Two-treatment response adaptive Group-Sequential Allocation Design For Count data

Preet Paul, Souvik Das, Sahil Dutta

Presidency University, Kolkata

June 9, 2025

Introduction

- **Underutilized Potential of GSDs:** Group-sequential designs offer ethical and statistical efficiency but remain underused in clinical trials due to computational and analytical complexities—especially beyond normal or binary responses.

Introduction

- **Underutilized Potential of GSDs:** Group-sequential designs offer ethical and statistical efficiency but remain underused in clinical trials due to computational and analytical complexities—especially beyond normal or binary responses.
- **Need for Count Data Models:** Real-world medical studies increasingly yield count-type outcomes (e.g., seizure counts, readmissions), which are better modeled by Poisson-type distributions rather than classical ones.

Introduction

- **Underutilized Potential of GSDs:** Group-sequential designs offer ethical and statistical efficiency but remain underused in clinical trials due to computational and analytical complexities—especially beyond normal or binary responses.
- **Need for Count Data Models:** Real-world medical studies increasingly yield count-type outcomes (e.g., seizure counts, readmissions), which are better modeled by Poisson-type distributions rather than classical ones.
- **Our Contribution:** We develop a two-treatment response-adaptive GSD specifically for count data, bridging a significant methodological gap in biostatistics and clinical trial design.

Group Sequential Design

- **Purpose & Advantage:** GSDs allow interim analyses and early stopping (for efficacy/futility), reducing patient burden and accelerating access to effective treatments—while maintaining control over Type I and II errors.

Group Sequential Design

- **Purpose & Advantage:** GSDs allow interim analyses and early stopping (for efficacy/futility), reducing patient burden and accelerating access to effective treatments—while maintaining control over Type I and II errors.
- **Efficiency:** Compared to fixed-sample designs, GSDs improve statistical and ethical efficiency by lowering the Average Sample Number (ASN) needed to reach a decision.

Group Sequential Design

- **Purpose & Advantage:** GSDs allow interim analyses and early stopping (for efficacy/futility), reducing patient burden and accelerating access to effective treatments—while maintaining control over Type I and II errors.
- **Efficiency:** Compared to fixed-sample designs, GSDs improve statistical and ethical efficiency by lowering the Average Sample Number (ASN) needed to reach a decision.
- **Relevance for Count Data:** Count outcomes naturally arise in settings such as: Number of seizures (epilepsy), Asthma attacks per patient, 30-day hospital re-admissions, Number of ulcers healed.

Group Sequential Design

- **Purpose & Advantage:** GSDs allow interim analyses and early stopping (for efficacy/futility), reducing patient burden and accelerating access to effective treatments—while maintaining control over Type I and II errors.
- **Efficiency:** Compared to fixed-sample designs, GSDs improve statistical and ethical efficiency by lowering the Average Sample Number (ASN) needed to reach a decision.
- **Relevance for Count Data:** Count outcomes naturally arise in settings such as: Number of seizures (epilepsy), Asthma attacks per patient, 30-day hospital re-admissions, Number of ulcers healed.
- **Proposed Approach:** We develop a two-treatment response-adaptive GSD that dynamically updates patient allocation based on interim outcomes—ensuring both efficiency and ethical consideration.

Objective

- Let, X_k be the number of recurrences of the symptoms with treatment k ; where $k = A, B$.

Objective

- Let, X_k be the number of recurrences of the symptoms with treatment k ; where $k = A, B$.
- We assume, $X_k \sim Poisson(\lambda_k)$, $k = A, B$, independently

Objective

- Let, X_k be the number of recurrences of the symptoms with treatment k ; where $k = A, B$.
- We assume, $X_k \sim Poisson(\lambda_k)$, $k = A, B$, independently
- Here, λ_k be the average number of recurrence of the symptoms with treatment $'k'$.

Objective

- Let, X_k be the number of recurrences of the symptoms with treatment k ; where $k = A, B$.
- We assume, $X_k \sim Poisson(\lambda_k)$, $k = A, B$, independently
- Here, λ_k be the average number of recurrence of the symptoms with treatment $'k'$.
- In our study, we want to test,

$$\begin{aligned} & H_0 \quad : \quad A \preceq B \text{ i.e. } \lambda_A \geq \lambda_B \\ \text{against} \quad & H_1 \quad : \quad A \succ B \text{ i.e. } \lambda_A < \lambda_B \end{aligned}$$

Choosing Suitable Transformation

- Let, N = Total sample size to be allowed to take.

Choosing Suitable Transformation

- Let, N = Total sample size to be allowed to take.
- We consider maximum "K" interim look of the Group Sequential process.

Choosing Suitable Transformation

- Let, N = Total sample size to be allowed to take.
- We consider maximum "K" interim look of the Group Sequential process.
- With equal observations, let, m_{A_k} be the number of patients recieving treatment A in k^{th} interim and m_{B_k} be the number of patients recieving treatment B in k^{th} interim such that $m_{A_k} + m_{B_k} = r = n_k =$ size of k^{th}group ; $k = 1(1)K$.

Choosing Suitable Transformation

- Let, N = Total sample size to be allowed to take.
- We consider maximum "K" interim look of the Group Sequential process.
- With equal observations, let, m_{A_k} be the number of patients recieving treatment A in k^{th} interim and m_{B_k} be the number of patients recieving treatment B in k^{th} interim such that $m_{A_k} + m_{B_k} = r = n_k$ = size of k^{th}group ; $k = 1(1)K$.
- We also define, $n_{A_k} = m_{A_1} + m_{A_2} + ... + m_{A_k}$ = cumulative sample size upto k^{th} group with treatment A and $n_{B_k} = m_{B_1} + m_{B_2} + ... + m_{B_k}$ = cumulative sample size upto k^{th} group with treatment B ; $k = 1(1)K$.

Choosing Suitable Transformation

- Let, N = Total sample size to be allowed to take.
- We consider maximum "K" interim look of the Group Sequential process.
- With equal observations, let, m_{A_k} be the number of patients recieving treatment A in k^{th} interim and m_{B_k} be the number of patients recieving treatment B in k^{th} interim such that $m_{A_k} + m_{B_k} = r = n_k$ = size of k^{th}group ; $k = 1(1)K$.
- We also define, $n_{A_k} = m_{A_1} + m_{A_2} + ... + m_{A_k}$ = cumulative sample size upto k^{th} group with treatment A and $n_{B_k} = m_{B_1} + m_{B_2} + ... + m_{B_k}$ = cumulative sample size upto k^{th} group with treatment B ; $k = 1(1)K$.
- Now, we want to check for which transformation, the poisson data more effectively exhibits asymptotic normality.

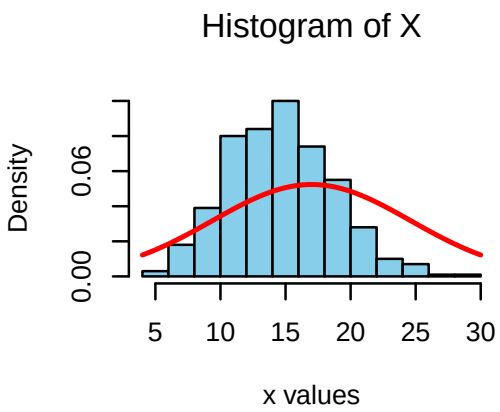
Choosing Suitable Transformation

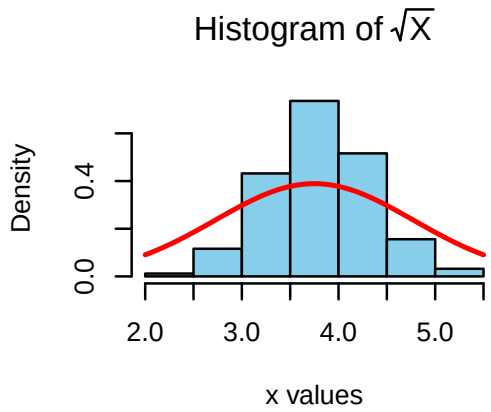
- Let, N = Total sample size to be allowed to take.
- We consider maximum "K" interim look of the Group Sequential process.
- With equal observations, let, m_{A_k} be the number of patients recieving treatment A in k^{th} interim and m_{B_k} be the number of patients recieving treatment B in k^{th} interim such that $m_{A_k} + m_{B_k} = r = n_k$ = size of k^{th}group ; $k = 1(1)K$.
- We also define, $n_{A_k} = m_{A_1} + m_{A_2} + ... + m_{A_k}$ = cumulative sample size upto k^{th} group with treatment A and $n_{B_k} = m_{B_1} + m_{B_2} + ... + m_{B_k}$ = cumulative sample size upto k^{th} group with treatment B ; $k = 1(1)K$.
- Now, we want to check for which transformation, the poisson data more effectively exhibits asymptotic normality.
- Suppose $X \sim poisson(\lambda = 15)$

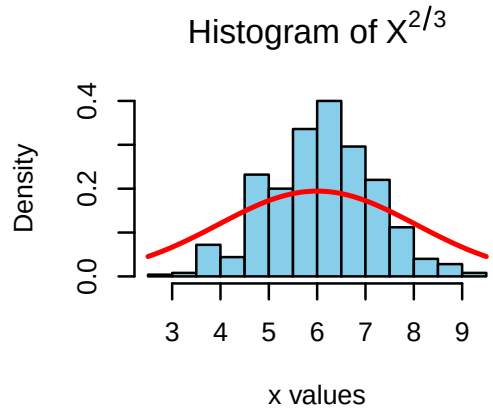
P-Values for Kolmogorov-Smrinov under suitable transformations

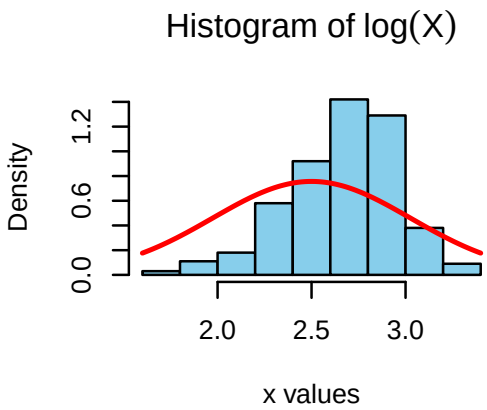
Transformation	P_Value
OrgSample	0.0245251871
sqrt	0.0337430991
two_thirds	0.0877515261
log	0.0005209938
log_of_sqrt	0.0005209938

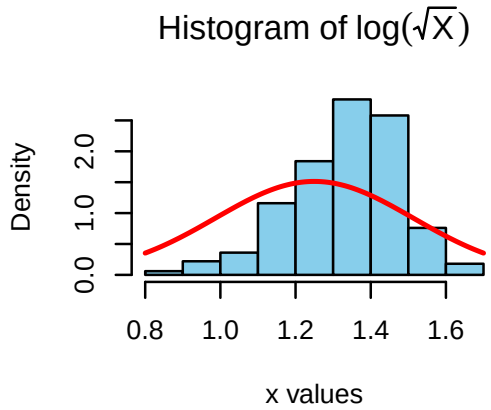
Histograms of the Data under Different Transformations











Test Statistic

- Based on the *Kolmogorov - Smrinov* test results and the histogram, we will use the $g(X) = X^{2/3}$ transformation for our analyses

Test Statistic

- Based on the *Kolmogorov - Smrinov* test results and the histogram, we will use the $g(X) = X^{2/3}$ transformation for our analyses
- Using CLT and delta method, the test statistic for k^{th} interim is given by,

$$Z_k = \frac{\bar{X}_{A_k}^{2/3} - \bar{X}_{B_k}^{2/3}}{\sqrt{\frac{4}{9}\hat{\lambda_k}^{1/3}(\frac{1}{n_{A_k}} + \frac{1}{n_{B_k}})}} \; ; k = 1, 2, ..., K$$

Test Statistic

- Based on the *Kolmogorov - Smrinov* test results and the histogram, we will use the $g(X) = X^{2/3}$ transformation for our analyses
- Using CLT and delta method, the test statistic for k^{th} interim is given by,

$$Z_k = \frac{\bar{X}_{A_k}^{2/3} - \bar{X}_{B_k}^{2/3}}{\sqrt{\frac{4}{9}\hat{\lambda_k}^{1/3}(\frac{1}{n_{A_k}} + \frac{1}{n_{B_k}})}} \; ; k = 1, 2, ..., K$$

- where,

$$\hat{\lambda_k} = \frac{n_{A_k}\bar{X}_{A_k} + n_{B_k}\bar{X}_{B_k}}{n_{A_k} + n_{B_k}} \; ; k = 1, 2, ..., K$$

Test Procedure

- Then, the sequential test procedure for first stage can be written as,

Test Procedure

- Then, the sequential test procedure for first stage can be written as,
- (i) If, $Z_k < a_k$;

Test Procedure

- Then, the sequential test procedure for first stage can be written as,
- (i) If, $Z_k < a_k$;
- $\Rightarrow$ We reject H_0 i.e. we accept H_1

Test Procedure

- Then, the sequential test procedure for first stage can be written as,
- (i) If, $Z_k < a_k$;
- $\Rightarrow$ We reject H_0 i.e. we accept H_1
- (ii) If, $Z_k > b_k$;

Test Procedure

- Then, the sequential test procedure for first stage can be written as,
- (i) If, $Z_k < a_k$;
- $\Rightarrow$ We reject H_0 i.e. we accept H_1
- (ii) If, $Z_k > b_k$;
- $\Rightarrow$ We accept H_0

Test Procedure

- Then, the sequential test procedure for first stage can be written as,
- (i) If, $Z_k < a_k$;
- $\Rightarrow$ We reject H_0 i.e. we accept H_1
- (ii) If, $Z_k > b_k$;
- $\Rightarrow$ We accept H_0
- (ii) If, $a_k \leq Z_k \leq b_k$

Test Procedure

- Then, the sequential test procedure for first stage can be written as,
- (i) If, $Z_k < a_k$;
- $\Rightarrow$ We reject H_0 i.e. we accept H_1
- (ii) If, $Z_k > b_k$;
- $\Rightarrow$ We accept H_0
- (ii) If, $a_k \leq Z_k \leq b_k$
- $\Rightarrow$ inconclusive about acceptance of $H_i; i = 0, 1$ and we go for the next stage.

Boundary Points

- Let, $\alpha = \alpha_1 + \alpha_2 + ... + \alpha_K =$ the total size of the test procedure and $\beta = \beta_1 + \beta_2 + ...\beta_K =$ the total type-II error probability spent in the test.

Boundary Points

- Let, $\alpha = \alpha_1 + \alpha_2 + ... + \alpha_K$= the total size of the test procedure and $\beta = \beta_1 + \beta_2 + ...\beta_K$ = the total type-II error probability spent in the test.
- Here, the boundary points a_1, b_1 can be chosen from,

Boundary Points

- Let, $\alpha = \alpha_1 + \alpha_2 + ... + \alpha_K$= the total size of the test procedure and $\beta = \beta_1 + \beta_2 + ...\beta_K$ = the total type-II error probability spent in the test.
- Here, the boundary points a_1, b_1 can be chosen from,
- (The Size Condition)

$$\alpha_k = P_{H_0}(a_1 \leq Z_1 \leq b_1 \ , ..., \ Z_k \leq a_k)$$

Boundary Points

- Let, $\alpha = \alpha_1 + \alpha_2 + ... + \alpha_K$= the total size of the test procedure and $\beta = \beta_1 + \beta_2 + ...\beta_K$ = the total type-II error probability spent in the test.
- Here, the boundary points a_1, b_1 can be chosen from,
- (The Size Condition)

$$\alpha_k = P_{H_0}(a_1 \leq Z_1 \leq b_1 \ , ..., \ Z_k \leq a_k)$$

- (The Type-II error probability)

$$\beta_k = P_{H_1}(a_1 \leq Z_1 \leq b_1 \ , ..., \ Z_k > b_k)$$

Boundary Points

- Let, $\alpha = \alpha_1 + \alpha_2 + ... + \alpha_K$= the total size of the test procedure and $\beta = \beta_1 + \beta_2 + ...\beta_K$ = the total type-II error probability spent in the test.
- Here, the boundary points a_1, b_1 can be chosen from,
- (The Size Condition)

$$\alpha_k = P_{H_0}(a_1 \leq Z_1 \leq b_1 \ , ..., \ Z_k \leq a_k)$$

- (The Type-II error probability)

$$\beta_k = P_{H_1}(a_1 \leq Z_1 \leq b_1 \ , ..., \ Z_k > b_k)$$

- We will use $K = 3$ for our study.

Boundary Points

- Let, $\alpha = \alpha_1 + \alpha_2 + ... + \alpha_K =$ the total size of the test procedure and $\beta = \beta_1 + \beta_2 + ...\beta_K =$ the total type-II error probability spent in the test.
- Here, the boundary points a_1, b_1 can be chosen from,
- (The Size Condition)

$$\alpha_k = P_{H_0}(a_1 \leq Z_1 \leq b_1 \ , ..., \ Z_k \leq a_k)$$

- (The Type-II error probability)

$$\beta_k = P_{H_1}(a_1 \leq Z_1 \leq b_1 \ , ..., \ Z_k > b_k)$$

- We will use $K = 3$ for our study.
- So, we will consider $a_3 = b_3$ for the third stage.

Average Sample Number (ASN)

- We consider, $n_i = n_{A_i} + n_{B_i}$; $i = 1, 2, ..., K$

Average Sample Number (ASN)

- We consider, $n_i = n_{A_i} + n_{B_i}$; $i = 1, 2, ..., K$

n_i	probability of terminating at i^{th} stage (p_i)
n_1	$P(Z_1 < a_1)P(Z_1 > b_1) = 1 - P(a_1 \leq Z_1 \leq b_1)$
n_2	$P[(a_1 \leq Z_1 \leq b_1) \cap \{(Z_2 < a_2) \cup (Z_2 > b_2)\}]$
n_3	$P_{H_0}[(a_1 \leq Z_1 \leq b_1) \cap (a_2 \leq Z_2 \leq b_2) \cap (Z_3 \leq b_3)]$

Average Sample Number (ASN)

- We consider, $n_i = n_{A_i} + n_{B_i}$; $i = 1, 2, ..., K$

n_i	probability of terminating at i^{th} stage (p_i)
n_1	$P(Z_1 < a_1)P(Z_1 > b_1) = 1 - P(a_1 \leq Z_1 \leq b_1)$
n_2	$P[(a_1 \leq Z_1 \leq b_1) \cap \{(Z_2 < a_2) \cup (Z_2 > b_2)\}]$
n_3	$P_{H_0}[(a_1 \leq Z_1 \leq b_1) \cap (a_2 \leq Z_2 \leq b_2) \cap (Z_3 \leq b_3)]$

- Then, average sample number can be defined as,

$$ASN = E(N)$$

Average Sample Number (ASN)

- We consider, $n_i = n_{A_i} + n_{B_i}$; $i = 1, 2, ..., K$

n_i	probability of terminating at i^{th} stage (p_i)
n_1	$P(Z_1 < a_1)P(Z_1 > b_1) = 1 - P(a_1 \leq Z_1 \leq b_1)$
n_2	$P[(a_1 \leq Z_1 \leq b_1) \cap \{(Z_2 < a_2) \cup (Z_2 > b_2)\}]$
n_3	$P_{H_0}[(a_1 \leq Z_1 \leq b_1) \cap (a_2 \leq Z_2 \leq b_2) \cap (Z_3 \leq b_3)]$

- Then, average sample number can be defined as,

$$ASN = E(N)$$

- i.e.

$$ASN = n_1 p_1 + n_2 p_2 + n_3 p_3$$

Computation

- We fix the sample of each group $n_1 = n_2 = n_3 = 100$.

Computation

- We fix the sample of each group $n_1 = n_2 = n_3 = 100$.
- so, $N = 300$.

Computation

- We fix the sample of each group $n_1 = n_2 = n_3 = 100$.
- so, $N = 300$.
- We allocate equal number of treatment A and treatment B to the patients, i.e. $m_{A_k} = m_{B_k} = 50 \; ; \; k = 1, 2, 3$.

Computation

- We fix the sample of each group $n_1 = n_2 = n_3 = 100$.
- so, $N = 300$.
- We allocate equal number of treatment A and treatment B to the patients, i.e. $m_{A_k} = m_{B_k} = 50\ ;\ k = 1, 2, 3$.
- We choose $\alpha = 0.05$ and $\beta = 0.05$ such that $\alpha_1 = 0.02,\ \alpha_2 = 0.02,\ \alpha_3 = 0.01$ and $\beta_1 = 0.015,\ \beta_2 = 0.015,\ \beta_3 = 0.02$, for now.

Computation

- We fix the sample of each group $n_1 = n_2 = n_3 = 100$.
- so, $N = 300$.
- We allocate equal number of treatment A and treatment B to the patients, i.e. $m_{A_k} = m_{B_k} = 50\ ;\ k = 1, 2, 3$.
- We choose $\alpha = 0.05$ and $\beta = 0.05$ such that $\alpha_1 = 0.02,\ \alpha_2 = 0.02,\ \alpha_3 = 0.01$ and $\beta_1 = 0.015,\ \beta_2 = 0.015,\ \beta_3 = 0.02$, for now.
- We simulate 50 samples each from $poisson(\lambda_A)$ and $poisson(\lambda_B)$ for the first interim and carry out the procedure to find the boundary points.

Computation

- We fix the sample of each group $n_1 = n_2 = n_3 = 100$.
- so, $N = 300$.
- We allocate equal number of treatment A and treatment B to the patients, i.e. $m_{A_k} = m_{B_k} = 50\ ;\ k = 1, 2, 3$.
- We choose $\alpha = 0.05$ and $\beta = 0.05$ such that $\alpha_1 = 0.02,\ \alpha_2 = 0.02,\ \alpha_3 = 0.01$ and $\beta_1 = 0.015,\ \beta_2 = 0.015,\ \beta_3 = 0.02$, for now.
- We simulate 50 samples each from $poisson(\lambda_A)$ and $poisson(\lambda_B)$ for the first interim and carry out the procedure to find the boundary points.
- Then, in second and third stage, we simulate data from $poisson(\hat{\lambda_A})$ and $poisson(\hat{\lambda_B})$; where $\hat{\lambda_A}=\bar{X_{A_1}}$ and $\hat{\lambda_B}=\bar{X_{B_1}}$.

Computation

- We fix the sample of each group $n_1 = n_2 = n_3 = 100$.
- so, $N = 300$.
- We allocate equal number of treatment A and treatment B to the patients, i.e. $m_{A_k} = m_{B_k} = 50\ ;\ k = 1, 2, 3$.
- We choose $\alpha = 0.05$ and $\beta = 0.05$ such that $\alpha_1 = 0.02,\ \alpha_2 = 0.02,\ \alpha_3 = 0.01$ and $\beta_1 = 0.015,\ \beta_2 = 0.015,\ \beta_3 = 0.02$, for now.
- We simulate 50 samples each from $poisson(\lambda_A)$ and $poisson(\lambda_B)$ for the first interim and carry out the procedure to find the boundary points.
- Then, in second and third stage, we simulate data from $poisson(\hat{\lambda_A})$ and $poisson(\hat{\lambda_B})$; where $\hat{\lambda_A}=\bar{X_{A_1}}$ and $\hat{\lambda_B}=\bar{X_{B_1}}$.
- We fix $\lambda_A = 2$.

ASN for Different $\lambda's$

	lambda_B	ASN_H0	ASN_H1
1	2.0	291.3	287.8
2	2.2	290.0	274.4
3	2.4	288.1	245.6
4	2.6	282.6	201.4
5	2.8	273.8	154.0
6	3.0	259.7	123.1
7	3.2	237.3	107.3
8	3.4	220.9	100.9
9	3.6	209.5	100.3
10	3.8	203.6	100.0
11	4.0	197.4	100.0

Different Choices of Error Spendings

- Now, we will find and plot ASN for different choices of the error spending (α_k, β_k) ; $k = 1, 2, 3$ (keeping the total size $\alpha = 0.05$ and total type II probability β=0.05 fixed) in multiple line diagrams against different $\lambda'_B s$.

Different Choices of Error Spendings

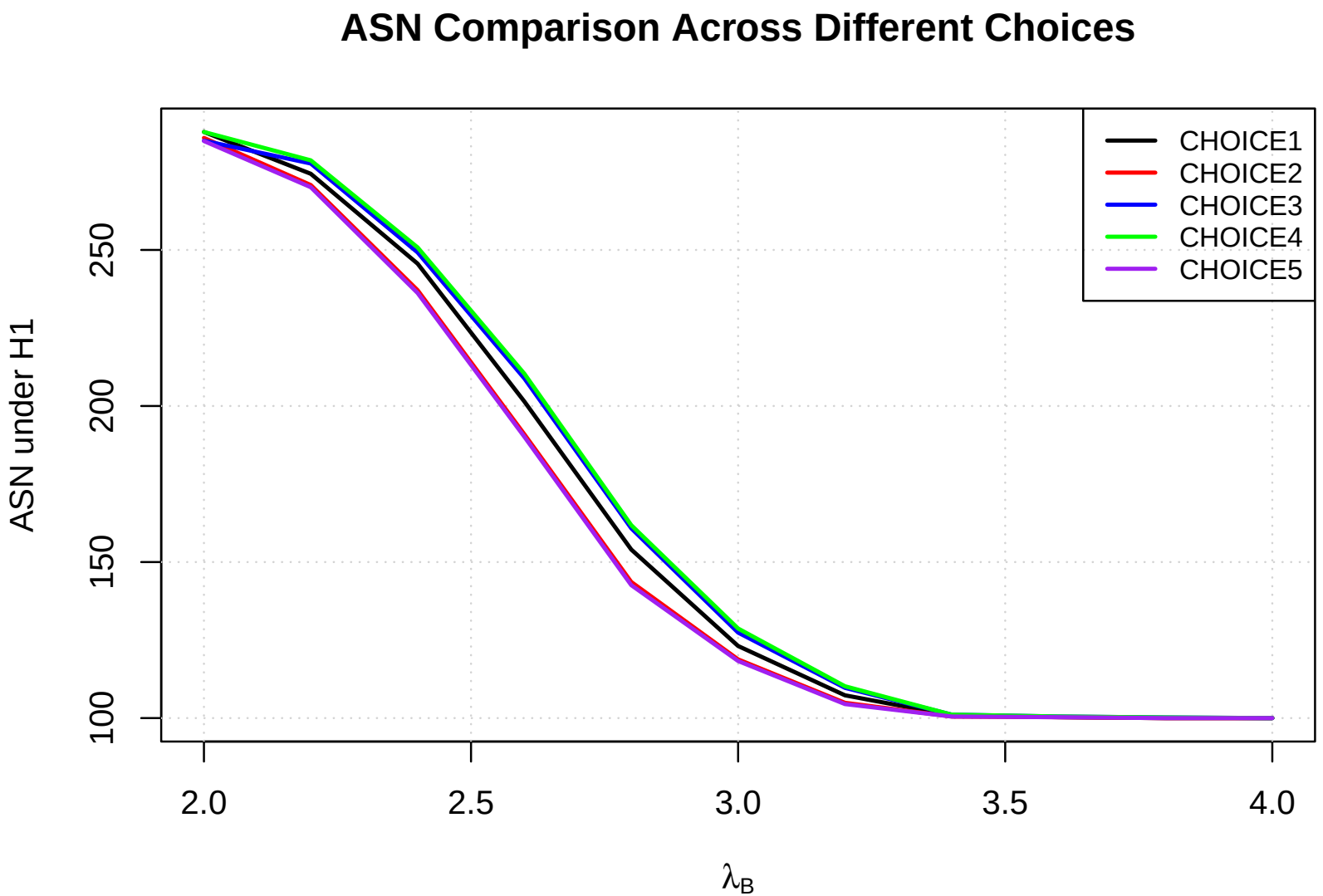
- Now, we will find and plot ASN for different choices of the error spending (α_k, β_k) ; $k = 1, 2, 3$ (keeping the total size $\alpha = 0.05$ and total type II probability β=0.05 fixed) in multiple line diagrams against different $\lambda'_B s$.
- We take the choices of (α, β) as,

Different Choices of Error Spendings

- Now, we will find and plot ASN for different choices of the error spending (α_k, β_k) ; $k = 1, 2, 3$ (keeping the total size $\alpha = 0.05$ and total type II probability β=0.05 fixed) in multiple line diagrams against different $\lambda'_B s$.
- We take the choices of (α, β) as,
-

Choices	α_1	α_2	α_3	β_1	β	β_3
1	0.02	0.02	0.01	0.015	0.015	0.02
2	0.03	0.01	0.01	0.02	0.02	0.01
3	0.015	0.025	0.01	0.03	0.01	0.01
4	0.015	0.015	0.02	0.025	0.01	0.015
5	0.03	0.015	0.005	0.02	0.025	0.005

ASN for Different (α_k, β_k) and Different $\lambda's$



ASN table for $\alpha = (0.03, 0.015, 0.005)$, $\beta = (0.02, 0.025, 0.005)$

	lambda_B	ASN_H0	ASN_H1
1	2.0	287.9	284.9
2	2.2	286.6	270.1
3	2.4	282.2	236.2
4	2.6	275.8	190.1
5	2.8	261.4	142.6
6	3.0	239.4	118.3
7	3.2	222.8	104.5
8	3.4	210.1	100.5
9	3.6	202.6	100.3
10	3.8	197.7	100.0
11	4.0	195.0	100.0

Adaptive Group Sequential Design

- **Need for Adaptation:** Traditional fixed-sample and classical GSDs lack flexibility and can be ethically limiting, especially when interim evidence suggests one treatment is clearly better.

Adaptive Group Sequential Design

- **Need for Adaptation:** Traditional fixed-sample and classical GSDs lack flexibility and can be ethically limiting, especially when interim evidence suggests one treatment is clearly better.
- **Statistical and Ethical Integration:** Adaptive GSD blends sequential testing with evolving allocation rules, reducing Average Sample Number (ASN) while ethically favoring superior treatments.

Adaptive Group Sequential Design

- **Need for Adaptation:** Traditional fixed-sample and classical GSDs lack flexibility and can be ethically limiting, especially when interim evidence suggests one treatment is clearly better.
- **Statistical and Ethical Integration:** Adaptive GSD blends sequential testing with evolving allocation rules, reducing Average Sample Number (ASN) while ethically favoring superior treatments.
- **Dynamic Allocation:** Instead of static equal randomization, treatment probabilities are updated based on accumulating evidence, ensuring more patients receive the potentially better treatment over time.

Adaptive Group Sequential Design

- **Need for Adaptation:** Traditional fixed-sample and classical GSDs lack flexibility and can be ethically limiting, especially when interim evidence suggests one treatment is clearly better.
- **Statistical and Ethical Integration:** Adaptive GSD blends sequential testing with evolving allocation rules, reducing Average Sample Number (ASN) while ethically favoring superior treatments.
- **Dynamic Allocation:** Instead of static equal randomization, treatment probabilities are updated based on accumulating evidence, ensuring more patients receive the potentially better treatment over time.
- **Practical Impact:** Enhances patient welfare, improves trial efficiency, and maintains rigorous Type I/II error control—especially vital in trials involving serious or life-threatening conditions.

Entry Stage Adaptive Group Sequential Design

- **In the first stage,** we simulate 50 samples X_{A_1} from $poisson(\lambda_A)$ and 50 samples X_{B_1} from $poisson(\lambda_B)$ and we carry out the sequential test procedure for first stage as described in the group sequential design.

Entry Stage Adaptive Group Sequential Design

- **In the first stage,** we simulate 50 samples X_{A_1} from $poisson(\lambda_A)$ and 50 samples X_{B_1} from $poisson(\lambda_B)$ and we carry out the sequential test procedure for first stage as described in the group sequential design.
- **In second stage,** we simulate 50 samples X_{A_2} from $poisson(\hat{\lambda}_A)$ and 50 samples $X_{B_2}$from $poisson(\hat{\lambda}_B)$ and carry out GSD; where,

$$\hat{\lambda}_A = \bar{X}_{A_1} = \frac{1}{50}\sum_{j=1}^{50} X_{A_1}^{(j)} \text{ and } \hat{\lambda}_B = \bar{X}_{B_1} = \frac{1}{50}\sum_{j=1}^{50} X_{B_1}^{(j)}$$

Entry Stage Adaptive Group Sequential Design

- **In the first stage,** we simulate 50 samples X_{A_1} from $poisson(\lambda_A)$ and 50 samples X_{B_1} from $poisson(\lambda_B)$ and we carry out the sequential test procedure for first stage as described in the group sequential design.
- **In second stage,** we simulate 50 samples X_{A_2} from $poisson(\hat{\lambda}_A)$ and 50 samples $X_{B_2}$from $poisson(\hat{\lambda}_B)$ and carry out GSD; where,

$$\hat{\lambda}_A = \bar{X}_{A_1} = \frac{1}{50}\sum_{j=1}^{50} X_{A_1}^{(j)} \text{ and } \hat{\lambda}_B = \bar{X}_{B_1} = \frac{1}{50}\sum_{j=1}^{50} X_{B_1}^{(j)}$$

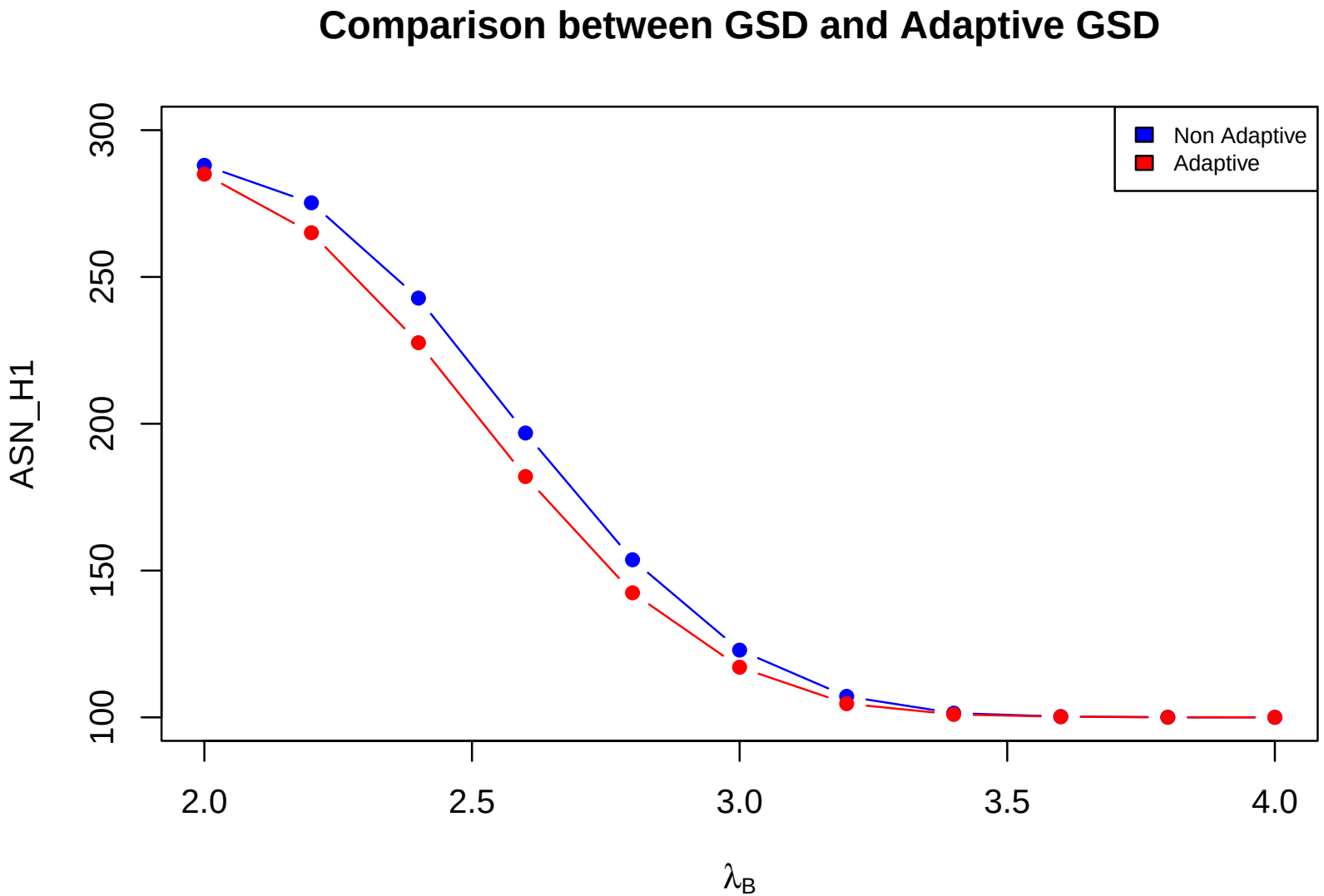
- **In third stage,** we simulate 50 samples X_{A_3} from $poisson(\hat{\lambda}_A^*)$ and 50 samples X_{B_3} from $poisson(\hat{\lambda}_B^*)$ and carry out GSD; where,

$$\hat{\lambda}_A^* = \bar{X}_{A_2} = \frac{1}{50}\sum_{j=1}^{50} X_{B_1}^{(j)} \text{ and } \hat{\lambda}_B^* = \bar{X}_{B_2} = \frac{1}{50}\sum_{j=1}^{50} X_{B_2}^{(j)}$$

ASN table for Entry Stage Adaptive Group Sequential Design

	lambda_B	ASN_H0	ASN_H1
1	2.0	289.23	283.74
2	2.2	288.14	262.65
3	2.4	278.54	223.19
4	2.6	251.82	175.71
5	2.8	218.46	136.37
6	3.0	199.60	112.70
7	3.2	195.02	102.83
8	3.4	195.02	100.67
9	3.6	195.02	100.10
10	3.8	195.02	100.04
11	4.0	195.02	100.02

Comparison of ASN between Non-Adaptive and Entry Stage Adaptive GSD For different λ_B



Fully Adaptive Group Sequential Design

- In such designs, allocation probabilities are adjusted at each interim stage based on the accumulating evidence.

Fully Adaptive Group Sequential Design

- In such designs, allocation probabilities are adjusted at each interim stage based on the accumulating evidence.
- Specifically: As the trial progresses and evidence accumulates in favor of Treatment A, the randomization scheme is adaptively modified to assign more patients to Treatment A and fewer to Treatment B.

Fully Adaptive Group Sequential Design

- In such designs, allocation probabilities are adjusted at each interim stage based on the accumulating evidence.
- Specifically: As the trial progresses and evidence accumulates in favor of Treatment A, the randomization scheme is adaptively modified to assign more patients to Treatment A and fewer to Treatment B.
- This ensures that more patients receive the better treatment, enhancing the ethical integrity of the trial without sacrificing statistical rigor.

Fully Adaptive Group Sequential Design

- In such designs, allocation probabilities are adjusted at each interim stage based on the accumulating evidence.
- Specifically: As the trial progresses and evidence accumulates in favor of Treatment A, the randomization scheme is adaptively modified to assign more patients to Treatment A and fewer to Treatment B.
- This ensures that more patients receive the better treatment, enhancing the ethical integrity of the trial without sacrificing statistical rigor.
- Here, we have discussed two methods of allocating treatments in fully adaptive group sequential design.

Adaptive Allocation (R_A)

- In our scenario, the alternative hypothesis propose treatment A is superior than the treatment B.

Adaptive Allocation (R_A)

- In our scenario, the alternative hypothesis propose treatment A is superior than the treatment B.
- Then for ethical purpose, when we get stronger evidence against the null hypothesis, we wish to allocate treatment A to the $i^{th}(i = 1, ..., n_k; k = 1, 2, ..., K)$ patient with higher probability.

Adaptive Allocation (R_A)

- In our scenario, the alternative hypothesis propose treatment A is superior than the treatment B.
- Then for ethical purpose, when we get stronger evidence against the null hypothesis, we wish to allocate treatment A to the $i^{th}(i = 1, ..., n_k; k = 1, 2, ..., K)$ patient with higher probability.
- Let, R_A be the probability that a randomly entered(i^{th}) patient will receive treatment A

Adaptive Allocation (R_A)

- In our scenario, the alternative hypothesis propose treatment A is superior than the treatment B.
- Then for ethical purpose, when we get stronger evidence against the null hypothesis, we wish to allocate treatment A to the $i^{th}(i = 1, ..., n_k; k = 1, 2, ..., K)$ patient with higher probability.
- Let, R_A be the probability that a randomly entered(i^{th}) patient will receive treatment A
- We propose,

$$R_A = \frac{\lambda_B}{\lambda_A + \lambda_B}$$

Adaptive Allocation (R_A)

- In our scenario, the alternative hypothesis propose treatment A is superior than the treatment B.
- Then for ethical purpose, when we get stronger evidence against the null hypothesis, we wish to allocate treatment A to the $i^{th}(i = 1, ..., n_k; k = 1, 2, ..., K)$ patient with higher probability.
- Let, R_A be the probability that a randomly entered(i^{th}) patient will receive treatment A
- We propose,

$$R_A = \frac{\lambda_B}{\lambda_A + \lambda_B}$$

- where, $\lambda_A < \lambda_B \Rightarrow$ treatment A is better than treatment B

Allocation Procedure

- We generate few samples (say, 4)
  $X_{A_k}^{[4]} = (X_{A_k}^{(1)}, X_{A_k}^{(2)}, X_{A_k}^{(3)}, X_{A_k}^{(4)})$ from $poisson(\lambda_{A_k})$ and same number of samples $X_{B_k}^{[4]}$ from $poisson(\lambda_{B_k})$; $k = 1, 2, ..., K$

Allocation Procedure

- We generate few samples (say, 4) $X_{A_k}^{[4]} = (X_{A_k}^{(1)}, X_{A_k}^{(2)}, X_{A_k}^{(3)}, X_{A_k}^{(4)})$ from $poisson(\lambda_{A_k})$ and same number of samples $X_{B_k}^{[4]}$ from $poisson(\lambda_{B_k})$; $k = 1, 2, ..., K$
- We draw a random number say r_{i_k} $(i = 9, ..., n_k; k = 1, 2, , , , K)$ from 0 to 1 (i.e. we generate a sample from $Uniform(0, 1)$)

Allocation Procedure

- We generate few samples (say, 4) $X_{A_k}^{[4]} = (X_{A_k}^{(1)}, X_{A_k}^{(2)}, X_{A_k}^{(3)}, X_{A_k}^{(4)})$ from $poisson(\lambda_{A_k})$ and same number of samples $X_{B_k}^{[4]}$ from $poisson(\lambda_{B_k})$; $k = 1, 2, ..., K$
- We draw a random number say r_{i_k} $(i = 9, ..., n_k; k = 1, 2, , , , K)$ from 0 to 1 (i.e. we generate a sample from $Uniform(0, 1)$)
- Then, if $r_{i_k} \leq R_{A_k}^{(i-1)}$, we draw $X_{A_k}^{(i)}$ from $poisson(\lambda_{A_k})$; $i = 9, ..., n_k$; $k = 1, 2, ..., K$

Allocation Procedure

- We generate few samples (say, 4) $X_{A_k}^{[4]} = (X_{A_k}^{(1)}, X_{A_k}^{(2)}, X_{A_k}^{(3)}, X_{A_k}^{(4)})$ from $poisson(\lambda_{A_k})$ and same number of samples $X_{B_k}^{[4]}$ from $poisson(\lambda_{B_k})$; $k = 1, 2, ..., K$
- We draw a random number say r_{i_k} $(i = 9, ..., n_k; k = 1, 2, , , , K)$ from 0 to 1 (i.e. we generate a sample from $Uniform(0, 1)$)
- Then, if $r_{i_k} \leq R_{A_k}^{(i-1)}$, we draw $X_{A_k}^{(i)}$ from $poisson(\lambda_{A_k})$; $i = 9, ..., n_k$; $k = 1, 2, ..., K$
- otherwise, we draw $X_{B_k}^{(i)}$ from $poisson(\lambda_{B_k})$; $i = 9, ..., n_k$; $k = 1, 2, ..., K$

ASN Table for Fully Adaptive GSD under Adaptive Allocation (R_A)

	lambda_B	ASN_H0	ASN_H1	RA	Prop_A	Prop_A_SE
1	2.0	289.1	282.9	0.5063556	0.5053500	0.1340708
2	2.2	288.9	277.2	0.5212328	0.5203600	0.1304991
3	2.4	289.1	276.9	0.5356348	0.5329733	0.1296204
4	2.6	288.8	269.6	0.5501091	0.5482433	0.1368455
5	2.8	288.2	269.4	0.5658189	0.5615400	0.1271016
6	3.0	288.5	262.1	0.5774070	0.5726267	0.1283543
7	3.2	287.3	255.0	0.5907565	0.5841400	0.1251406
8	3.4	286.4	250.6	0.6090878	0.6012033	0.1220593
9	3.6	288.2	237.5	0.6184434	0.6081033	0.1281298
10	3.8	282.7	233.6	0.6287941	0.6201900	0.1185039
11	4.0	284.2	214.3	0.6432668	0.6331767	0.1211721

Adaptive Allocation (R_A^*)

- In the response adaptive allocation as described in the previous part, we can clearly see the RA values and the proportion of patients receiving treatment A ($Prop(A)$) is increasing as we move away from the null.

Adaptive Allocation (R_A^*)

- In the response adaptive allocation as described in the previous part, we can clearly see the RA values and the proportion of patients receiving treatment A ($Prop(A)$) is increasing as we move away from the null.
- But, we are still interested in some better choices of R_A , so that we can have more increase in the $Prop(A)$.

Adaptive Allocation (R_A^*)

- In the response adaptive allocation as described in the previous part, we can clearly see the RA values and the proportion of patients receiving treatment A ($Prop(A)$) is increasing as we move away from the null.
- But, we are still interested in some better choices of R_A , so that we can have more increase in the $Prop(A)$.
- So, we introduce another version of R_A (say, R_A^*); which can be defined as follows,

$$R_A^* = P(X_A < X_B) + (\frac{1}{2}) \times P(X_A = X_B)$$

Adaptive Allocation (R_A^*)

- In the response adaptive allocation as described in the previous part, we can clearly see the RA values and the proportion of patients receiving treatment A ($Prop(A)$) is increasing as we move away from the null.
- But, we are still interested in some better choices of R_A , so that we can have more increase in the $Prop(A)$.
- So, we introduce another version of R_A (say, R_A^*); which can be defined as follows,

$$R_A^* = P(X_A < X_B) + (\frac{1}{2}) \times P(X_A = X_B)$$

- Here, the first term $P(X_A < X_B)$ allocates positive probability when the treatment A is perform better than the treatment B; and the second term $(\frac{1}{2}) \times P(X_A = X_B)$ allocates equal probabilities when treatment A and treatment B performs similar.

Allocation Procedure

- we generate few samples (say, 4) $X_{A_k}^{[4]}$ from $poisson(\lambda_{A_k})$ and same number of samples $X_{B_k}^{[4]}$ from $poisson(\lambda_{B_k})$; $k = 1, 2, ..., K$

Allocation Procedure

- we generate few samples (say, 4) $X_{A_k}^{[4]}$ from $poisson(\lambda_{A_k})$ and same number of samples $X_{B_k}^{[4]}$ from $poisson(\lambda_{B_k})$; $k = 1, 2, ..., K$
- We draw a random number say r_{i_k} $(i = 9, ..., n_k; k = 1, 2, , , , K)$ from 0 to 1 (i.e. we generate a sample from $Uniform(0, 1)$)

Allocation Procedure

- we generate few samples (say, 4) $X_{A_k}^{[4]}$ from $poisson(\lambda_{A_k})$ and same number of samples $X_{B_k}^{[4]}$ from $poisson(\lambda_{B_k})$; $k = 1, 2, ..., K$
- We draw a random number say r_{i_k} $(i = 9, ..., n_k; k = 1, 2, , , , K)$ from 0 to 1 (i.e. we generate a sample from $Uniform(0, 1)$)
- The R_A^* is to be calculated empirically.

Allocation Procedure

- we generate few samples (say, 4) $X_{A_k}^{[4]}$ from $poisson(\lambda_{A_k})$ and same number of samples $X_{B_k}^{[4]}$ from $poisson(\lambda_{B_k})$; $k = 1, 2, ..., K$
- We draw a random number say r_{i_k} $(i = 9, ..., n_k; k = 1, 2, , , , K)$ from 0 to 1 (i.e. we generate a sample from $Uniform(0, 1)$)
- The R_A^* is to be calculated empirically.
- We simulate 50 samples from $poisson(\lambda_{A_k})$ and 50 samples from $poisson(\lambda_{B_k})$.

Allocation Procedure

- we generate few samples (say, 4) $X_{A_k}^{[4]}$ from $poisson(\lambda_{A_k})$ and same number of samples $X_{B_k}^{[4]}$ from $poisson(\lambda_{B_k})$; $k = 1, 2, ..., K$
- We draw a random number say r_{i_k} $(i = 9, ..., n_k; k = 1, 2, , , , K)$ from 0 to 1 (i.e. we generate a sample from $Uniform(0, 1)$)
- The R_A^* is to be calculated empirically.
- We simulate 50 samples from $poisson(\lambda_{A_k})$ and 50 samples from $poisson(\lambda_{B_k})$.
- So, we get total 2500 pair of observations $(X_{A_k}^{(i)}, X_{B_k}^{(j)})$.

Allocation Procedure

- Then, we can calculate,

$$P(X_{A_k} < X_{B_k}) = \frac{\text{number of } X_{A_k}^{(i)} < X_{B_k}^{(j)}}{2500} \; ; i, j = 1(1)50; \; k = 1(1)K$$

and

$$P(X_{A_k} = X_{B_k}) = \frac{\text{number of } X_{A_k}^{(i)} = X_{B_k}^{(j)}}{2500} \; ; i, j = 1(1)50; \; k = 1(1)K$$

Allocation Procedure

- Then, we can calculate,

$$P(X_{A_k} < X_{B_k}) = \frac{\text{number of } X_{A_k}^{(i)} < X_{B_k}^{(j)}}{2500} \; ; i, j = 1(1)50; \; k = 1(1)K$$

and

$$P(X_{A_k} = X_{B_k}) = \frac{\text{number of } X_{A_k}^{(i)} = X_{B_k}^{(j)}}{2500} \; ; i, j = 1(1)50; \; k = 1(1)K$$

- Then, if $r_{i_k} \leq R_{A_k}^{*(i-1)}$, we draw $X_{A_k}^{(i)}$ from $poisson(\lambda_{A_k})$; $i = 9, ..., n_k$; $k = 1, 2, ..., K$

Allocation Procedure

- Then, we can calculate,

$$P(X_{A_k} < X_{B_k}) = \frac{\text{number of } X_{A_k}^{(i)} < X_{B_k}^{(j)}}{2500} \; ; i, j = 1(1)50; \; k = 1(1)K$$

and

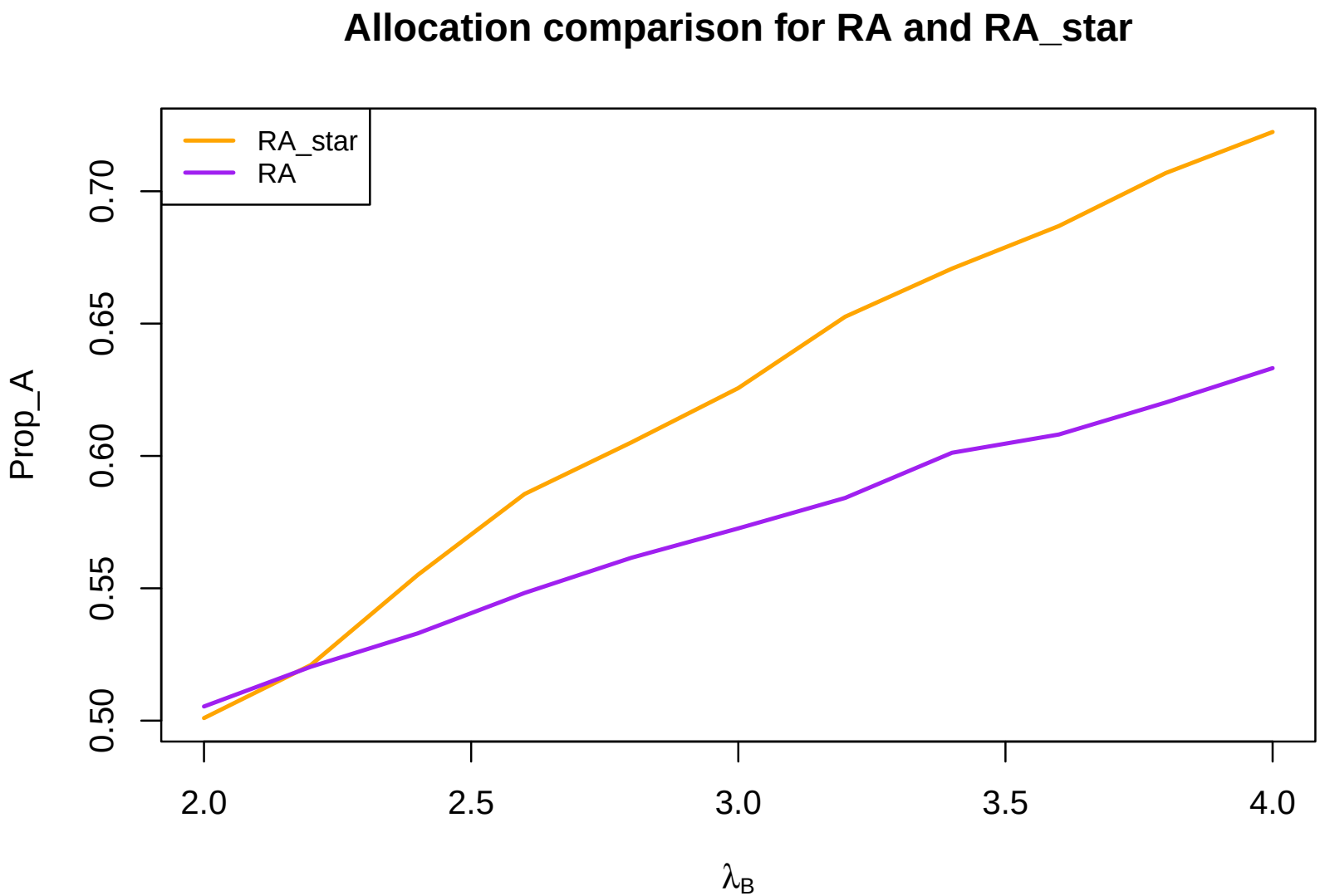
$$P(X_{A_k} = X_{B_k}) = \frac{\text{number of } X_{A_k}^{(i)} = X_{B_k}^{(j)}}{2500} \; ; i, j = 1(1)50; \; k = 1(1)K$$

- Then, if $r_{i_k} \leq R_{A_k}^{*(i-1)}$, we draw $X_{A_k}^{(i)}$ from $poisson(\lambda_{A_k})$; $i = 9, ..., n_k \; ; k = 1, 2, ..., K$
- otherwise, we draw $X_{B_k}^{(i)}$ from $poisson(\lambda_{B_k})$; $i = 9, ..., n_k \; ; k = 1, 2, ..., K$

ASN Table for Fully Adaptive GSD under Adaptive Allocation (R_A^*)

	lambda_B	ASN_H0	ASN_H1	RA_Star	Prop_A	Prop_A_SE
1	2.0	288.7	282.0	0.5005146	0.5009600	0.2144455
2	2.2	288.7	279.0	0.5221844	0.5210067	0.2098777
3	2.4	288.8	275.3	0.5566484	0.5550300	0.2162207
4	2.6	287.9	276.7	0.5938794	0.5856133	0.2052927
5	2.8	288.3	266.0	0.6148290	0.6051300	0.2031611
6	3.0	287.6	260.7	0.6385272	0.6256400	0.1997961
7	3.2	286.6	256.6	0.6620340	0.6525900	0.1978750
8	3.4	284.3	256.9	0.6886046	0.6707867	0.1896226
9	3.6	284.2	253.7	0.7017788	0.6868700	0.1856287
10	3.8	283.5	237.2	0.7242718	0.7068800	0.1843832
11	4.0	276.5	230.0	0.7403032	0.7224000	0.1797703

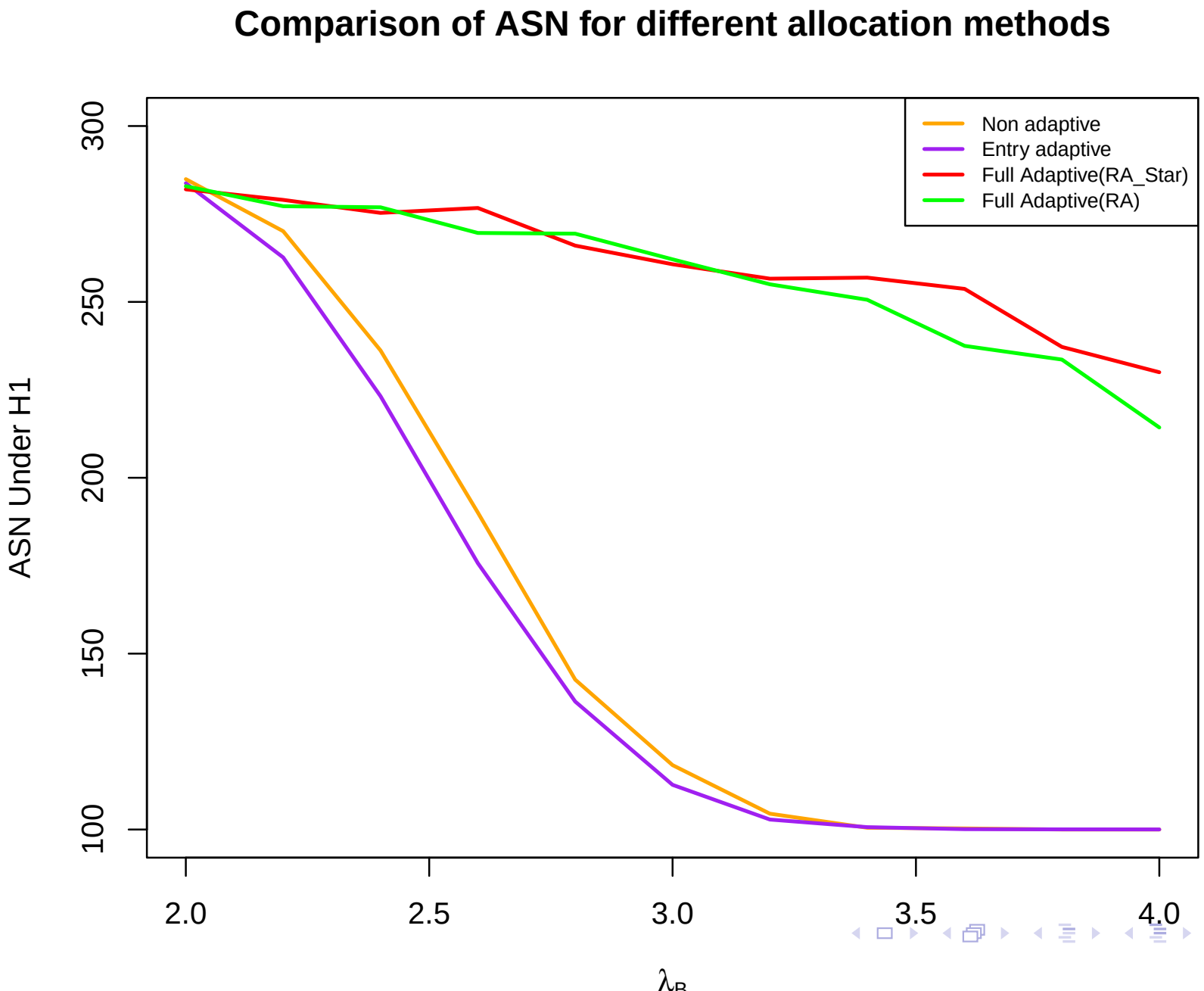
Allocation comparison for R_A and R_A^*



Comparison of ASN for all methods

	Lambda_B	Non Ada	Entry Ada	RA	RA_star
[1,]	2.0	284.9	283.74	282.9	282.0
[2,]	2.2	270.1	262.65	277.2	279.0
[3,]	2.4	236.2	223.19	276.9	275.3
[4,]	2.6	190.1	175.71	269.6	276.7
[5,]	2.8	142.6	136.37	269.4	266.0
[6,]	3.0	118.3	112.70	262.1	260.7
[7,]	3.2	104.5	102.83	255.0	256.6
[8,]	3.4	100.5	100.67	250.6	256.9
[9,]	3.6	100.3	100.10	237.5	253.7
[10,]	3.8	100.0	100.04	233.6	237.2
[11,]	4.0	100.0	100.02	214.3	230.0

Comparison of ASN for all methods



Group Sequential Design Under Bivariate Setup

- **Motivation:** Many clinical trials involve multiple correlated count outcomes (e.g., disease events and healthcare utilization), making univariate analysis insufficient for capturing joint treatment effects.

Group Sequential Design Under Bivariate Setup

- **Motivation:** Many clinical trials involve multiple correlated count outcomes (e.g., disease events and healthcare utilization), making univariate analysis insufficient for capturing joint treatment effects.
- **Need for Joint Modeling:** Correlated outcomes often share underlying risk factors (e.g., disease severity), and joint analysis improves efficiency and provides more clinically relevant insights.

Group Sequential Design Under Bivariate Setup

- **Motivation:** Many clinical trials involve multiple correlated count outcomes (e.g., disease events and healthcare utilization), making univariate analysis insufficient for capturing joint treatment effects.
- **Need for Joint Modeling:** Correlated outcomes often share underlying risk factors (e.g., disease severity), and joint analysis improves efficiency and provides more clinically relevant insights.
- **Bivariate GSD Advantage:** Allows interim evaluations and early stopping based on joint outcomes, maintaining both statistical rigor and ethical patient treatment allocation.

Group Sequential Design Under Bivariate Setup

- **Motivation:** Many clinical trials involve multiple correlated count outcomes (e.g., disease events and healthcare utilization), making univariate analysis insufficient for capturing joint treatment effects.
- **Need for Joint Modeling:** Correlated outcomes often share underlying risk factors (e.g., disease severity), and joint analysis improves efficiency and provides more clinically relevant insights.
- **Bivariate GSD Advantage:** Allows interim evaluations and early stopping based on joint outcomes, maintaining both statistical rigor and ethical patient treatment allocation.
- **Examples:** Asthma attacks & inhaler use, seizures & ER visits, infections & antibiotic prescriptions, ulcers healed & follow-up visits — all naturally modeled as bivariate counts.

Objective

- Let, for treatment A, $U_A \sim Poisson(\lambda_A)$, $V_A \sim Poisson(\theta_A)$ and $W_A \sim Poisson(\phi_A)$ and U_A, V_A and W_A are independently distributed.

Objective

- Let, for treatment A, $U_A \sim Poisson(\lambda_A)$, $V_A \sim Poisson(\theta_A)$ and $W_A \sim Poisson(\phi_A)$ and U_A, V_A and W_A are independently distributed.
- Then,

$$X_A = U_A + W_A \overset{marginally}{\sim} Poisson(\lambda_A + \phi_A)$$

$$Y_A = V_A + W_A \overset{marginally}{\sim} Poisson(\theta_A + \phi_A)$$

Objective

- Let, for treatment A, $U_A \sim Poisson(\lambda_A)$, $V_A \sim Poisson(\theta_A)$ and $W_A \sim Poisson(\phi_A)$ and U_A, V_A and W_A are independently distributed.
- Then,

$$X_A = U_A + W_A \overset{marginally}{\sim} Poisson(\lambda_A + \phi_A)$$

$$Y_A = V_A + W_A \overset{marginally}{\sim} Poisson(\theta_A + \phi_A)$$

- Then, jointly, (X_A, Y_A) follows a probability distribution called $BVPoisson(\lambda_A, \theta_A, \phi_A)$ with pmf,

$$e^{-(\lambda_A+\theta_A+\phi_A)} \lambda_A^{x_A} \theta_A^{y_A} \sum_{r=0}^{min\{x_A, y_A\}} \left(\frac{\phi_A}{\lambda_A \theta_A}\right)^r \frac{1}{(x_A - r)!(y_A - r)! r!}$$

Objective

- Here, $Cov(X_A, Y_A) = \phi_A$

Objective

- Here, $Cov(X_A, Y_A) = \phi_A$
- We are interested to test,

$$H_0 : B \succeq A \quad \text{vs} \quad H_1 : B \prec A$$

$$\text{i.e. } H_0 : \lambda_A + \phi_A \geq \lambda_B + \phi_B \quad \text{vs} \quad H_1 : \lambda_A + \phi_A < \lambda_B + \phi_B$$

$$\text{or, } \theta_A + \phi_A \geq \theta_B + \phi_B \qquad \text{and, } \theta_A + \phi_A < \theta_B + \phi_B$$

Test Statistic

- Let, $Z_1 = \bar{X}_A^{2/3} - \bar{X}_B^{2/3}$ and $Z_2 = \bar{Y}_A^{2/3} - \bar{Y}_B^{2/3}$

Test Statistic

- Let, $Z_1 = \bar{X}_A^{2/3} - \bar{X}_B^{2/3}$ and $Z_2 = \bar{Y}_A^{2/3} - \bar{Y}_B^{2/3}$
- Then, we define three statistics which are given by,

Test Statistic

- Let, $Z_1 = \bar{X}_A^{2/3} - \bar{X}_B^{2/3}$ and $Z_2 = \bar{Y}_A^{2/3} - \bar{Y}_B^{2/3}$
- Then, we define three statistics which are given by,
-

$$T^{(1)} = min\{Z_1, Z_2\}$$

Test Statistic

- Let, $Z_1 = \bar{X}_A^{2/3} - \bar{X}_B^{2/3}$ and $Z_2 = \bar{Y}_A^{2/3} - \bar{Y}_B^{2/3}$
- Then, we define three statistics which are given by,
- $$T^{(1)} = min\{Z_1, Z_2\}$$
- $$T^{(2)} = max\{Z_1, Z_2\}$$

Test Statistic

- Let, $Z_1 = \bar{X}_A^{2/3} - \bar{X}_B^{2/3}$ and $Z_2 = \bar{Y}_A^{2/3} - \bar{Y}_B^{2/3}$
- Then, we define three statistics which are given by,
- $$T^{(1)} = min\{Z_1, Z_2\}$$
- $$T^{(2)} = max\{Z_1, Z_2\}$$
- $$T^{(3)} = \frac{T^{(1)} + T^{(2)}}{2}$$

Test Procedure

- The sequential test procedure for k^{th} group can be written as,

Test Procedure

- The sequential test procedure for k^{th} group can be written as,
-

(i) if, $T_k^{(s)} < a_k \Rightarrow$ We reject H_0 i.e. we accept H_1

(ii) if, $T_k^{(s)} > b_k \Rightarrow$ We accept H_0

(ii) if, $a_k \leq T_k^{(s)} \leq b_k \Rightarrow$ go for next group

Test Procedure

- The sequential test procedure for k^{th} group can be written as,
-

(i) if, $T_k^{(s)} < a_k \Rightarrow$ We reject H_0 i.e. we accept H_1

(ii) if, $T_k^{(s)} > b_k \Rightarrow$ We accept H_0

(ii) if, $a_k \leq T_k^{(s)} \leq b_k \Rightarrow$ go for next group

- We calculate the boundary points and the ASN similarly as univariate setup.

Justification of The Statistic

- Here, we have defined the statistic $T^{(2)}$ in such a way that it will prioritize the alternative hypothesis more since when the maximum of Z_1 and Z_2 will be small, then the alternative is accepted (i.e., $max\{Z_1, Z_2\} < a_1 \Longleftarrow Z_1 < a_1, Z_2 < a_1$).
- Unlike $T^{(2)}$, the other test statistic $T^{(1)}$ will prioritize the null hypothesis more since when the minimum of Z_1 and Z_2 will be large enough, then the null hypothesis will be accepted (i.e., $min\{Z_1, Z_2\} > b_1^* \Longleftarrow W_1 > b_1^*, W_2 > b_1^*$).
- The statistic $T^{(3)}$ should perform equally good for null and alternative, as we have taken the average of the other two statistics.

Computation

- We fix the sample of each group $n_1 = n_2 = n_3 = 100$. So, $N = 300$.

Computation

- We fix the sample of each group $n_1 = n_2 = n_3 = 100$. So, $N = 300$.
- We allocate equal number of treatment A and treatment B to the patients, i.e. $m_{A_k} = m_{B_k} = 50 \; ; \; k = 1, 2, 3$.

Computation

- We fix the sample of each group $n_1 = n_2 = n_3 = 100$. So, $N = 300$.
- We allocate equal number of treatment A and treatment B to the patients, i.e. $m_{A_k} = m_{B_k} = 50 \; ; \; k = 1, 2, 3$.
- As, directly simulation from bivariate poisson is difficult, so we simulate 50 samples each from $poisson(\lambda_A)$, $poisson(\lambda_B)$, $poisson(\theta_A)$ and $poisson(\theta_B)$ seperately for the first interim and carry out the procedure to find the boundary points.

Computation

- We fix the sample of each group $n_1 = n_2 = n_3 = 100$. So, $N = 300$.
- We allocate equal number of treatment A and treatment B to the patients, i.e. $m_{A_k} = m_{B_k} = 50\ ;\ k = 1, 2, 3$.
- As, directly simulation from bivariate poisson is difficult, so we simulate 50 samples each from $poisson(\lambda_A)$, $poisson(\lambda_B)$, $poisson(\theta_A)$ and $poisson(\theta_B)$ seperately for the first interim and carry out the procedure to find the boundary points.
- Then, in second and third stage, we simulate data from $poisson(\hat{\lambda}_A)$, $poisson(\hat{\lambda}_B)$, $poisson(\hat{\theta}_A)$ and $poisson(\hat{\theta}_B)$; where $\hat{\lambda}_A = \bar{X}_{A_1}$ and $\hat{\lambda}_B = \bar{X}_{B_1}$.

Computation

- We fix the sample of each group $n_1 = n_2 = n_3 = 100$. So, $N = 300$.
- We allocate equal number of treatment A and treatment B to the patients, i.e. $m_{A_k} = m_{B_k} = 50\ ;\ k = 1, 2, 3$.
- As, directly simulation from bivariate poisson is difficult, so we simulate 50 samples each from $poisson(\lambda_A)$, $poisson(\lambda_B)$, $poisson(\theta_A)$ and $poisson(\theta_B)$ seperately for the first interim and carry out the procedure to find the boundary points.
- Then, in second and third stage, we simulate data from $poisson(\hat{\lambda}_A)$, $poisson(\hat{\lambda}_B)$, $poisson(\hat{\theta}_A)$ and $poisson(\hat{\theta}_B)$; where $\hat{\lambda}_A = \bar{X}_{A_1}$ and $\hat{\lambda}_B = \bar{X}_{B_1}$.
- We fix the nuisance parameter $\phi_A = \phi_B = \phi$ for our computational purposes.

ASN for Different $\lambda's$ and θ's (for $T^{(1)}$)

	lambda_B	theta_B	ASN_H0	ASN_H1
1	2.0	2.5	290.9	291.4
2	2.2	2.7	272.7	274.2
3	2.4	2.9	232.4	236.4
4	2.6	3.1	171.2	178.9
5	2.8	3.3	127.0	131.0
6	3.0	3.5	105.9	106.1
7	3.2	3.7	100.0	100.0
8	3.4	3.9	100.0	100.0
9	3.6	4.1	100.0	100.0
10	3.8	4.3	100.0	100.0
11	4.0	4.5	100.0	100.0

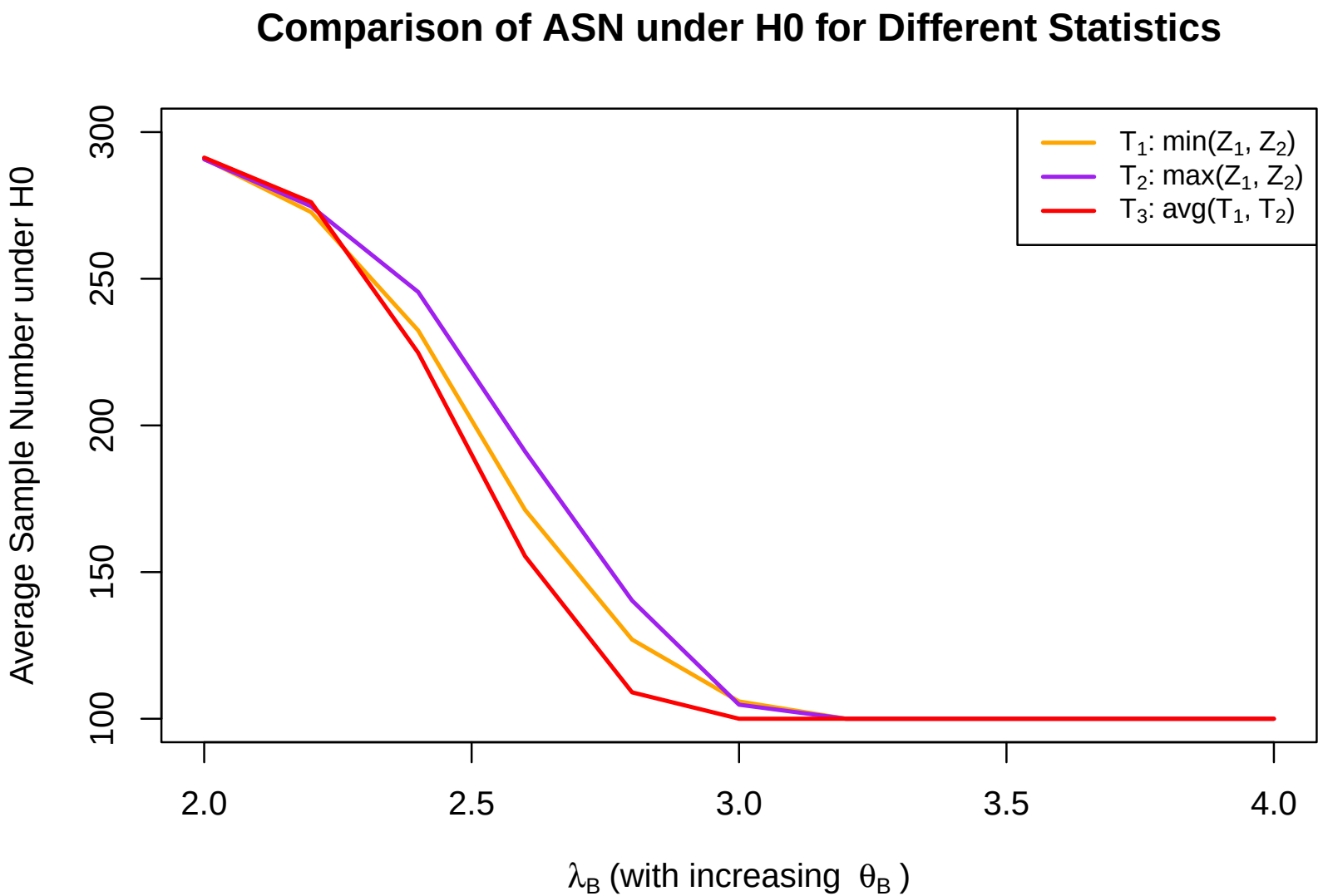
ASN for Different λ's and θ's (for $T^{(2)}$)

	lambda_B	theta_B	ASN_H0	ASN_H1
1	2.0	2.5	290.7	288.5
2	2.2	2.7	274.7	263.7
3	2.4	2.9	245.5	212.8
4	2.6	3.1	191.1	162.8
5	2.8	3.3	140.3	120.7
6	3.0	3.5	104.8	103.4
7	3.2	3.7	100.0	100.0
8	3.4	3.9	100.0	100.0
9	3.6	4.1	100.0	100.0
10	3.8	4.3	100.0	100.0
11	4.0	4.5	100.0	100.0

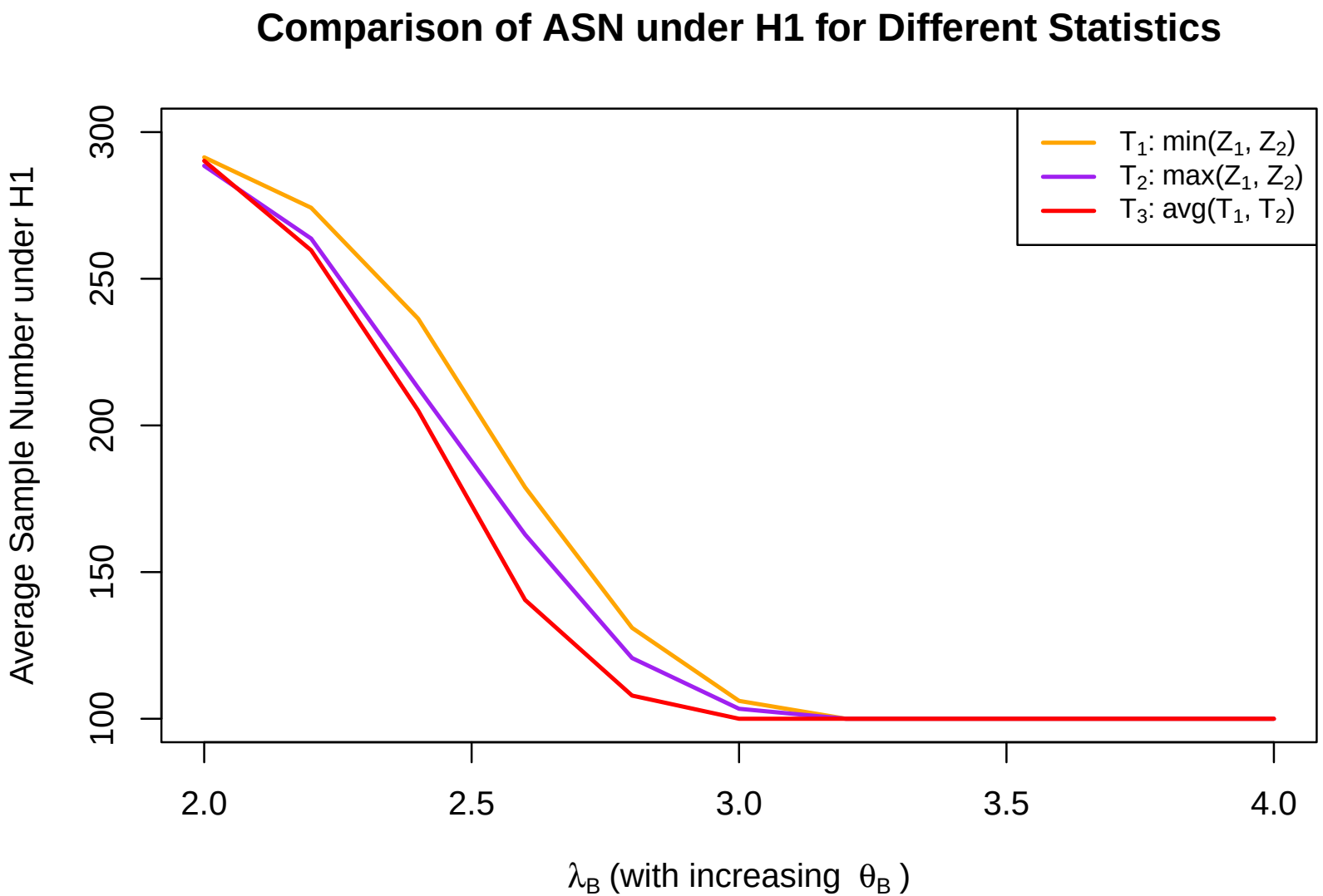
ASN for Different λ's and θ's (for $T^{(3)}$)

	lambda_B	theta_B	ASN_H0	ASN_H1
1	2.0	2.5	291.3	290.2
2	2.2	2.7	276.1	259.7
3	2.4	2.9	224.8	205.1
4	2.6	3.1	155.4	140.5
5	2.8	3.3	109.0	107.9
6	3.0	3.5	100.0	100.0
7	3.2	3.7	100.0	100.0
8	3.4	3.9	100.0	100.0
9	3.6	4.1	100.0	100.0
10	3.8	4.3	100.0	100.0
11	4.0	4.5	100.0	100.0

ASN Under H_0 for Different statistics



ASN Under H_1 for Different statistics



Different Choices of Error Spendings

- We fix $\lambda_A = 2, \theta_A = 2.5$. Now, we will find and plot ASN for different choices of the error spending (α_k, β_k) .

Different Choices of Error Spendings

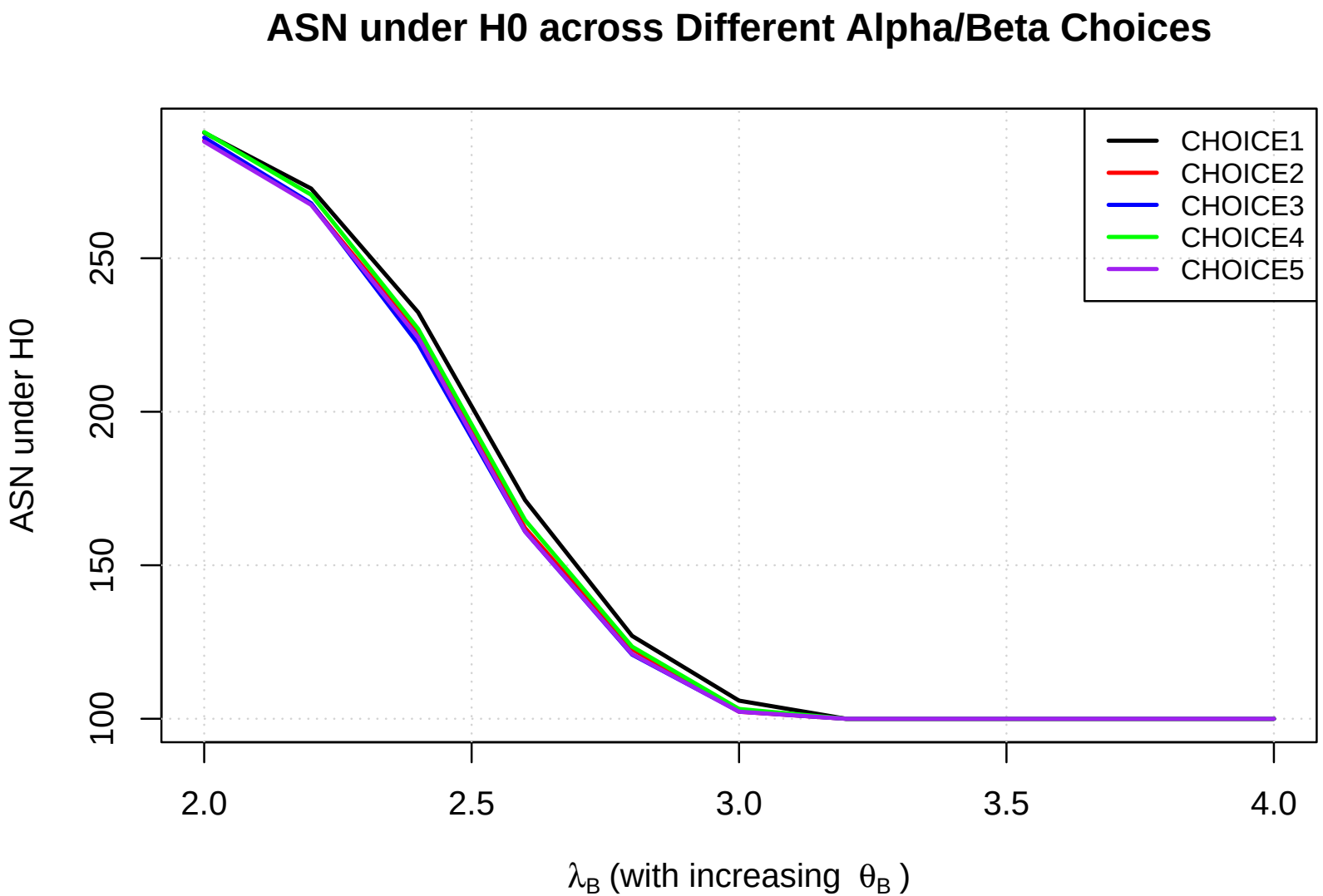
- We fix $\lambda_A = 2, \theta_A = 2.5$. Now, we will find and plot ASN for different choices of the error spending (α_k, β_k) .
- We take the choices of (α, β) as,

Different Choices of Error Spendings

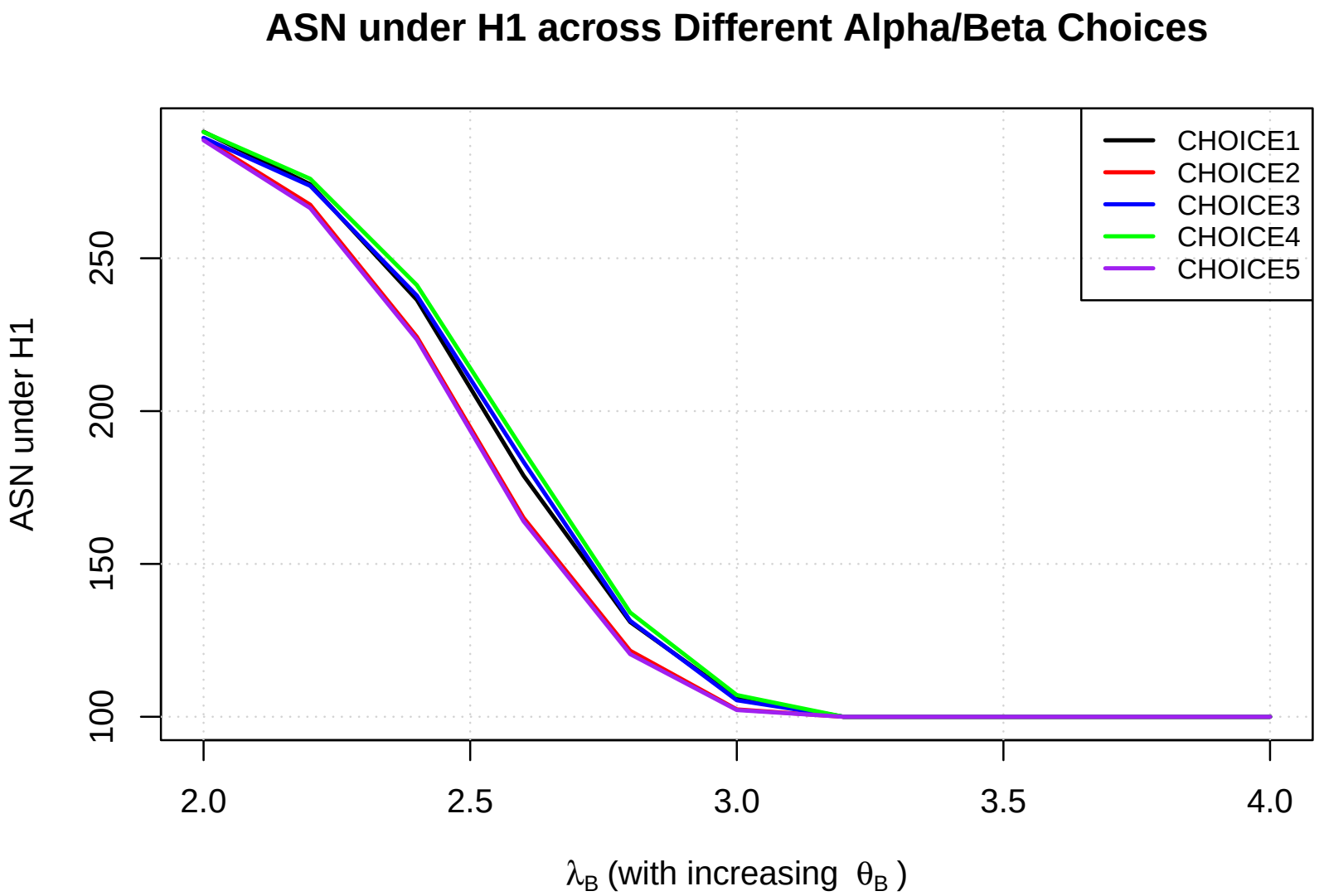
- We fix $\lambda_A = 2, \theta_A = 2.5$. Now, we will find and plot ASN for different choices of the error spending (α_k, β_k) .
- We take the choices of (α, β) as,

Choices	α_1	α_2	α_3	β_1	β	β_3
1	0.02	0.02	0.01	0.015	0.015	0.02
2	0.03	0.01	0.01	0.02	0.02	0.01
3	0.015	0.025	0.01	0.03	0.01	0.01
4	0.015	0.015	0.02	0.025	0.01	0.015
5	0.03	0.015	0.005	0.02	0.025	0.005

ASN Under H_0 for Different (α_k, β_k)



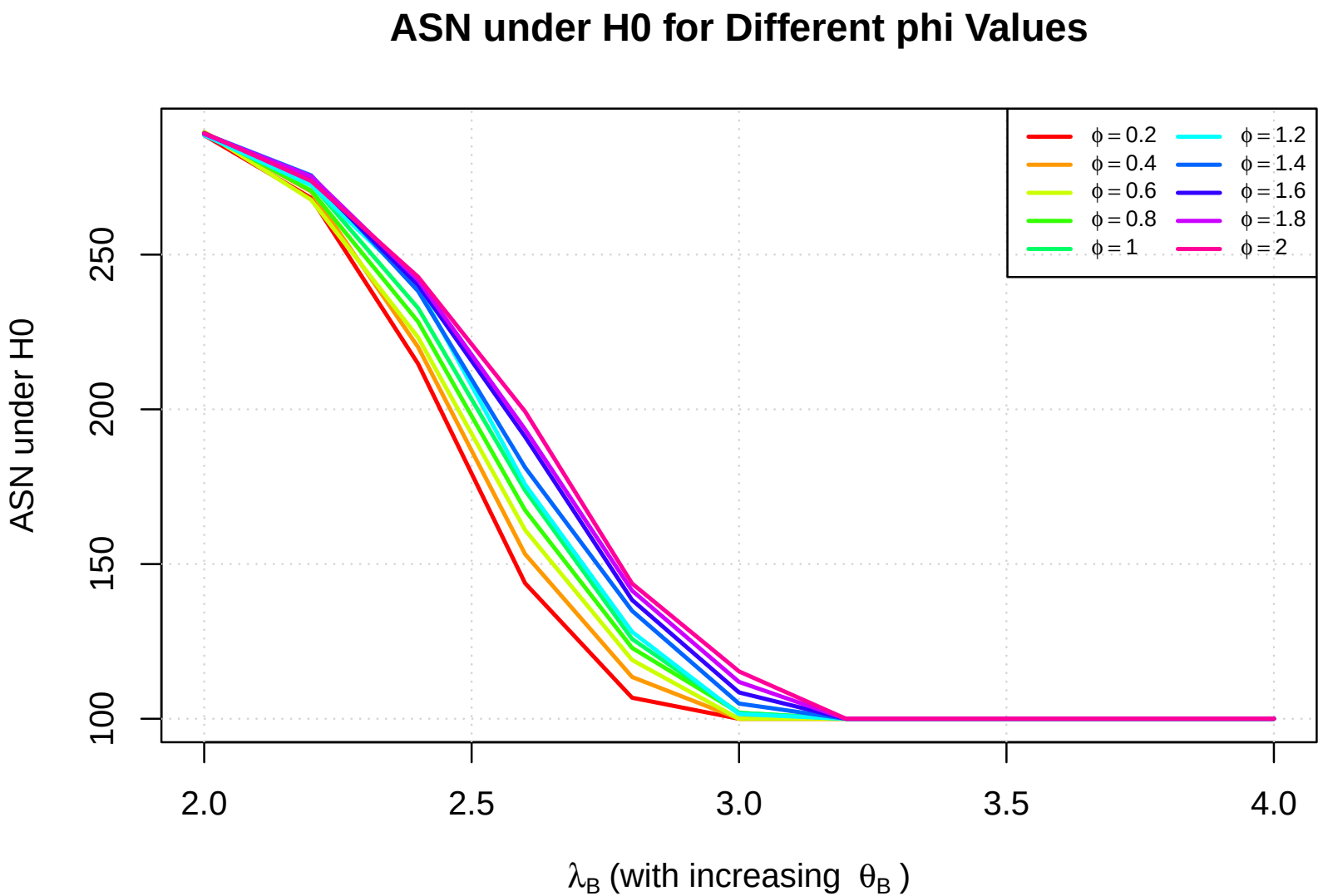
ASN Under H_1 for Different (α_k, β_k)



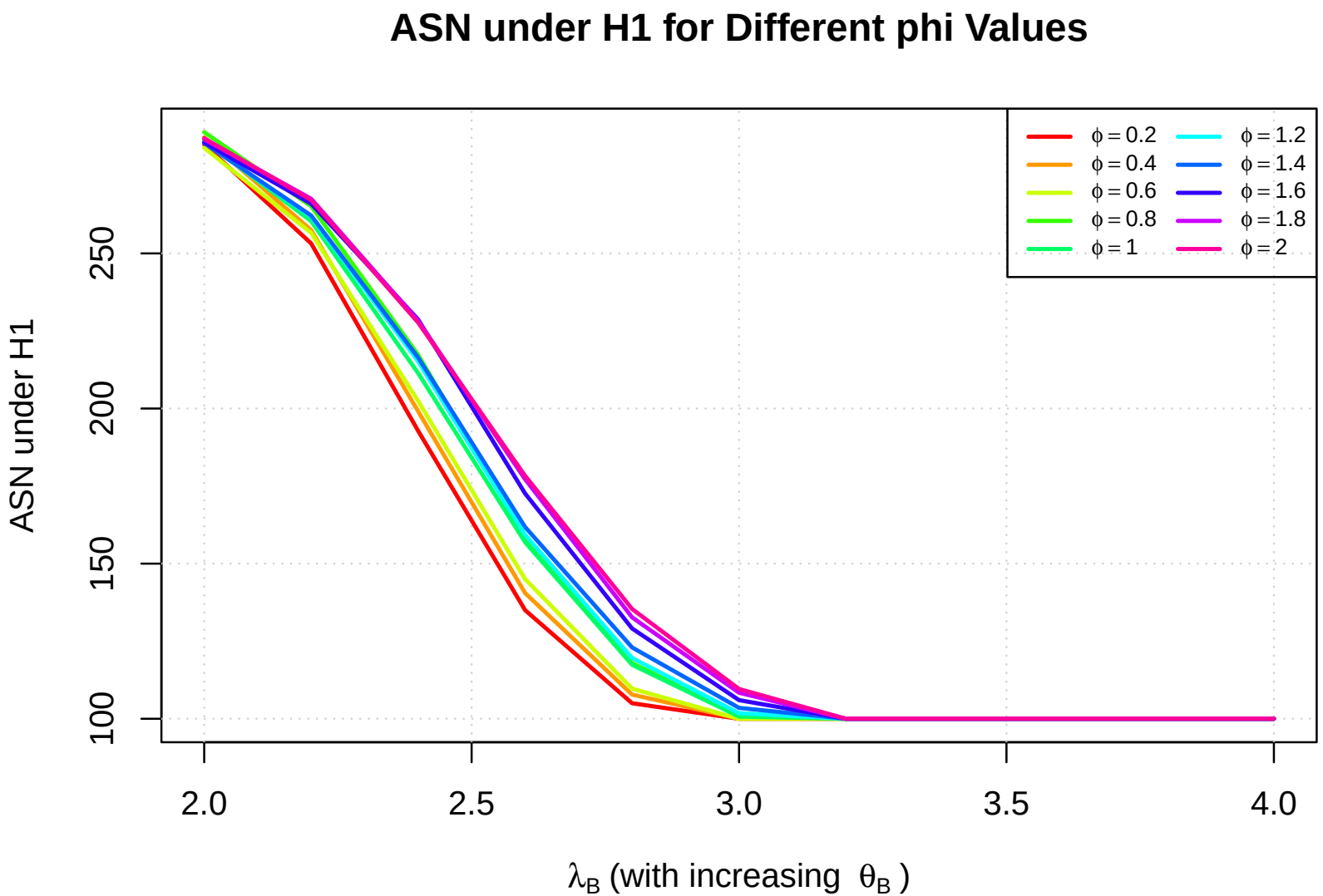
ASN table for $\alpha = (0.03, 0.015, 0.005)$, $\beta = (0.02, 0.025, 0.005)$

	lambda_B	theta_B	ASN_H0	ASN_H1
1	2.0	2.5	287.6	287.5
2	2.2	2.7	268.4	256.0
3	2.4	2.9	214.0	195.5
4	2.6	3.1	146.4	134.1
5	2.8	3.3	104.8	105.3
6	3.0	3.5	100.0	100.0
7	3.2	3.7	100.0	100.0
8	3.4	3.9	100.0	100.0
9	3.6	4.1	100.0	100.0
10	3.8	4.3	100.0	100.0
11	4.0	4.5	100.0	100.0

ASN Under H_0 for Different ϕ



ASN Under H_1 for Different ϕ



Adaptive Group Sequential Designs Under Bivariate Setup

- **Motivation:** Many modern trials involve two correlated count outcomes that must be evaluated jointly for clinical insight and patient safety.

Adaptive Group Sequential Designs Under Bivariate Setup

- **Motivation:** Many modern trials involve two correlated count outcomes that must be evaluated jointly for clinical insight and patient safety.
- **Adaptive Component:** Treatment allocation and model parameters are adaptively updated at each interim stage based on joint evidence from both outcomes.

Adaptive Group Sequential Designs Under Bivariate Setup

- **Motivation:** Many modern trials involve two correlated count outcomes that must be evaluated jointly for clinical insight and patient safety.
- **Adaptive Component:** Treatment allocation and model parameters are adaptively updated at each interim stage based on joint evidence from both outcomes.
- **Sequential Framework:** Interim analyses still maintain statistical rigor, allowing for early stopping based on combined treatment effects.

Adaptive Group Sequential Designs Under Bivariate Setup

- **Motivation:** Many modern trials involve two correlated count outcomes that must be evaluated jointly for clinical insight and patient safety.
- **Adaptive Component:** Treatment allocation and model parameters are adaptively updated at each interim stage based on joint evidence from both outcomes.
- **Sequential Framework:** Interim analyses still maintain statistical rigor, allowing for early stopping based on combined treatment effects.
- **Ethical and Efficient:** Ensures more patients receive the superior treatment across both outcomes, balancing ethical responsibility and inferential accuracy in complex trials.

Entry Stage Adaptive Group Sequential Design

- **In the first stage,** we simulate 50 samples of $\binom{X_{A_1}}{Y_{A_1}}$ from $BVPoisson(\lambda_A,\theta_A,\phi_A)$ and 50 samples of $\binom{X_{B_1}}{Y_{B_1}}$ from $BVPoisson(\lambda_B,\theta_B,\phi_B)$. Then we carry out the sequential test procedure for first stage as described in the group sequential design.

Entry Stage Adaptive Group Sequential Design

- **In the first stage,** we simulate 50 samples of $\binom{X_{A_1}}{Y_{A_1}}$ from $BVPoisson(\lambda_A,\theta_A,\phi_A)$ and 50 samples of $\binom{X_{B_1}}{Y_{B_1}}$ from $BVPoisson(\lambda_B,\theta_B,\phi_B)$. Then we carry out the sequential test procedure for first stage as described in the group sequential design.
- **In second stage,** we simulate 50 samples $\binom{X_{A_2}}{Y_{A_2}}$ from $BVPoisson(\hat{\lambda}_A,\hat{\theta}_A,\phi_A)$ and 50 samples $\binom{X_{B_2}}{Y_{B_2}}$ from $BVPoisson(\hat{\lambda}_B, \hat{\theta}_B, \phi_B)$ where,

$$\begin{pmatrix}\hat{\lambda}_A\\ \hat{\theta}_A\end{pmatrix} = \begin{pmatrix}\bar{X}_{A_1}\\ \bar{Y}_{A_1}\end{pmatrix} \text{ and } \begin{pmatrix}\hat{\lambda}_B\\ \hat{\theta}_B\end{pmatrix} = \begin{pmatrix}\bar{X}_{B_1}\\ \bar{Y}_{B_1}\end{pmatrix}$$

Entry Stage Adaptive Group Sequential Design

- **In the first stage,** we simulate 50 samples of $\binom{X_{A_1}}{Y_{A_1}}$ from $BVPoisson(\lambda_A,\theta_A,\phi_A)$ and 50 samples of $\binom{X_{B_1}}{Y_{B_1}}$ from $BVPoisson(\lambda_B,\theta_B,\phi_B)$. Then we carry out the sequential test procedure for first stage as described in the group sequential design.
- **In second stage,** we simulate 50 samples $\binom{X_{A_2}}{Y_{A_2}}$ from $BVPoisson(\hat{\lambda}_A,\hat{\theta}_A,\phi_A)$ and 50 samples $\binom{X_{B_2}}{Y_{B_2}}$ from $BVPoisson(\hat{\lambda}_B,\hat{\theta}_B,\phi_B)$ where,

$$\begin{pmatrix}\hat{\lambda}_A\\ \hat{\theta}_A\end{pmatrix} = \begin{pmatrix}\bar{X}_{A_1}\\ \bar{Y}_{A_1}\end{pmatrix} \text{ and } \begin{pmatrix}\hat{\lambda}_B\\ \hat{\theta}_B\end{pmatrix} = \begin{pmatrix}\bar{X}_{B_1}\\ \bar{Y}_{B_1}\end{pmatrix}$$

- Then we carry out the group sequential test procedure.

- **In third stage,** we simulate 50 samples $\binom{X_{A_3}}{Y_{A_3}}$ from $BVPoisson(\hat{\lambda^*}_A, \hat{\theta^*}_A, \phi_A)$ and 50 samples of $\binom{X_{B_3}}{Y_{B_3}}$ from $BVPoisson(\hat{\lambda^*}_A, \hat{\theta^*}_A, \phi_B)$; where,

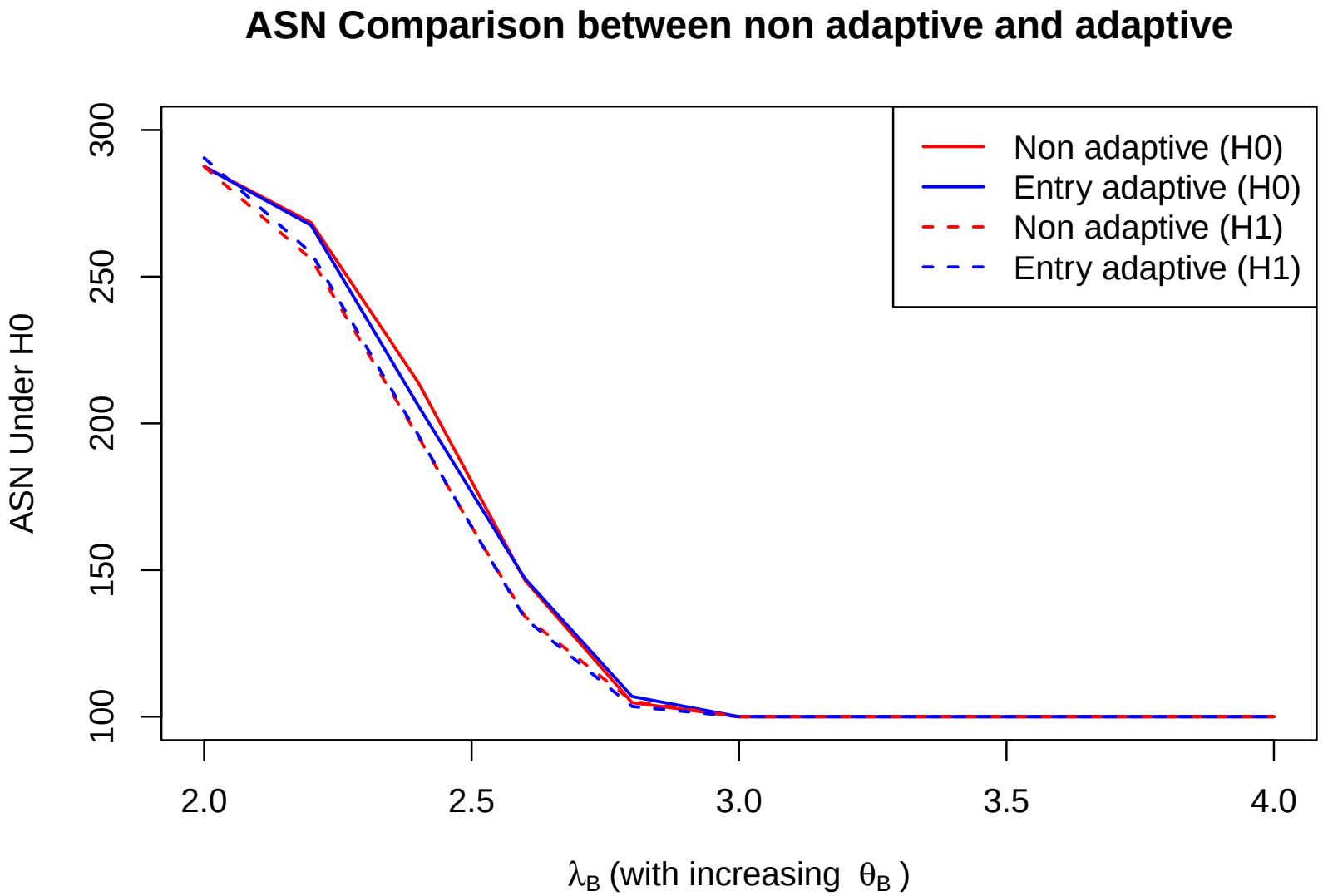
$$\begin{pmatrix} \hat{\lambda^*}_A \\ \hat{\theta^*}_A \end{pmatrix} = \begin{pmatrix} \bar{X}_{A_2} \\ \bar{Y}_{A_2} \end{pmatrix} \text{ and } \begin{pmatrix} \hat{\lambda^*}_B \\ \hat{\theta^*}_B \end{pmatrix} = \begin{pmatrix} \bar{X}_{B_2} \\ \bar{Y}_{B_2} \end{pmatrix}$$

- Then we carry out the group sequential test procedure.

ASN table for Entry Stage Adaptive Group Sequential Design

	lambda_B	theta_B	ASN_H0	ASN_H1
1	2.0	2.5	287.5	290.5
2	2.2	2.7	267.5	258.1
3	2.4	2.9	206.1	196.1
4	2.6	3.1	147.0	133.4
5	2.8	3.3	106.9	103.5
6	3.0	3.5	100.0	100.0
7	3.2	3.7	100.0	100.0
8	3.4	3.9	100.0	100.0
9	3.6	4.1	100.0	100.0
10	3.8	4.3	100.0	100.0
11	4.0	4.5	100.0	100.0

Comparison of ASN between Non-Adaptive GSD and Entry Stage Adaptive GSD



Fully Adaptive Group Sequential Design

- The entry-stage adaptive group sequential designs helped us in reducing sample size.

Fully Adaptive Group Sequential Design

- The entry-stage adaptive group sequential designs helped us in reducing sample size.
- But still we have ethical concerns.

Fully Adaptive Group Sequential Design

- The entry-stage adaptive group sequential designs helped us in reducing sample size.
- But still we have ethical concerns.
- To deal with that, also in bivariate setup, we introduce fully adaptive group sequential design under bivariate setup.

Fully Adaptive Group Sequential Design

- The entry-stage adaptive group sequential designs helped us in reducing sample size.
- But still we have ethical concerns.
- To deal with that, also in bivariate setup, we introduce fully adaptive group sequential design under bivariate setup.
- We will discuss two methods to work with this.

Adaptive Allocation (R_A)

- When we get stronger evidence against the null hypothesis, we wish to allocate treatment A to the $i^{th}(i = 1, ..., n_k; k = 1, 2, ..., K)$ patient with higher probability.

Adaptive Allocation (R_A)

- When we get stronger evidence against the null hypothesis, we wish to allocate treatment A to the $i^{th}(i = 1, ..., n_k; k = 1, 2, ..., K)$ patient with higher probability.
- Let, R_A be the probability that a randomly entered(i^{th}) patient will receive treatment A

Adaptive Allocation (R_A)

- When we get stronger evidence against the null hypothesis, we wish to allocate treatment A to the $i^{th}(i = 1, ..., n_k; k = 1, 2, ..., K)$ patient with higher probability.
- Let, R_A be the probability that a randomly entered(i^{th}) patient will receive treatment A
- We propose,

$$R_A = \frac{\lambda_B + \theta_B}{\lambda_A + \theta_A + \lambda_B + \theta_B}$$

Adaptive Allocation (R_A)

- When we get stronger evidence against the null hypothesis, we wish to allocate treatment A to the $i^{th}(i = 1, ..., n_k; k = 1, 2, ..., K)$ patient with higher probability.
- Let, R_A be the probability that a randomly entered(i^{th}) patient will receive treatment A
- We propose,

$$R_A = \frac{\lambda_B + \theta_B}{\lambda_A + \theta_A + \lambda_B + \theta_B}$$

- where, $\binom{\lambda_A}{\theta_A} < \binom{\lambda_B}{\theta_B} \Rightarrow$ treatment A is better than treatment B

Allocation Procedure

- We generate few samples (say, 4)
  $\binom{X_{A_k}^{[4]}}{Y_{A_k}^{[4]}} = \left(\binom{X_{A_k}^{(1)}}{Y_{A_k}^{(1)}}, \binom{X_{A_k}^{(2)}}{Y_{A_k}^{(2)}}, \binom{X_{A_k}^{(3)}}{Y_{A_k}^{(3)}}, \binom{X_{A_k}^{(4)}}{Y_{A_k}^{(4)}} \right)$ from
  $BVPoisson(\lambda_{A_k}, \theta_{A_k}, \phi_A)$ and same number of samples $\binom{X_{B_k}^{[4]}}{Y_{B_k}^{[4]}}$
  from $BVPoisson(\lambda_{B_k}, \theta_{B_k}, \phi_B)$

Allocation Procedure

- We generate few samples (say, 4)
  $\binom{X_{A_k}^{[4]}}{Y_{A_k}^{[4]}} = \left(\binom{X_{A_k}^{(1)}}{Y_{A_k}^{(1)}}, \binom{X_{A_k}^{(2)}}{Y_{A_k}^{(2)}}, \binom{X_{A_k}^{(3)}}{Y_{A_k}^{(3)}}, \binom{X_{A_k}^{(4)}}{Y_{A_k}^{(4)}} \right)$ from
  $BVPoisson(\lambda_{A_k}, \theta_{A_k}, \phi_A)$ and same number of samples $\binom{X_{B_k}^{[4]}}{Y_{B_k}^{[4]}}$
  from $BVPoisson(\lambda_{B_k}, \theta_{B_k}, \phi_B)$
- We draw a random number say
  r_{i_k} $(i = 9, ..., n_k; k = 1, 2, , , , K)$ from 0 to 1 (i.e. we generate a sample from $Uniform(0, 1)$)

Allocation Procedure

- We generate few samples (say, 4)
  $\binom{X_{A_k}^{[4]}}{Y_{A_k}^{[4]}} = \left(\binom{X_{A_k}^{(1)}}{Y_{A_k}^{(1)}}, \binom{X_{A_k}^{(2)}}{Y_{A_k}^{(2)}}, \binom{X_{A_k}^{(3)}}{Y_{A_k}^{(3)}}, \binom{X_{A_k}^{(4)}}{Y_{A_k}^{(4)}} \right)$ from
  $BVPoisson(\lambda_{A_k}, \theta_{A_k}, \phi_A)$ and same number of samples $\binom{X_{B_k}^{[4]}}{Y_{B_k}^{[4]}}$
  from $BVPoisson(\lambda_{B_k}, \theta_{B_k}, \phi_B)$
- We draw a random number say
  r_{i_k} $(i = 9, ..., n_k; k = 1, 2, , , , K)$ from 0 to 1 (i.e. we generate a sample from $Uniform(0, 1)$)
- Then, if $r_{i_k} \leq R_{A_k}^{(i-1)}$,$\binom{X_{A_k}^{(i)}}{Y_{A_k}^{(i)}}$ from $BVPoisson(\lambda_{A_k}, \theta_{A_k}, \phi_A)$;
  $i = 9, ..., n_k$; $k = 1, 2, ..., K$

Allocation Procedure

- We generate few samples (say, 4)
  $\binom{X_{A_k}^{[4]}}{Y_{A_k}^{[4]}} = \left(\binom{X_{A_k}^{(1)}}{Y_{A_k}^{(1)}}, \binom{X_{A_k}^{(2)}}{Y_{A_k}^{(2)}}, \binom{X_{A_k}^{(3)}}{Y_{A_k}^{(3)}}, \binom{X_{A_k}^{(4)}}{Y_{A_k}^{(4)}} \right)$ from
  $BVPoisson(\lambda_{A_k}, \theta_{A_k}, \phi_A)$ and same number of samples $\binom{X_{B_k}^{[4]}}{Y_{B_k}^{[4]}}$
  from $BVPoisson(\lambda_{B_k}, \theta_{B_k}, \phi_B)$
- We draw a random number say
  r_{i_k} $(i = 9, ..., n_k; k = 1, 2, , , , K)$ from 0 to 1 (i.e. we generate a sample from $Uniform(0, 1)$)
- Then, if $r_{i_k} \leq R_{A_k}^{(i-1)}$, $\binom{X_{A_k}^{(i)}}{Y_{A_k}^{(i)}}$ from $BVPoisson(\lambda_{A_k}, \theta_{A_k}, \phi_A)$;
  $i = 9, ..., n_k$; $k = 1, 2, ..., K$
- otherwise, we draw $\binom{X_{B_k}^{(i)}}{Y_{B_k}^{(i)}}$ from $BVPoisson(\lambda_{B_k}, \theta_{B_k}, \phi_B)$;
  $i = 9, ..., n_k$; $k = 1, 2, ..., K$

ASN for Fully Adaptive GSD under Adaptive Allocation (R_A)

	lambda_B	theta_B	ASN_H0	ASN_H1	RA	Prop_A	Prop_A_SE
1	2.0	2.5	288.9	282.0	0.50	0.50	0.11
2	2.2	2.7	289.0	276.2	0.52	0.52	0.10
3	2.4	2.9	288.3	274.5	0.54	0.53	0.10
4	2.6	3.1	288.2	266.2	0.55	0.55	0.10
5	2.8	3.3	287.3	255.2	0.57	0.57	0.10
6	3.0	3.5	287.3	246.5	0.58	0.58	0.10
7	3.2	3.7	281.4	238.0	0.60	0.59	0.09
8	3.4	3.9	281.3	224.0	0.61	0.60	0.10
9	3.6	4.1	280.2	217.8	0.63	0.61	0.09
10	3.8	4.3	273.3	201.7	0.63	0.62	0.09
11	4.0	4.5	273.2	199.9	0.64	0.63	0.09

Adaptive Allocation (R_A^*)

- Now, we introduce another version of R_A (say, R_A^*); which can be defined as follows,

$$
\begin{aligned}
R_A^* = \quad & (1/4)\{P(X_A = X_B, Y_A > Y_B) \\
& + P(X_A > X_B, Y_A = Y_B)\} \\
& + (3/4)\{P(X_A = X_B, Y_A < Y_B) \\
& + P(X_A < X_B, Y_A = Y_B)\} \\
& + (1/2)\{P(X_A > X_B, Y_A < Y_B) \\
& + P(X_A < X_B, Y_A > Y_B) \\
& + P(X_A = X_B, Y_A = Y_B)\} + P(X_A < X_B, Y_A < Y_B)
\end{aligned}
$$

Allocation Procedure

- we generate few samples (say, 4)
  $\binom{X_{A_k}^{[4]}}{Y_{A_k}^{[4]}} = \left(\binom{X_{A_k}^{(1)}}{Y_{A_k}^{(1)}}, \binom{X_{A_k}^{(2)}}{Y_{A_k}^{(2)}}, \binom{X_{A_k}^{(3)}}{Y_{A_k}^{(3)}}, \binom{X_{A_k}^{(4)}}{Y_{A_k}^{(4)}} \right)$ from
  $BVPoisson(\lambda_{A_k}, \theta_{A_k}, \phi_A)$ and same number of samples $\binom{X_{B_k}^{[4]}}{Y_{B_k}^{[4]}}$
  from $BVPoisson(\lambda_{B_k}, \theta_{B_k}, \phi_B)$

Allocation Procedure

- we generate few samples (say, 4)
  $\binom{X_{A_k}^{[4]}}{Y_{A_k}^{[4]}} = \left(\binom{X_{A_k}^{(1)}}{Y_{A_k}^{(1)}}, \binom{X_{A_k}^{(2)}}{Y_{A_k}^{(2)}}, \binom{X_{A_k}^{(3)}}{Y_{A_k}^{(3)}}, \binom{X_{A_k}^{(4)}}{Y_{A_k}^{(4)}} \right)$ from
  $BVPoisson(\lambda_{A_k}, \theta_{A_k}, \phi_A)$ and same number of samples $\binom{X_{B_k}^{[4]}}{Y_{B_k}^{[4]}}$
  from $BVPoisson(\lambda_{B_k}, \theta_{B_k}, \phi_B)$
- We simulate 50 samples from $poisson(\lambda_{A_k})$ and 50 samples from $poisson(\lambda_{B_k})$.

Allocation Procedure

- we generate few samples (say, 4)
  $\binom{X_{A_k}^{[4]}}{Y_{A_k}^{[4]}} = \left(\binom{X_{A_k}^{(1)}}{Y_{A_k}^{(1)}}, \binom{X_{A_k}^{(2)}}{Y_{A_k}^{(2)}}, \binom{X_{A_k}^{(3)}}{Y_{A_k}^{(3)}}, \binom{X_{A_k}^{(4)}}{Y_{A_k}^{(4)}} \right)$ from
  $BVPoisson(\lambda_{A_k}, \theta_{A_k}, \phi_A)$ and same number of samples $\binom{X_{B_k}^{[4]}}{Y_{B_k}^{[4]}}$
  from $BVPoisson(\lambda_{B_k}, \theta_{B_k}, \phi_B)$
- We simulate 50 samples from $poisson(\lambda_{A_k})$ and 50 samples from $poisson(\lambda_{B_k})$.
- Then we calculate the probability terms in $R_{A_k}^*$ empirically by simulation as in the univariate setup.

Allocation Procedure

- We draw a random number say r_{i_k} $(i = 9, ..., n_k; k = 1, 2, , , , K)$ from 0 to 1 (i.e. we generate a sample from $Uniform(0, 1)$)

Allocation Procedure

- We draw a random number say r_{i_k} $(i = 9, ..., n_k; k = 1, 2, , , , K)$ from 0 to 1 (i.e. we generate a sample from $Uniform(0, 1)$)
- Then, if $r_{i_k} \leq R_{A_k}^{*(i-1)}$, $\binom{X_{A_k}^{(i)}}{Y_{A_k}^{(i)}}$ from $BVPoisson(\lambda_{A_k}, \theta_{A_k}, \phi_A)$; $i = 9, ..., n_k$; $k = 1, 2, ..., K$

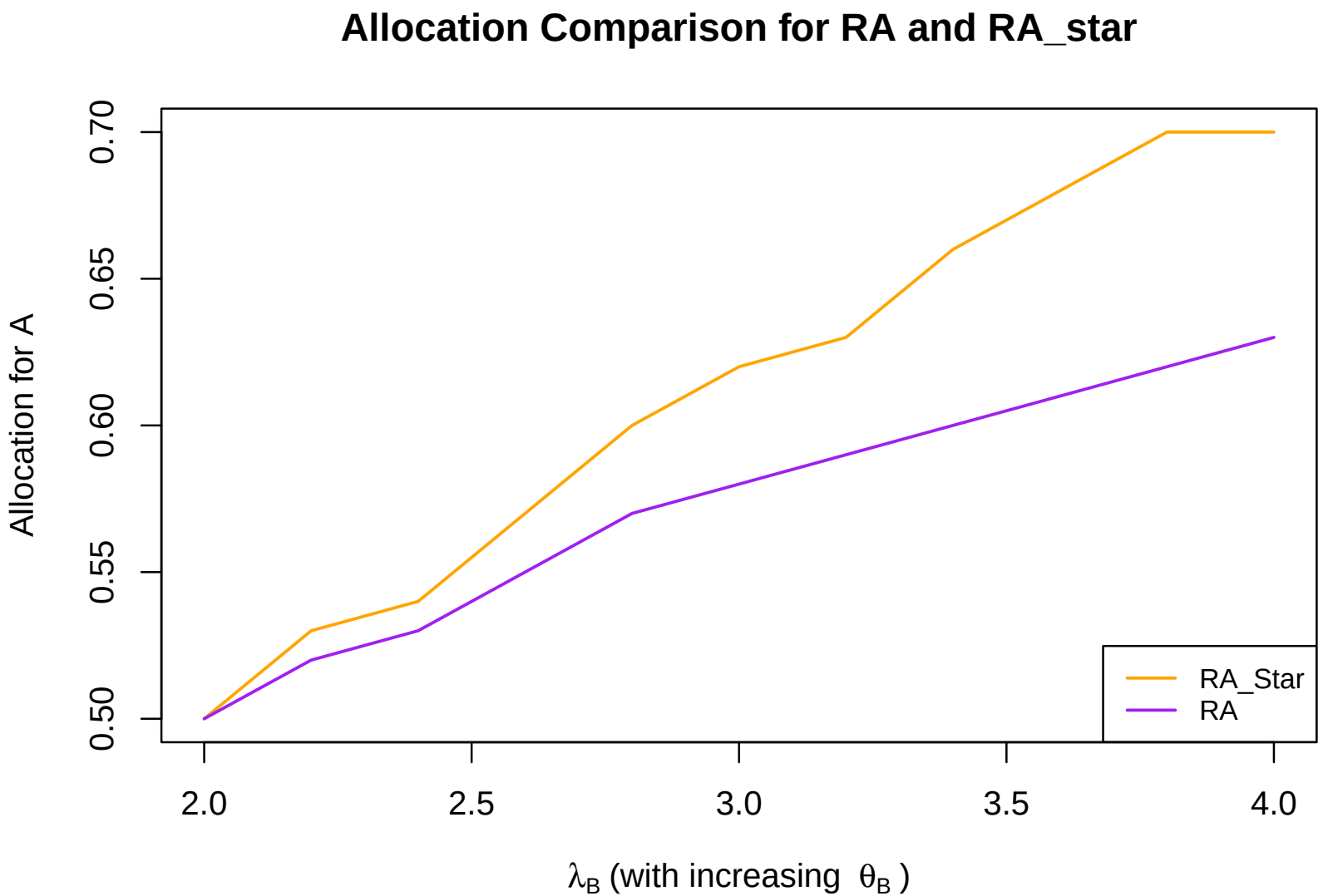
Allocation Procedure

- We draw a random number say r_{i_k} $(i = 9, ..., n_k; k = 1, 2, , , , K)$ from 0 to 1 (i.e. we generate a sample from $Uniform(0, 1)$)
- Then, if $r_{i_k} \leq R_{A_k}^{*(i-1)}$, $\binom{X_{A_k}^{(i)}}{Y_{A_k}^{(i)}}$ from $BVPoisson(\lambda_{A_k}, \theta_{A_k}, \phi_A)$; $i = 9, ..., n_k$; $k = 1, 2, ..., K$
- otherwise, we draw $\binom{X_{B_k}^{(i)}}{Y_{B_k}^{(i)}}$ from $BVPoisson(\lambda_{B_k}, \theta_{B_k}, \phi_B)$; $i = 9, ..., n_k$; $k = 1, 2, ..., K$

ASN for Fully Adaptive GSD under Adaptive Allocation (R_A^*)

	lambda_B	theta_B	ASN_H0	ASN_H1	RA	Prop_A	Prop_A_SE
1	2.0	2.5	289.1	283.5	0.51	0.50	0.15
2	2.2	2.7	289.0	278.2	0.53	0.53	0.15
3	2.4	2.9	288.3	276.0	0.54	0.54	0.15
4	2.6	3.1	288.2	266.0	0.58	0.57	0.15
5	2.8	3.3	287.7	252.1	0.60	0.60	0.15
6	3.0	3.5	288.4	241.8	0.62	0.62	0.15
7	3.2	3.7	284.4	238.9	0.64	0.63	0.15
8	3.4	3.9	285.8	227.6	0.66	0.66	0.14
9	3.6	4.1	284.7	216.9	0.68	0.68	0.14
10	3.8	4.3	262.9	188.6	0.70	0.70	0.13
11	4.0	4.5	272.9	191.3	0.70	0.70	0.13

Allocation Comparison for R_A and R_A^*

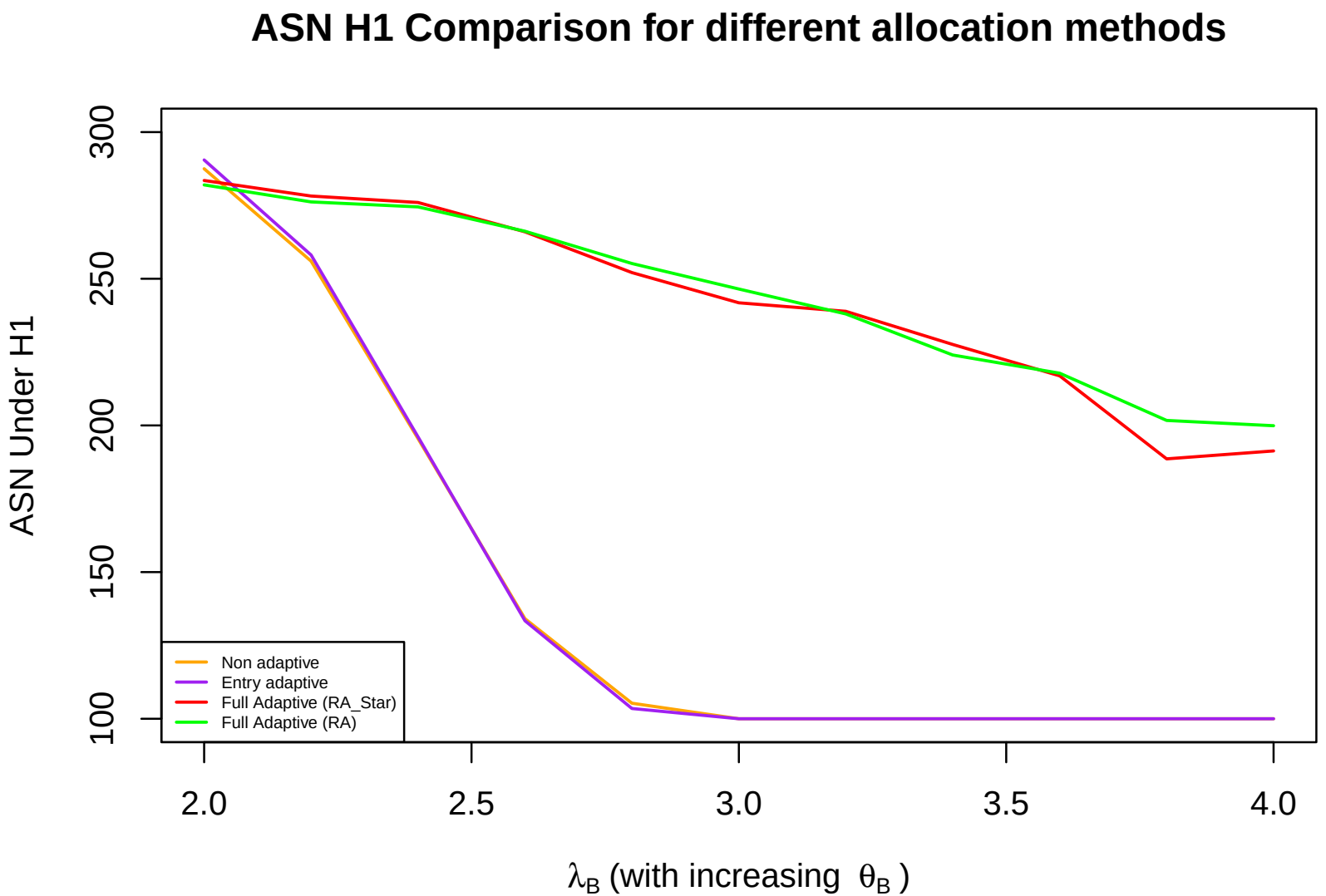


Comparison of ASN for All Methods

Comparison of ASN for different methods :

	Lambda_B	Theta_B	Non Ada	Entry Ada	RA	RA_star
[1,]	2.0	2.5	287.5	290.5	282.0	283.5
[2,]	2.2	2.7	256.0	258.1	276.2	278.2
[3,]	2.4	2.9	195.5	196.1	274.5	276.0
[4,]	2.6	3.1	134.1	133.4	266.2	266.0
[5,]	2.8	3.3	105.3	103.5	255.2	252.1
[6,]	3.0	3.5	100.0	100.0	246.5	241.8
[7,]	3.2	3.7	100.0	100.0	238.0	238.9
[8,]	3.4	3.9	100.0	100.0	224.0	227.6
[9,]	3.6	4.1	100.0	100.0	217.8	216.9
[10,]	3.8	4.3	100.0	100.0	201.7	188.6
[11,]	4.0	4.5	100.0	100.0	199.9	191.3

Comparison of ASN for All Methods



Conclusion

- Developed and compared univariate and bivariate group sequential designs (GSDs) for count data, incorporating adaptive allocation rules to improve ethical treatment assignment.
- Adaptive designs improved patient allocation toward better treatments but led to increased average sample number (ASN) compared to non-adaptive methods — highlighting a trade-off between ethics and efficiency.
- Extended the framework to bivariate Poisson models capturing correlated outcomes (e.g., seizures & hospital visits); observed similar trade-offs, especially as correlation (φ) increased.

Future Directions

- **Covariate-Adaptive Extensions:** Incorporate patient-specific covariates to guide allocation and improve personalized treatment strategies.
- **Estimating ϕ:** Develop methods to estimate and update ϕ during interim analyses for improved modeling accuracy.
- **Multi-Arm and Multi-Endpoint Trials:** Extend the framework to trials involving more than two treatments or multiple outcomes (e.g., include quality-of-life measures).
- **Utility-Based or Bayesian Approaches:** Integrate utility functions or Bayesian priors that align with clinical priorities to guide ethical and efficient decision-making.

Thank You

All R codes are accessible from the following GitHub repository:

`https://github.com/Sahil01S/STAT1092-Research-Project`

Happy to take any questions.