A Gate-keeping Approach for Selecting Adaptive Interventions under General SMART Designs

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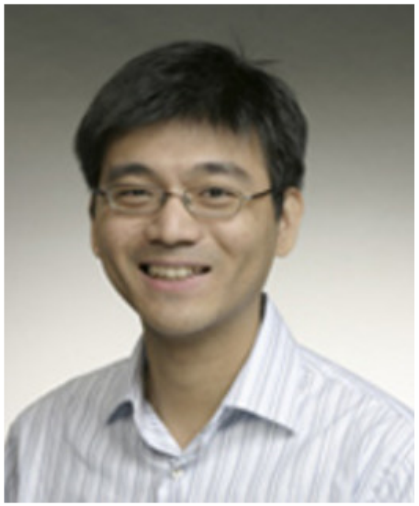

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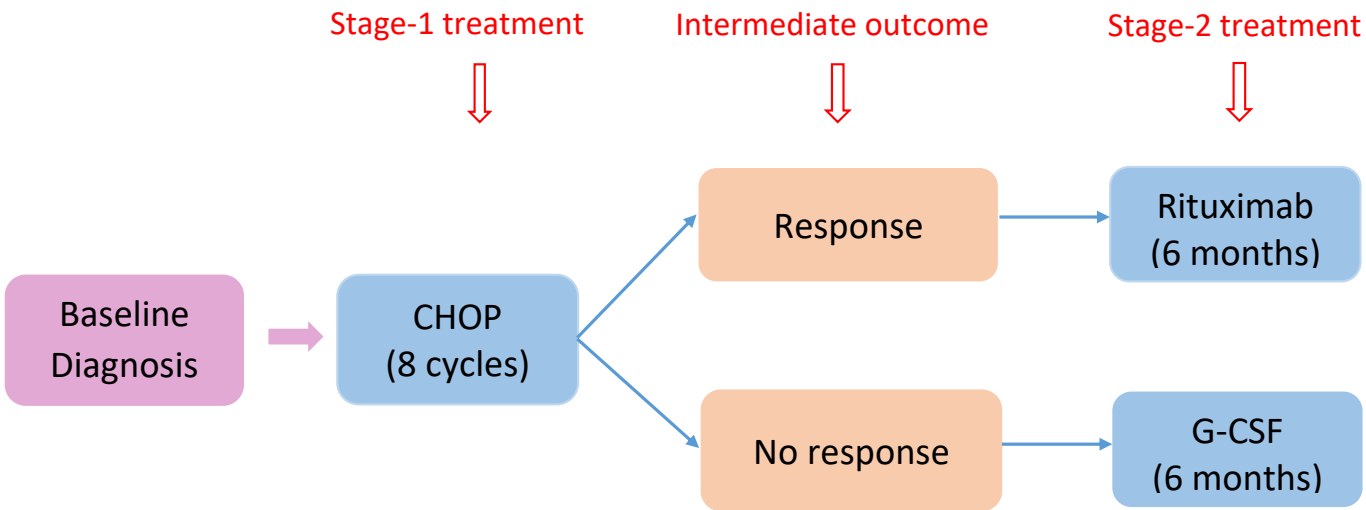
Adaptive Intervention

- For chronic diseases (e.g. cancer, depression)
  - Clinicans often need to make a sequence of treatment decisions throughout the course of a patient's clinical care
  - Such decisions are usually adapted to the patient's individual response to previous treatments
  - **Adaptive intervention** formalizes the mechanism of such a sequence of decision makings.
  - It provides an opportunity to optimize a patient's long-term response

Example 1: Oncology Intervention

- Example of adaptive intervention for Lymphoma patients[1]



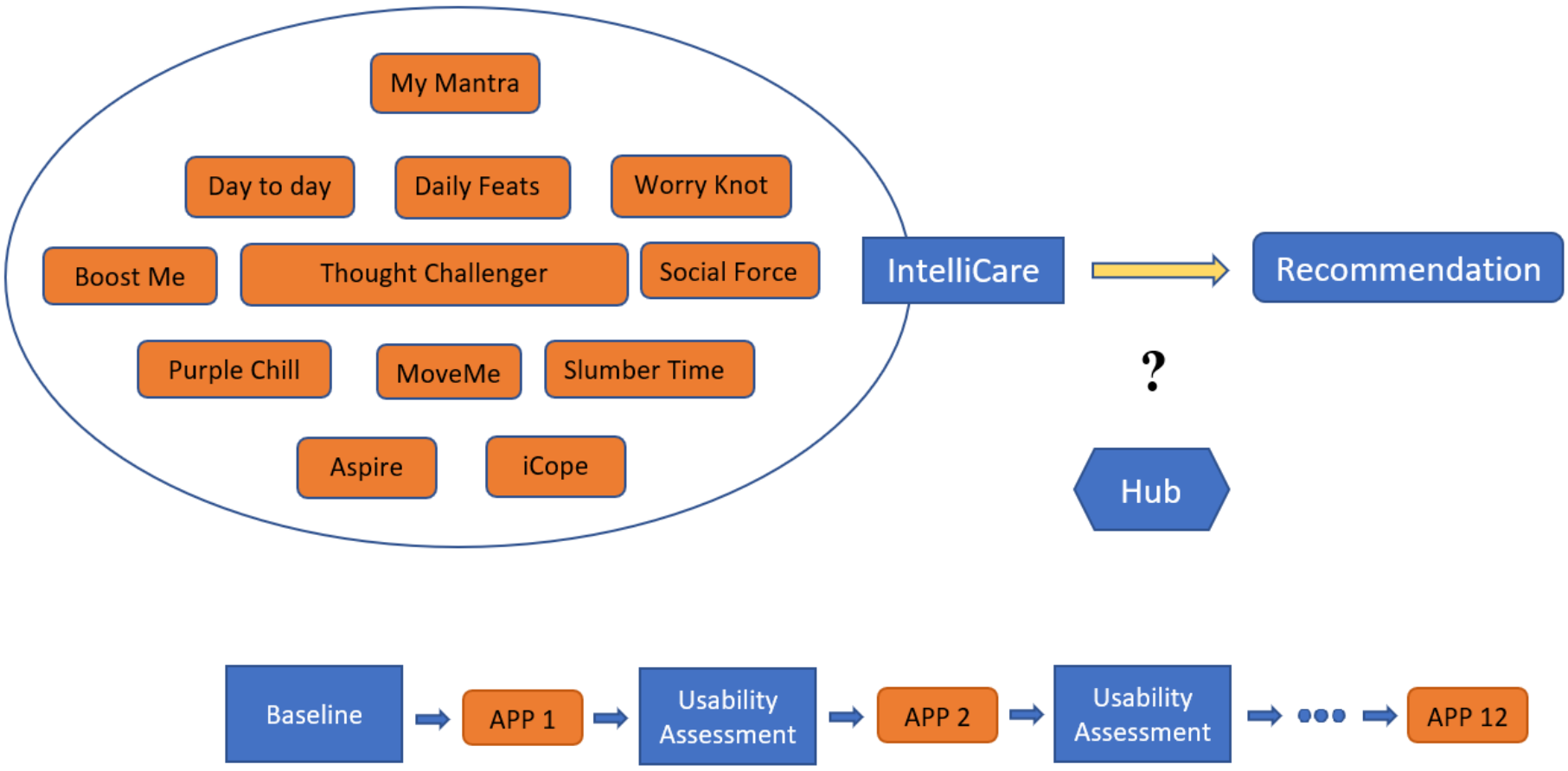
- CHOP: **C**yclophosphamide (750 mg/m^2), **H**ydroxydaunorubicin (50 mg/m^2), **O**ncovin (1.4 mg/m^2), **P**rednisone (40 mg/m^2)
- Response: complete/partial remission; Non-response: otherwise
- G-CSF: Granulocyte colony-stimulating factor

[1] Habermann et al. *J Clin Oncol*, 2006

Example 2: Depression Intervention

- Smartphone apps can be effective in managing depression
  - Pro1: more flexible than PC-based internet intervention
  - Pro2: collect individual information in real-time settings
  - Pro3: an active market provides more and more products
- Using smartphone apps for depression management has its own challenge
  - Simple apps are in favor
  - A wide variety of psychological strategies (e.g., goal setting, cognitive restructure, behavioral activation etc.) can be useful for patients with common mental health issues.
  - How to use the simple weapons to solve complicate problem?

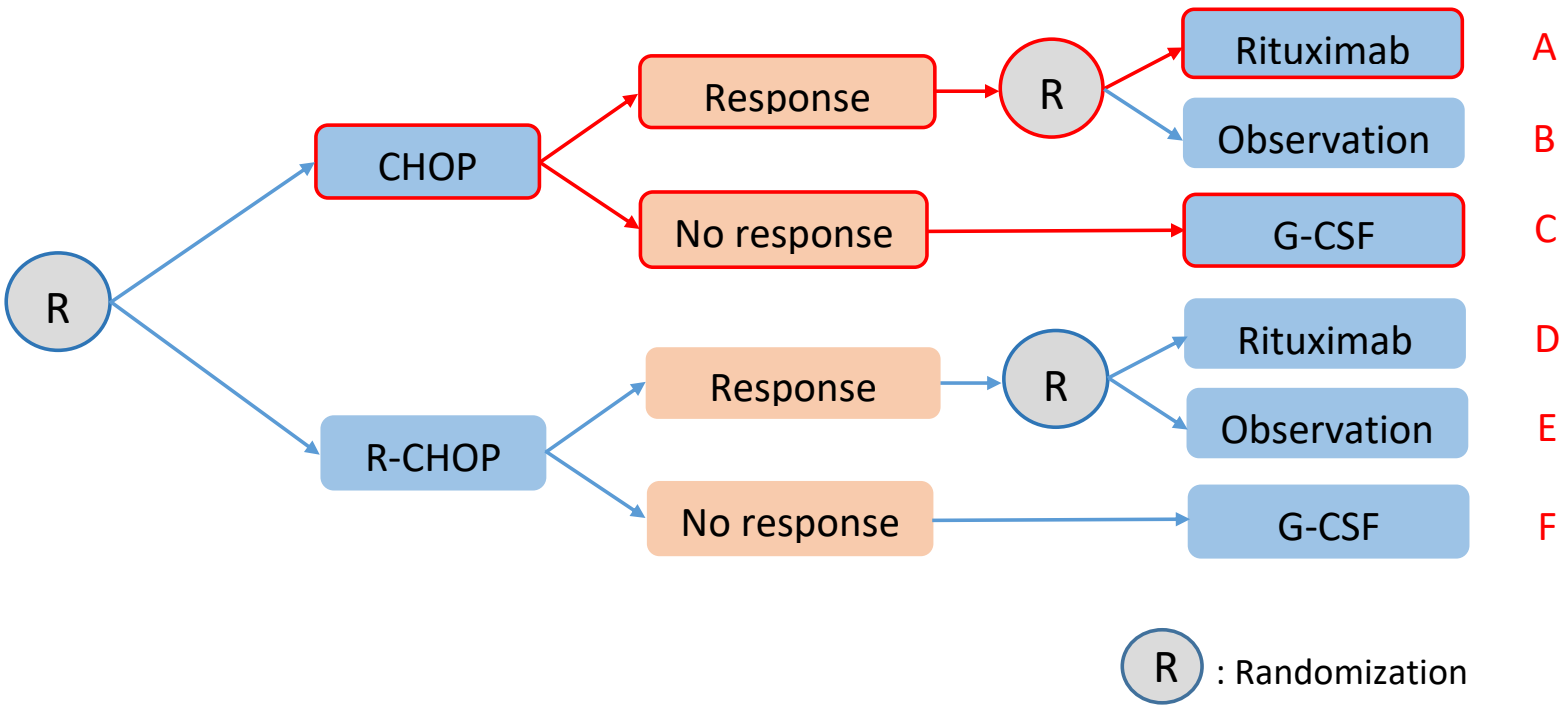
Example 2: IntelliCare (Cheung et al., 2018)



SMART Design

- Sequential multiple assignment randomized trial (SMART) is a clinical trial design that can be used to compare multiple adaptive interventions
  - SMART randomly assigns patients to **a collection of adaptive interventions** that may overlap in terms of treatment decisions
  - By virtue of randomization, it provides information for directly **comparing multiple adaptive interventions**

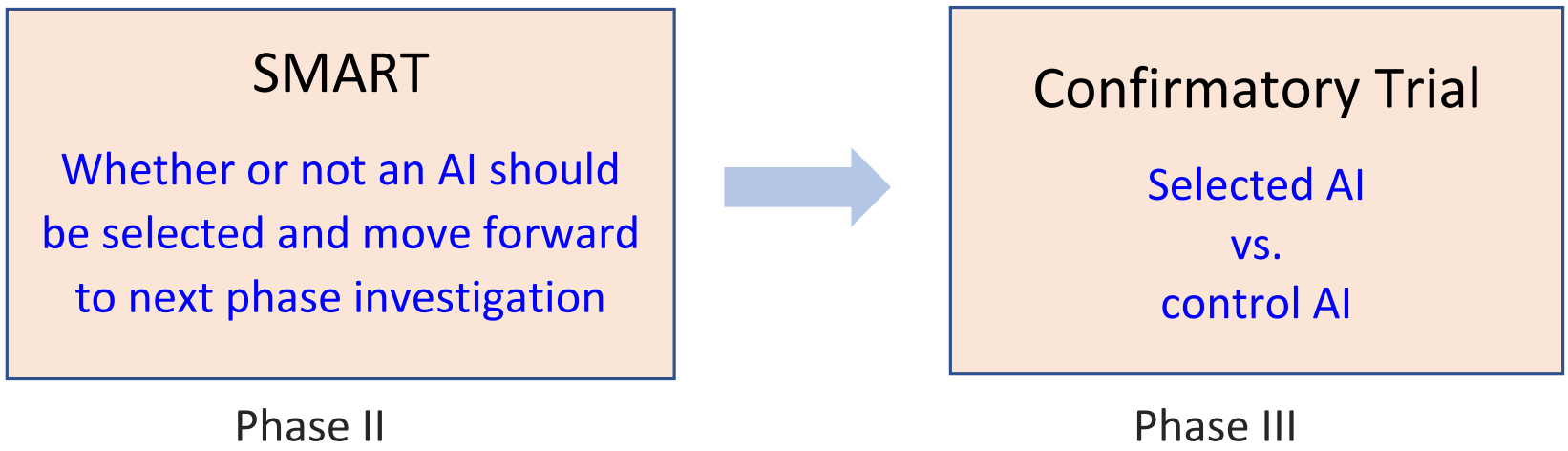
SMART Example: DLBCL Trial



There are 4 adaptive interventions embedded in this SMART, including

(A + C), (B + C), (D + F), (E + F)

Research Question



Statistical issue: multiple comparisons of adaptive interventions (AI)

Pairwise Comparison

- Pairwise comparison is commonly used for selecting adaptive interventions (AIs) embedded in a SMART
  - Conduct a series of pairwise tests based on the estimated values of all the AIs
    - e.g. Inverse probability weighted estimation (IPWE) [2]
  - Entail multiple comparisons
    - e.g. Bonferroni adjustment
- A SMART typically consists of numerous AIs
  - Inferential procedures based on pairwise comparisons of all interventions may suffer **substantial loss in power** after accounting for multiplicity

[2] Murphy, *Stat Med*, 2005

Gate-Keeping Approach

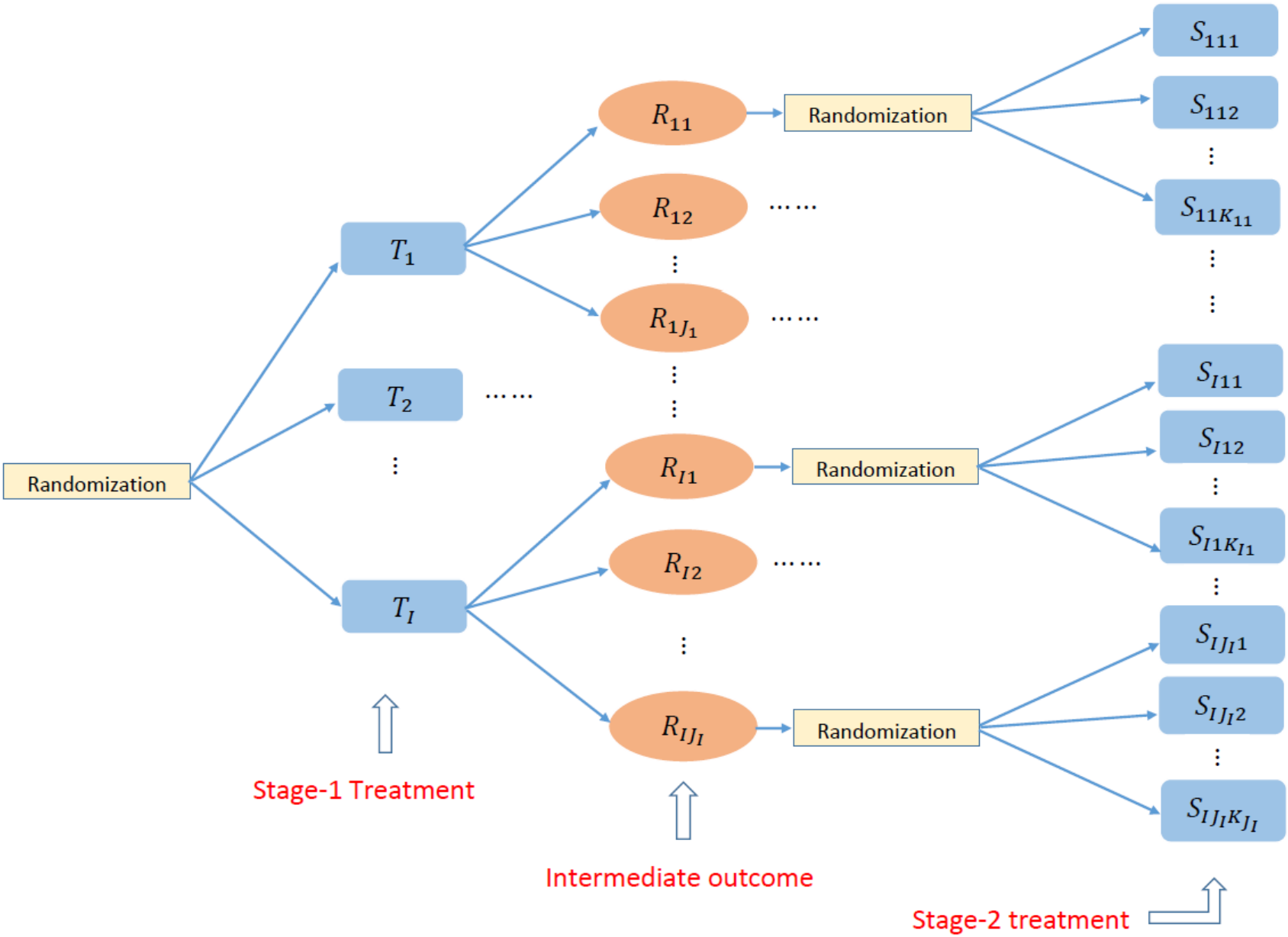
- Gate-keeping approach to avoid exhaustive search
  - Step 1: **conduct a gate-keeping test** with the null hypothesis that all the adaptive interventions have the same value
  - Step 2: **select the best adaptive intervention** only after the null hypothesis of the gate-keeping test is rejected
- Existing gate-keeping test for SMART
  - Wald test based on inverse probability weighted estimation (IPWE)[3]
    - can be used to control familywise type I error rate
    - less efficient (e.g., unbalanced randomization)
    - asymptotic properties of the test statistics has not been thoroughly studied
    - performance of selecting adaptive intervention remains unclear

[3] Ogabagabar, Karp and Wahed, *Stat Med*, 2016

The Proposed Gate-keeping Test

- We proposed a **likelihood-based** gate-keeping test for selecting the optimal adaptive intervention
  - derived the asymptotic distribution of test statistics and studied its properties
  - derived a formal sample size calculation formula
  - studied the finite sample performance of using the proposed gate-keeping approach for selecting the optimal adaptive intervention under different SMART settings, and compare it with the two existing methods

A General Two-stage SMART Design



Notation and Model

- Data for a patient can be summarized as (U, X, V, Y)
  - U: the stage-1 treatment
  - X: the intermediate response
  - V: the stage-2 treatment
  - Y: the final primary outcome
- Assuming (U, X, V, Y) to be i.i.d. distributed with

$$\Pr(U = T_i) = \pi_i,\ i = 1, \ldots, I,$$

$$\Pr(X = R_{ij} | U = T_i) = p_{ij},\ j = 1, \ldots, J_i, i = 1, \ldots, I,$$

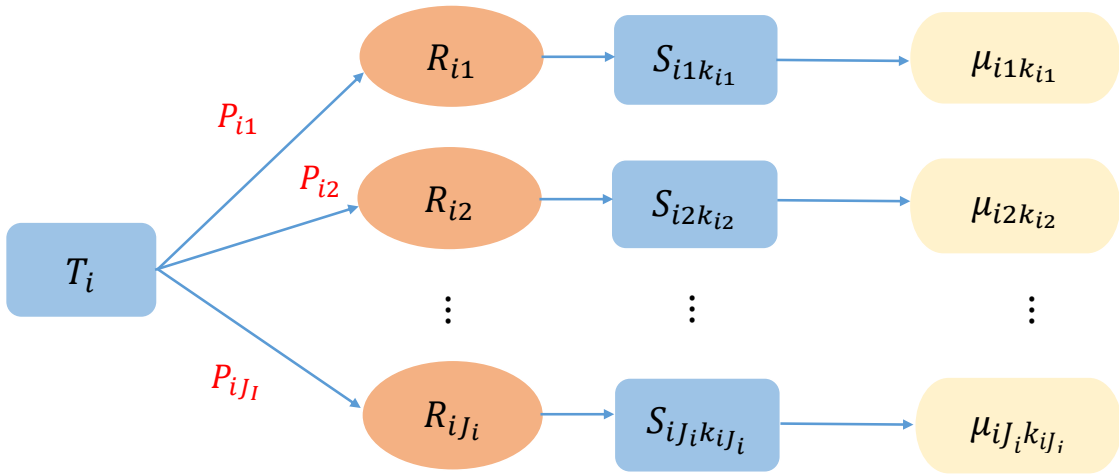
$$\Pr(V = S_{ijk} | U = T_i, X = R_{ij}) = \pi_{ijk},\ k = 1, \ldots, K_{ij}, j = 1, \ldots, J_i, i = 1, \ldots, I,$$

$$Y|(U = T_i, X = R_{ij}, V = S_{ijk}) \sim f\left(y|\mu_{ijk}, \tau_{ijk}\right),$$

$$\text{e.g. } Y|(U = T_i, X = R_{ij}, V = S_{ijk}) \overset{iid}{\sim} N\left(y|\mu_{ijk}, \sigma^2_{ijk}\right)$$

Estimand of Interest: Intervention Value

- Let $d_{i;k_{i1},\ldots,k_{iJ_i}} = (T_i; S_{i1k_{i1}}, \ldots, S_{iJ_ik_{iJ_i}})$ be an AI



- The value of an AI is defined as

$$\theta_{i;k_{i1},\ldots,k_{iJ_i}} = \sum_{j=1}^{J_i} p_{ij}\mu_{ijk_{ij}}.$$

MLE of AI Value

- MLE of an AI value

$$\hat{\theta}_{i;k_{i1},\ldots,k_{iJ_i}} = \sum_{j=1}^{J_i} \hat{p}_{ij}\hat{\mu}_{ijk_{ij}},$$

where $\hat{p}_{ij}$ and $\hat{\mu}_{ijk_{ij}}$ are obtained from maximizing the joint distribution of (U, X, V, Y).

Asymptotic Distribution

- Let $\boldsymbol{\Theta} = (\theta_1, \ldots, \theta_G)^T$ be all the adaptive intervention values embedded in a SMART. As $n \to \infty$,

$$\sqrt{n}(\hat{\boldsymbol{\Theta}} - \boldsymbol{\Theta}) \xrightarrow{d} N(\mathbf{0}, \boldsymbol{\Sigma}),$$

where

$$\boldsymbol{\Sigma} = \begin{pmatrix} \boldsymbol{\Sigma}_1 & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \boldsymbol{\Sigma}_2 & \ddots & \vdots \\ \vdots & \ddots & \ddots & \mathbf{0} \\ \mathbf{0} & \cdots & \mathbf{0} & \boldsymbol{\Sigma}_I \end{pmatrix},$$

and

$$\text{rank}\left(\boldsymbol{\Sigma}_i\right) = \sum_{j=1}^{J_i} K_{ij} - J_i + 1. \tag{1}$$

Likelihood-based Wald Test

- Hypothesis:

$$H_0 : \theta_1 = \ldots = \theta_G \text{ vs. } H_1 : \theta\text{'s are not all equal.}$$

- Wald test:

$$Q = n(C\hat{\boldsymbol{\Theta}})^T (C\hat{\boldsymbol{\Sigma}}C^T)^- (C\hat{\boldsymbol{\Theta}}), \tag{2}$$

where $Q \xrightarrow{d} \chi^2_\nu$ under H_0 and $Q \xrightarrow{d} \chi^2_\nu(\lambda^*)$ under H_1.

- Degrees of freedom

$$\nu = \sum_{i=1}^{I} \sum_{j=1}^{J_i} K_{ij} - \sum_{i=1}^{I} J_i + I - 1. \tag{3}$$

Sample Size Calculation

- Conduct sample size calculation based on Wald test
  - Step 1: specify the study design

$$\{T_i, R_{ij}, S_{ijk}, \pi_i, \pi_{ijk}\}$$

  - Step 2: obtain λ^* by solving

$$\chi^2_{\nu,1-\beta}(\lambda^*) = \chi^2_{\nu,\alpha}(0) \tag{4}$$

  - Step 3: calculate the effect size

$$\Delta = (C\boldsymbol{\Theta}^*)^T (C\boldsymbol{\Sigma}^* C^T)^- (C\boldsymbol{\Theta}^*) \tag{5}$$

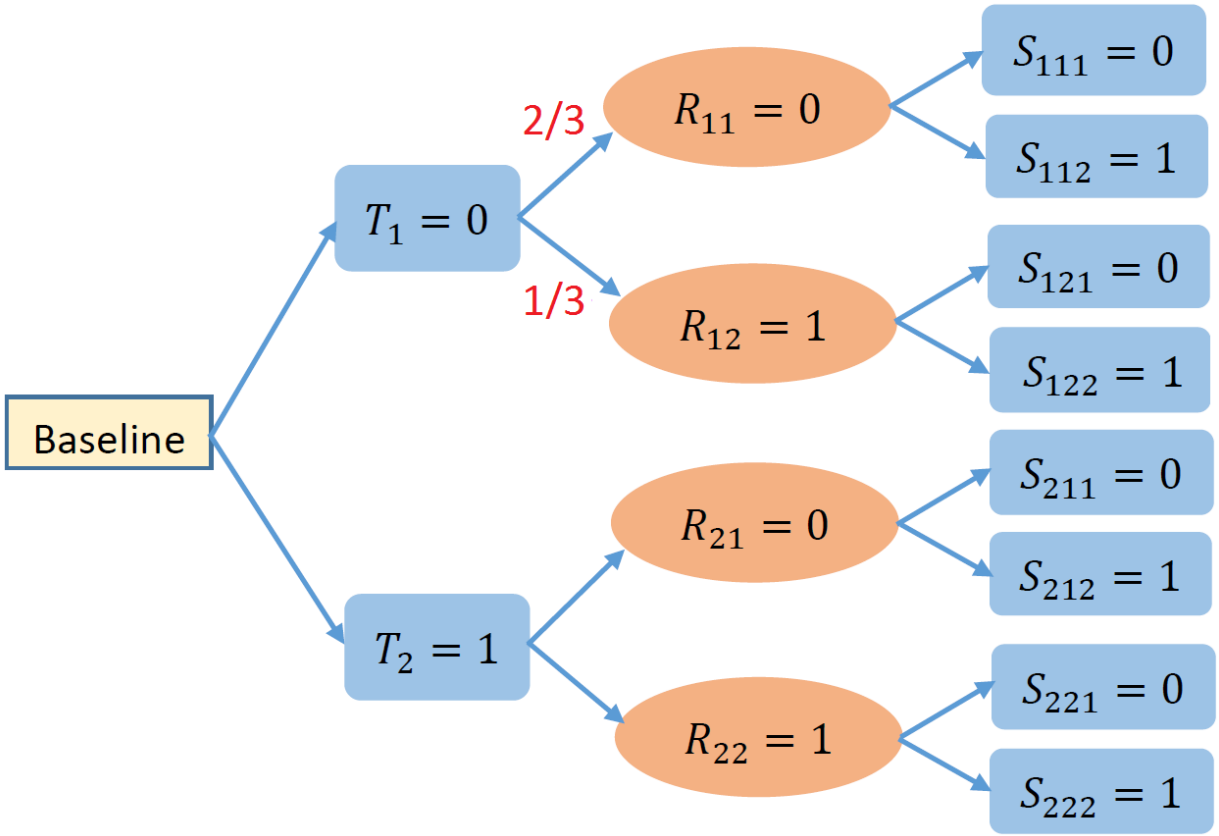
  - Step 4: total sample size of SMART

$$n = \frac{\lambda^*}{\Delta}. \tag{6}$$

Simulation Study

- Compare the type I error controls and the statistical powers
  1. Likelihood-based Wald test
  2. IPWE-based Wald test
  3. Pairwise tests with Bonferroni adjustment
     - Claim overall significance if any pairwise test is significant
- Assess the selection properties of the proposed gate-keeping approach
  - Step 1: conduct likelihood-based Wald test. If not significant, stop and claim no overall difference, otherwise, go to step 2
  - Step 2: select the best AI with the greatest observed value

Simulation: Design Structure



Simulation: Randomization

- Balanced randomization
  - $\Pr(U = 1) = 0.5$
  - $\Pr(V = 1|U, X) = 0.5$
- Unbalanced randomization
  - $\Pr(U = 1) = 0.7$
  - $\Pr(V = 1|U, X) = 0.7$
- Randomized play-the-winner
  - $\Pr(U = 1) = 0.5$
  - $\Pr(V = U|U, X = 1) = 0.7$
  - $\Pr(V = U|U, X = 0) = 0.3$

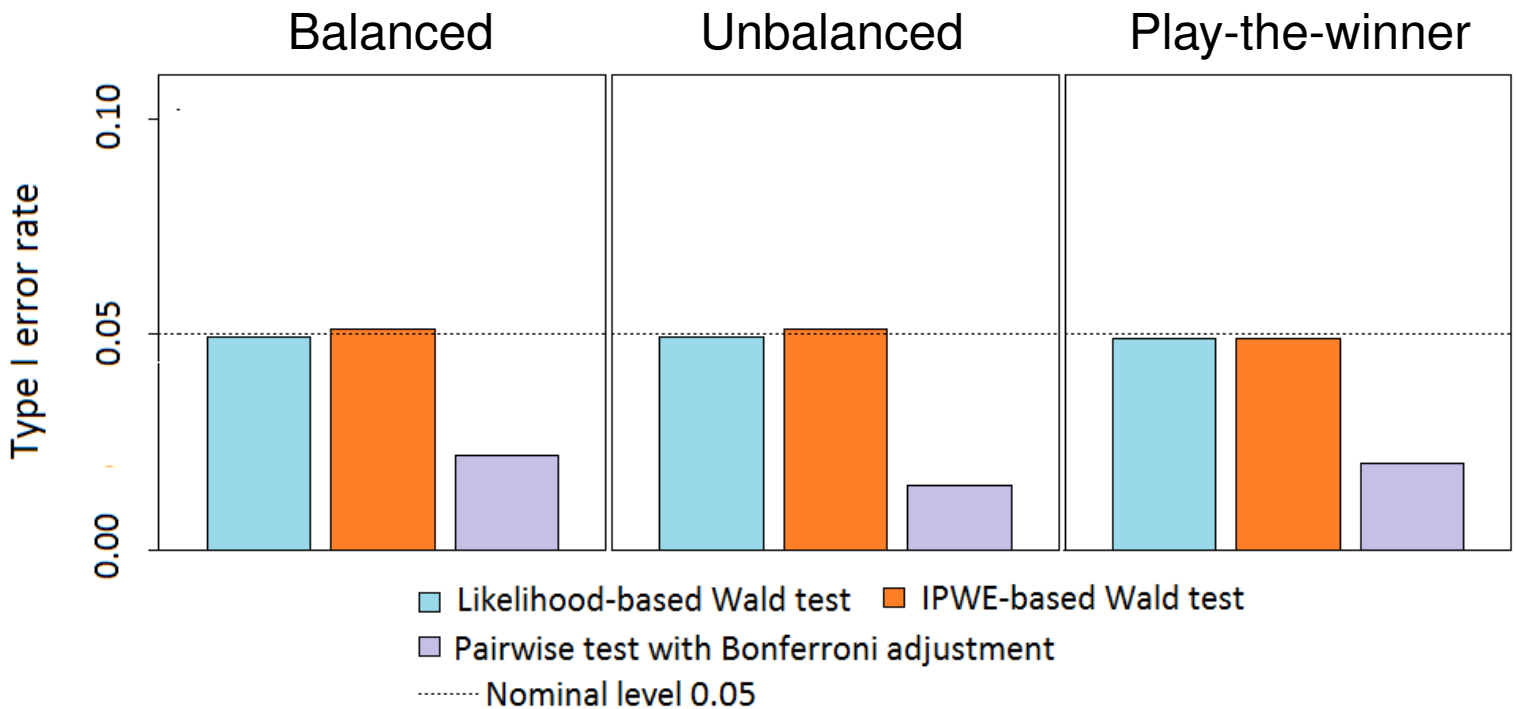
Simulation: Data Generation

- 5000 simulation replicates
- Sample size: $n = 200$
- Effect size: $\Delta = 0.10$
- Data generation
  - Intermediate response rates:
    - $\Pr(X = 1|U) = 1/3$ for $U = 0, 1$
  - Primary outcome

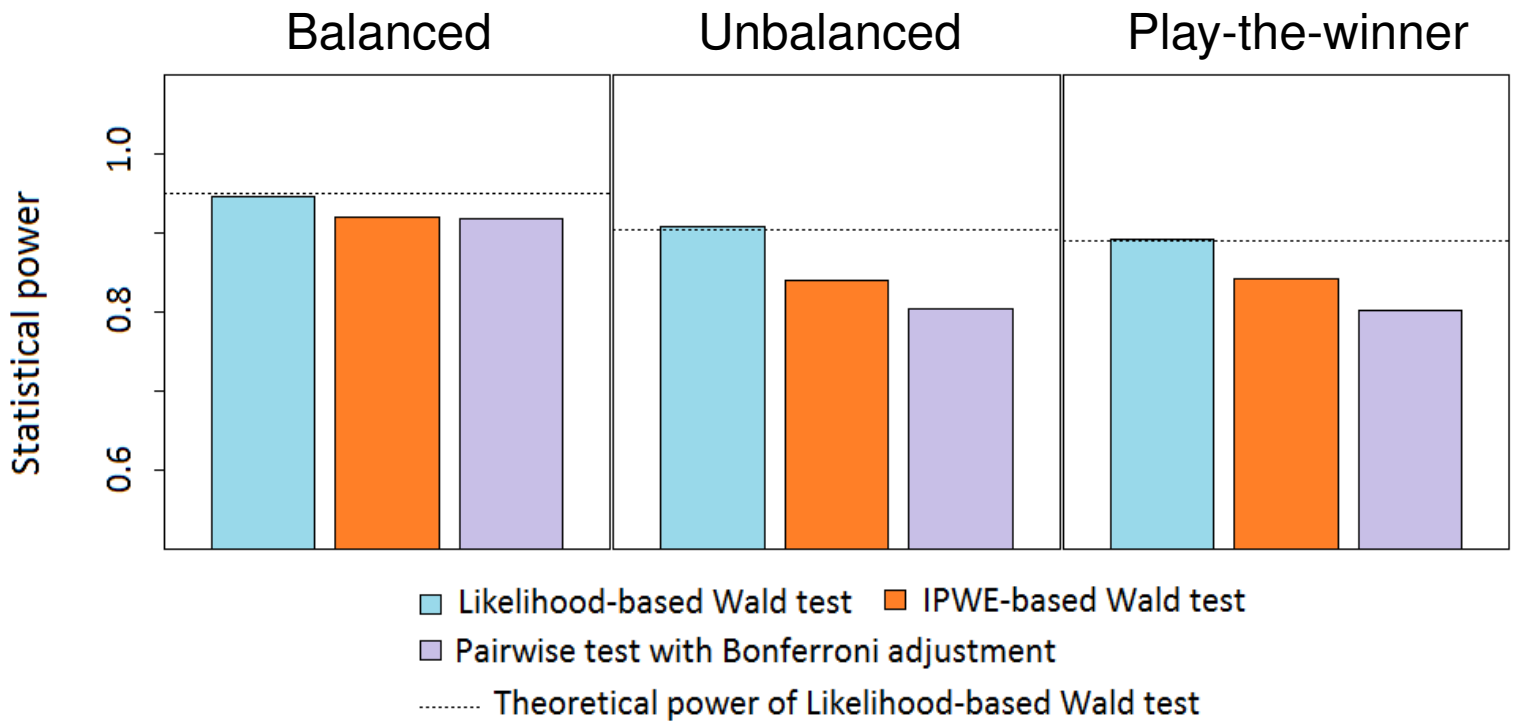
$$Y_{ijk} \overset{iid}{\sim} N(\mu_{ijk}, \sigma^2_{ijk})$$

    - $\sigma^2_{ijk} = 10^2$
    - $\mu_{ijk} = \beta_0 + \beta_1 T_i + \beta_2 R_{ij} + \beta_3 S_{ijk} + \beta_4 T_i R_{ij} + \beta_5 T_i S_{ijk} + \beta_6 R_{ij} S_{ijk} + \beta_7 T_i R_{ij} S_{ijk}$

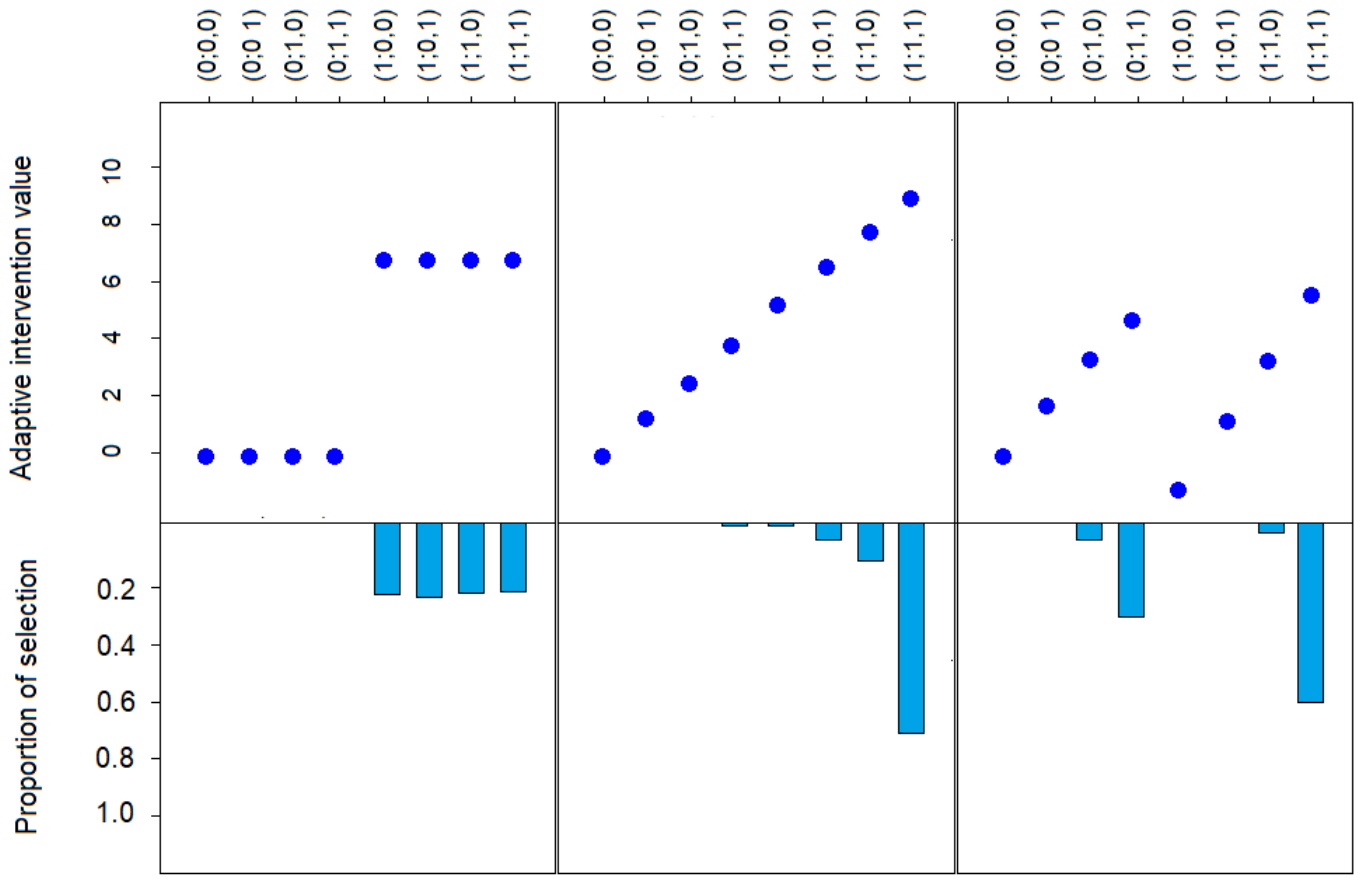
Results: Type I Error Rates (n=200)



Results: Statistical Powers (n=200)



Selection Properties: Results (n=200)



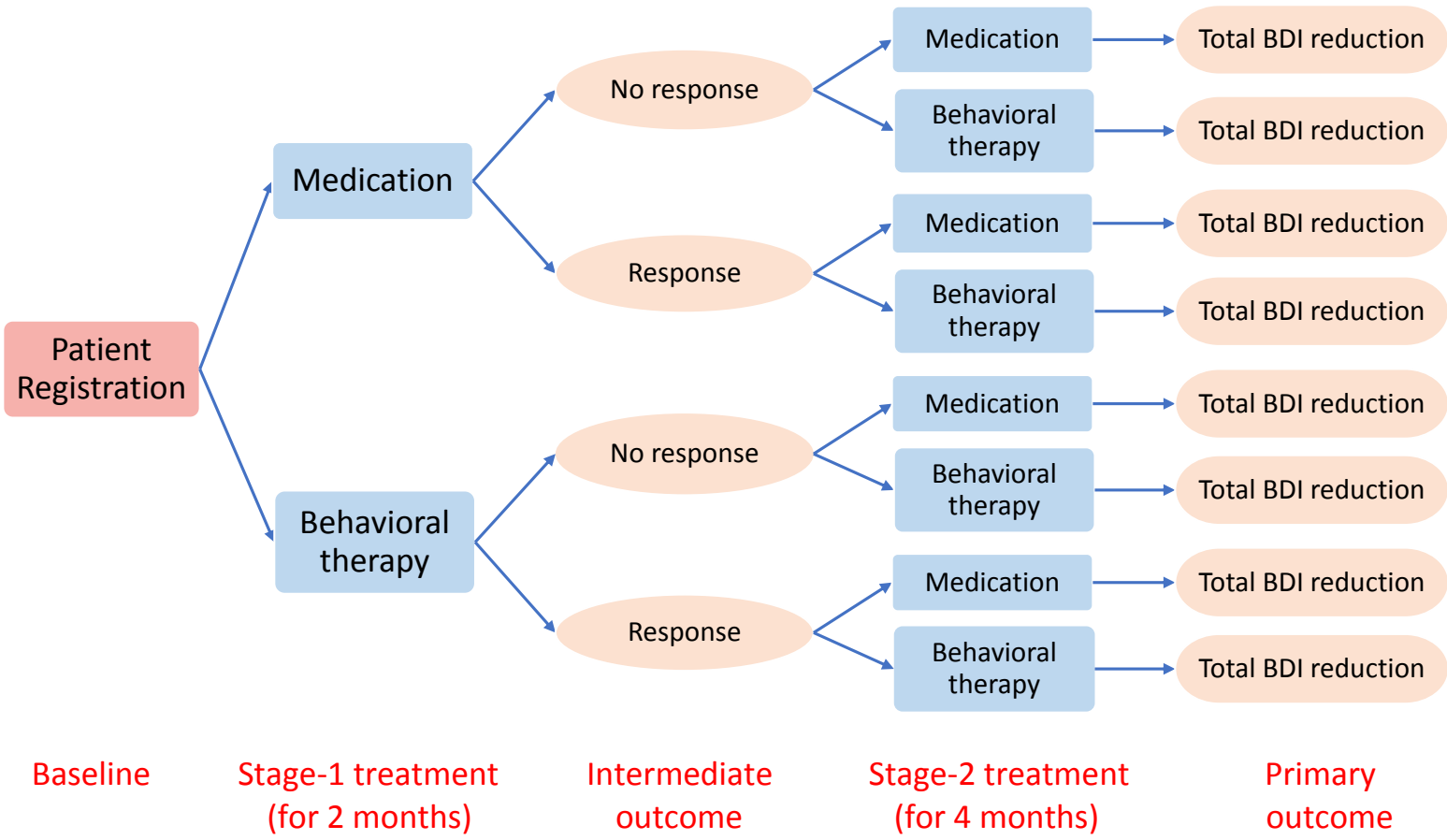
Note: under balanced randomization with effect size $\Delta = 0.10$

Real Data Analysis: CODIACS

- Comparison of Depression Interventions after Acute Coronary Syndromes (CODIACS)[4]
  - The study aimed to assess quality of depression care
  - The primary endpoint was reduction in the level of depression measured by Beck Depression Inventory (BDI)
  - More BDI reduction indicates a better treatment effect

[4] Cheung *et al. Biometrics*, 2015

CODIACS: Design Structure



CODIACS: Selecting the Best Strategy

- The objective was to select the optimal adaptive intervention to move forward to the next phase investigation

g	MLE	p-value
1	6.27	0.135
2	3.33	0.049
3	10.69	0.434
4	7.76	0.210
5	15.45	-
6	9.46	0.320
7	14.23	0.201
8	8.24	0.236

- Gate-keeping approach
  - Step 1: Likelihood-based Wald test ($p < 0.0001$)
  - Step 2: select $g = 5$ as the optimal
- Pairwise comparisons with Bonferroni's adjustment
  - Require a $p < 0.0018$ to achieve overall significance at 5%
  - No overall significance

Conclusion

- In this study
  - we explored the asymptotic distribution of the test statistics and its properties of the proposed likelihood-based Wald test
  - we derived a sample size calculation formula
- Pro: Likelihood-based Wald test
  - outperform the other two existing methods with better power
  - it can applied to varying design structures, randomization schemes and types of outcomes belonging to exponential family
- Con: The performance of likelihood-based test relies on the distributional assumption

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Thank You !

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