Modified Simon's Two-Stage Design with RShiny application

Two-Stage Design for Phase IIa Clinical Trials

A small group of patients is enrolled in the first stage. The joining, in the second stage, of the second group of patients is conditioned by the outcome of the first one.

Adaptive designs → Trials where a change or a **decision** is made when the trial is still going on.

- Early stopping → Lack of efficacy
- Sample size re-estimation →
  - To have an appropriate sample size for our study
  - A sample size which balance ethical and practical aspects (validity costs, regulatory…)

- More flexibility
- Give control over the trial to the trialist

Use the available information to **decrease time** and **costs**

Two-stage designs are adaptive designs and are used especially in **phase IIa** clinical trials.

Phase II clinical trials:
- Proof-of-content and dose-finding
- Have **high failure rate** (this is why adaptive design are useful here).

→ **Phase IIa** emphasizes a **quick evaluation** and the **early futility assessment.**

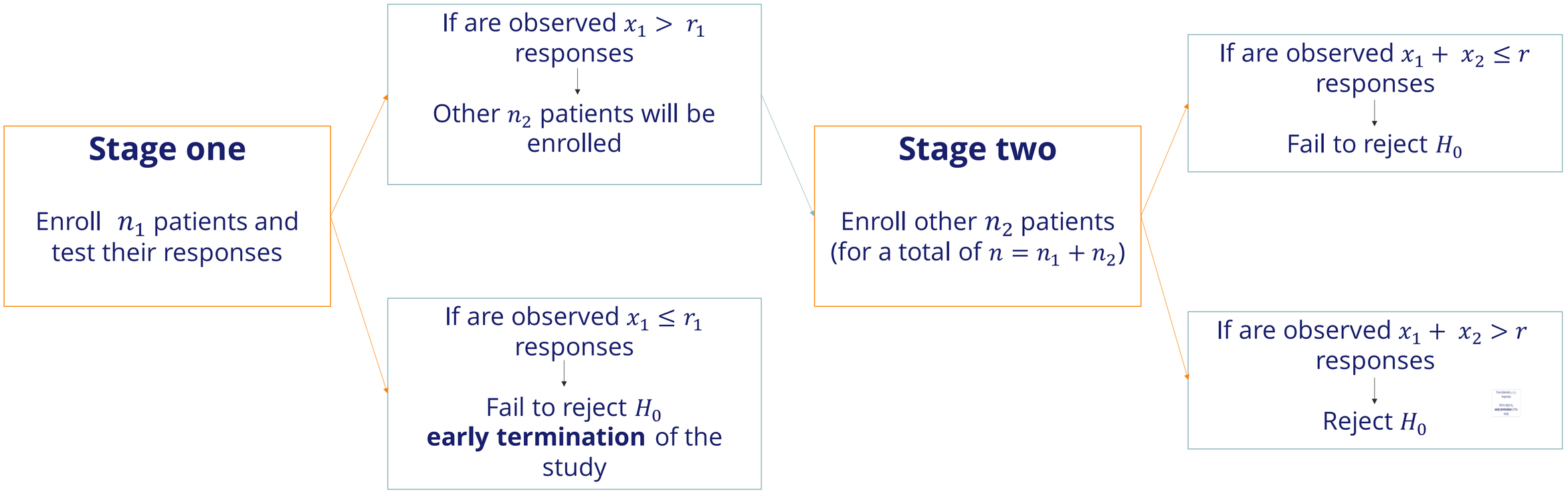
→ Phase IIb studies the unknown dose response curve to get the right model and doses.

The **purpose** is to find proof of **positive response** for a proposed treatment to recommend it for **further clinical trial evaluations.**

Simon's Two-Stage Design

One of the most popular two-stage design is the **Simon's two-stage design:**

- Used in **single-arm** trials → often in **oncology trials**;
- It allows to **stop early for futility**;
- The objective is trying to establish whether the proportion of responses is sufficiently high to recommend the next steps of the clinical trial phases.
- It follows this scheme:



Simon's Two-Stage Design

The theory

- Let $X \sim Bi(n, p)$ the random variable that describes the binary responses of n subjects with probability of success p;

- The notation used to identify a two-stage design is $(r_1/n_1, r/n)$, where
  - n_1 and n are the **number of patients** to be accrued at the first stage and the maximum sample size $(n = n_1 + n_2)$;
  - r_1 and r are the **boundary values** at stage one and at the end of the study.

- To determine these values, identifying the possible two-stage designs, we must satisfy the **conditions** given by the **pre-specified design parameters**:
  - Let p_0 and p_1 denote, respectively, the maximum unacceptable and the minimum acceptable probability of response, with $p_0 < p_1$;
  - We want to test $\begin{cases} H_0: p < p_0 \\ H_1: p \geq p_1 \end{cases}$, with type I error probability α and a power $1 - \beta$.

So, given the design parameters $(\boldsymbol{p_0, p_1, \alpha, \beta})$ we can identify all the suitable designs $(\boldsymbol{r_1/n_1, r/n})$ which satisfy the conditions.

Simon's Two-Stage Design

The theory

Given $b(\cdot\,;\ p,\ m)$ the binomial probability density function and $B(\cdot\,;\ p,\ m)$ its distribution function with probability of success p and m the number of trials, for a **two-stage design** we have:

- $Pet(p) = B(r_1;\ p,\ n_1) = P(X\ \leq\ r_1, n; p) \longrightarrow$ **probability of early termination after stage one**;
- $R(p) = B(r_1;\ p,\ n_1) + \sum_{x=\,r_1+1}^{\min(n_1,r)} b(x;\ p,\ n_1)B(r\ -x;\ p,\ n_2) \longrightarrow$ **probability of rejecting the treatment** (accepting H_0);
- $EN =\ n_1 + \big(1 - Pet(p_0)\big)\cdot n_2 \longrightarrow$ **expected sample size under null hypothesis.**

> **Early termination** allowed when the drug has **low activity**;
> **Early acceptance** is **not** permitted.

Simon's Two-Stage Design

The algorithm

How works the search for the numbers of patients and boundary levels.

It is a **grid search**:

- N_{max} — For a fixed N_{max}
  - n — for each value of $n \in (1, N_{max})$
    - n_1 — for each value of $n_1 \in (1, n-1)$
      - r_1 — for each value of $r_1 \in (0, n_1)$
        - r — for each value of $r \in (r_1 + 1, n)$

For the j-th combination of these values $(r_1/n_1, r/n)_j$ calculate:

- $\alpha_j = 1 - R(p_0)$
- $\beta_j = R(p_1)$
- $Pet_j(p_0)$
- EN_j

If $\boldsymbol{\alpha_j \leq \alpha}$ and $\boldsymbol{\beta_j \leq \beta}$ (α and β design parameters) then the j-th combination is a **suitable design**

- The **minmax design** is the j-th design where $\boldsymbol{n_j}$ is the smallest;
- The **optimal design** is the j-th design where $\boldsymbol{EN_j}$ is the smallest.

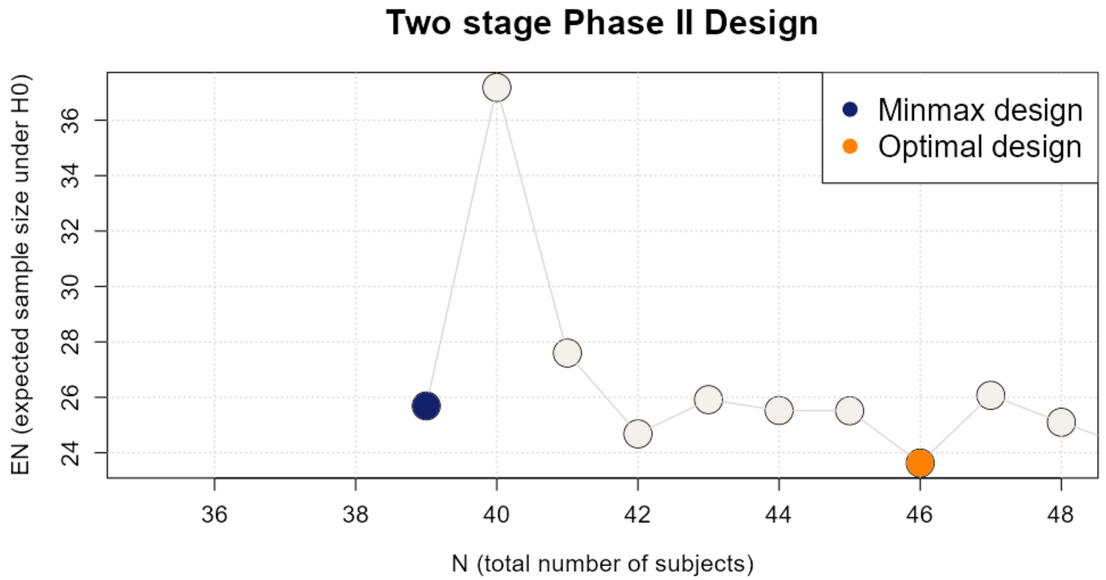
How to **choose between the two**: see how much the two designs differ, consider the accrual time, heterogeneous population…

Example 1

With the given the design parameters find **all the suitable Simon's two-stage designs**.

- Type I probability error $\alpha = 0.05$
- Power $1 - \beta = 0.80$
- Maximum unacceptable probability $p_0 = 0.30$
- Minimum acceptable probability $p_1 = 0.50$

	r1	n1	r	N	EN	Pet0
Minmax	6	19	16	39	25.69	0.67
2	15	37	16	40	37.18	0.94
3	4	15	17	41	27.6	0.52
4	6	18	17	42	24.68	0.72
5	8	22	17	43	25.92	0.81
6	5	16	18	44	25.53	0.66
7	6	18	18	45	25.51	0.72
Optimal	5	15	18	46	23.63	0.72
9	6	18	19	47	26.07	0.72
10	4	13	19	48	25.1	0.65



Here are displayed the first ten suitable designs.

According to the optimal design:

- to go at the second stage, we want to see at least 5 out of 15 responses at stage one;
- with a total number of 46 patients, we want to see 18 positive responses to reject H_0.

According to the minmax design:

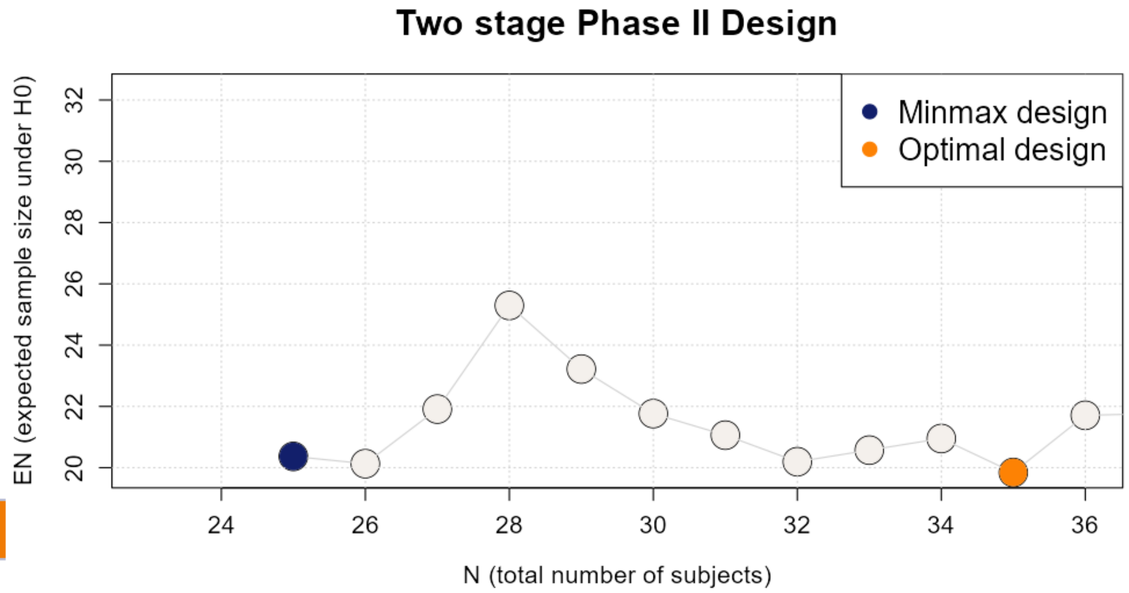
- to go at the second stage, we want to see at least 6 out of 19 responses at stage one;
- with a total number of 39 patients, we want to see 16 positive responses to reject H_0.

Example 2

With the given the design parameters find **all the suitable Simon's two-stage designs**.

- Type I probability error $\alpha = 0.10$
- Power $1 - \beta = 0.90$
- Maximum unacceptable probability $p_0 = 0.10$
- Minimum acceptable probability $p_1 = 0.30$

	r1	n1	r	N	EN	Pet0
Minmax	1	16	4	25	20.37	0.51
2	2	18	4	26	20.13	0.73
3	3	21	4	27	21.91	0.85
4	4	25	4	28	25.29	0.9
5	1	17	5	29	23.22	0.48
6	1	15	5	30	21.76	0.55
7	1	14	5	31	21.06	0.58
8	1	13	5	32	20.19	0.62
9	1	13	5	33	20.57	0.62
10	1	13	5	34	20.95	0.62
Optimal	1	12	5	35	19.84	0.66
12	1	13	6	36	21.71	0.62



For the optimal design: $n_1 = 12,\ N = 35,\ EN = 19.84$
For the minmax design: $n_1 = 16,\ N = 25,\ EN = 20.37$

- The expected sample sizes are similar;
- The optimal design exposes few patient (n_1) to a potentially inactive treatment;
- We might prefer larger n_1 when patients population is very heterogeneous;
- If the accrual rate is of 10 patients per year, it could take one year longer to complete the study with the optimal design;

Modified Simon's Two-Stage Design

The following modification delineates the conditional probability approach to the discrete binary response rate for the single-armed phase II trials.

Why we want to modify the Simon's two-stage design:

- These designs are rather **rigid** in their **settings** because of the **assumed response rate**, **pre-specified rejection rules** and **fixed sample sizes** at each stage;
- We could use the **information** given by the first stage to **redesign optimally** the second stage.

How we can modify:

→ **Adjusting the sample size** to enhance the power, using a **flexible monitoring schedule** for **interim analysis** and discussing the early termination also for **overwhelming efficacy**;

→ Using **conditional probability approach.**

The modification follows these steps:

1. Consider the **fixed sample size design** without any interim analysis to obtain the **maximal sample size.**
2. Conduct an **interim analysis**:
    - fix **the sample size for the interim analysis** and see the **number of responses observed**;
    - draw the **monitoring regions** to understand how to continue the study;
    - allow for **early termination** due to lack of efficacy and or overwhelming efficacy;
    - continue the study with the stage two by **adjusting the sample size** to enhance the power.

Modified Simon's Two-Stage Design

The fixed sample size design

- Let $X \sim Bi(N, p)$ the random variable that describes the binary responses of N subjects with probability of success p: $X_i = 1$ with probability p and $X_i = 0$ with probability $1 - p$, where $i = 1, \ldots, N$ with N is the total number of subjects.
- Let $X_n = \sum_{i=1}^{n} X_i$ denote the total number of responses out of n patients with $b(x\,;\, p,\ n)$ its binomial probability density function and $B(x\,;\, p,\ n)$ its distribution function.
- For binary data consider the hypothesis test $\begin{cases} H_0\colon\ p = \ p_0 \\ H_1\colon\ p = \ p_1 \end{cases}$, and assume $p_1 > p_0$.
- We would like to have a **power** of $1 - \beta$ and a **Type I error rate** α.

To determine the **sample size N** and the **critical boundary R** such that, if $X_N \geq R$ then we reject H_0 and claim the drug is worthy of further study, we must satisfy

- $P(\text{reject } H_0 | H_0 \text{ is true}) = P(X_N \geq R\ | p = \ p_0) = 1\ - B(R\ - 1,\ p_0,\ N) \leq \alpha$,
- $1\ - B(R\ - 1,\ p_1,\ N)\ \geq 1 - \ \beta$.

Modified Simon's Two-Stage Design

Trial monitoring: Simon's two-stage type of design and interim analysis

Consider now a **Simon's two-stage *type* of designs**: suppose we want to conduct an **interim analysis** when n_1^* patients complete the study (with $n_1^* \neq n_1$ where n_1 is the number of patients enrolled at the first stage of the Simon's two-stage of designs).

To **evaluate the result** of the **interim analysis** We need

- m the **threshold number** of responses needed for early termination for overwhelming efficacy;
- $\alpha_1 < \alpha$ the **alpha spent** to test the hypothesis at the interim analysis such that if

$$\alpha_1 = P\left(X_{n_1} \geq m \,\middle|\, p_0\right) = 1 - B(m - 1, p_0, n_1^*)$$

then to control the overall Type I error we have

$$P\left(X_{n_1^*} + X_{N - n_1^*} \geq R \,\middle|\, r_1^* \leq X_{n_1^*} < m\right) P(r_1^* \leq X_{n_1^*} < m) \leq \alpha - \alpha_1$$

thus

$$\sum_{y=r_1^*}^{m-1} \left(1 - B(R - y - 1, p_0, N - n_1^*)\right) b(y, p_0, n_1^*) \leq \alpha - \alpha_1$$

Once $\boldsymbol{m}$ and the timing $\boldsymbol{n_1^*}$ of the interim analysis are fixed:

1. Set $\boldsymbol{r_1^* = 0}$: futility is not used in "buying back" the alpha level;
2. Calculate $\boldsymbol{\alpha_1}$;
3. Adjust the critical value R of the fixed design to $\boldsymbol{R'}$ $(R' \geq R)$.
4. Draw the **monitoring region** and see where the result of the interim analysis falls.

Note that for **Simon's two-stage design** there is **no early stop for efficacy**, thus

- $\alpha_1 = 0$
- $m > n_1^*$

Modified Simon's Two-Stage Design

The conditional power

The monitoring regions are drawn by means of the **conditional power**.

The conditional power CP can be expressed under the

- **alternative hypothesis**: $CP_a = P(X_N \geq R' \mid p = p_1, X_{n_1^*} = x) = 1 - B(R' - x - 1, p_1, N - n_1^*)$;
- **current trend** $\hat{p} = \frac{X_{n_1^*}}{n_1^*}$: $CP_c = P\left(X_N \geq R' \mid p = \hat{p}, X_{n_1^*} = x\right) = 1 - B(R' - x - 1, \hat{p}, N - n_1^*)$, where another choice for p can be $\bar{p} = \frac{p_0 + p_1}{2}$.

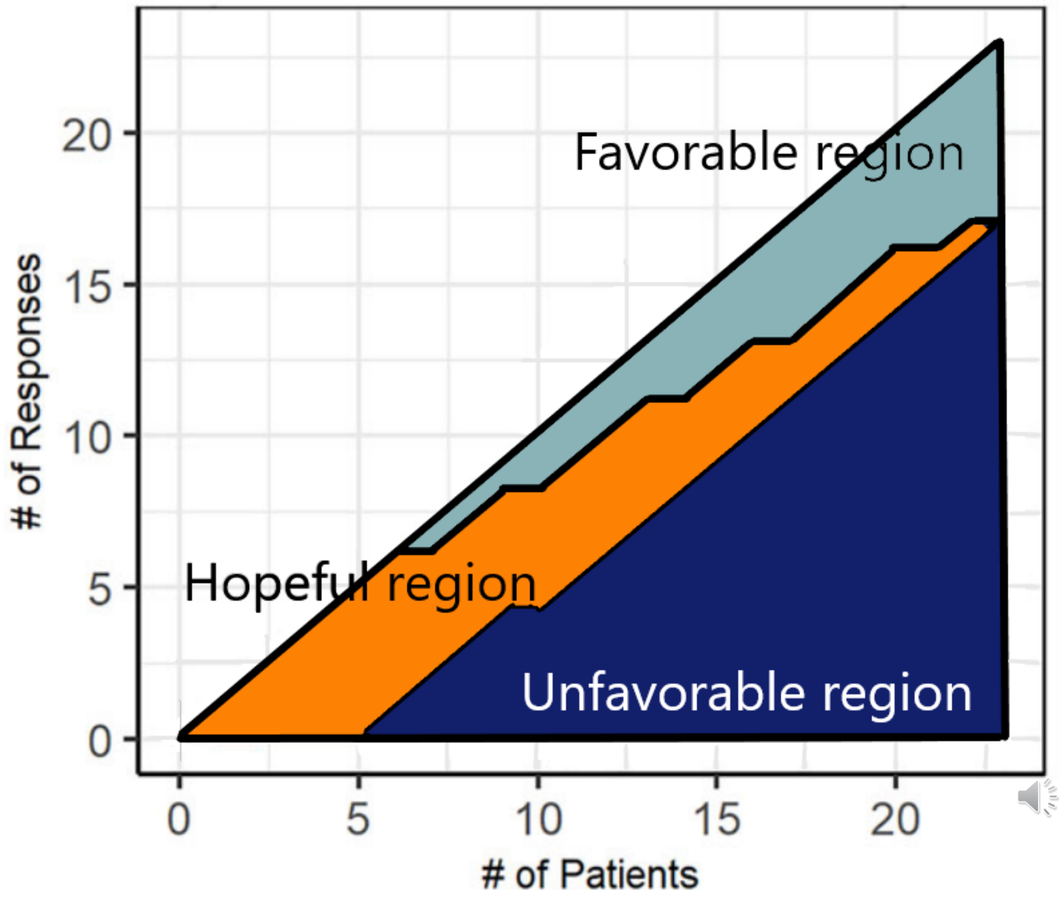
The conditional power allows to **define three regions** which help to understand the **direction** of the trial.

Modified Simon's Two-Stage Design

The monitoring regions

The interim analysis result can fall into **three different regions**:

- **Favorable region**: $CP \geq q_1$ ⟶ early termination of the trial for *overwhelming efficacy*.
- **Unfavorable region**: $CP < q_2$ ⟶ early termination of the trial for *lack of efficacy*;
- **Hopeful region**: $q_2 \leq CP < q_1$ ⟶ the trial should continue;



Modified Simon's Two-Stage Design

The monitoring regions

We can **stop** the trial if our interim analysis result falls into
- **Favorable region**: stop for **overwhelming efficacy**.
- **Unfavorable region**: stop for **lack efficacy**.

We can **continue** the study if our interim analysis' result fall into the **hopeful region**: we may want to

- **keep** the original sample size given by the fixed design;
- **increase** the sample size beyond N to **enhance the power**, depending on the observed response rate at interim.

To increase the sample size N to N^* and the rejection boundary R to R^* these two conditions must be satisfied:

i. $CP_0(N^*, R^*) \leq CP_0(N, R')$,

ii. $CP(N^*, R^*) = 1 - B(R^* - x - 1,\ p, N^* - n_1^*) \geq 1 - \beta'$

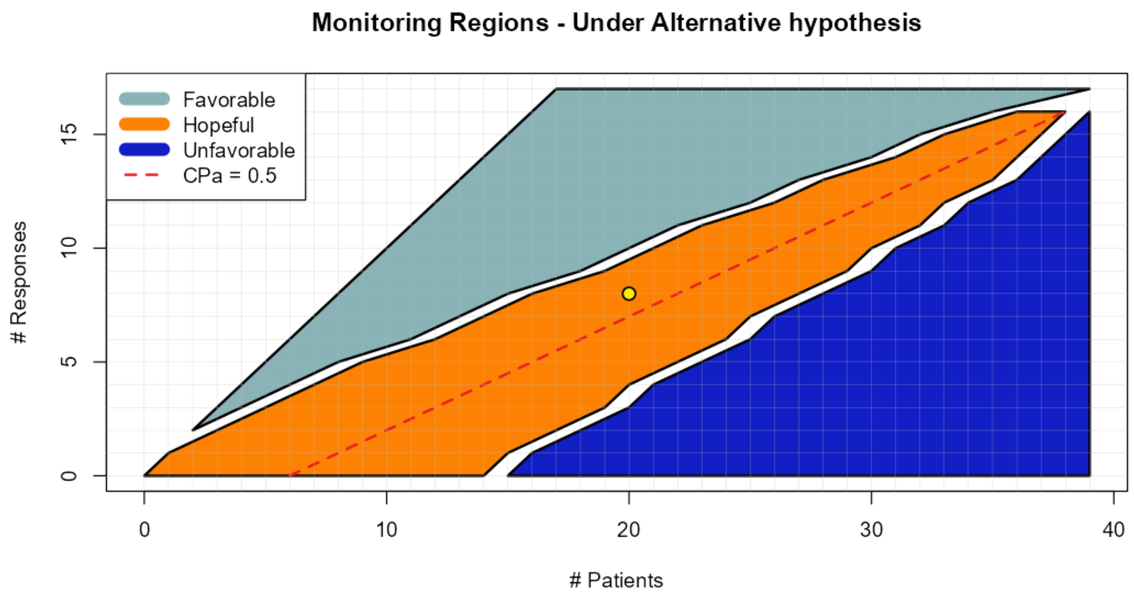
Where $p = p_1$ and $p = \hat{p}$ for the conditional power under alternative hypothesis and current trend, and where $1 - \beta'$ is the level of power we require to reach given the interim result.

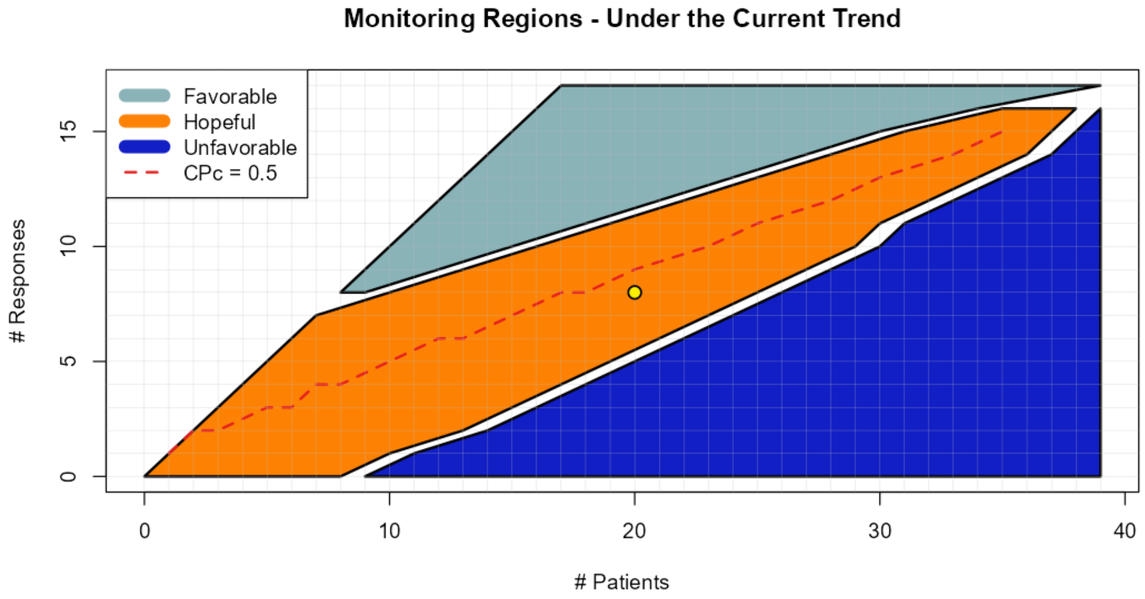
The **optimal solution** (N^*, R^*) is the one, among all the feasible solution, where N^* is the **smallest**.

Example 1 (continued)

Design parameters: $\alpha = 0.05$, $\beta = 0.20$, $p_0 = 0.30$ and $p_1 = 0.50$.

1. Consider the **fixed sample size design** to obtain the **maximal sample size** → $N = 39, R = 17$.
2. Suppose we want to conduct the **interim analysis** when $n_1^* = 20$ patients complete the study and suppose we observe $X_{n_1^*} = 8$ **positive responses**. → After the interim analysis we calculate R' $(R' \geq R)$, and we obtain $R' = 17$.
3. We set $0.05 \leq CP < 0.90$ for the hopeful region. The monitoring regions graphs are:





4. In both cases the result falls into the **hopeful region**;
5. We decide to go on with the study **adjusting the sample size** and the **rejection boundary** to **enhance the power** (for $CP \geq 0.87$);

→ $N^* = 58$, $R^* = 24$ under the alternative hypothesis

→ $N^* = 160$, $R^* = 58$ under the current trend

R Shiny application

The R code for the RShiny application can be found at the following GitHub repository.

https://github.com/AnnaMontin/SimonTwoStageDesign.git

Bibliography

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