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

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1 Introduction :

Group-sequential designs are known for their statistical and ethical efficiency, allowing researchers to reach conclusions about treatment efficacy using potentially smaller sample sizes and earlier stopping rules. This makes them especially attractive in clinical trials where patient welfare and resource optimization are of paramount importance. However, despite their advantages, such designs are still underutilized in practical clinical trial applications. One key reason is the computational and inferential complexity involved in implementing these designs, particularly when moving beyond classical distributions like the normal or binary responses.

Till now, most real-world applications of group-sequential designs have focused on outcomes following normal or binomial distributions, which are easier to handle analytically and computationally. While useful, these distributions are not always the most natural or informative models for many modern medical outcomes. In particular, count data are increasingly encountered in biostatistics and medical research due to the evolving nature of health surveillance and electronic health record systems.

In our work, while developing the two-treatment response-adaptive group sequential design we focus on count data responses which are emerging response distributions in the arena of biostatistics due to their wide applicability and unconventionality in this field. We will also try to improvise the prognostic factors in the existing design. Also we may extend the whole analysis for multi-treatment scenario. Moreover, the incorporation of adaptive elements in sequential frameworks provides greater flexibility and efficiency in clinical trial conduct. By allowing for interim analyses and possible early stopping, both ethical and economic considerations are better addressed. With the growing recognition of count data in medical and epidemiological studies, our proposed design can fill a significant methodological gap.

2 Group Sequential Design (GSD) :

In clinical research, it is often crucial to determine as early as possible whether a new treatment offers a superior therapeutic benefit compared to a standard or alternative intervention. Traditional fixed-sample single stage designs may require a large number of patients and long follow-up periods to detect treatment differences, which can delay potentially effective therapies from reaching the market and expose many patients to sub-optimal treatments.

To overcome these limitations, adaptive group sequential designs offer a promising alternative that combines early stopping rules for efficacy or futility with the flexibility to adjust aspects of the trial mid-course based on accumulating data. In GSD, data are evaluated at multiple predefined stages, and stopping rules are implemented to allow early decisions based on accumulating evidence. This framework enhances the statistical efficiency by potentially reducing the Average Sample Number (ASN) while maintaining control over Type I and Type II errors.

2.1 Some Practical Scenarios :

We illustrate four practical and impactful clinical scenarios where the outcomes of interest are count data, which naturally arise from repeated event occurrences over a period of time:

- **Number of seizures in epilepsy patients :** Epilepsy patients often experience seizures with varying frequency. New anti-epileptic drugs are continually developed, and comparing the efficacy of a new drug with a standard one using seizure counts over time offers a direct measure of treatment benefit.

- **Number of asthma attacks per patient :** Asthma is a chronic condition with episodic exacerbation. The goal of treatment is to reduce the frequency and severity of these attacks. Count data on asthma attacks over a defined monitoring period provides a reliable measure for evaluating and comparing treatment effects of new versus existing inhalers.

- **Number of hospital re-admissions within 30 days :** Hospital re-admissions are a significant burden on healthcare systems and a marker of quality of care. Comparing the effectiveness of two discharge planning or follow-up care interventions in reducing re-admissions provides actionable insight for health policy and clinical practice.

- **Number of ulcers healed in a clinical trial :** In dermatological or diabetic wound care trials, patients may have multiple ulcers. Tracking the number of ulcers that are healed under two treatment regimens (e.g., standard care vs. a new topical agent) offers a robust endpoint to assess efficacy.

All of these clinical contexts deal with outcomes best modeled by count data, typically assumed to follow a Poisson or Negative Binomial distribution. Such data often require flexible yet rigorous analytical methods. To enhance the efficiency and ethical standards of these studies, we propose a two-treatment response-adaptive group sequential design.

2.2 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 with pmf

$$P(X_k = x) = \frac{\lambda_k^x e^{-\lambda_k}}{x!};\ \lambda_k > 0\ ; x > 0\ ;\ k = A, B$$

Here, λ_k be the average number of recurrence of the symptoms with treatment $'k'$. If the response becomes smaller, then the treatment will become better. Hence,

$\lambda_A < \lambda_B$ <=> treatment A is better than treatment B ($\equiv A \succ B$)

$\lambda_A \geq \lambda_B$ <=> treatment A is not better than treatment B ($\equiv A \preceq B$)

In our study, we want to test,

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

Where, H_0 denotes the null hypothesis and H_1 denotes the alternative hypothesis.

Now, we will proceed with different type of designs to perform the test.

2.3 Choosing Suitable Transformation :

Let, Let, N = Total sample size to be allowed to take. We consider maximum "K" interim look of the Group Sequential process. K is chosen arbitrarily is treated as known apriori. Usually, K is chosen neither very small, nor too high. Practically, K can be taken as 3 or 4 or 5. Suppose, we consider equal group size ($= r$) in each group.

Let, Z_k be the test statistic for k^{th} group, $k = 1, 2, ..., K$. We choose $K = 3$ here.

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 up to 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 ; $k = 1(1)K$.

$$\begin{aligned} \bar{X}_{A_k} &= \text{sample mean response on treatment A from } k^{th} \text{ group} \\ &= \frac{1}{n_{A_k}} \sum_{j=1}^{n_{A_k}} X_{A_{k_j}}\ ;\ k = 1(1)K \end{aligned}$$

and similarly,

$$\begin{aligned} \bar{X}_{B_k} &= \text{sample mean response on treatment B from } k^{th} \text{ group} \\ &= \frac{1}{n_{B_k}} \sum_{j=1}^{n_{B_k}} X_{B_{k_j}}\ ;\ k = 1(1)K \end{aligned}$$

Now, we want to check for which transformation, the poisson data more effectively exhibits asymptotic normality. Suppose $X \sim poisson(\lambda = 15)$. We simulate 500 samples from X. We consider few transformations such as, $g(X) = \sqrt{X}, log(X), log(\sqrt{X})$ and $X^{2/3}$. We will do *Kolmogorov - Smrinov goodness-of-fit test* against standard normal and plot histograms for the X under mention transformations.

Table 1: Kolmogorov-Smrinov p-values for suitable transformations:

We apply *Kolmogorov-Smrinov Test* under different transformations and find p values for each. Here we want to test, $H_0 : \ F(x) = F_0(x)$ for all x vs $H1 : \ F(x) \neq F_0(x)$ for some x. Where, x be the observed value of X ; $F(\cdot)$ be the distribution function

of $poisson(\lambda = 15)$; $F_0(\cdot)$ be the distribution function of $Normal(\hat{\mu}, \hat{\sigma^2})$; $\hat{\mu}, \hat{\sigma^2}$ be the estimated mean and variance of X. Let, $F_n(x) = \frac{1}{n}\sum_{i=1}^{n} 1_{\{X_i \geq x\}}$. Then, the test statistics for the test wll be,

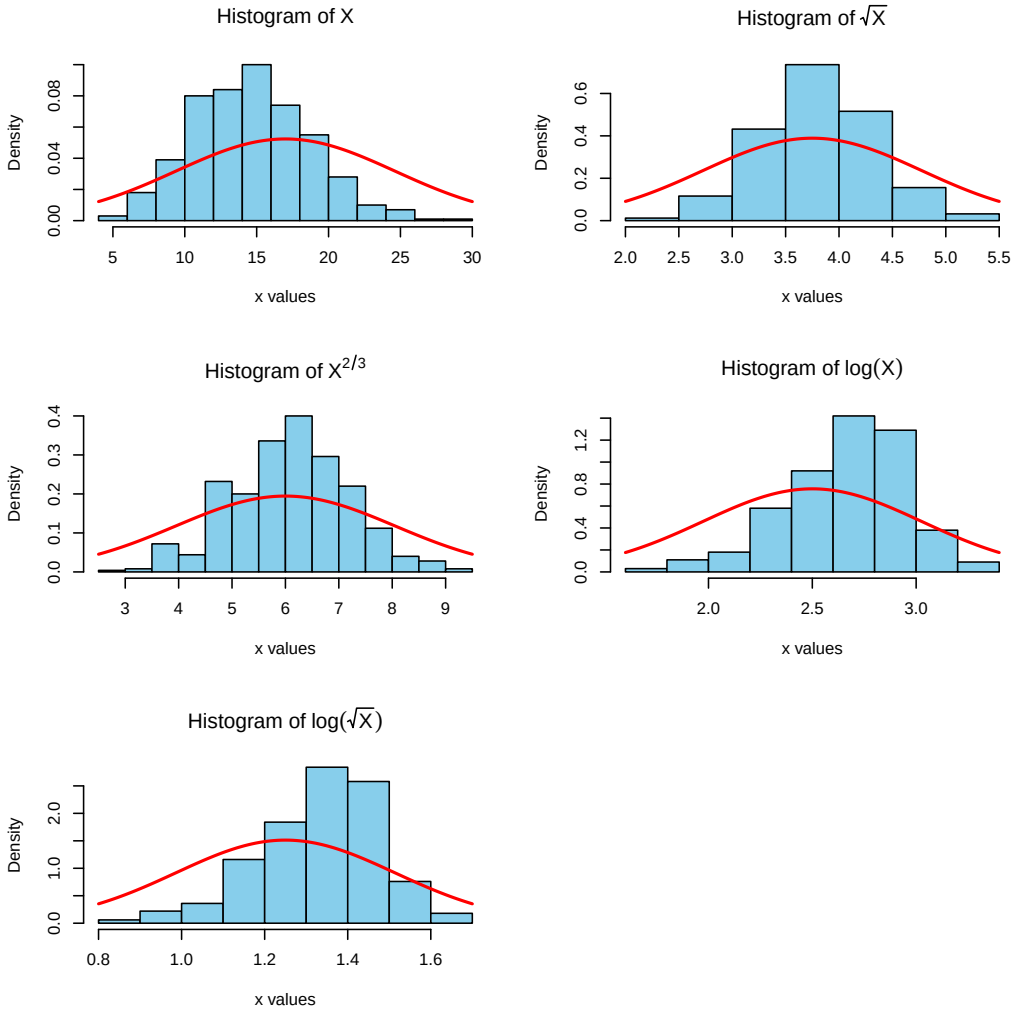
$$D_n = \sup_x |F_n(x) - F_0(x)|$$

We reject H_0 if $D_n > D_{n,\alpha}$; where $P_{H_0}(D_n > D_{n,\alpha}) = \alpha$.
Then, the p-values of the test,

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

Plot 1: Histograms of the Data under Different Transformations:

We plot histograms and compare them with the normal density curves in same plot for the above mentioned transformations.



Remark :

Based on the *Kolmogorov - Smrinov* test results and the histogram, we can see, for poisson data, the $g(X) = X^{2/3}$ transformation appears to produce a distribution that more closely approximates normality. So, we will use this transform for our group sequential test procedure.

2.4 Test Statistic :

Here, $X_{A_k} \sim poisson(\lambda_k)$ and $X_{B_k} \sim poisson(\lambda_k)$; $k = 1, 2, ..., K$

Then using central limit theorem,

$$\sqrt{n_{A_k}}(\bar{X}_{A_k} - \lambda_A) \xrightarrow{\mathcal{D}} N(0, \lambda_A); k = 1, 2, ..., K$$

Then, by delta method,

$$\sqrt{n_{A_k}}[g(\bar{X}_{A_k}) - g(\lambda_A)] \xrightarrow{\mathcal{D}} N(0, (g'(\lambda_A))^2\lambda_A) \ ; k = 1, 2, ..., K$$

Here,

$$\begin{aligned}
g(\bar{X}_{A_{ik}}) &= \bar{X}_{A_k}^{2/3} \\
\text{i.e.} \quad g(x) &= x^{2/3} \\
\Rightarrow g'(x) &= \frac{2}{3}x^{-\frac{1}{3}} \\
\text{Then,} \quad g'(\lambda_A) &= \frac{2}{3}\lambda_A^{-\frac{1}{3}} \\
\Rightarrow \sqrt{n_{A_1}}(\bar{X}_{A_1}^{2/3} - \lambda_A^{2/3}) &\xrightarrow{\mathcal{D}} N(0, \lambda_A \times (\frac{2}{3}\lambda_A^{-\frac{1}{3}})^2) \\
&\equiv N(0, \frac{4}{9}\lambda_A^{\frac{1}{3}}) \\
\text{Hence,} \quad \bar{X}_{A_k}^{2/3} &\sim N(\lambda_A^{2/3}, \frac{4}{9}\lambda_A^{\frac{1}{3}}) \ ; k = 1, 2, ..., K \\
\text{Similarly,} \quad \bar{X}_{B_k}^{2/3} &\sim N(\lambda_B^{2/3}, \frac{4}{9}\lambda_B^{\frac{1}{3}}) \ ; k = 1, 2, ..., K
\end{aligned}$$

The test statistic for k^{th} interim is given by,

$$\begin{aligned}
Z_k &= \frac{\bar{X}_{A_k}^{2/3} - \bar{X}_{B_k}^{2/3}}{\sqrt{\frac{4}{9}(\frac{\lambda_A^{\frac{1}{3}}}{n_{A_k}} + \frac{\lambda_B^{\frac{1}{3}}}{n_{B_k}})}} \sim N(\lambda_A^{2/3} - \lambda_B^{2/3}, 1) \ ; k = 1, 2, ..., K \\
\text{Under } H_0, \quad Z_k &= \frac{\bar{X}_{A_k}^{2/3} - \bar{X}_{B_k}^{2/3}}{\sqrt{\frac{4}{9}\hat{\lambda_k^{1/3}}(\frac{1}{n_{A_k}} + \frac{1}{n_{B_k}})}} \sim N(0, 1) \ ; k = 1, 2, ..., K
\end{aligned}$$

where,

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

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. We consider total number of interim, K=3 for now. Now we proceed with further interim analysis of the group sequential test procedure.

2.5 First Stage :

The test statistic for the first stage is given by,.

$$\begin{aligned} Z_1 &= \frac{\bar{X}_{A_1}^{2/3} - \bar{X}_{B_1}^{2/3}}{\sqrt{\frac{4}{9}(\frac{\lambda_A^{\frac{1}{3}}}{m_{A_1}} + \frac{\lambda_B^{\frac{1}{3}}}{m_{B_1}})}} \sim N(\lambda_A^{2/3} - \lambda_B^{2/3}, 1) \\ \text{Under } H_0, \quad Z_1 &= \frac{\bar{X}_1^{2/3} - \bar{X}_{B_1}^{2/3}}{\sqrt{\frac{4}{9}\hat{\lambda_1^{1/3}}(\frac{1}{m_{A_1}} + \frac{1}{m_{B_1}})}} \sim N(0,1) \end{aligned}$$

where,

$$\lambda_1 = \frac{m_{A_1}\bar{X}_{A_1} + m_{B_1}\bar{X}_{B_1}}{m_{A_1} + m_{B_1}}$$

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

If Z_1 is too small, we should accept H_1. But, if Z_1 is not too small, then we have two situations - (i) If Z_1 is quite high, we should accept H_0 or, (ii) If Z_1 is not high enough, we cannot accept any of H_0 or H_1. $\Rightarrow$ inconclusive / indecision. Mathematically, it can be written as,

(i) if, $Z_1 < a_1$ $\Rightarrow$ We reject H_0 i.e. we accept H_1
(ii) if, $Z_1 > b_1$ $\Rightarrow$ We accept H_0
(ii) if, $a_1 \leq Z_1 \leq b_1$ $\Rightarrow$ inconclusive about acceptance of $H_i; i = 0, 1$ and go for second group

where, the boundary points a_1, b_1 can be chosen from

$$\begin{aligned} \alpha_1 &= P_{H_0}(Z_1 < a_1) \\ &= P_{H_0}(H_0 \text{ is rejected at first stage}) \\ &= \text{a part of size of the test procedure obtained from interim 1} \end{aligned}$$

and

$$\begin{aligned} \beta_1 &= P_{H_1}(Z_1 > b_1) \\ &= P_{H_1}(H_0 \text{ is accepted at first stage}) \\ &= \text{a part of type-II error probability spent on interim 1} \end{aligned}$$

2.6 Second Stage :

Here, $n_{A_2} = m_{A_1} + m_{A_2}$ and $n_{B_2} = m_{B_1} + m_{B_2}$. The test statistic for the second stage is given by,

$$\begin{aligned} Z_2 &= \frac{\bar{X}_{A_2}^{2/3} - \bar{X}_{B_2}^{2/3}}{\sqrt{\frac{4}{9}(\frac{\lambda_A^{\frac{1}{3}}}{n_{A_2}} + \frac{\lambda_B^{\frac{1}{3}}}{n_{B_2}})}} \sim N(\lambda_A^{2/3} - \lambda_B^{2/3}, 1) \\ \text{Under } H_0, \quad Z_2 &= \frac{\bar{X}_2^{2/3} - \bar{X}_{B_2}^{2/3}}{\sqrt{\frac{4}{9}\hat{\lambda_2^{1/3}}(\frac{1}{n_{A_2}} + \frac{1}{n_{B_2}})}} \sim N(0,1) \end{aligned}$$

where,

$$\lambda_2 = \frac{n_{A_2}\bar{X}_{A_2} + n_{B_2}\bar{X}_{B_2}}{n_{A_2} + n_{B_2}}$$

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

(i) if, $a_1 \leq Z_1 \leq b_1$ and $Z_2 < a_2$ $\Rightarrow$ We reject H_0 i.e. we accept H_1
(ii) if, $a_1 \leq Z_1 \leq b_1$ and $Z_2 > b_2$ $\Rightarrow$ We accept H_0
(ii) if, $a_1 \leq Z_1 \leq b_1$ and $a_2 \leq Z_2 \leq b_2$ $\Rightarrow$ inconclusive about acceptance of $H_i; i = 0, 1$ and go for third group

where, the boundary points a_2, b_2 can be chosen from

$$\begin{aligned}
\alpha_2 &= P_{H_0}(a_1 \leq Z_1 \leq b_1 \ , \ Z_2 < a_2) \\
&= P_{H_0}(H_0 \text{ is rejected at second stage}) \\
&= \text{a part of size of the test procedure obtained from interim 2}
\end{aligned}$$

and

$$\begin{aligned}
\beta_2 &= P_{H_1}(a_1 \leq Z_1 \leq b_1 \ , \ Z_2 > b_2) \\
&= P_{H_1}(H_0 \text{ is accepted at second stage}) \\
&= \text{a part of type-II error probability spent on interim 2}
\end{aligned}$$

2.7 Third Stage (Final Stage) :

We have chosen K=3 for the group sequential test procedure. So, we wish to terminate the test procedure in this stage. Here, $n_{A_3} = m_{A_1} + m_{A_2} + m_{A_3}$ and $n_{B_2} = m_{B_1} + m_{B_2} + m_{B_3}$. The test statistic for the third stage is given by,

$$\begin{aligned}
Z_3 &= \frac{\bar{X}_{A_3}^{2/3} - \bar{X}_{B_3}^{2/3}}{\sqrt{\frac{4}{9}(\frac{\lambda_A^{\frac{1}{3}}}{n_{A_3}} + \frac{\lambda_B^{\frac{1}{3}}}{n_{B_3}})}} \sim N(\lambda_A^{2/3} - \lambda_B^{2/3}, 1) \\
\text{Under } H_0, \quad Z_3 &= \frac{\bar{X}_{A_3}^{2/3} - \bar{X}_{B_3}^{2/3}}{\sqrt{\frac{4}{9}\hat{\lambda_3^{1/3}}(\frac{1}{n_{A_3}} + \frac{1}{n_{B_3}})}} \sim N(0, 1)
\end{aligned}$$

where,

$$\lambda_3 = \frac{n_{A_3}\bar{X}_{A_3} + n_{B_3}\bar{X}_{B_3}}{n_{A_3} + n_{B_3}}$$

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

(i) if, $a_1 \leq Z_1 \leq b_1$; $a_2 \leq Z_2 \leq b_2$ and $Z_3 < a_3 = b_3$ $\Rightarrow$ We reject H_0 i.e. we accept H_1
(ii) if, $a_1 \leq Z_1 \leq b_1$; $a_2 \leq Z_2 \leq b_2$ and $Z_3 \geq a_3 = b_3$ $\Rightarrow$ We accept H_0

where, the boundary points $a_3 = b_3$ can be chosen from the size condition,

$$\begin{aligned}
\alpha_3 &= P_{H_0}(a_1 \leq Z_1 \leq b_1 \ , \ a_2 \leq Z_2 \leq b_2 \ , \ Z_3 \leq b_3) \\
&= P_{H_0}(H_0 \text{ is rejected at third stage}) \\
&= \text{a part of size of the test procedure obtained from group 3}
\end{aligned}$$

2.8 Average Sample Number (ASN) :

We consider the following table for our further calculation. We consider, $n_i = n_{A_i} + n_{B_i}$; $i = 1, 2, ..., K$

Table 2 :

sample size for i^{th} stage (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,

$$\begin{aligned} ASN &= E(N) \\ &= n_1 p_1 + n_2 p_2 + n_3 p_3 \end{aligned}$$

2.9 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. $m_{A_k} = m_{B_k} = 50$; $k = 1, 2, 3$. Also, $N = 300$. 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 compute the probabilities to calculate the boundary points (a_k, b_k) by simulating 1000 samples.

We fix $\lambda_A = 2$. Then, we find Average sample number (ASN) under H_0 and H_1 for different values of λ_B's .

Table 3 : 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

Remark :

We can see, the ASN is reducing significantly under $H_!$ in the group sequential setup.

2.10 Choosing Optimal Error Spendings :

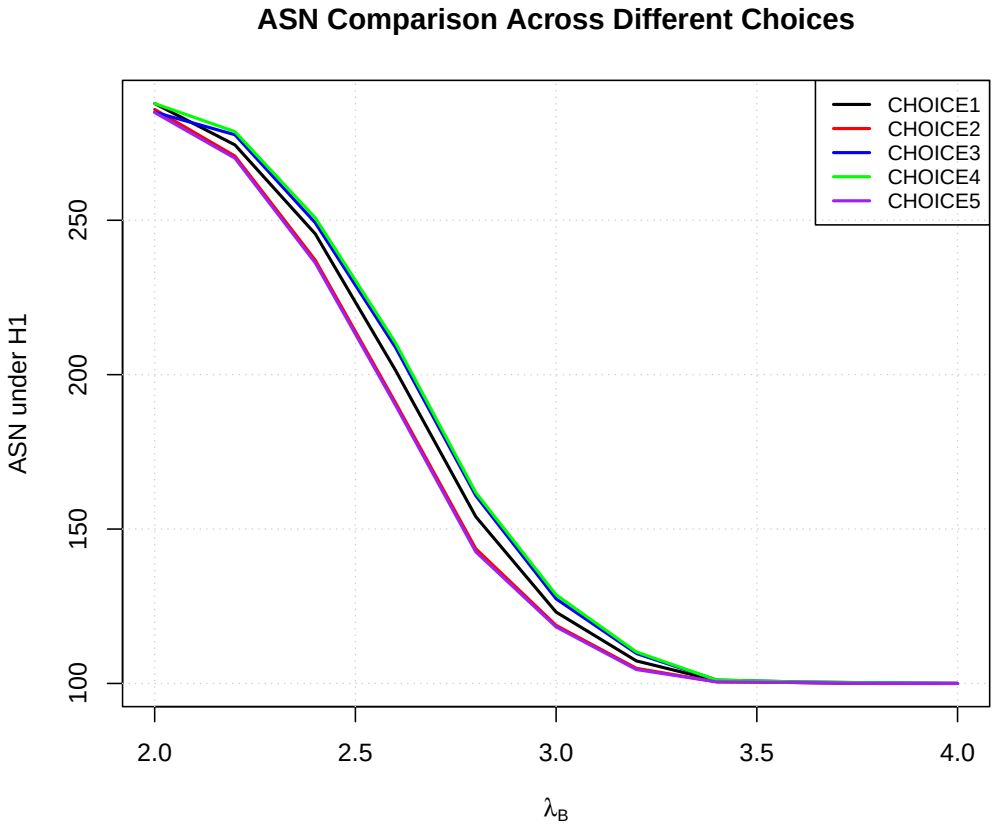
We fix $\lambda_A = 2$. Now, we find and plot ASN for different choices of the error spending (α_k, β_k) ; $k = 1, 2, 3$ (keeping the total size $\alpha = 0.05$ and total type II probability β=0.05 fixed) in multiple line diagrams against different $\lambda_B's$. We take the choices of (α, β) as,

Table 4 : Different choices of (α_k, β_k); $k = 1, 2, 3$:

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

Now, we plot the diagram.

Plot 2: ASN for Different (α_k, β_k) and Different $\lambda's$:



Remark :

We can clearly see, the choice 5, $\alpha = (0.03, 0.015, 0.005)$, $\beta = (0.02, 0.025, 0.005)$ is resulting lowest ASN values. So, we are going to use this choice for further analysis. The ASN table for this choice looks like,

Table 5 : 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

3 Adaptive Group Sequential Design (Adaptive GSD):

In modern clinical and experimental research, especially in biomedical and healthcare studies, it is crucial to design trials that are both statistically efficient and ethically responsible. Traditional fixed-sample designs, although widely used, are often inefficient in terms of resource utilization and may pose ethical concerns, particularly when clear differences between treatments emerge during the course of the study but are not acted upon due to rigid sample sizes.

To address these limitations, group sequential designs have gained prominence as they allow interim analyses, enabling early stopping of the trial for efficacy or futility. This approach can reduce the expected sample size (ASN), saving time, costs, and potential harm to participants. However, classical group sequential methods are based on fixed, pre-specified parameters and randomization schemes that do not adjust based on accruing data.

This motivates the development of adaptive group sequential designs, which combine the strengths of sequential testing with the flexibility of adaptive procedures. So, we proceed with some adaptive methods of group sequential design described as below.

3.1 Entry Stage Adaptive Group Sequential Design :

The Entry Stage Adaptive Group Sequential Design introduces an adaptive mechanism into the traditional group sequential framework, while maintaining a balance between statistical efficiency and operational simplicity. In this design, the adaptation occurs at the level of treatment effect estimation, not at the patient allocation level. Specifically, the design uses updated estimates of treatment parameters (λ_A, λ_B) from preceding stages to inform the simulation and decision-making process in subsequent stages. It can be described in 3 steps,

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

ii) **In second stage,** we simulate 50 samples X_{A_2} from $poisson(\hat{\lambda}_A)$ and 50 samples $X_{B_2}$from $poisson(\hat{\lambda}_B)$; where,

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

Then we carry out the sequential test procedure for second stage as described in the group sequential design.

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

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

Then we carry out the sequential test procedure for third stage as described in the group sequential design.

So, in the test procedure, we are adapting the (λ_A, λ_B) with the their estimates calculated from their previous stage. Now we compute the probabilities to calculate the boundary points (a_k, b_k) ; $k = 1, 2, 3$ for the *size* and *type-II* error condition by simulating 1000 samples. Then we also calculate the Average Sample Number (ASN) in the same way as described in the group sequential design.

Table 6 : ASN table for Entry Stage Adaptive Group Sequential Design :

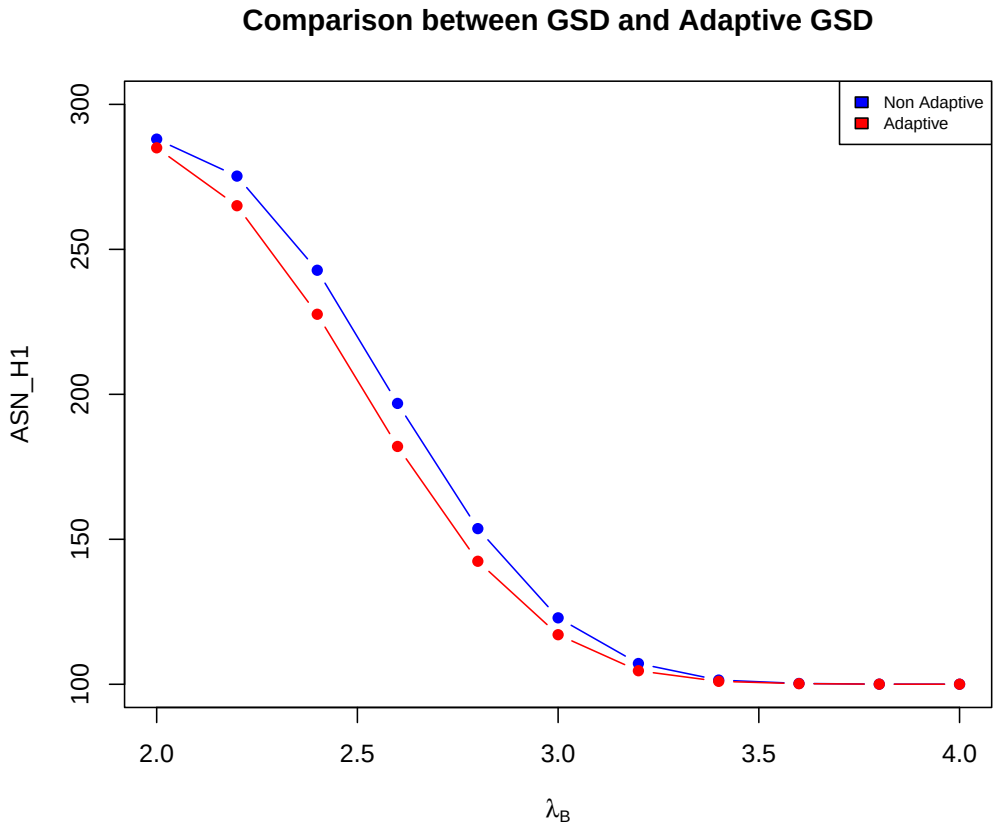
We fix $\lambda_A = 2$. Then, we find ASN under H_0 and H_1 for different values of λ_B's for the entry stage adaptive group sequential design.

	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

3.2 Comparing Entry Adaptive with Non Adaptive GSD :

To compare the results of entry stage adaptive GSD with the non-adaptive GSD, we plot the ASN values under H_1 against different values of λ_B (keeping $\lambda_A = 2$ fixed) in a multiple line diagram.

Plot 3: Comparison of ASN between Non-Adaptive and Entry Stage Adaptive GSD For different Values of λ_B :



Remark :

So we can see a clear reduction in the average sample number (ASN) in the entry stage adaptive adaptive group design.

3.3 Fully Adaptive Group Sequential Design :

While entry-stage adaptive group sequential designs offer a clear statistical advantage - notably in terms of reducing expected sample size, they fall short in addressing a critical concern in clinical trial design: ethical responsibility toward trial participants. In such designs, patients are allocated equally to the two treatments (Treatment A and Treatment B) at each stage of the trial, regardless of emerging evidence on their relative efficacy. This static allocation rule may be statistically efficient but possess a significant ethical concern, particularly when interim data begins to indicate a clear advantage for one treatment over the other.

In our scenario: Treatment A is a new or experimental treatment we are testing. Treatment B is the standard or existing treatment. The null hypothesis states that Treatment A is not better than Treatment B, while the alternative hypothesis says that Treatment A is superior to Treatment B.

Now, suppose interim results suggest we are moving away from the null hypothesis- i.e., evidence is accumulating that Treatment A may indeed be more effective. In an entry-stage adaptive design, we continue to randomize patients equally to Treatments A and B regardless of this emerging evidence. This design choice becomes ethically questionable because patients who are assigned to the potentially inferior Treatment B are, knowingly or unknowingly, exposed to a less beneficial treatment, even when growing evidence suggests a better alternative exists. The design fails to prioritize patient welfare, especially in serious or life-threatening conditions, where even small gains in treatment efficacy can significantly impact quality of life or survival.

This leads us to the fully adaptive group sequential design, where ethical concerns are addressed more directly and dynamically. 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 few methods of allocating treatments in fully adaptive group sequential design.

3.3.1 Adaptive Allocation (R_A):

Here, we define an indicator variable,

$$\delta_i = \begin{cases} 1 & ; \text{ if } i^{th} \text{ individual gets treatment A} \\ 0 & ; \text{ if } i^{th} \text{ individual gets treatment B} \end{cases}$$

We denote,

$$\begin{aligned} R_A &= P(\delta_i = 1) \\ &= P(\text{randomly entered}(i^{th}) \text{ patient will receive treatment A}) \end{aligned}$$

similarly,

$$\begin{aligned} R_B &= P(\delta_i = 0) \\ &= 1 - R_A \\ &= P(\text{randomly entered patient will recieve treatment B}) \end{aligned}$$

K be the number of interim. n_k be the sample size of the k^{th} interim. When i^{th} patient $(i = 1, ..., n_k; k = 1, 2, ..., K)$ is ready to be randomized, we allocate treatment A to i^{th} patient $(i = 1, ..., n_k; k = 1, 2, ..., K)$ with probability R_A and we allocate treatment B with probability R_B. 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} patient with higher probability. So, considering this fact in mind, we propose,

$$R_A = \frac{\lambda_B}{\lambda_A + \lambda_B} \quad \text{and similarly,} \quad R_B = \frac{\lambda_A}{\lambda_A + \lambda_B}$$

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

Here, we can clearly see, as we move away from the null hypothesis, i.e. the values of λ_A and λ_B will move far away, then the value of R_A (probability of receiving treatment A) will increase and the value of R_B (probability of receiving treatment B) will decrease in the same manner. Now we can do further interim analysis using these probabilities. For computation purpose, we can describe the whole procedure in the following steps.

i) Here, $X_A \sim poisson(\lambda_A)$ and $X_B \sim poisson(\lambda_B)$. K denotes the number of interim. We first equally allocate some treatments (treatment A and treatment B) to small number of patients. Mathematically we can say, 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 $X_{B_k}^{[4]} = (X_{B_k}^{(1)}, X_{B_k}^{(2)}, X_{B_k}^{(3)}, X_{B_k}^{(4)})$from $poisson(\lambda_{B_k})$; $k = 1, 2, ..., K$. Where,

$$\lambda_{A_k} = \frac{1}{4}\sum_{j=1}^{4} X_{A_k}^{(j)} \text{ and } \lambda_{B_k} = \frac{1}{4}\sum_{j=1}^{4} X_{B_k}^{(j)} \; ; \; k = 1, 2, ..., K$$

ii) 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 $Uniform(0, 1)$) . We also define,

$$R_{A_k}^{(i)} = \frac{\lambda_{B_k}}{\lambda_{A_k} + \lambda_{B_k}} \; ; i = 9, ..., n_k \; ; k = 1, 2, ..., K$$

iii) then,

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

iv) If the 9^{th} patient gets treatment A, then we adapt λ_{A_k} and λ_{B_k} from the new sample as,

$$\lambda_{A_k} = \frac{1}{5}\sum_{j=1}^{5} X_{A_k}^{(j)} \text{ and } \lambda_{B_k} = \frac{1}{4}\sum_{j=1}^{4} X_{B_k}^{(j)} \; ; \; k = 1, 2, ..., K$$

and if the 9^{th} patient gets treatment B, then we adapt λ_{A_k} and $\lambda_{B_k}$from the new sample as,

$$\lambda_{A_k} = \frac{1}{4}\sum_{j=1}^{4} X_{A_k}^{(j)} \text{ and } \lambda_{B_k} = \frac{1}{5}\sum_{j=1}^{5} X_{B_k}^{(j)} \; ; \; k = 1, 2, ..., K$$

v) We repeat the step (ii) and step (iii) , then we again adapt the λ_{A_k} and λ_{B_k} from the new sample until we generate total $n_k(k = 1, 2, , , , K)$ number of observations, i.e. until $n_k(k = 1, 2, , , , K)$ patients are assigned by any treatment (A or B).

vi) After we have generated $n_k(k = 1, 2, , , , K)$ number of observations, then we calculate the test statistic $Z_k(k = 1, 2, , , , K)$ and carry out the sequential test procedure as described in the group sequential design. We also calculate the boundary points $(a_k, b_k; k = 1, 2, , , , K)$ from the size condition and from the *type-II error* probabilities to calculate the termination probabilities of the test procedure as described in the group sequential design.

vii) we repeat step (i) to step (vi) for all of the K stages of the group sequential test procedure. We also incorporate entry stage adaptive group sequential design to adapt λ_{A_k} and λ_{B_k} by estimating them with the mean of the total samples generated in the previous stages for each of the K stages.

viii) We calculate the proportion of patients receiving treatment A and treatment B as,

$$\text{prop(A)} = \frac{\text{number of patients recieving treatment A}}{\text{total number of patients } (n)}$$

and,

$$\begin{aligned}\text{prop(B)} &= \frac{\text{number of patients recieving treatment B}}{\text{total number of patients } (n)} \\ &= 1 - \text{prop(A)}\end{aligned}$$

We also calculate the expected sample size (ASN) as,

$$\begin{aligned}ASN &= E(N) \\ &= \sum_{i=1}^{K} n_i p_i\end{aligned}$$

where, p_i probability of terminating the test procedure at i^{th} stage ; $i = 1, 2, ..., K$

Table 7 : ASN for Fully Adaptive GSD under Adaptive Allocation (R_A):

Here, we fix $\lambda_A = 2$. We calculate ASN, R_A, Prop(A) = Proportion of patients receiving treatment A, and the standard error of the Prop(A) in the table for different values of λ_B. We iterate the procedure 1000 times R_A and Prop(A). Here, in the table, *RA* denotes the R_A values, *ASN_H0* denotes Average sample number under H_0 and *ASN_H1* denotes Average sample number under H_1 , *Prop_A* denotes the proportion of patients receiving treatment A and *Prop_A_SE* denotes the standard error of the proportion.

	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

Remark :

We can see, as we move away from the null, the value of R_A and proportion of patients receiving treatment A is increasing. We face lower reduction in ASN than the non-adaptive GSD or entry stage adaptive GSD, but here our interest is to serve ethical purpose. So, after allocation better treatment to more patients, we still have successfully reduced the sample size, which completely serves our interest.

3.3.2 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)* . We define R_A as earlier,

Here, we define an indicator variable,

$$\begin{aligned} R_A^* &= P(\delta_i = 1) \\ &= P(i^{th} \text{ patient will recieve treatment A}) \end{aligned}$$

where,

$$\delta_i = \begin{cases} 1 & ; \text{ if } i^{th} \text{ individual gets treatment A} \\ 0 & ; \text{ if } i^{th} \text{ individual gets treatment B} \end{cases}$$

Now, instead of comparing the estimated parameters (λ_A and λ_B), we may wish to estimate the probability (R_A) directly (i.e. empirically). So, we introduce another version of R_A (say, R_A^*); which can be defined as follows,

$$\begin{aligned} R_A^* &= P(\delta_i = 1) \\ &= P(X_A < X_B) \times P(\delta_i = 1/X_A < X_B) + P(X_A = X_B) \times P(\delta_i = 1/X_A = X_B) + \\ &\quad P(X_A > X_B) \times P(\delta_i = 1/X_A > X_B) \\ &= 1 \times P(X_A < X_B) + (1/2) \times P(X_A = X_B) + 0 \times P(X_A > X_B) \\ &= P(X_A < X_B) + (\frac{1}{2}) \times P(X_A = X_B) \end{aligned}$$

similarly,

$$\begin{aligned} R_B^* &= P(\delta_i = 0) \\ &= P(X_A < X_B) \times P(\delta_i = 0/X_A < X_B) + P(X_A = X_B) \times P(\delta_i = 0/X_A = X_B) + \\ &\quad P(X_A > X_B) \times P(\delta_i = 0/X_A > X_B) \\ &= 0 \times P(X_A < X_B) + (1/2) \times P(X_A = X_B) + 1 \times P(X_A > X_B) \\ &= P(X_A > X_B) + (\frac{1}{2}) \times P(X_A = X_B) \end{aligned}$$

So, we can also see that, $R_A^* + R_B^* = 1$

where, $X_A \sim poisson(\lambda_A)$ and $X_B \sim poisson(\lambda_B)$ independently.

Here, the first term $P(X_A < X_B)$ allocates positive probability when the treatment A is perform worse 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. It can be carried out in some following steps,

i) Here, $X_A \sim poisson(\lambda_A)$ and $X_B \sim poisson(\lambda_B)$. K denotes the number of interim. We first equally allocate some treatments (treatment A and treatment B) to small number of patients. Mathematically we can say, 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 $X_{B_k}^{[4]} = (X_{B_k}^{(1)}, X_{B_k}^{(2)}, X_{B_k}^{(3)}, X_{B_k}^{(4)})$from $poisson(\lambda_{B_k})$; $k = 1, 2, ..., K$. Where,

$$\lambda_A^{(k)} = \frac{1}{4}\sum_{j=1}^{4} X_{A_k}^{(j)} \text{ and } \lambda_B^{(k)} = \frac{1}{4}\sum_{j=1}^{4} X_{B_k}^{(j)} \; ; \; k = 1, 2, ..., K$$

ii) 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 $Uniform(0, 1)$) . We also define,

$$R_A^* = P(X_{A_k} < X_{B_k}) + (\frac{1}{2}) \times P(X_{A_k} = X_{B_k}) \;\; ; i = 9, ..., n_k \; ; k = 1, 2, ..., K$$

iii) The R_A^* is to be calculated empirically. We simulate 50 samples $X_{A_k}^{[50]} = (X_{A_k}^{(1)}, X_{A_k}^{(2)}, ..., X_{A_k}^{(50)})$ from $poisson(\lambda_A)$ and 50 samples $X_{B_k}^{[50]} = (X_{B_k}^{(1)}, X_{B_k}^{(2)}, ..., X_{B_k}^{(50)})$ from $poisson(\lambda_B)$. Here, total number of permutations = 2500. So, we get total 2500 pair of observations $(X_{A_k}^{(i)}, X_{B_k}^{(j)})$; $i = 1, 2, ..., 50$; $j = 1, 2, ..., 50$; $k = 1, 2, ..., K$. 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

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

iv) then,

$$\begin{aligned} \text{if } r_k^{(i)} \leq R_{A_k}^{*(i-1)} \quad &, \quad \text{we draw } X_{A_k}^{(i)} \text{ from } poisson(\lambda_{A_k}) \\ &\quad ; \; i = 9, ..., n_k \; ; k = 1, 2, ..., K \\ \text{otherwise} \quad &, \quad \text{we draw } X_{B_k}^{(i)} \text{ from } poisson(\lambda_{B_k}) \\ &\quad ; \; i = 9, ..., n_k \; ; k = 1, 2, ..., K \end{aligned}$$

v) If the 9^{th} patient gets treatment A; we update X_{A_k} by adding the new observation $X_{A_k}^{(5)}$. Then we also adapt λ_{A_k} and λ_{B_k} from the new sample as,

$$\lambda_{A_k} = \frac{1}{5}\sum_{j=1}^{5} X_{A_k}^{(j)} \text{ and } \lambda_{B_k} = \frac{1}{4}\sum_{j=1}^{4} X_{B_k}^{(j)} \; ; \; k = 1, 2, ..., K$$

and if the 9^{th} patient gets treatment B; we update X_{B_k} by adding the new observation $X_{B_k}^{(5)}$. Then we also adapt λ_{A_k} and λ_{B_k} from the new sample as,

$$\lambda_{A_k} = \frac{1}{4}\sum_{j=1}^{4} X_{A_k}^{(j)} \text{ and } \lambda_{B_k} = \frac{1}{5}\sum_{j=1}^{5} X_{B_k}^{(j)} \; ; \; k = 1, 2, ..., K$$

vi) We repeat the step (ii) , (iii) and step (iv) , then we again adapt the λ_{A_k} and λ_{B_k} from the new sample and we continue adding new samples in X_{A_k} and X_{B_k} until we generate total $n_k(k = 1, 2, , , , K)$ number of observations, i.e. until $n_k(k = 1, 2, , , , K)$ patients are assigned by either treatment A or treatment B.

vii) After we have generated $n_k(k = 1, 2, , , , K)$ number of observations, then we calculate the test statistic $Z_k(k = 1, 2, ..., K)$ and carry out the sequential test procedure as described in the group sequential design. We also calculate the boundary points $(a_k, b_k; k = 1, 2, , , , K)$ from the size condition and from the *type-II error* probabilities

to calculate the termination probabilities of the test procedure as described in the group sequential design.

viii) we repeat step (i) to step (vii) for all of the K stages of the group sequential test procedure. We also incorporate entry stage adaptive group sequential design to adapt λ_{A_k} and λ_{B_k} by estimating them with the mean of the total samples generated in the previous stages for each of the K stages.

ix) We calculate the proportion of patients receiving treatment A and treatment B as,

$$\text{prop(A)} = \frac{\text{number of patients recieving treatment A}}{\text{total number of patients } (n)}$$

and,

$$\begin{aligned}\text{prop(B)} &= \frac{\text{number of patients recieving treatment B}}{\text{total number of patients } (n)} \\ &= 1 - \text{prop(A)}\end{aligned}$$

We also calculate the expected sample size (ASN) as,

$$\begin{aligned}ASN &= E(N) \\ &= \sum_{i=1}^{K} n_i p_i\end{aligned}$$

where, p_i probability of terminating the test procedure at i^{th} stage ; $i = 1, 2, ..., K$

Table 8 : ASN for Fully Adaptive GSD under Adaptive Allocation (R_A^*) :

Here, we fix $\lambda_A = 2$. We calculate ASN, R_A, Prop(A) = Proportion of patients receiving treatment A, and the standard error of the Prop(A) in the table for different values of λ_B. We have simulated 1000 times to calculate R_A and Prop(A). Here, in the table, *RA_Star* denotes the R_A^* values, *ASN_H0* denotes Average sample number under H_0 and *ASN_H1* denotes Average sample number under H_1 , *Prop_A* denotes the proportion of patients receiving treatment A and *Prop_A_SE* denotes the standard error of the proportion.

	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

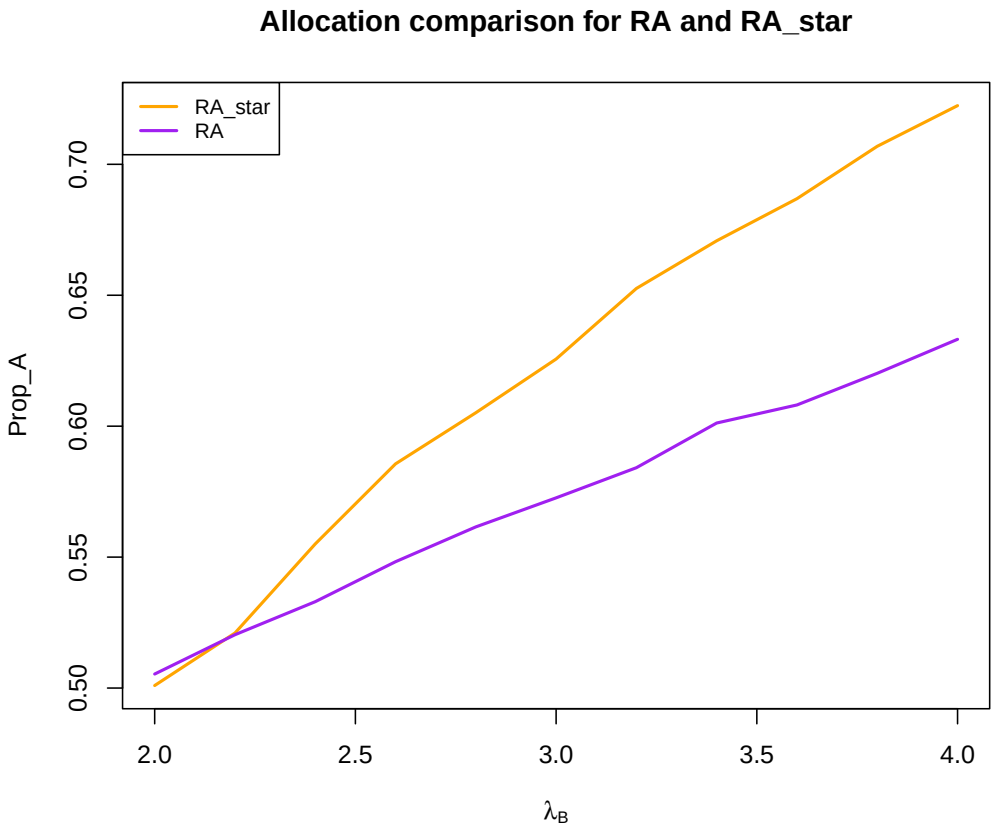
Remark :

We can see, as we move away from the null, the value of R_A^* and proportion of patients receiving treatment A is increasing.

3.4 Comparing Adaptive Allocation Methods Using R_A and R_A^* :

Now, we wish to compare the proportion of patients receiving treatment A for different between the adaptive allocation methods using R_A and R_A^*. We fix $\lambda_A = 2$. Now, we plot *propA* for diiferent values of λ_B for these two methods.

Plot 4 : Allocation comparison for R_A and R_A^* :



Remark :

We find that, the allocation method using R_A^* is allocating treatment A to more patients than the method using R_A.

3.5 Overall Comparison :

Table 9 : 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

Remark :

Compared to the non-adaptive method, the entry-adaptive approach achieves a similar average sample number (ASN) under the alternative hypothesis (H1) while providing a better allocation proportion toward the superior treatment.

In contrast, the fully adaptive method results in a significantly higher ASN under H1. However, its primary goal is to enhance response-based allocation, and in that regard, it achieves a substantially higher proportion of allocation to the better treatment. Between R_A and R_A^*, the latter demonstrates an even more favorable allocation proportion.

4 Group Sequential Design Under Bivariate Setup :

While the majority of GSD applications in the literature focus on univariate outcomes such as survival time, binary responses, or single-event counts, many clinical situations inherently involve multiple correlated outcomes. In particular, count data arising from recurrent events such as the number of disease flare-ups and healthcare utilization (e.g., hospital or doctor visits) are common endpoints in chronic disease management trials. Such data are not only important individually but also provide richer insight when analyzed jointly, as they often share an underlying latent risk factor (e.g., disease severity, patient susceptibility). This motivates the need for a bivariate group sequential testing procedure that can efficiently and ethically evaluate joint treatment effects on correlated count outcomes.

4.1 Some Practical Scenarios :

Below are other practical clinical examples where bivariate count data naturally arise:

- **Number of asthma attacks and number of rescue inhaler uses:** These counts are jointly informative of both the frequency and management of the disease.
- **Number of epileptic seizures and ER visits:** Seizure frequency and emergency interventions often co-occur.
- **Number of infections and antibiotic prescriptions in immunocompromised patients:** Joint analysis captures both disease burden and treatment demand.
- **No of ulcers healed and follow-up dressing appointments in diabetic patients:** Correlated outcomes to assess effectiveness and clinical effort.

Each of these cases benefits from a joint modeling framework, especially under a group sequential setting where early insights from interim data can drive ethical and efficient trial conclusions.

4.2 Objective :

To illustrate this framework, consider a chronic disease trial (e.g., for rheumatoid arthritis or COPD), where the two primary endpoints are:

Let, X : the number of chronic disease occurrences (flare-ups or exacerbations) during a fixed observation window, and Y : the number of doctor or clinic visits within the same period. These two endpoints are not independent. Patients experiencing more frequent flare-ups are likely to visit healthcare providers more often, making the pair (X,Y) a suitable candidate for bivariate Poisson modeling. In this context, a new treatment may aim to simultaneously reduce the frequency of both disease events and associated healthcare visits, compared to a standard therapy. Tracking these outcomes jointly and adaptively allows for a more comprehensive and efficient assessment of treatment effectiveness.

We assume, X_k = No. of recurrence of the symptoms (before some action is taken) with treatment k ; $k = A, B$.

and Y_k = No. of visits to a doctor's clinic after the occurrence of the disease with treatment k ; $k = A, B$.

In our study, we want to test,

$$H_0 : \text{ treatment A } \not\succ \text{ treatment B } \text{ vs. } H_1 : \text{ treatment A } \succ \text{ treatment B}$$

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,

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

and

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

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

$$\begin{aligned}
P(X_A = x_A, Y_A = y_A) &= P(U_A + W_A = x_A, V_A + W_A = y_A) \\
&= \sum_r P(U_A + W_A = x_A, V_A + W_A = y_A, W_A = r) \\
&= \sum_r P(U_A + r = x_A, V_A + r = y_A, W_A = r) \\
&= \sum_{r \le x_A, y_A} P(U_A = x_A - r) \times P(V_A = y_A - r) \times P(W_A = r) \\
&= \sum_{r=0}^{min\{x_A, y_A\}} \frac{e^{-\lambda_A} \lambda_A^{x_A - r}}{(x_A - r)!} \times \frac{e^{-\theta_A} \theta_A^{y_A - r}}{(y_A - r)!} \times \frac{e^{-\phi_A} \phi_A^{x_A - r}}{r!} \\
&= e^{-(\lambda_A + \theta_A + \phi_A)} \lambda_A^{x_A} \theta_A^{y_A} \sum_{r=0}^{min\{x_A, y_A\}} (\frac{\phi_A}{\lambda_A \theta_A})^r \times \frac{1}{(x_A - r)!(y_A - r)! r!}
\end{aligned}$$

Similarly, for treatment B,

$U_B \sim Poisson(\lambda_B)$, $V_B \sim Poisson(\theta_B)$ and $W_B \sim Poisson(\phi_B)$ and U_B, V_B and W_B are independently distributed. Then,

$$X_B = U_B + W_B \overset{marginally}{\sim} Poisson(\lambda_B + \phi_B)$$

and,

$$Y_A = V_B + W_B \overset{marginally}{\sim} Poisson(\theta_B + \phi_B)$$

Then, jointly,

$$(X_B, Y_B) \sim \ BVPoisson(\lambda_B, \theta_B, \phi_B)$$

with pmf,

$$\begin{aligned}
P(X_B = x_B, Y_B = y_B) &= P(U_B + W_B = x_B, V_B + W_B = y_B) \\
&= \sum_r P(U_B + W_B = x_B, V_B + W_B = y_B, W_B = r) \\
&= \sum_r P(U_B + r = x_B, V_B + r = y_B, W_B = r) \\
&= \sum_{r \le x_B, y_B} P(U_B = x_B - r) \times P(V_B = y_B - r) \times P(W_B = r) \\
&= \sum_{r=0}^{min\{x_B, y_B\}} \frac{e^{-\lambda_B} \lambda_B^{x_B - r}}{(x_B - r)!} \times \frac{e^{-\theta_B} \theta_B^{y_B - r}}{(y_B - r)!} \times \frac{e^{-\phi_B} \phi_B^{x_B - r}}{r!} \\
&= e^{-(\lambda_B + \theta_B + \phi_B)} \lambda_B^{x_B} \theta_B^{y_B} \sum_{r=0}^{min\{x_B, y_B\}} (\frac{\phi_B}{\lambda_B \theta_B})^r \times \frac{1}{(x_B - r)!(y_B - r)! r!}
\end{aligned}$$

Now, for treatment A,

$$\begin{aligned} Cov(X_A, Y_A) &= Cov(U_A + W_A, V_A + W_A) \\ &= Cov(W_A, W_A) \text{ (as } (U_A, V_A, W_A) \text{ are independently distributed)} \\ &= Var(W_A) \\ &= \phi_A \end{aligned}$$

Similarly, for treatment B,

$$\begin{aligned} Cov(X_B, Y_B) &= Cov(U_B + W_B, V_B + W_B) \\ &= Cov(W_B, W_B) \text{ (as } (U_B, V_B, W_B) \text{ are independently distributed)} \\ &= Var(W_B) \\ &= \phi_B \end{aligned}$$

We are interested to test,

$$\begin{aligned} H_0 : B \preceq A \quad &\text{vs} \quad H_1 : B \succ A \\ \text{i.e. } H_0 : \lambda_A + \phi_A \geq \lambda_B + \phi_B \quad &\text{vs} \quad H_1 : \lambda_A + \phi_A < \lambda_A + \phi_A \\ \text{or, } \theta_A + \phi_A \geq \theta_B + \phi_B \quad &\text{or, } \theta_A + \phi_A < \theta_B + \phi_B \end{aligned}$$

4.3 Test Statistics :

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 two statistics which are given by,

$$\begin{aligned} T^{(1)} &= min\{\bar{X}_A^{2/3} - \bar{X}_B^{2/3}, \bar{Y}_A^{2/3} - \bar{Y}_B^{2/3}\} \\ &= min\{Z_1, Z_2\} \end{aligned}$$

$$\begin{aligned} T^{(2)} &= max\{\bar{X}_A^{2/3} - \bar{X}_B^{2/3}, \bar{Y}_A^{2/3} - \bar{Y}_B^{2/3}\} \\ &= max\{Z_1, Z_2\} \end{aligned}$$

$$T^{(3)} = \frac{T^{(1)} + T^{(2)}}{2}$$

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. K be the total number of interims. We consider total number of interim, K=3 for now. Now we proceed with further interim analysis of the group sequential test procedure.

4.4 First Stage :

In first stage, we are working with m_{A_1} observations of type A and m_{B_1} observations of type B.

$T_1^{(s)}$ be the test statistics ; $s = 1, 2, 3$ given by,

$$T_1^{(1)} = min\{\bar{X}_{A_1}^{2/3} - \bar{X}_{B_1}^{2/3}, \bar{Y}_{A_1}^{2/3} - \bar{Y}_{B_1}^{2/3}\}$$

$$T_1^{(2)} = max\{\bar{X}_{A_1}^{2/3} - \bar{X}_{B_1}^{2/3}, \bar{Y}_{A_1}^{2/3} - \bar{Y}_{B_1}^{2/3}\}$$

$$T_1^{(3)} = \frac{T_1^{(1)} + T_1^{(2)}}{2}$$

where,

$$\begin{pmatrix} X_{A_1} \\ Y_{A_1} \end{pmatrix} \sim BVPoisson(\lambda_A, \theta_A, \phi_A)$$

$$\begin{pmatrix} X_{B_1} \\ Y_{B_1} \end{pmatrix} \sim BVPoisson(\lambda_B, \theta_B, \phi_B)$$

Also,

$$\begin{pmatrix} \bar{X}_{A_1} \\ \bar{Y}_{A_1} \end{pmatrix} = \frac{1}{m_{A_1}} \sum_{j=1}^{m_{A_1}} \begin{pmatrix} X_{A_1}^{(j)} \\ Y_{A_1}^{(j)} \end{pmatrix}$$

$$\begin{pmatrix} \bar{X}_{B_1} \\ \bar{Y}_{B_1} \end{pmatrix} = \frac{1}{m_{B_1}} \sum_{j=1}^{m_{B_1}} \begin{pmatrix} X_{B_1}^{(j)} \\ Y_{B_1}^{(j)} \end{pmatrix}$$

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

(i) if, $T_1^{(s)} < a_1 \Rightarrow$ We reject H_0 i.e. we accept H_1

(ii) if, $T_1^{(s)} > b_1 \Rightarrow$ We accept H_0

(ii) if, $a_1 \leq T_1^{(s)} \leq b_1 \Rightarrow$ inconclusive about acceptance of $H_i; i = 0, 1$ and go for second group

where, the boundary points a_1, b_1 can be chosen from

$$\begin{aligned} \alpha_1 &= P_{H_0}(T_1^{(s)} < a_1) \\ &= P_{H_0}(H_0 \text{ is rejected at first stage}) \\ &= \text{a part of size of the test procedure obtained from interim 1} \end{aligned}$$

and

$$\begin{aligned} \beta_1 &= P_{H_1}(T_1^{(s)} > b_1) \\ &= P_{H_1}(H_0 \text{ is accepted at first stage}) \\ &= \text{a part of type-II error probability spent on interim 1} \end{aligned}$$

4.5 Second Stage :

Here, $n_{A_2} = m_{A_1} + m_{A_2}$ and $n_{B_2} = m_{B_1} + m_{B_2}$. The test statistic for the second stage is given by,

$$T_2^{(1)} = min\{\bar{X}_{A_2}^{2/3} - \bar{X}_{B_2}^{2/3}, \bar{Y}_{A_2}^{2/3} - \bar{Y}_{B_2}^{2/3}\}$$

$$T_2^{(2)} = max\{\bar{X}_{A_2}^{2/3} - \bar{X}_{B_2}^{2/3}, \bar{Y}_{A_2}^{2/3} - \bar{Y}_{B_2}^{2/3}\}$$

$$T_2^{(3)} = \frac{T_2^{(1)} + T_2^{(2)}}{2}$$

where,

$$\begin{pmatrix} X_{A_2} \\ Y_{A_2} \end{pmatrix} \sim BVPoisson(\hat{\lambda}_A, \hat{\theta}_A, \phi_A)$$

$$\begin{pmatrix} X_{B_2} \\ Y_{B_2} \end{pmatrix} \sim BVPoisson(\hat{\lambda}_B, \hat{\theta}_B, \phi_B)$$

$$\begin{pmatrix}\hat{\lambda}_A\\ \hat{\theta}_A\end{pmatrix}=\begin{pmatrix}\bar{X}_{A_1}\\ \bar{Y}_{A_1}\end{pmatrix}=\frac{1}{n_{A_2}}\sum_{j=1}^{n_{A_2}}\begin{pmatrix}X_{A_1}^{(j)}\\ Y_{A_1}^{(j)}\end{pmatrix}\text{ and }\begin{pmatrix}\hat{\lambda}_B\\ \hat{\theta}_B\end{pmatrix}=\begin{pmatrix}\bar{X}_{B_1}\\ \bar{Y}_{B_1}\end{pmatrix}=\frac{1}{n_{B_2}}\sum_{j=1}^{n_{B_2}}\begin{pmatrix}X_{B_1}^{(j)}\\ Y_{B_1}^{(j)}\end{pmatrix}$$

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

(i) if, $a_1 \le T_2^{(s)} \le b_1$ and $T_2^{(s)} < a_2$ $\Rightarrow$ We reject H_0 i.e. we accept H_1
(ii) if, $a_1 \le T_2^{(s)} \le b_1$ and $T_2^{(s)} > b_2$ $\Rightarrow$ We accept H_0
(ii) if, $a_1 \le T_2^{(s)} \le b_1$ and $a_2 \le T_2^{(s)} \le b_2$ $\Rightarrow$ inconclusive about acceptance of $H_i; i = 0, 1$ and go for third group

where, the boundary points a_2, b_2 can be chosen from

$$\begin{aligned}\alpha_2 &= P_{H_0}(a_1 \le T_2^{(s)} \le b_1\ ,\ T_2^{(s)} < a_2)\\ &= P_{H_0}(H_0 \text{ is rejected at second stage})\\ &= \text{a part of size of the test procedure obtained from interim 2}\end{aligned}$$

and

$$\begin{aligned}\beta_2 &= P_{H_1}(a_1 \le T_2^{(s)} \le b_1\ ,\ T_2^{(s)} > b_2)\\ &= P_{H_1}(H_0 \text{ is accepted at second stage})\\ &= \text{a part of type-II error probability spent on interim 2}\end{aligned}$$

4.6 Third Stage (Final Stage) :

We have chosen K=3 for the group sequential test procedure. So, we wish to terminate the test procedure in this stage. Here, $n_{A_3} = m_{A_1} + m_{A_2} + m_{A_3}$ and $n_{B_2} = m_{B_1} + m_{B_2} + m_{B_3}$. The test statistic for the third stage is given by,

$$T_3^{(1)} = min\{\bar{X}_{A_3}^{2/3} - \bar{X}_{B_3}^{2/3}, \bar{Y}_{A_3}^{2/3} - \bar{Y}_{B_3}^{2/3}\}$$

$$T_3^{(2)} = max\{\bar{X}_{A_3}^{2/3} - \bar{X}_{B_3}^{2/3}, \bar{Y}_{A_3}^{2/3} - \bar{Y}_{B_3}^{2/3}\}$$

$$T_3^{(3)} = \frac{T_2^{(1)} + T_2^{(2)}}{2}$$

where,

$$\begin{pmatrix}X_{A_3}\\ Y_{A_3}\end{pmatrix} \sim BVPoisson(\hat{\lambda}_A, \hat{\theta}_A, \phi_A)$$

$$\begin{pmatrix}X_{B_2}\\ Y_{B_2}\end{pmatrix} \sim BVPoisson(\hat{\lambda}_B, \hat{\theta}_B, \phi_B)$$

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

(i) if, $a_1 \le T_3^{(s)} \le b_1$; $a_2 \le T_3^{(s)} \le b_2$ and $T_3^{(s)} < a_3 = b_3$ $\Rightarrow$ We reject H_0 i.e. we accept H_1
(ii) if, $a_1 \le T_3^{(s)} \le b_1$; $a_2 \le T_3^{(s)} \le b_2$ and $T_3^{(s)} \ge a_3 = b_3$ $\Rightarrow$ We accept H_0

where, the boundary points $a_3 = b_3$ can be chosen from the size condition,

$$\begin{aligned}\alpha_3 &= P_{H_0}(a_1 \leq T_3^{(s)} \leq b_1\ ,\ a_2 \leq T_3^{(s)} \leq b_2\ ,\ T_3^{(s)} \leq b_3) \\ &= P_{H_0}(H_0 \text{ is rejected at third stage}) \\ &= \text{a part of size of the test procedure obtained from group 3}\end{aligned}$$

4.7 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., $max\{Z_1, Z_2\} < a_1 \Longleftarrow Z_1 < a_1, Z_2 < a_1$). Hence, it if $T^{(2)} < a_1$, i.e. it will strongly accept the alternative hypothesis i.e. to say, we will say that, treatment A is better than treatment B in our testing procedure.

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., $min\{Z_1, Z_2\} > b_1^* \Longleftarrow W_1 > b_1^*, W_2 > b_1^*$). Hence, it if $T^{(2)} > b_1^*$, it strongly accepts the null hypothesis i.e. to say, we will say that, treatment A is not better than treatment B in our testing procedure.

The statistic $T^{(3)}$ should perform equally for null and alternative, as we have taken the average of the other two statistics.

4.8 Average Sample Number (ASN) :

We consider the following table for our further calculation. We consider, $n_i = n_{A_i} + n_{B_i}\ ;\ i = 1, 2, ..., K$

Table 10:

sample size for i^{th} stage (n_i)	probability of terminating at i^{th} stage (p_i)
n_1	$P(T_1^{(s)} < a_1)P(T_1^{(s)} > b_1) \ = \ 1 - P(a_1 \leq T_1^{(s)} \leq b_1)$
n_2	$P[(a_1 \leq T_2^{(s)} \leq b_1) \ \cap \ \{(T_2^{(s)} < a_2) \cup (T_2^{(s)} > b_2)\}]$
n_3	$P_{H_0}[(a_1 \leq T_3^{(s)} \leq b_1) \ \cap \ (a_2 \leq T_3^{(s)} \leq b_2) \ \cap \ (T_3^{(s)} \leq b_3)]$

Then, average sample number can be defined as,

$$\begin{aligned}ASN &= E(N) \\ &= n_1p_1 + n_2p_2 + n_3p_3\end{aligned}$$

We will do equal allocation for now. So, we assume, $n_1 = n_2 = n_3$. Also, as ϕ_A and ϕ_B are nuisance parameter, we fix them from beginning for our computation purpose. Also, we assume for both the treatments, the measure of association is equivalenty, so we keep them equal.

4.9 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. $m_{A_k} = m_{B_k} = 50\ ;\ k = 1, 2, 3$. Also, $N = 300$. We fix $\phi_A = \phi_B = 0.1$. 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.

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 compute the probabilities to calculate the boundary points (a_k, b_k) by simulating 1000 samples.

We fix $\lambda_A = 2$ and $\theta_A = 2.5$. Then, we find Average sample number (ASN) under H_0 and H_1 for different values of λ_B's and θ_B's.

Table 11 : 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

Table 12 : ASN for Different $\lambda's$ 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

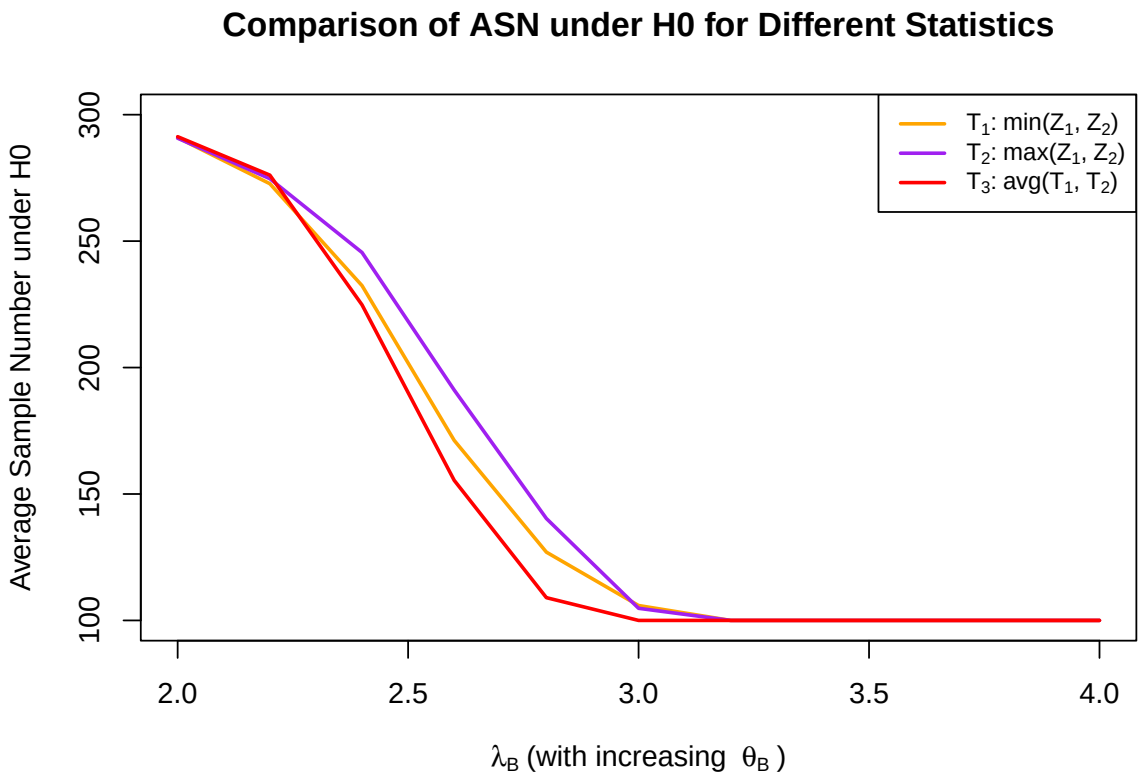
Table 13: ASN for Different $\lambda's$ and θ's (for $T^{(3)}$) :

	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

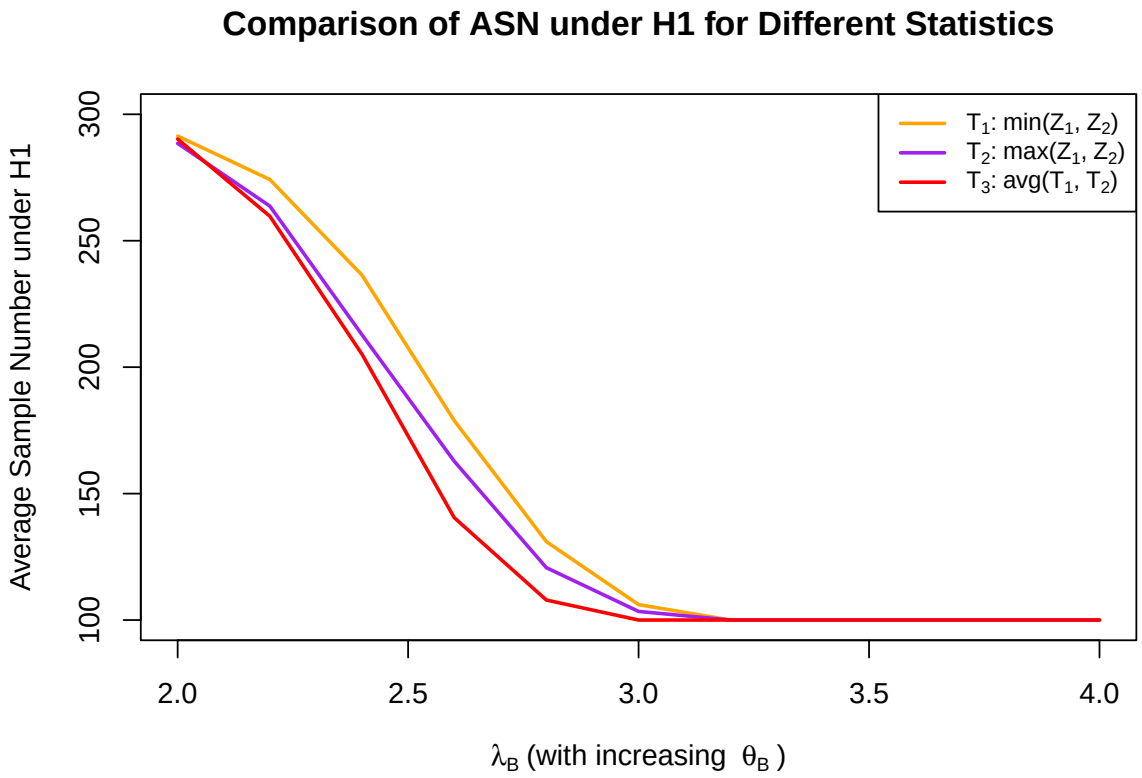
```
9       3.6     4.1  100.0  100.0
10      3.8     4.3  100.0  100.0
11      4.0     4.5  100.0  100.0
```

Now, we plot The ASN under H_0 and H_1 in two different plots for $T^{(1)}$, $T^{(2)}$, $T^{(3)}$.

Plot 5: ASN_H0 for Different statistics :



Plot 6: ASN_H1 for Different statistics :



Remark :

We can clearly see, $T^{(1)}$ is performing better under null hypothesis, and $T^{(2)}$ is performing better under the alternative hypothesis (as we discussed in section 4.7). We also found that, $T^{(3)}$ has reduced the ASN significantly more than other two. So, we will work with $T^{(3)}$ for our further analysis.

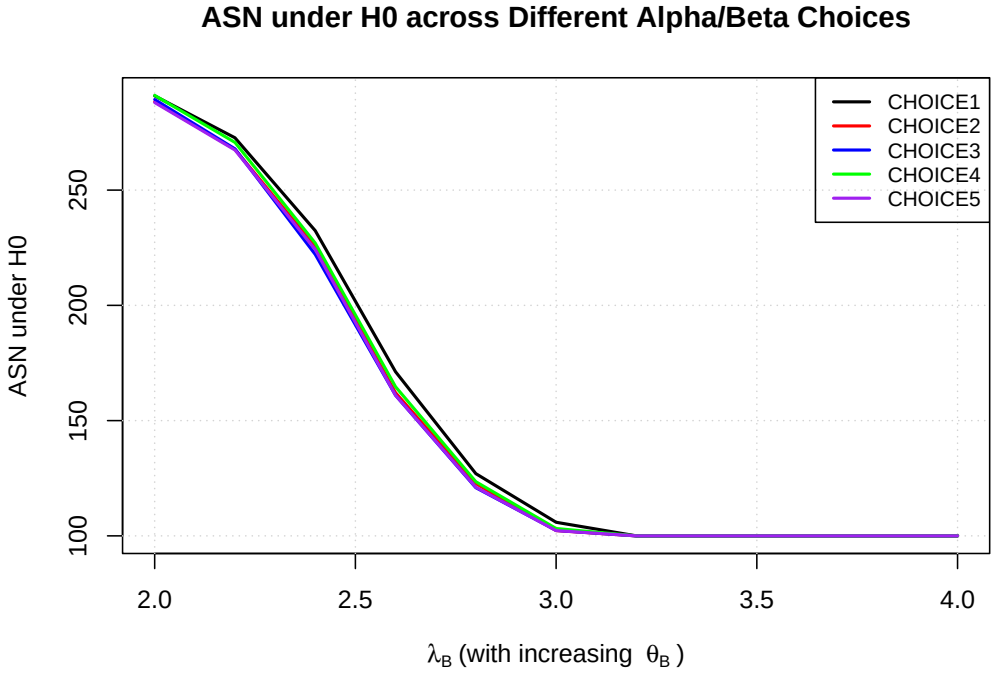
4.10 Choosing Optimal Error Spendings :

We fix $\lambda_A = 2$,$\theta_A = 2.5$ Now, we 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,

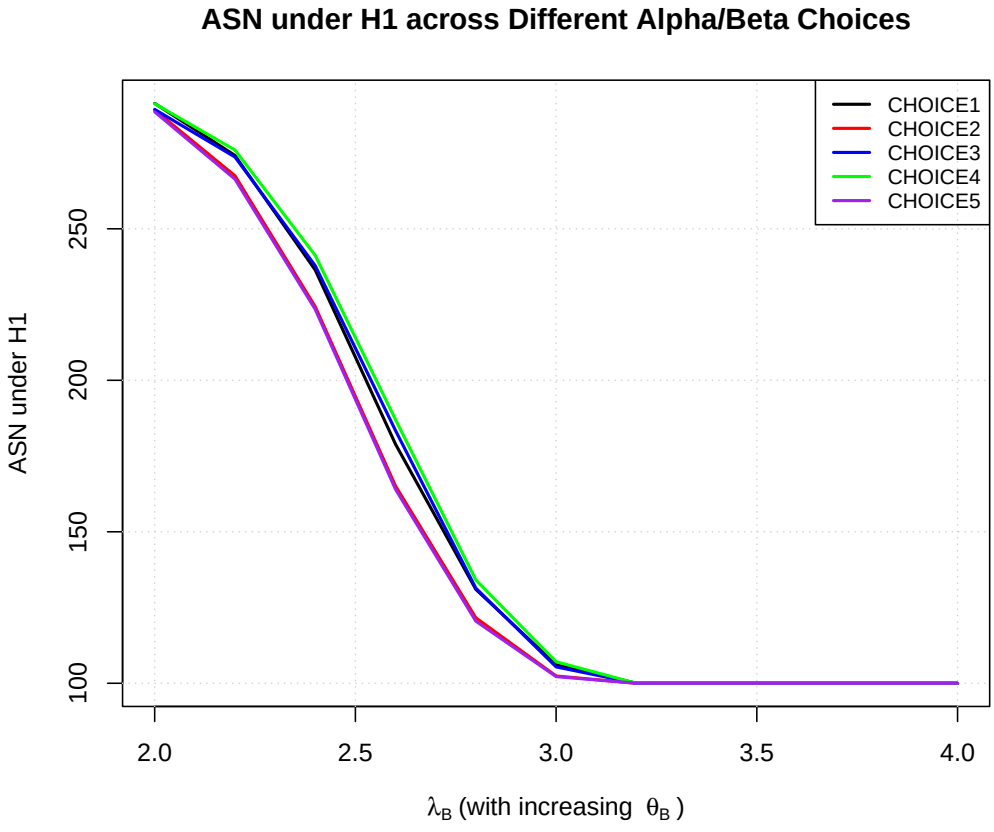
Table 14 : Different choices of (α_k, β_k); $k = 1, 2, 3$:

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

Plot 7 : ASN_H0 for Different (α_k, β_k) :



Plot 8 : ASN_H1 for Different (α_k, β_k) :



Remark :

Looking at both plots, we can see the choice 5, $\alpha = (0.03, 0.015, 0.005)$, $\beta = (0.02, 0.025, 0.005)$ is resulting better ASN values. So, we are going to use this choice for our further work. The ASN table for this choice looks like,

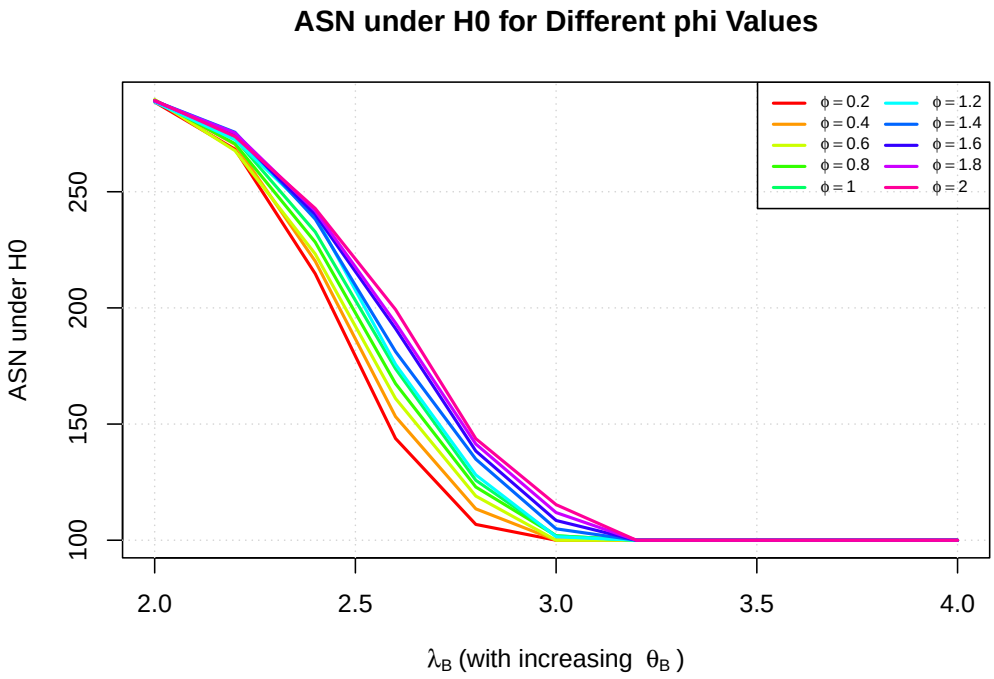
Table 15 : ASN table for $\alpha = (0.03, 0.015, 0.005)$, $\beta = (0.02, 0.025, 0.005)$:

	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

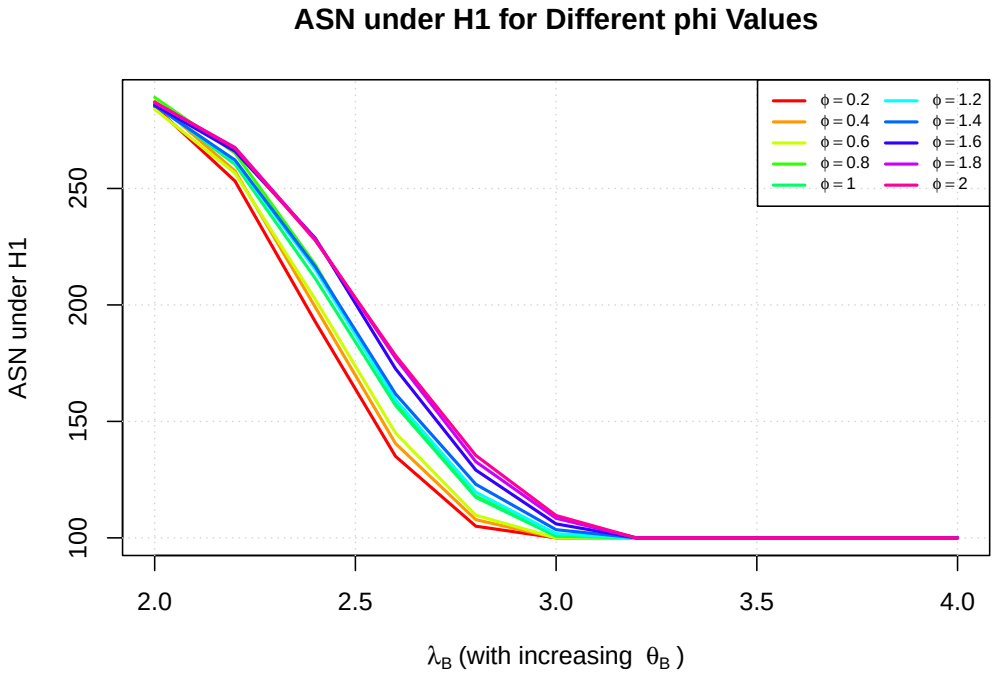
4.11 Choosing Optimal $\phi(= \phi_A = \phi_B)$:

Now, we will find and plot ASN for different choices of the ϕ (from 0.2 to 2). We have assumed, $\phi_A = \phi_B = \phi$

Plot 9 : ASN_H0 for Different ϕ :



Plot 10 : ASN_H1 for Different ϕ :



Remark :

We can clearly see, ASN is increasing as we increase the ϕ values. In bivariate setup, if X and Y are highly correlated (i.e. high ϕ), they provide less independent information. So, although we observe both treatments, we gain less total new information per subject, causing the test require more samples to reach a terminal decision. So, we stick to our choice of low value of ϕ for our further analysis.

5 Adaptive Group Sequential Design Under Bivariate Setup:

Now, we wish to ethically allocate treatments under bivariate setup, too. So, we go for adaptive group sequential design. The adaptive component enables modifications based on accumulating joint data, such as re-estimation of parameters, refinement of allocation probabilities, or updating stopping boundaries. At the same time, the group sequential structure ensures rigorous interim decision-making. Together, this approach provides a dynamic and ethically responsible trial design that adapts to real-time evidence across both outcomes simultaneously, making it particularly suited for modern clinical research where multivariate count responses are common.

5.1 Entry Stage Adaptive Group Sequential Design :

Very similarly to the univariate case, The adaptive group sequential design for bivariate data can also be structured in three stages.

i) **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.

ii) **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,

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

Then we carry out the sequential test procedure for second stage as described in the group sequential design.

iii) **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,

$$\begin{pmatrix}\hat{\lambda^*}_A\\ \hat{\theta^*}_A\end{pmatrix} = \begin{pmatrix}\bar{X}_{A_2}\\ \bar{Y}_{A_2}\end{pmatrix} = \frac{1}{50}\sum_{j=1}^{50}\begin{pmatrix}X_{A_2}^{(j)}\\ Y_{A_2}^{(j)}\end{pmatrix} \text{ and } \begin{pmatrix}\hat{\lambda^*}_B\\ \hat{\theta^*}_B\end{pmatrix} = \begin{pmatrix}\bar{X}_{B_2}\\ \bar{Y}_{B_2}\end{pmatrix} = \frac{1}{50}\sum_{j=1}^{50}\begin{pmatrix}X_{B_2}^{(j)}\\ Y_{B_2}^{(j)}\end{pmatrix}$$

Then we carry out the sequential test procedure for third stage as described in the group sequential design.

So, in the test procedure, we are adapting the $\left(\binom{\lambda_A}{\theta_A}, \binom{\lambda_B}{\theta_B}\right)$ with the estimates calculated from the previous stage. Now, we compute the probabilities to calculate the boundary points $(a_k, b_k); k = 1, 2, 3$ for the $size$ and $type - II$ error condition by simulating 1000 samples. Then, we also calculate the Average Sample Number (ASN) in the same way as described in the group sequential design.

Table 16 : ASN table for Entry Stage Adaptive Group Sequential Design :

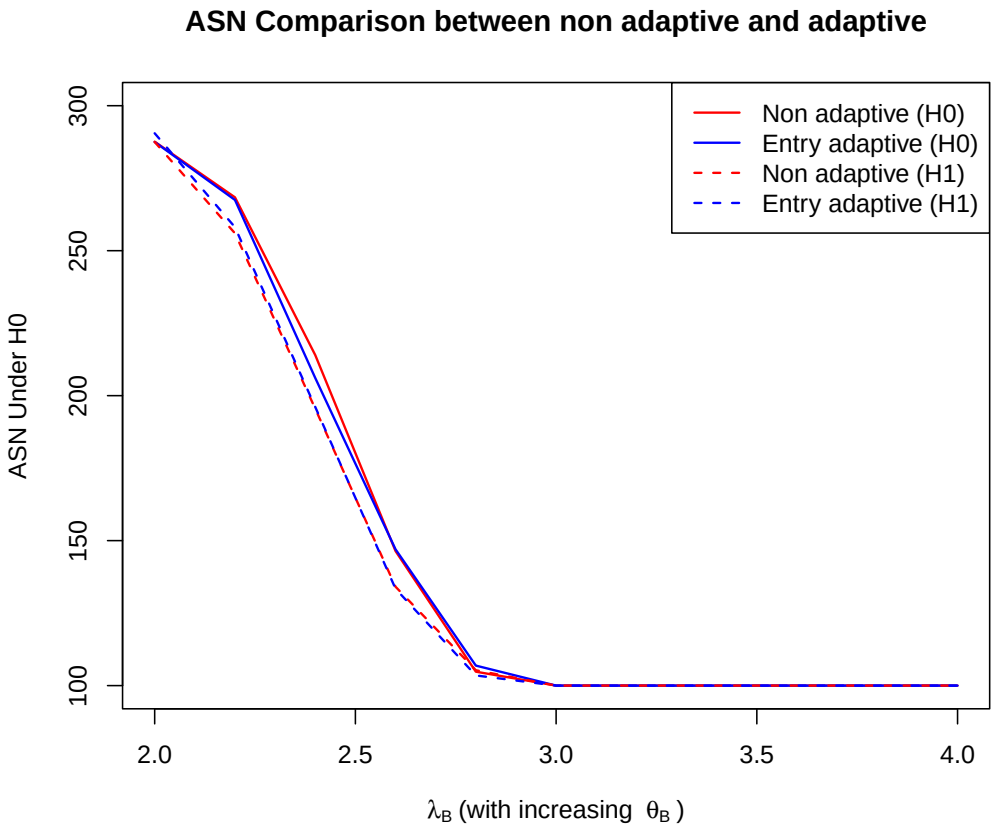
We fix $\lambda_A = 2$ and $\lambda_B = 2.5$. Then, we find Average sample number (ASN) under H_0 and H_1 for different values of λ_B's for the entry stage adaptive group sequential design.

	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

5.2 Comparing Entry Adaptive with Non Adaptive GSD :

To compare the results of entry stage adaptive group sequential design with the non-adaptive group sequential design, we plot the ASN values under H_0 against different values of λ_B and θ_B (keeping $\lambda_A = 2$,$\theta_A = 2.5$, fixed) in a multiple line diagram.

Plot 11 : Comparison of ASN between Non-Adaptive Group Sequential Design and Entry Stage Adaptive Group Sequential Design :



Remark :

We can see, when we deviate away from the null, in few cases entry adaptive is performing better i.e. reducing ASN more; again in few cases non adaptive is performing better (for both under H_0 and H_1) . We will use the entry adaptive mechanism in our further study.

5.3 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.

5.3.1 Adaptive Allocation (R_A):

Here, we define an indicator variable,

$$\delta_i = \begin{cases} 1 & ; \text{ if } i^{th} \text{ individual gets treatment A} \\ 0 & ; \text{ if } i^{th} \text{ individual gets treatment B} \end{cases}$$

We denote,

$$\begin{aligned} R_A &= P(\delta_i = 1) \\ &= P(\text{randomly entered}(i^{th}) \text{ patient will receive treatment A}) \end{aligned}$$

similarly,

$$\begin{aligned} R_B &= P(\delta_i = 0) \\ &= 1 - P(\delta_i = 1) \\ &= 1 - R_A \\ &= P(\text{randomly entered patient will recieve treatment B}) \end{aligned}$$

K be the number of interim. n_k be the sample size of the k^{th} interim. When i^{th} patient $(i = 1, ..., n_k; k = 1, 2, ..., K)$ is ready to be randomized, we allocate treatment A to i^{th} patient $(i = 1, ..., n_k; k = 1, 2, ..., K)$ with probability R_A and we allocate treatment B with probability R_B. 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} patient with higher probability. So, considering this fact in mind, we propose,

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

and similarly,

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

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

Here, we can clearly see, as we move away from the null hypothesis, i.e. the values of $\binom{\lambda_A}{\theta_A}$ and $\binom{\lambda_B}{\theta_B}$ will move far away, then the value of R_A (probability of receiving treatment A) will increase and the value of R_B (probability of receiving treatment B) will decrease in the same manner. Now we can do further interim analysis using these probabilities. For computation purpose, we can describe the whole procedure in the following steps.

i) Here, $(X_A, Y_A) \sim BVPoisson(\lambda_A, \theta_A, \phi_A)$ and $(X_B, Y_B) \sim BVPoisson(\lambda_B, \theta_B, \phi_B)$. K denotes the number of interim. We first equally allocate some treatments (treatment A and treatment B) to small number of patients deterministically. Mathematically, we can say, we generate few samples (say, 4); $\binom{X^{[4]}_{A_k}}{Y^{[4]}_{A_k}} = \left(\binom{X^{(1)}_{A_k}}{Y^{(1)}_{A_k}}, \binom{X^{(2)}_{A_k}}{Y^{(2)}_{A_k}}, \binom{X^{(3)}_{A_k}}{Y^{(3)}_{A_k}}, \binom{X^{(4)}_{A_k}}{Y^{(4)}_{A_k}} \right)$ from $BVPoisson(\lambda_{A_k}, \theta_{A_k}, \phi_A)$and same number of samples $\binom{X^{[4]}_{B_k}}{Y^{[4]}_{B_k}} = \left(\binom{X^{(1)}_{B_k}}{Y^{(1)}_{B_k}}, \binom{X^{(2)}_{B_k}}{Y^{(2)}_{B_k}}, \binom{X^{(3)}_{B_k}}{Y^{(3)}_{B_k}}, \binom{X^{(4)}_{B_k}}{Y^{(4)}_{B_k}} \right); k = 1, 2, ..., K$ from $BVPoisson(\lambda_{B_k}, \theta_{B_k}, \phi_B)$.

Where,

$$\begin{pmatrix}\lambda_{A_k}\\ \theta_{A_k}\end{pmatrix} = \frac{1}{4}\sum_{j=1}^{4}\begin{pmatrix}X_{A_k}^{(j)}\\ Y_{A_k}^{(j)}\end{pmatrix} \text{ and } \begin{pmatrix}\lambda_{B_k}\\ \theta_{B_k}\end{pmatrix} = \frac{1}{4}\sum_{j=1}^{4}\begin{pmatrix}X_{B_k}^{(j)}\\ Y_{B_k}^{(j)}\end{pmatrix} \text{ ; k = 1,2,...,K}$$

Where,

$$\lambda_{A_k} = \frac{1}{4}\sum_{j=1}^{4} X_{A_k}^{(j)} \text{ and } \lambda_{B_k} = \frac{1}{4}\sum_{j=1}^{4} X_{B_k}^{(j)} \text{ ; } k = 1, 2, ..., K$$

ii) 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 $Uniform(0, 1)$) . We also define,

$$R_{A_k}^{(i)} = \frac{\lambda_{B_k} + \theta_{B_k}}{\lambda_{A_k} + \theta_{A_k} + \lambda_{B_k} + \theta_{B_k}}; i = 9, ..., n_k; k = 1, 2, ..., K$$

iii) then,

$$\begin{aligned}\text{if } r_{i_k} \leq R_{A_k}^{(i-1)} \quad &, \quad \text{we draw } \begin{pmatrix}X_{A_k}^{(i)}\\ Y_{A_k}^{(i)}\end{pmatrix} \text{ from } BVPoisson(\lambda_{A_k}, \theta_{A_k}, \phi_A)\\ &\quad ; \ i = 9, ..., n_k \ ; k = 1, 2, ..., K\\ \text{otherwise} \quad &, \quad \text{we draw } X_{B_k}^{(i)} \text{ from } BVPoisson(\lambda_{B_k}, \theta_{B_k}, \phi_B)\\ &\quad ; \ i = 9, ..., n_k \ ; k = 1, 2, ..., K\end{aligned}$$

iv) If the 9^{th}patient gets treatment A, then we adapt $\binom{\lambda_{A_k}}{\theta_{A_k}}$ and $\binom{\lambda_{B_k}}{\theta_{B_k}}$ from the new sample as,

$$\begin{pmatrix}\lambda_{A_k}\\ \theta_{A_k}\end{pmatrix} = \frac{1}{5}\sum_{j=1}^{5}\begin{pmatrix}X_{A_k}^{(j)}\\ Y_{A_k}^{(j)}\end{pmatrix} \text{ and } \begin{pmatrix}\lambda_{B_k}\\ \theta_{B_k}\end{pmatrix} = \frac{1}{4}\sum_{j=1}^{4}\begin{pmatrix}X_{B_k}^{(j)}\\ Y_{B_k}^{(j)}\end{pmatrix} \text{ ; k = 1,2,...,K}$$

and if the 9^{th}patient gets treatment B, then we adapt $\binom{\lambda_{A_k}}{\theta_{A_k}}$ and $\binom{\lambda_{B_k}}{\theta_{B_k}}$ from the new sample as,

$$\begin{pmatrix}\lambda_{A_k}\\ \theta_{A_k}\end{pmatrix} = \frac{1}{4}\sum_{j=1}^{4}\begin{pmatrix}X_{A_k}^{(j)}\\ Y_{A_k}^{(j)}\end{pmatrix} \text{ and } \begin{pmatrix}\lambda_{B_k}\\ \theta_{B_k}\end{pmatrix} = \frac{1}{5}\sum_{j=1}^{5}\begin{pmatrix}X_{B_k}^{(j)}\\ Y_{B_k}^{(j)}\end{pmatrix} \text{ ; k = 1,2,...,K}$$

v) We repeat the step (ii) and step (iii) , then we again adapt the $\binom{\lambda_{A_k}}{\theta_{A_k}}$ and $\binom{\lambda_{B_k}}{\theta_{B_k}}$ from the new sample until we generate total $n_k(k = 1, 2, , , , K)$ number of observations, i.e. until $n_k(k = 1, 2, , , , K)$ patients are assigned by any treatment (A or B).

vi) After we have generated $n_k(k = 1, 2, , , , K)$ number of observations, then we calculate the test statistic $Z_k(k = 1, 2, , , , K)$ and carry out the sequential test procedure as described in the group sequential design. We also calculate the boundary points $(a_k, b_k; k = 1, 2, , , , K)$ from the size condition and from the *type-II error* probabilities to calculate the termination probabilities of the test procedure as described in the group sequential design.

vii) we repeat step (i) to step (vi) for all of the K stages of the group sequential test procedure. We also incorporate entry stage adaptive group sequential design to adapt $\binom{\lambda_{A_k}}{\theta_{A_k}}$ and $\binom{\lambda_{B_k}}{\theta_{B_k}}$ by estimating them with the mean of the total samples generated in the previous stages for each of the K stages.

viii) We calculate the proportion of patients receiving treatment A and treatment B as,

$$\text{prop(A)} = \frac{\text{number of patients recieving treatment A}}{\text{total number of patients } (n)}$$

and,

$$\begin{aligned}\text{prop(B)} &= \frac{\text{number of patients recieving treatment B}}{\text{total number of patients } (n)} \\ &= 1 - \text{prop(A)}\end{aligned}$$

We also calculate the expected sample size (ASN) as,

$$\begin{aligned}ASN &= E(N) \\ &= \sum_{i=1}^{K} n_i p_i\end{aligned}$$

where, p_i probability of terminating the test procedure at i^{th} stage ; $i = 1, 2, ..., K$

Table 17 : ASN for Fully Adaptive GSD under Adaptive Allocation (R_A):

Here, we fix $\lambda_A = 2$ and $\theta_A = 2.5$. We calculate ASN, R_A, Prop(A) = Proportion of patients receiving treatment A, and the standard error of the Prop(A) in the table for different values of λ_B. We iterate the procedure 1000 times R_A and Prop(A). Here, in the table, *RA* denotes the R_A values, *ASN_H0* denotes Average sample number under H_0 and *ASN_H1* denotes Average sample number under H_1 , *Prop_A* denotes the proportion of patients receiving treatment A and *Prop_A_SE* denotes the standard error of the proportion.

	lambda_B	theta_B	ASN_H0	ASN_H1	RA	Prop_A	Prop_A_SE
1	2.0	2.5	288.9	282.0	0.5036791	0.5022333	0.10978888
2	2.2	2.7	289.0	276.2	0.5156898	0.5168633	0.10290776
3	2.4	2.9	288.3	274.5	0.5379178	0.5341433	0.09789600
4	2.6	3.1	288.2	266.2	0.5514714	0.5470500	0.10319961
5	2.8	3.3	287.3	255.2	0.5732740	0.5685067	0.10251760
6	3.0	3.5	287.3	246.5	0.5815798	0.5760000	0.09901472
7	3.2	3.7	281.4	238.0	0.5976686	0.5888467	0.09499605
8	3.4	3.9	281.3	224.0	0.6054343	0.6004033	0.09732002
9	3.6	4.1	280.2	217.8	0.6260322	0.6143633	0.09366175
10	3.8	4.3	273.3	201.7	0.6261073	0.6197700	0.09269529
11	4.0	4.5	273.2	199.9	0.6352020	0.6269467	0.09235214

Remark :

We can see, as we move away from the null, the value of R_A and proportion of patients receiving treatment A is increasing. We face lower reduction in ASN than the non-adaptive GSD or entry stage adaptive GSD, but here our interest is to serve ethical purpose. So, after allocation better treatment to more patients, we still have successfully reduced the sample size, which completely serves our interest.

5.3.2 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)* . We define R_A as earlier,

Here, we define an indicator variable,

$$\begin{aligned} R_A &= P(\delta_i = 1) \\ &= P(i^{th} \text{ patient will recieve treatment A}) \end{aligned}$$

where,

$$\delta_i = \begin{cases} 1 & ; \text{ if } i^{th} \text{ individual gets treatment A} \\ 0 & ; \text{ if } i^{th} \text{ individual gets treatment B} \end{cases}$$

Now, instead of comparing the estimated parameters $\binom{\lambda_A}{\theta_A}$ and $\binom{\lambda_B}{\theta_B}$, we may wish to estimate the probability (R_A) directly (i.e. empirically). So, we introduce another version of R_A (say, R_A^*); which can be defined as follows,

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

It can be carried out in some following steps,

i) Here, $(X_A, Y_A) \sim BVPoisson(\lambda_A, \theta_A, \phi_A)$ and $(X_B, Y_B) \sim BVPoisson(\lambda_B, \theta_B, \phi_B)$. K denotes the number of interims. We first equally allocate some treatments (treatment A and treatment B) to small number of patients deterministically. Mathematically, we can say, 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 $\binom{X_{B_k}^{[4]}}{Y_{B_k}^{[4]}} = \left(\binom{X_{B_k}^{(1)}}{Y_{B_k}^{(1)}}, \binom{X_{B_k}^{(2)}}{Y_{B_k}^{(2)}}, \binom{X_{B_k}^{(3)}}{Y_{B_k}^{(3)}}, \binom{X_{B_k}^{(4)}}{Y_{B_k}^{(4)}} \right); k = 1, 2, ..., K$ from $BVPoisson(\lambda_{B_k}, \theta_{B_k}, \phi_B)$.

ii) 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 $Uniform(0, 1)$) . We also define,

$$\begin{aligned} R_A^* \;=\; & (1/4) \times P(X_{A_k} = X_{B_k}, Y_{A_k} > Y_{B_k}) + (1/4) \times P(X_{A_k} > X_{B_k}, Y_{A_k} = Y_{B_k}) + \\ & (3/4) \times P(X_{A_k} = X_{B_k}, Y_{A_k} < Y_{B_k}) + (3/4) \times P(X_{A_k} < X_{B_k}, Y_{A_k} = Y_{B_k}) + \\ & (1/2) \times P(X_{A_k} > X_{B_k}, Y_{A_k} < Y_{B_k}) + (1/2) \times P(X_{A_k} < X_{B_k}, Y_{A_k} > Y_{B_k}) \\ & (1/2) \times P(X_{A_k} = X_{B_k}, Y_{A_k} = Y_{B_k}) + P(X_{A_k} < X_{B_k}, Y_{A_k} < Y_{B_k}) \\ & ; k = 1, 2, ..., K \end{aligned}$$

iii) The R_A^* is to be calculated empirically. We simulate 50 samples $X_{A_k}^{[50]} = (X_{A_k}^{(1)}, X_{A_k}^{(2)}, ..., X_{A_k}^{(50)})$ from $poisson(\lambda_A + \phi)$, 50 samples $X_{B_k}^{[50]} = (X_{B_k}^{(1)}, X_{B_k}^{(2)}, ..., X_{B_k}^{(50)})$ from $poisson(\lambda_B + \phi)$, 50 samples $Y_{A_k}^{[50]} = (Y_{A_k}^{(1)}, Y_{A_k}^{(2)}, ..., Y_{A_k}^{(50)})$ from $poisson(\theta_A + \phi)$, 50 samples $Y_{B_k}^{[50]} = (Y_{B_k}^{(1)}, Y_{B_k}^{(2)}, ..., Y_{B_k}^{(50)})$ from $poisson(\lambda_B + \phi)$. Here, total number of permutations = 2500. So, we get total 2500 pair of observations $(X_{A_k}^{(i)}, X_{B_k}^{(j)})$; $i = 1, 2, , , 50$; $j = 1, 2, ..., 50$; $k =$

$1, 2, ..., K$. and total 2500 pair of observations $(Y_{A_k}^{(i)}, Y_{B_k}^{(j)})$; $i = 1, 2, , , 50$; $j = 1, 2, ..., 50$; $k = 1, 2, ..., K$. Then, we can calculate,

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

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

Similarly, we can calculate the other probability terms, too.

iv)then,

$$\begin{aligned} \text{if } r_{i_k} \leq R_{A_k}^{(i-1)} \quad , \quad & \text{we draw } \binom{X_{A_k}^{(i)}}{Y_{A_k}^{(i)}} \text{ from } BVPoisson(\lambda_{A_k}, \theta_{A_k}, \phi_A) \\ & ; \; i = 9, ..., n_k \; ; k = 1, 2, ..., K \\ \text{otherwise} \quad , \quad & \text{we draw } X_{B_k}^{(i)} \text{ from } BVPoisson(\lambda_{B_k}, \theta_{B_k}, \phi_B) \\ & ; \; i = 9, ..., n_k \; ; k = 1, 2, ..., K \end{aligned}$$

v) If the 9^{th}patient gets treatment A, then we adapt $\binom{\lambda_{A_k}}{\theta_{A_k}}$ and $\binom{\lambda_{B_k}}{\theta_{B_k}}$ from the new sample as,

$$\binom{\lambda_{A_k}}{\theta_{A_k}} = \frac{1}{5} \sum_{j=1}^{5} \binom{X_{A_k}^{(j)}}{Y_{A_k}^{(j)}} \text{ and } \binom{\lambda_{B_k}}{\theta_{B_k}} = \frac{1}{4} \sum_{j=1}^{4} \binom{X_{B_k}^{(j)}}{Y_{B_k}^{(j)}} \text{ ; k = 1,2,...,K}$$

and if the 9^{th}patient gets treatment B, then we adapt $\binom{\lambda_{A_k}}{\theta_{A_k}}$ and $\binom{\lambda_{B_k}}{\theta_{B_k}}$ from the new sample as,

$$\binom{\lambda_{A_k}}{\theta_{A_k}} = \frac{1}{4} \sum_{j=1}^{4} \binom{X_{A_k}^{(j)}}{Y_{A_k}^{(j)}} \text{ and } \binom{\lambda_{B_k}}{\theta_{B_k}} = \frac{1}{5} \sum_{j=1}^{5} \binom{X_{B_k}^{(j)}}{Y_{B_k}^{(j)}} \text{ ; k = 1,2,...,K}$$

vi) We repeat the step (ii) , (iii) and step (iv) , then we again adapt the λ_{A_k} and λ_{B_k} from the new sample and we continue adding new samples in X_{A_k} and X_{B_k} until we generate total $n_k(k = 1, 2, , , K)$ number of observations, i.e. until $n_k(k = 1, 2, , , K)$ patients are assigned by either treatment A or treatment B.

vii) After we have generated $n_k(k = 1, 2, , , K)$ number of observations, then we calculate the test statistic $T_k^{(s)}(s = 1, 2, 3; k = 1, 2, , , K)$ and carry out the sequential test procedure as described in the group sequential design. We also calculate the boundary points $(a_k, b_k; k = 1, 2, , , K)$ from the size condition and from the *type-II error* probabilities to calculate the termination probabilities of the test procedure as described in the group sequential design.

viii) we repeat step (i) to step (vii) for all of the K stages of the group sequential test procedure. We also incorporate entry stage adaptive group sequential design to adapt λ_{A_k} and λ_{B_k} by estimating them with the mean of the total samples generated in the previous stages for each of the K stages.

ix) We calculate the proportion of patients receiving treatment A and treatment B as,

$$\text{prop(A)} \; = \frac{\text{number of patients recieving treatment A}}{\text{total number of patients } (n)}$$

and,

$$\begin{aligned} \text{prop(B)} &= \frac{\text{number of patients recieving treatment B}}{\text{total number of patients } (n)} \\ &= 1 - \text{prop(A)} \end{aligned}$$

We also calculate the expected sample size (ASN) as,

$$\begin{aligned} ASN &= E(N) \\ &= \sum_{i=1}^{K} n_i p_i \end{aligned}$$

where, p_i probability of terminating the test procedure at i^{th} stage ; $i = 1, 2, ..., K$

Table 18: ASN for Fully Adaptive GSD under Adaptive Allocation (R_A^*) :

Here, we fix $\lambda_A = 2$ and $\theta_A = 2.5$. We calculate ASN, R_A^*, Prop(A) = Proportion of patients receiving treatment A, and the standard error of the Prop(A) in the table for different values of λ_B. We have simulated 1000 times to calculate R_A and Prop(A). Here, in the table, *RA_Star* denotes the R_A^* values, *ASN_H0* denotes Average sample number under H_0 and *ASN_H1* denotes Average sample number under H_1, *Prop_A* denotes the proportion of patients receiving treatment A and *Prop_A_SE* denotes the standard error of the proportion.

	lambda_B	theta_B	ASN_H0	ASN_H1	RA	Prop_A	Prop_A_SE
1	2.0	2.5	289.1	283.5	0.510270	0.5034700	0.1495623
2	2.2	2.7	289.0	278.2	0.529005	0.5268467	0.1486632
3	2.4	2.9	288.3	276.0	0.543905	0.5443867	0.1485932
4	2.6	3.1	288.2	266.0	0.575915	0.5722200	0.1455187
5	2.8	3.3	287.7	252.1	0.601805	0.5997367	0.1494518
6	3.0	3.5	288.4	241.8	0.624145	0.6218700	0.1503975
7	3.2	3.7	284.4	238.9	0.639580	0.6312600	0.1452108
8	3.4	3.9	285.8	227.6	0.655970	0.6554533	0.1412290
9	3.6	4.1	284.7	216.9	0.681490	0.6776100	0.1376827
10	3.8	4.3	262.9	188.6	0.704795	0.7008967	0.1300240
11	4.0	4.5	272.9	191.3	0.703360	0.7035467	0.1318772

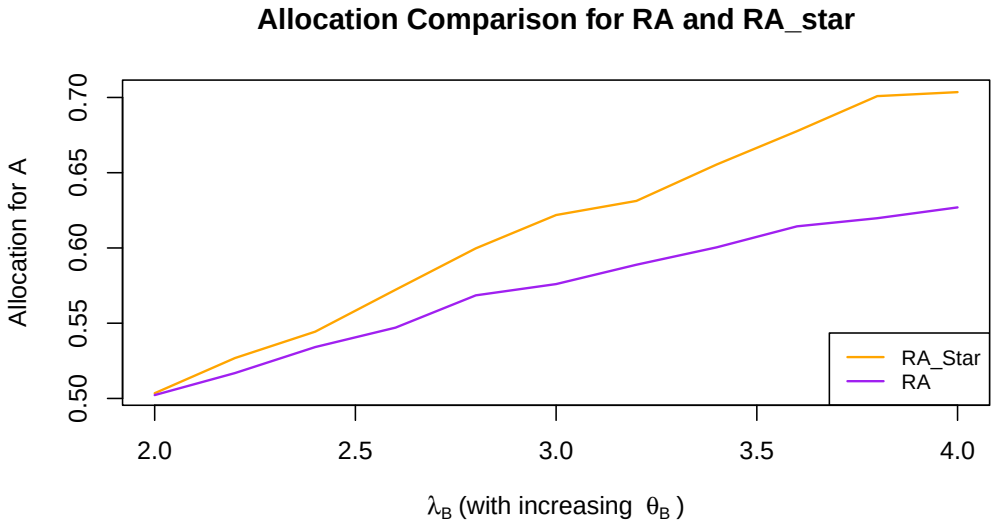
Remark :

We can see, as we move away from the null, the value of R_A^* and proportion of patients receiving treatment A is increasing.

5.4 Comparing Adaptive Allocation Methods Using R_A and R_A^* :

Now, we wish to compare the proportion of patients receiving treatment A for different between the adaptive allocation methods using R_A and R_A^*. We fix $\lambda_A = 2$ and $\theta_A = 2.5$. Now, we plot *propA* for diiferent values of (λ_B, θ_B) for these two methods.

Plot 12 : Allocation Comparison for R_A and R_A^* :



Remark :

We can find that, using R_A^*, the procedure is allocating treatment A to more patients than the procedure using R_A. Also from the tables, we can see, it is reducing the sample size more than the previous test procedure using R_A.

5.5 Overall Comparison :

Table 19 : Comparison of ASN (Under H_1) for different methods :

```
Comparison of ASN (Under H1) 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
```

Remark :

We can observe similar patterns (as in the univariate setup) in the bivariate setup as well.

6 Conclusion :

In this study, we developed and evaluated a sequence of trial designs for comparing two treatments based on count data, beginning with univariate group sequential designs (GSDs) and extending them to adaptive and ethically informed frameworks. Our univariate analysis showed that while adaptive allocation rules like improved ethical treatment assignment, they came at the cost of increased average sample number (ASN) than non adaptive framework, highlighting a trade-off between ethical allocation and statistical efficiency.

Building upon this, we extended our approach to a bivariate Poisson setup, modeling two correlated count outcomes (e.g., disease episodes and doctor visits), which better captures the complexity of many real-world clinical trials. We implemented a fully adaptive bivariate GSD using a similar allocation logic and observed consistent patterns: adaptive designs improved ethical allocation, though with increased ASN—especially with higher correlation (via shared parameter ϕ)

Looking forward, several promising directions can enhance our framework:

- Incorporating baseline covariates (e.g., age, comorbidities) to allow covariate - adjusted allocation rules and stratified analysis.
- Exploring alternative correlation structures, such as using copula-based or negative binomial bivariate models.
- Extending to more than two treatment arms or multi-dimensional endpoints, such as including quality-of-life metrics alongside clinical counts.
- Incorporate utility functions or Bayesian priors that reflect clinical priorities.

In summary, our work presents a flexible, ethically aware design framework for trials with count data, with strong potential for further extension in practical, multi-dimensional clinical research settings.

7 References :

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8 Appendix :

In the course of developing and implementing the methodologies discussed in this project, we have written and executed several comprehensive R programs to perform simulations, create tables and generate visualizations that support our theoretical findings and empirical results. These R scripts encapsulate the full scope of our analytical workflow, including data generation under bivariate Poisson models, adaptive allocation mechanisms, interim analysis procedures, and graphical representations of test statistics, allocation patterns, and average sample numbers (ASN).

To ensure transparency, reproducibility, and accessibility of our work, we have compiled and organized all relevant R codes, datasets, and outputs into a dedicated GitHub repository. This repository serves as a centralized resource for anyone interested in exploring our computational framework, replicating our results, or extending the methodology for further research. The repository will remain publicly available and is structured with clear documentation and modular code files to facilitate understanding and reuse.

All R codes are accessible from the following GitHub repository:
https://github.com/Sahil01S/STAT1092-Research-Project