clinical benefit and any side effects associated with long-term use after the drug has been approved and marketed.

Source: Wikipedia

Conventional Phase 2 & Phase 3



Seamless Adaptive Designs



Clinical Trials in Pre-cirrhotic Non-alcoholic Steatohepatitis (NASH)

- NASH has been recognized as one of the leading causes of cirrhosis in adults and NASH-related cirrhosis is currently the second indication for liver transplants in the United States (Younossi et al., 2016).
- In a recently published study of 108 non-alcoholic fatty liver disease (NAFLD) patients who had serial biopsies, 47% of patients with NASH had a progression of fibrosis, and 18%, had spontaneous regression of fibrosis over a median follow-up period of 6.6 years (McPherson et al., 2015).
- Question: Can a clinical trial for treating NASH be conducted in less than 6.6 years? With innovative designs?

Four Types of Two-Stage Seamless Adaptive Designs

Study Objectives	Study Endpoint (Same/Different)	
Same (S)	I= (S, S)	II= (S, D)
Different (D)	III= (D, S)	IV= (D, D)

Source: Chow SC and Lin M, 2015.

Analysis for Category II Adaptive Design

- Let x_i be the observed value of the surrogate endpoint in Stage 1,i=1…,n, and y_j be the observed primary clinical endpoint in Stage 2, j=1…,m.

Suppose $y_i = \beta_0 + \beta_1 x_i + \varepsilon$,

where $x_{i \sim iid} N(v, \tau^2)$ and $y_{i \sim iid} N(\mu, \sigma^2)$ and ε is independent of x_i.

$$\hat{\mu} = \omega\bar{\hat{y}} + (1-\omega)\,\bar{y},$$ where $\bar{\hat{y}} = \frac{1}{n}\sum_{i=1}^{n} y_i$ and $\bar{y} = \frac{1}{n}\sum_{i=1}^{m} y_i$.

- Note that the first stage clinical outcome $\hat{y}_i$ will be combined with those collected at Stage 2. One special case is that no IA conducted for clinical endpoint after the end of Stage 1 and before the end of Stage 2.

Source: Chow SC and Lin M, 2015.

FDA Accelerated Approval Program

- *Guidance for Industry-Expedited Programs for Serious Conditions—Drugs & Biologics* (FDA, 2014*)* states the following:

The accelerated approval provisions of FDASIA in section 506(c) of the FD&C Act provide that FDA may grant accelerated approval to:

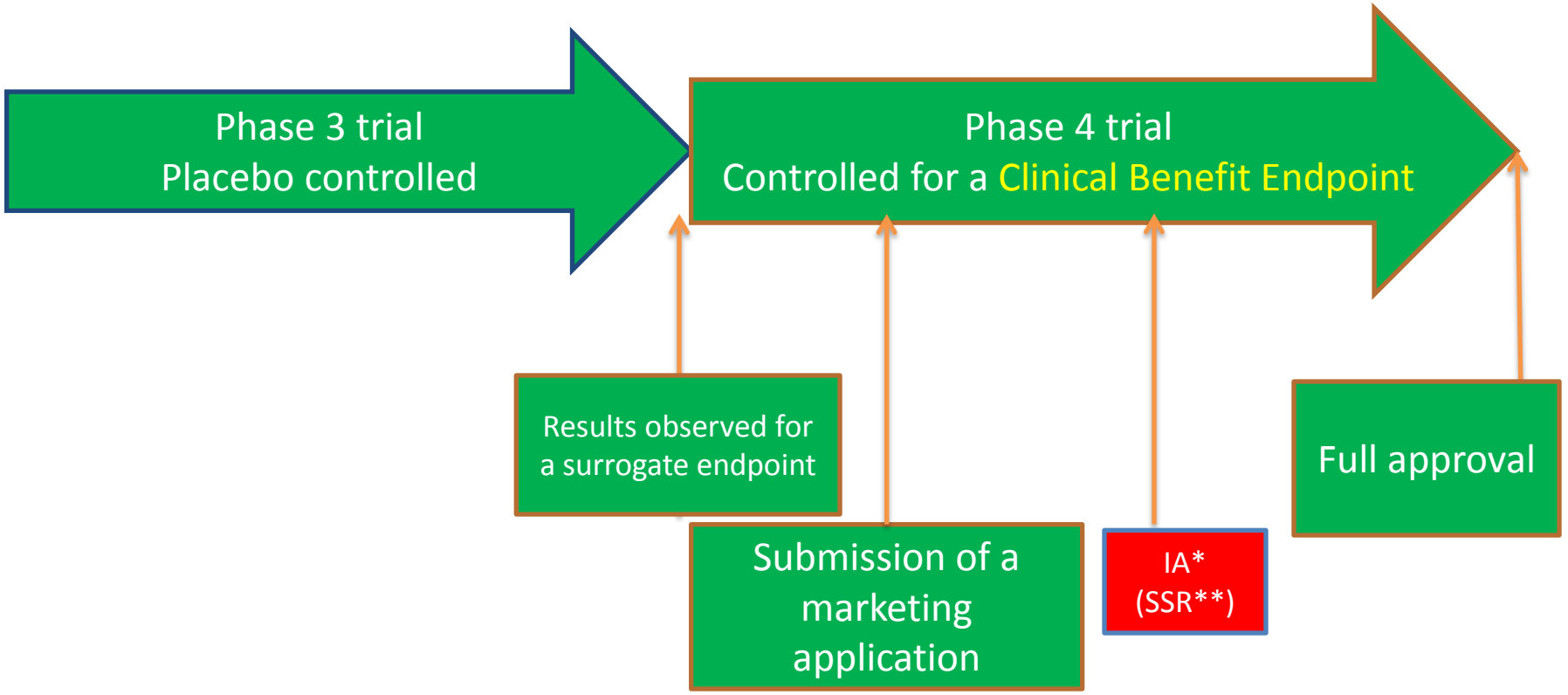
> . . . a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

For drugs granted accelerated approval, postmarketing confirmatory trials have been required to verify and describe the anticipated effect on IMM or other clinical benefit (see sections VII.D.2. and VII.D.3.).[16]

FDA Guidance -Adaptive Design-

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf.%20

Phase 3/4 Seamless Design for Accelerated Approval



*Interim Analysis, ** Sample Size Re-estimation

Challenges with Accelerated Approval Trials

- Need to plan far in advance for the entire phase 3/4 trial with the Statistical Analysis Plan submitted prior to trial initiation
- Retention of patients in a placebo-controlled trial after marketing approval
  - Placebo control is the best
  - Potential for use of historical control, but lacking data for NASH at this time.

  Question: Can we consider other types of design?
- FDA Guidance for Industry—*E10 Choice of Control Group and Related Issues in Clinical Trials* (FDA, 2001)

Primary Endpoint – NASH Program

Phase 3 (binary)

- Based on histological measurement
  - Can be co-primary endpoints
  1. Resolution of NASH without worsening of fibrosis
  2. Reduction of fibrosis without worsening of NASH

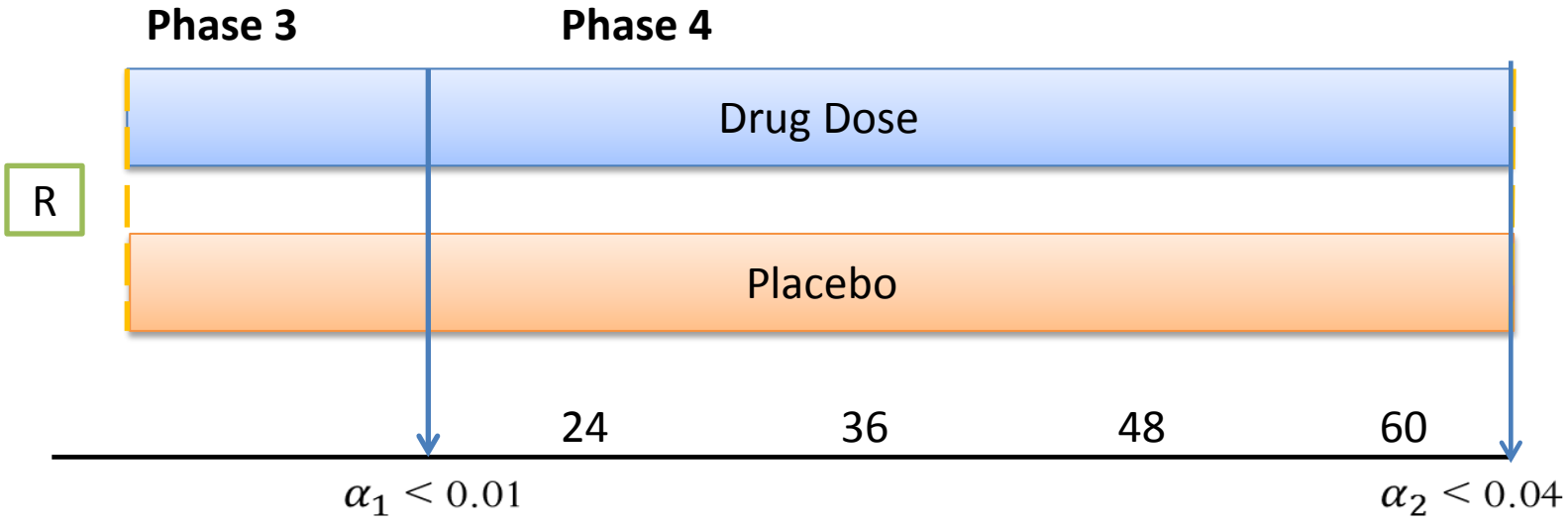
Phase 4 (survival)

- Time to all-cause mortality and liver-related clinical outcomes, which may include but not limited to:
  - Death (all cause)
  - Model of end stage liver disease (MELD) score ≥15
  - Liver transplant
  - Hospitalization

How to control overall Type I error rate?

- The overall alpha of 0.05 needs to be adjusted for the phase 3/4 trial
  - Should we consider **$(\alpha_3, \alpha_4)=(0.05, 0.05)$?**
- If only one single phase 3/4 trial is submitted for the marketing application, a much smaller alpha less than 0.05 may be considered (e.g., total $p< 0.00125$).
  - FDA Guidance—*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (FDA, 1998)

Proposed Phase 3/4 Seamless Adaptive Design for NASH



IA when p% of the population complete month 18
Efficacy based on histology: co-primary endpoints
1-Resolution of NASH without worsening of fibrosis
2-Reduction in fibrosis without worsening of NASH

Composite endpoint for Phase 4 based on

- **Progression to cirrhosis (histology)**
- **Overall mortality and liver clinical outcomes**

Evaluation of Type I Error Controls

- In order to control the study-wise Type I error rate at 0.05, the following procedures are considered:
  - 0.05 for both phases 3 and 4 ($p_1<0.05$ & $p_2<0.05$)
  - 0.01 for phase 3 and 0.04 for phase 4 ($p_1<0.01$ & $p_2<0.04$)
  - 0.01 for phase 3 ($p_1<0.01$)
  - 0.04 for phase 4 ($p_2<0.04$)
  - 0.01 for phase 3. If $p_1<0.01$, then use 0.05, otherwise 0.04 for phase 4 (0.01/0.04/0.05)

Data Generation for Simulations

- Simulate two sets of repeated measurements by:

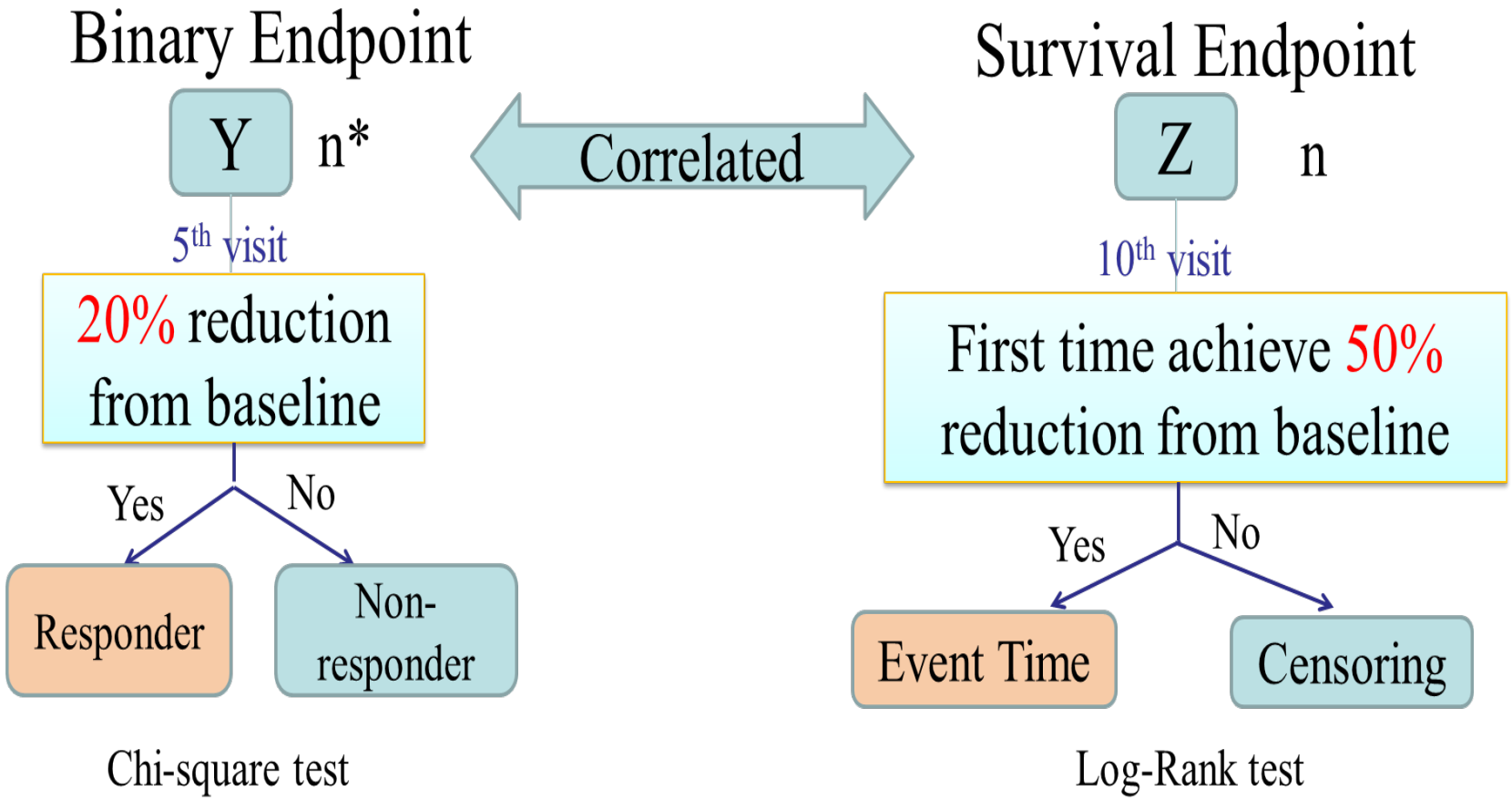
$$y_{ijk_1} = \alpha_{ik_1} + B_{k_1} + C_j + \varepsilon_{ijk_1}$$
$$z_{ijk_2} = \alpha^*_{ik_2} + B^*_{k_2} + C_j + \varepsilon^*_{ijk_2}$$

i: treatment; j: subject; k: visit ($k_1 = 5, k_2 = 10$)
α: treatment effect (fixed); B: visit effect (random);
C: subject effect (random); ε: random error

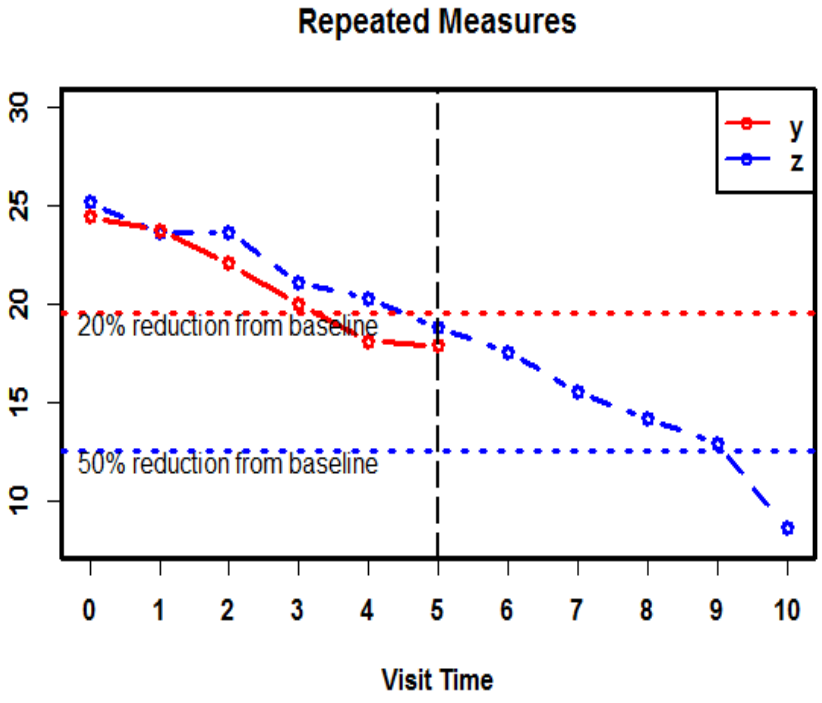
$$B \sim MVN(\mathbf{0}, V); C \sim normal(0, \sigma_c^2);\ \varepsilon \sim normal(0, \sigma_\varepsilon^2)$$

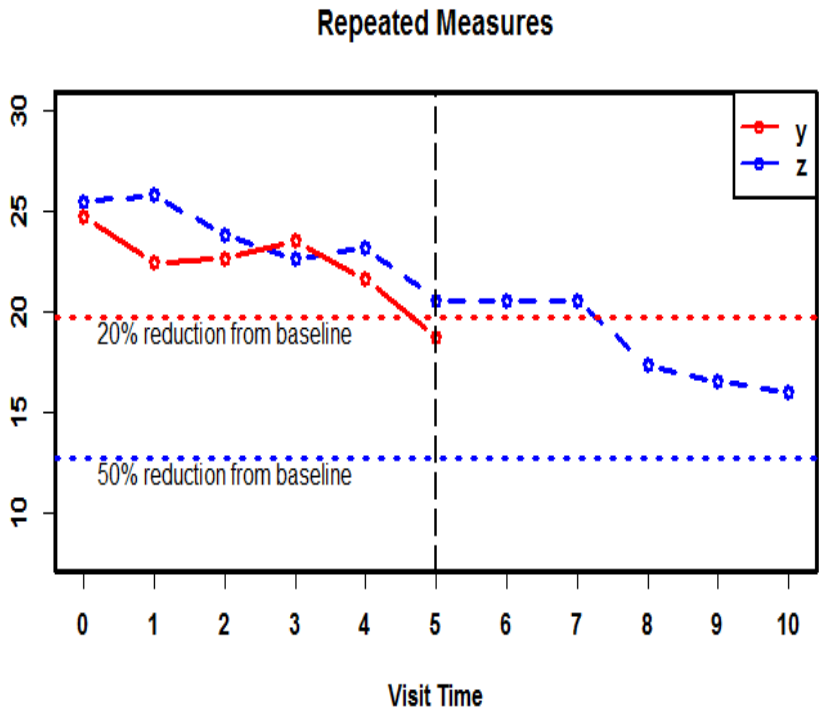
- Considering non-informative dropouts

Data Conversion



Example of Patient Profiles





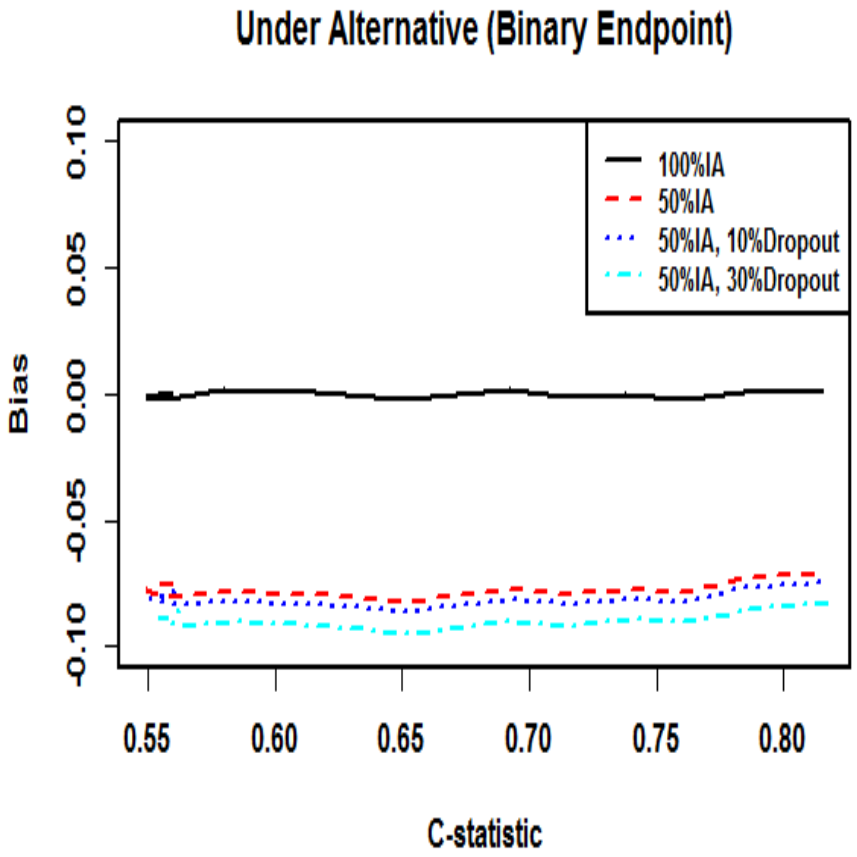
Simulation Settings

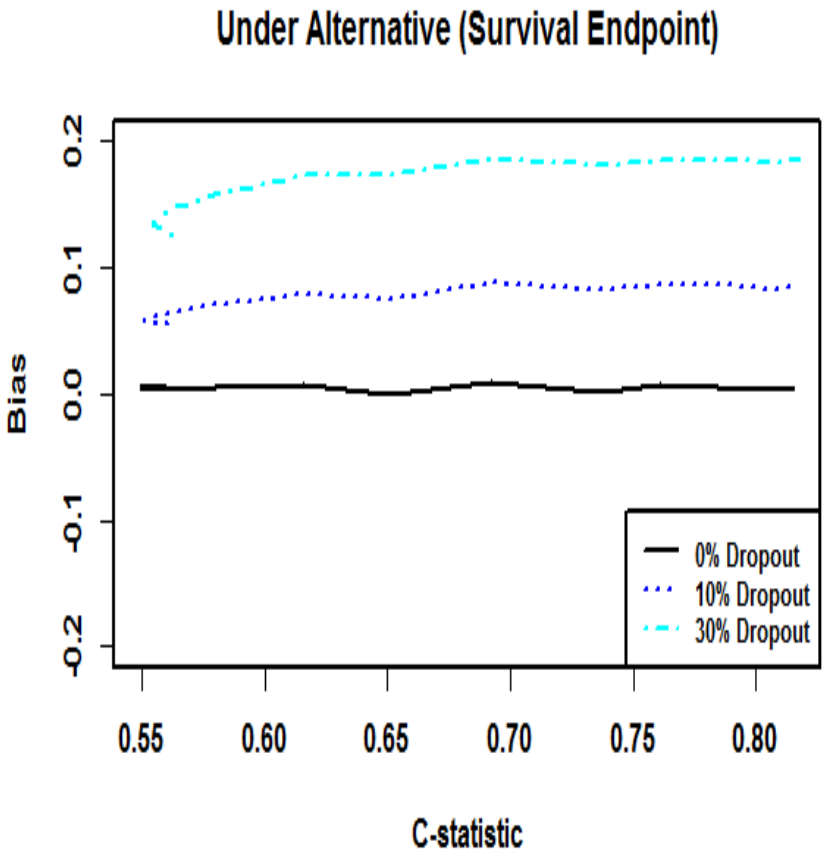
- n = 200/arm
- Fixed effect parameter setup

	Intercept	Drug Slope	Placebo Slope
Null	20	-2.7 /-1.6	-2.7 /-1.6
Alternative	20	-3/-2	-2.6/-1.7

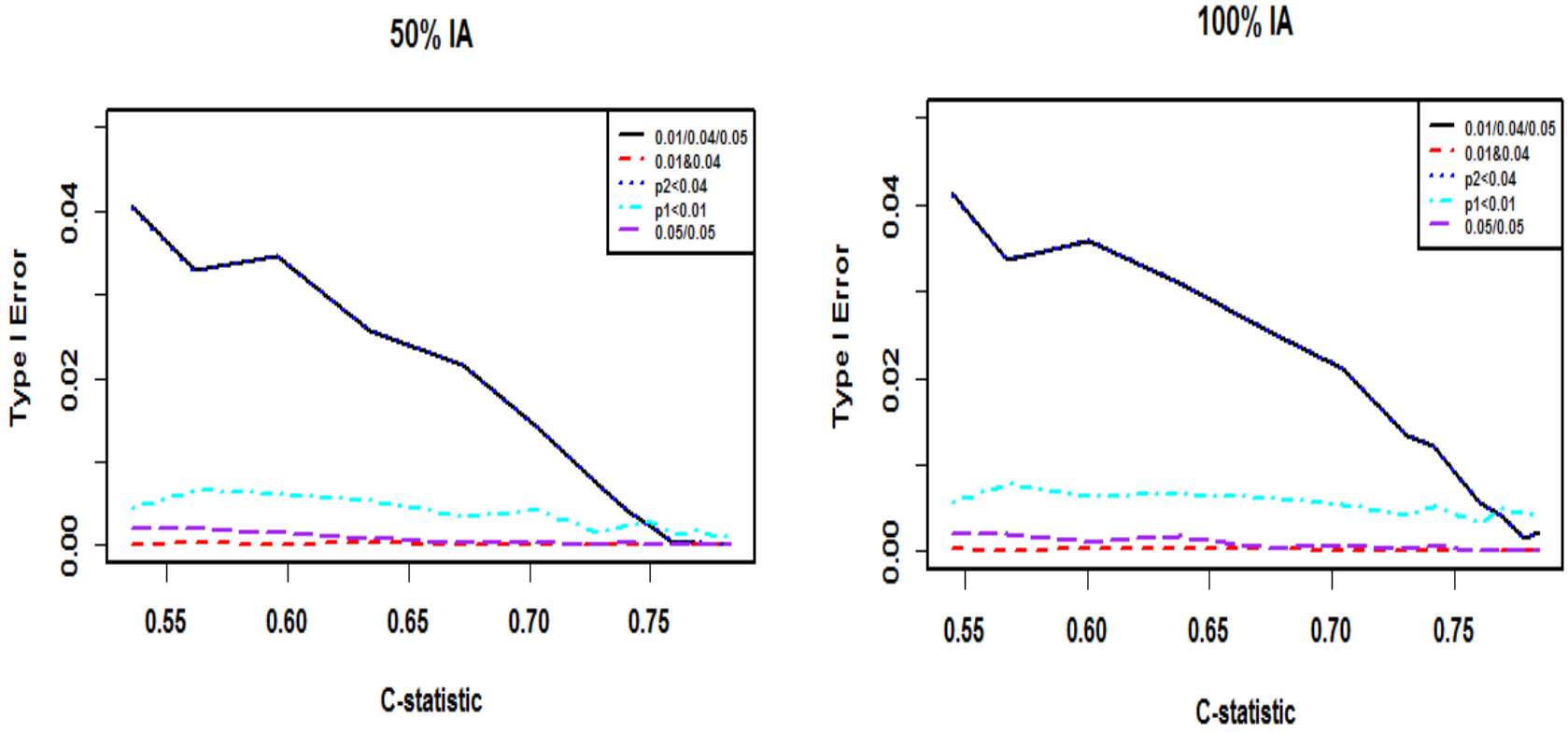
Replicate 10,000 times

Larger Biases With IA Conducted Earlier and More Dropouts

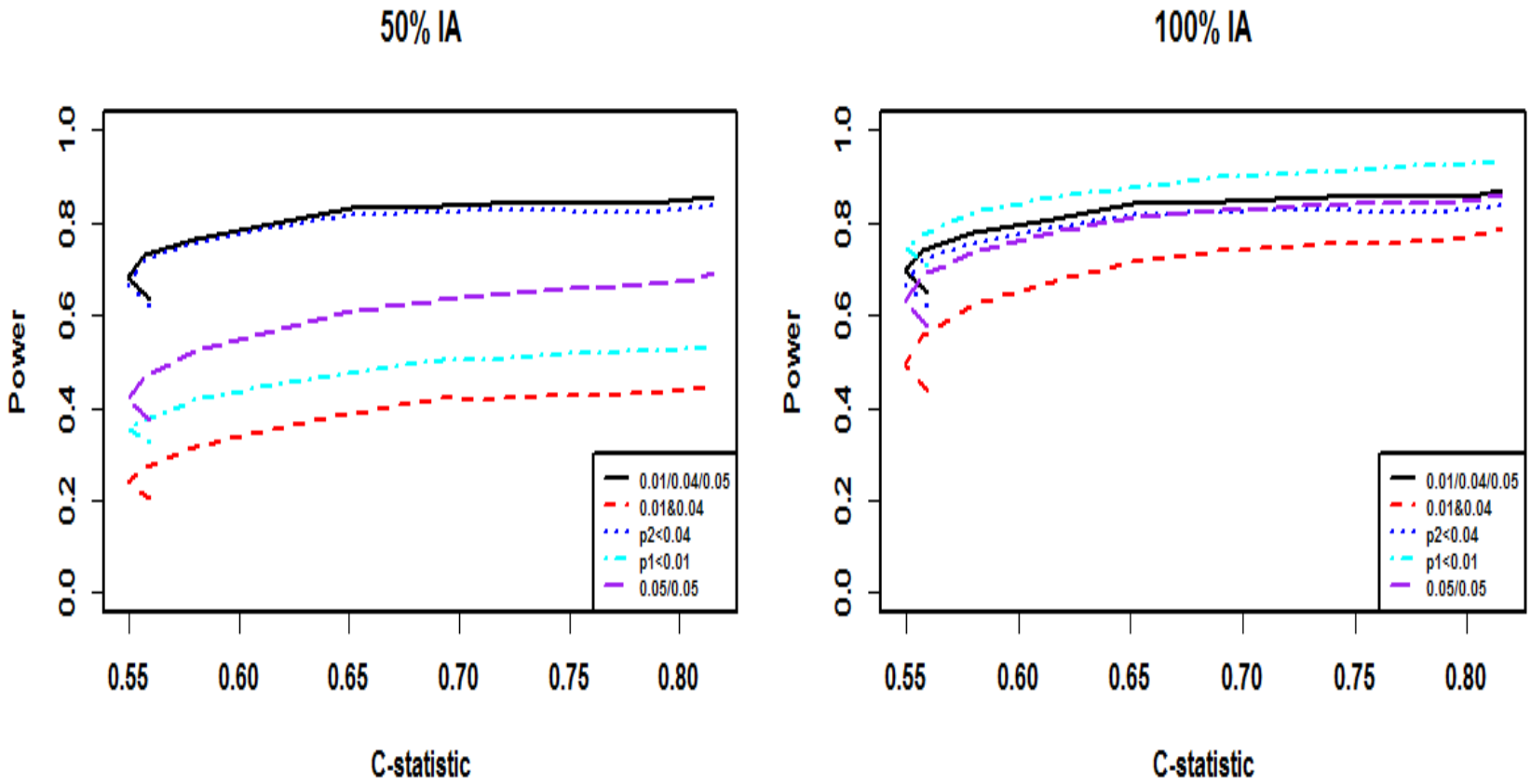




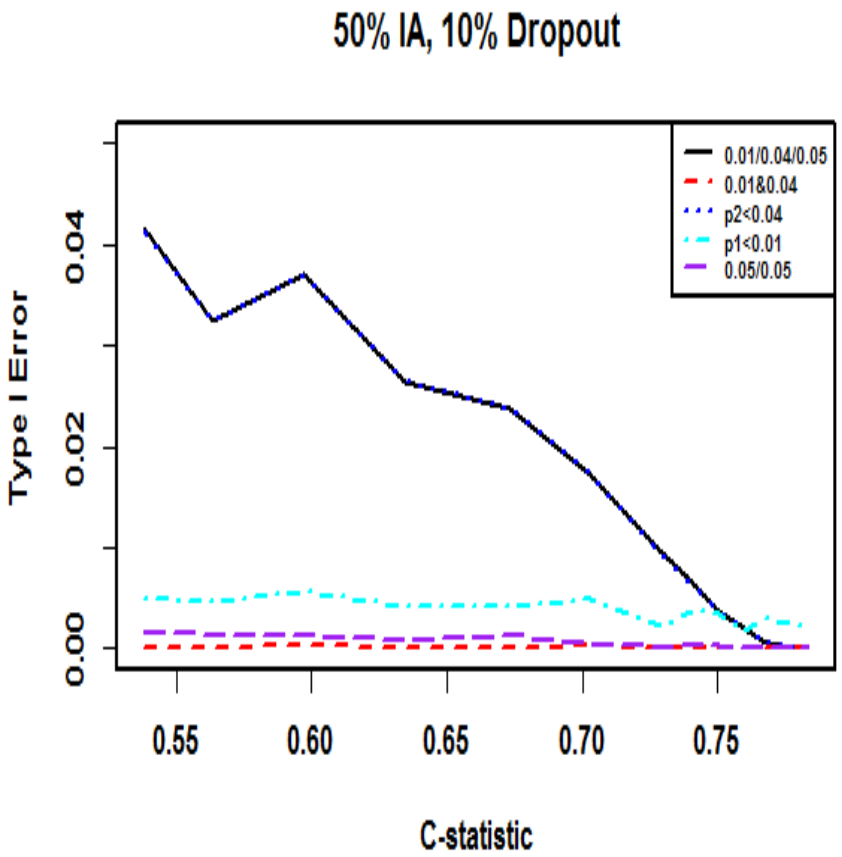
Type I Error Controlled But Conservative When C-statistic ↑

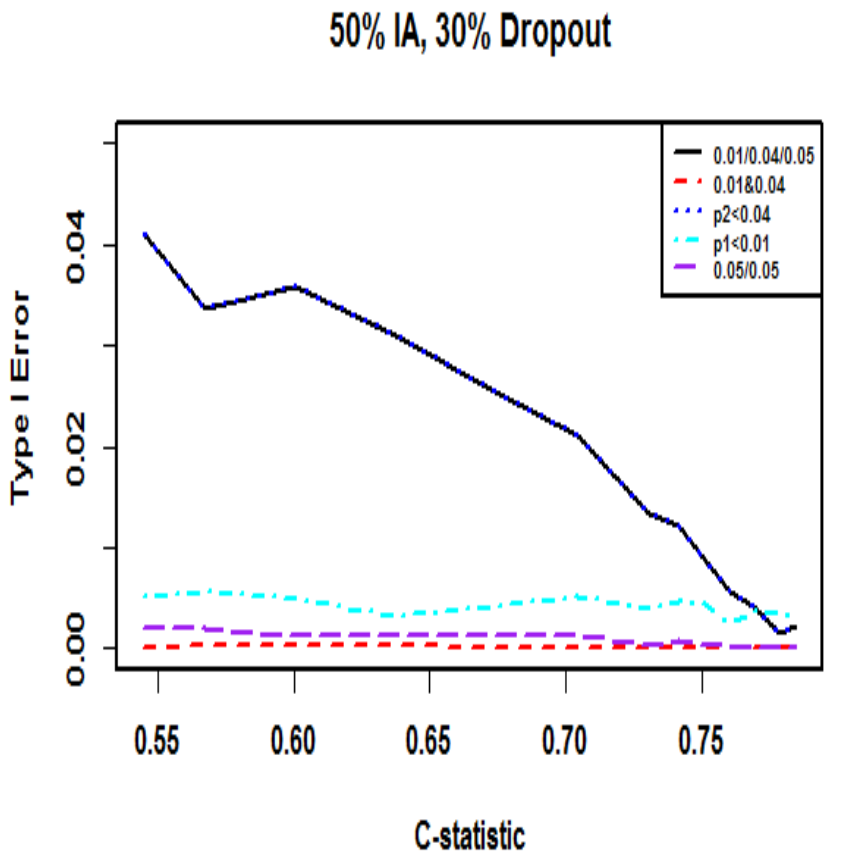


Power Increases as C-statistic ↑

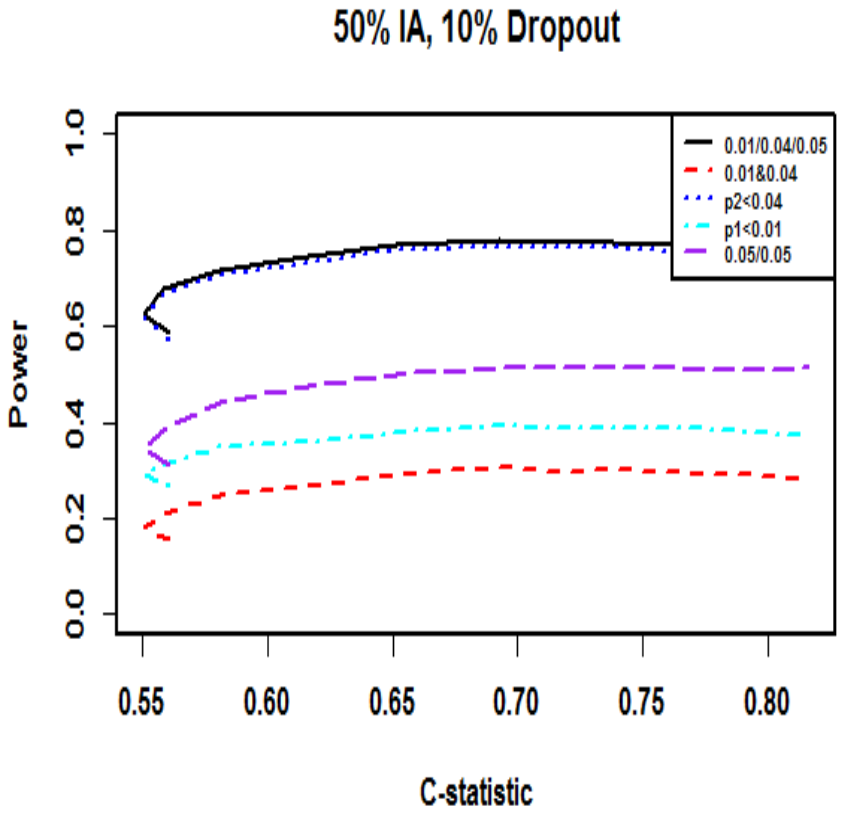


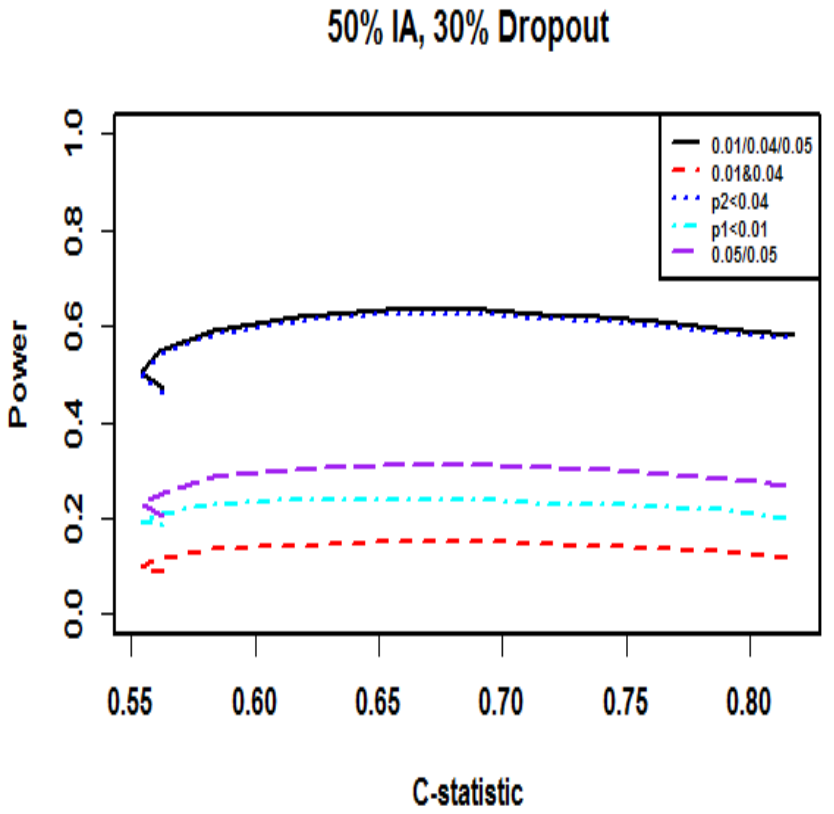
Type I Error Rate ↑ When Dropout ↑





Power ↓ When Dropout Rate ↑





Case Example

- Two NASH trials are planned; one uses a phase 2/3/4 seamless design; the other one uses a phase 3/4 design.

Question 1:

What is a better approach to identifying safe and effective doses in phase 2 that can be further examined in phases 3 and 4?

Consider interim efficacy or futility analysis?

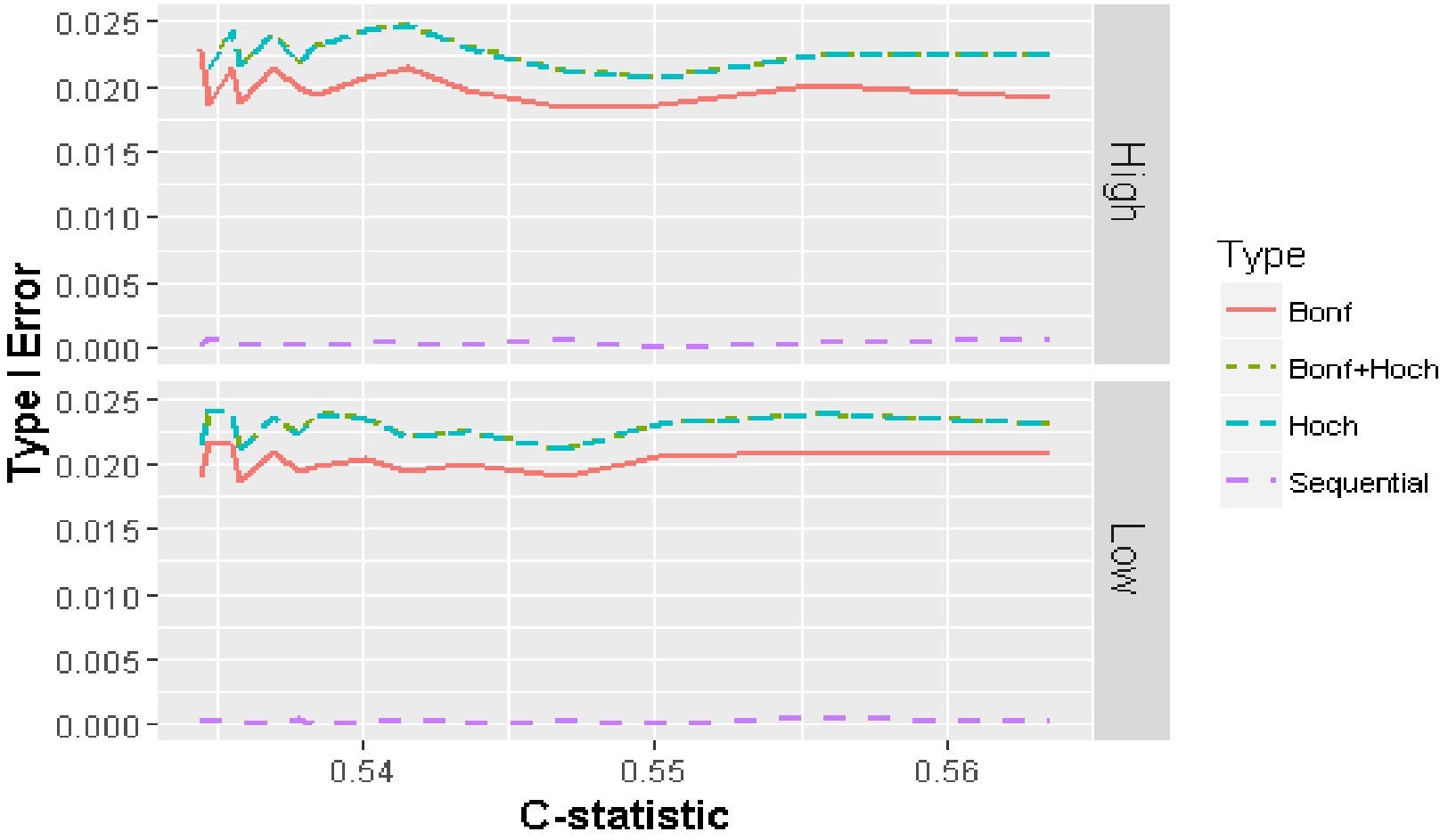
Question 2:

Can the phase 4 data be combined from two separate trials and tested at α=0.05? **No!**

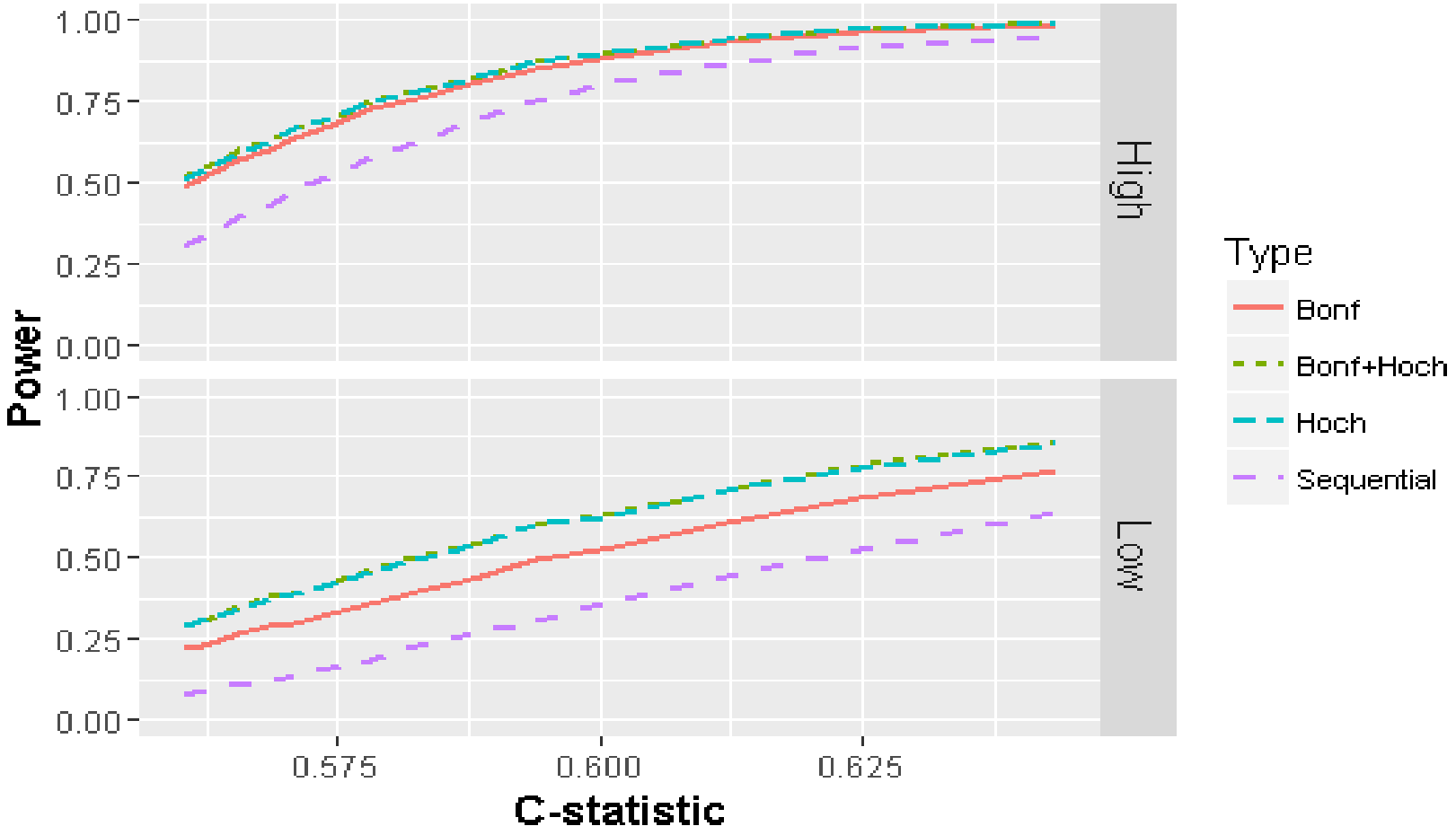
Considering Two Doses in Phase 3/4

- We compared four procedures
  - (1) Sequential: $(\alpha_3, \alpha_4)=(0.05/2, 0.05/2)$ for each dose
  - (2) Bonferroni: $(\alpha_3, \alpha_4)=(0.01/2, 0.04/2)$ with a recycled alpha
  - (3) $\text{Bonferoni}_3 + \text{Hochberg}_4$
    - If winning on both doses, the phase 4 uses Hochberg 0.05
    - If winning on only one dose, the phase 4 uses Hochberg 0.045
    - If failing on both doses, the phase 4 uses Hochberg 0.04
  - (4) $\text{Hochberg}_{3\&4}$
    - If winning on both doses, the phase 4 uses Hochberg 0.05
    - If winning on only one dose, the phase 4 uses Hochberg 0.04
    - If failing on both doses, the phase 4 uses Hochberg 0.04

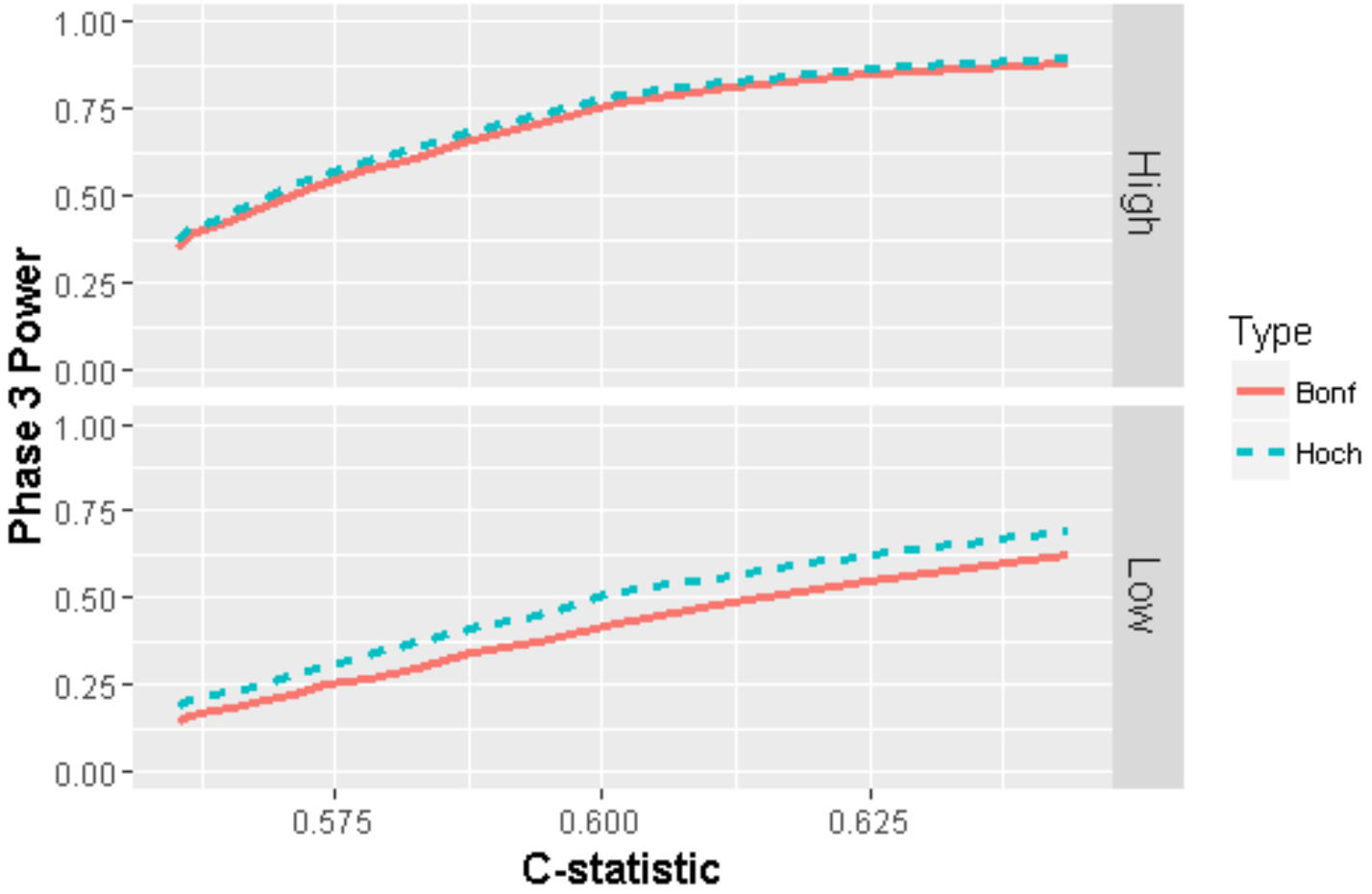
Type I errors are controlled



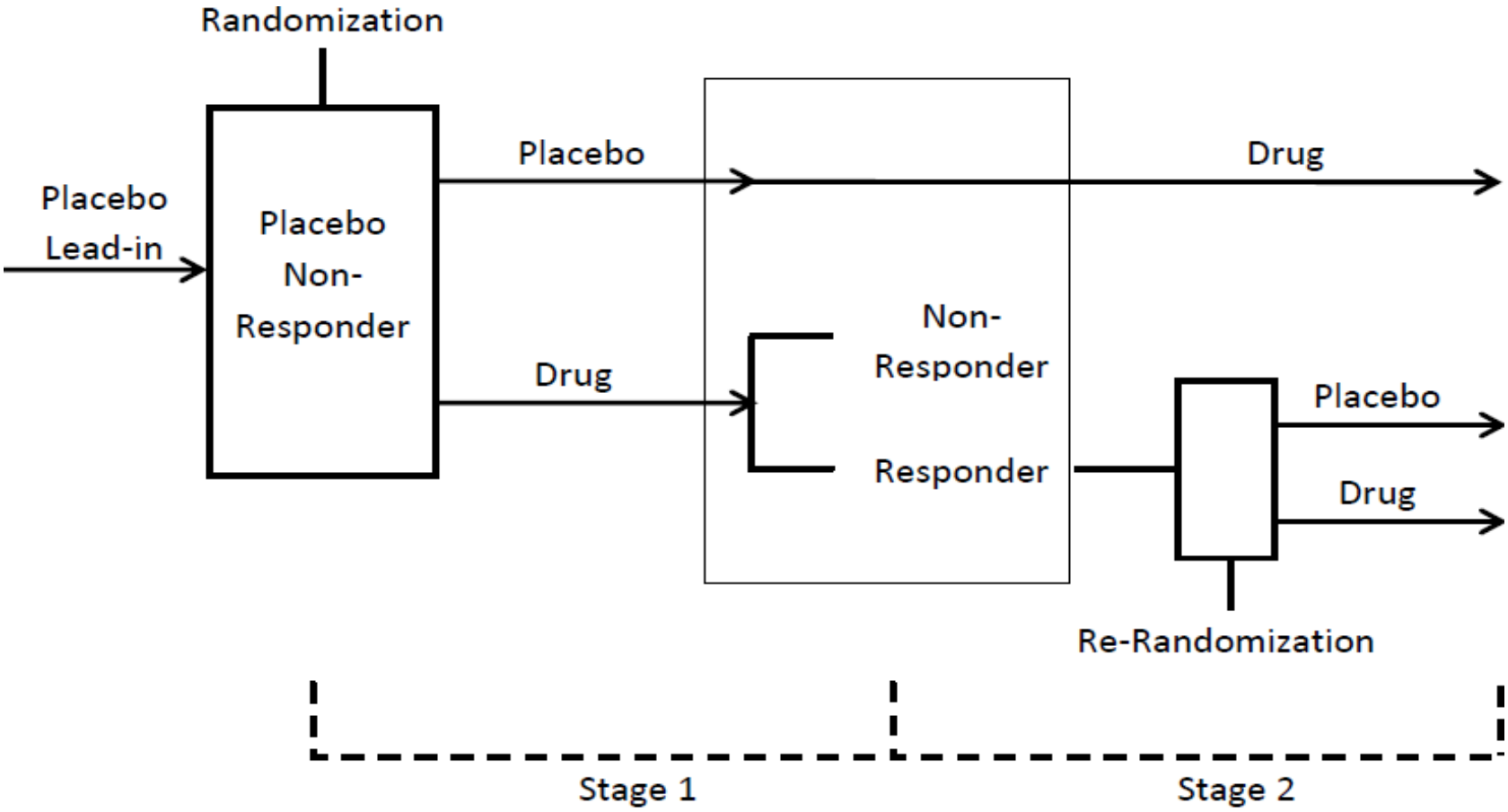
$Bonf_3$+ $Hoch_4$ and $Hochberg_{3\&4}$ are equally powerful



Hochberg is more powerful at phase 3



SED (Chen et al., 2014) for Handling Placebo Dropouts at Phase 4



For NASH trials, the placebo lead-in could be replaced by Vitamin E non-responders.

External Control in Phase 4

- To address the issues (e.g., ethical concern, extensive dropouts) associated with the inclusion of a long term placebo arm
- To eliminate biases with external controls and to maintain the integrity
  - matching methods (e.g., propensity scores) to optimize comparability of similar participating subjects
  - Survival analyses to adjust for important baseline covariates
- May need to consider a conservative method for handling intermittent missing data in the external control arm

Take-Home Messages

- A two-stage seamless adaptive design can speed up the drug development process.
- We studied several procedures that aimed to control the overall Type I error rate. The sequential testing procedure is conservative but not powerful.
- When the surrogate and clinical endpoints are highly correlated, the studied procedures appear to be too conservative and thus more research is needed to enhance trial efficiency.
- To avoid bias due to potential extensive dropouts from placebo patients in phase 4, different designs including adding an external control can be considered, but the Statistical Analysis Plan needs to be specified prospectively.

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