Internship presentation

Biostatistics of classical and adaptive designs and application to clinical trial simulations

Hussein Jouni

Danone Nutricia Research

Biometry and data sciences department

Supervised by Laurent Quinquis

6 November 2017

Summary

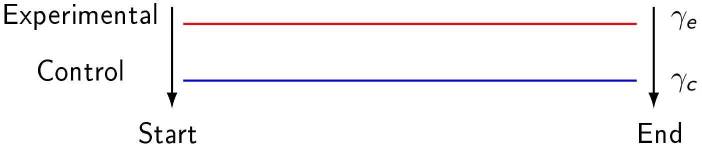
1. Context
   (a) Clinical designs
   (b) Introduction to clinical trial simulations
2. A clinical study
3. Classical designs
   (a) Elements of biostatistics
   (b) Probability of success
4. Adaptive designs
   (a) Group Sequential Design
   (b) Sample-size re-estimation Design
   (c) Enrichment Design

CONTEXT

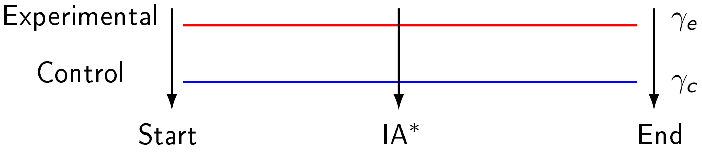
Context
a) Clinical designs

Classical designs : no analysis during the study

Example : Parallel designs

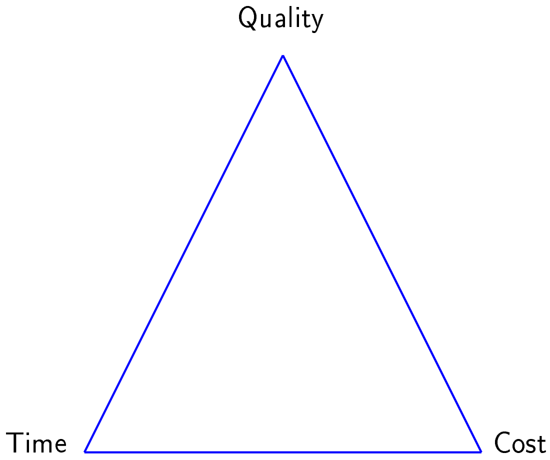


Adaptive designs : decision making is allowed during the study



IA* : Interim Analysis

Context
b) Clinical designs



Input parameters → Algorithm → Output parameters

Input parameters:

Treatment effect

Sample-size

Errors α, β

...

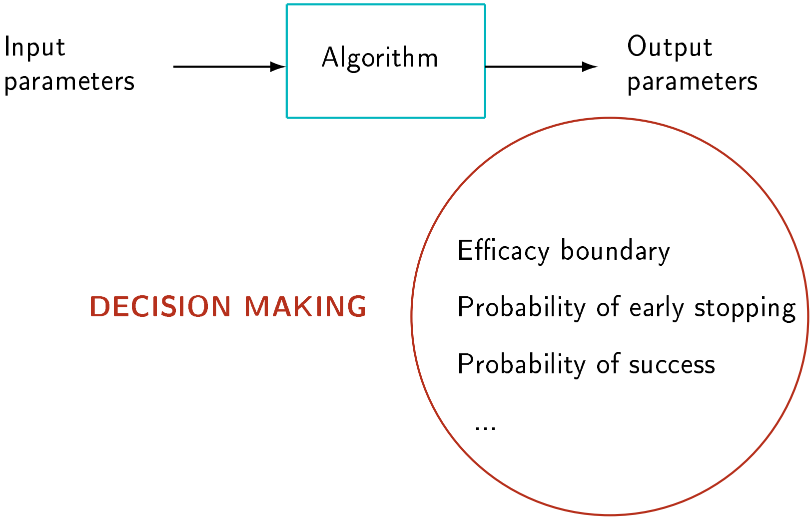
Output parameters:

Efficacy boundary

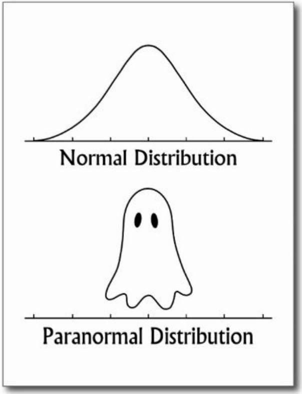
Probability of early stopping

Probability of success

...

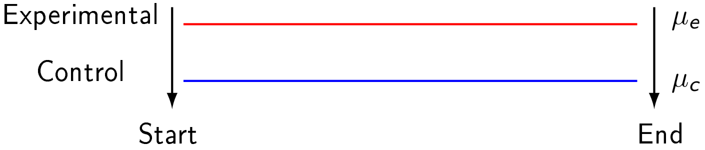

Input parameters
Algorithm
Output parameters
DECISION MAKING
Efficacy boundary
Probability of early stopping
Probability of success
...

A CLINICAL STUDY



A clinical study

- Primary endpoint : Average of a given value (**continuous**)



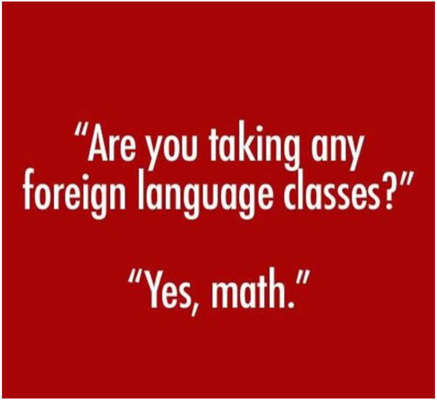
Treatment effect : $\theta = \mu_e - \mu_c$

A clinical study

- Population
  - Subgroup 1 : Ω_1
  - Subgroup 2 : Ω_2
- Hypotheses on Ω_1
  - $\theta = 7$
  - $\sigma = 15$

$$\boxed{N = 144 \text{ subjects}}$$

CLASSICAL DESIGNS



Hypothesis testing for superiority

$$H_0 : \theta = 0 \qquad H_a : \theta > 0$$

Z-Statistics (Wald statistics) :

$$z = \frac{\widehat{\theta}\,\sqrt{N}}{2\,\widehat{\sigma}}$$

- $\widehat{\theta}$: Observed effect
- $\widehat{\sigma}$: Observed standard deviation

Before the study

Experimental (μ_e, σ)

Placebo (μ_c, σ)

SUPPOSED

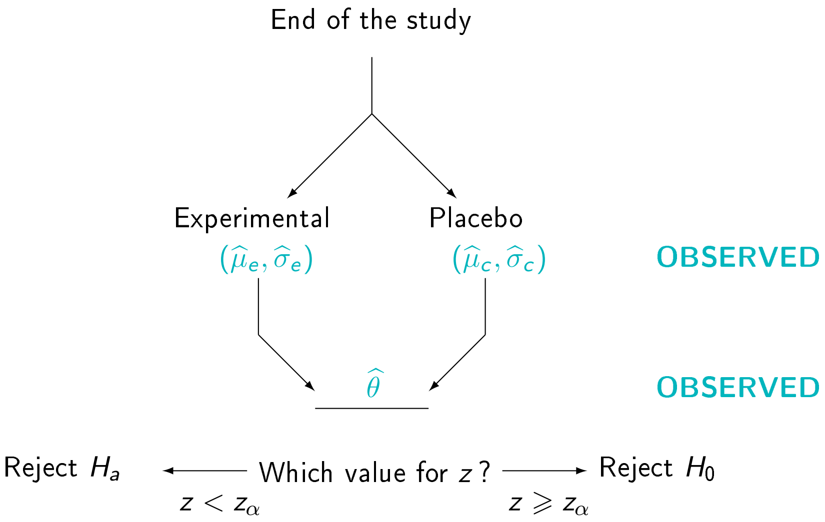
$\theta \sim \mathcal{N}$

SUPPOSED

$$z \sim \mathcal{N}(0,1) \xleftarrow{H_0} \text{Which value for } z\,? \xrightarrow{H_a} z \sim \mathcal{N}\left(\frac{\theta\sqrt{N}}{2\,\sigma}, 1\right)$$

Classical designs

a) Elements of biostatistics



Values taken from a previous study on $m = 50$ subjects per arm :

$$d = \{5, 6, 7\} \qquad s = \{15, 25, 35\}$$

Problem

GREAT UNCERTAINTY ON θ

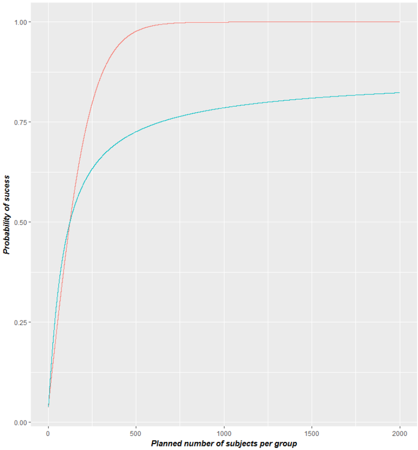
What are the chances of demonstrating an effect ?

Power vs. Probability of success

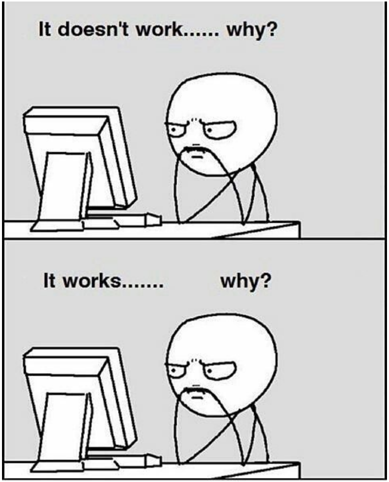
Probability of rejecting H_0

- **Power** : $\theta = k$
- **Probability of sucess** : $\theta \sim \pi$

Bayesians considerations

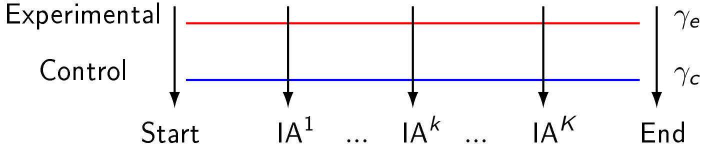


ADAPTIVE DESIGNS



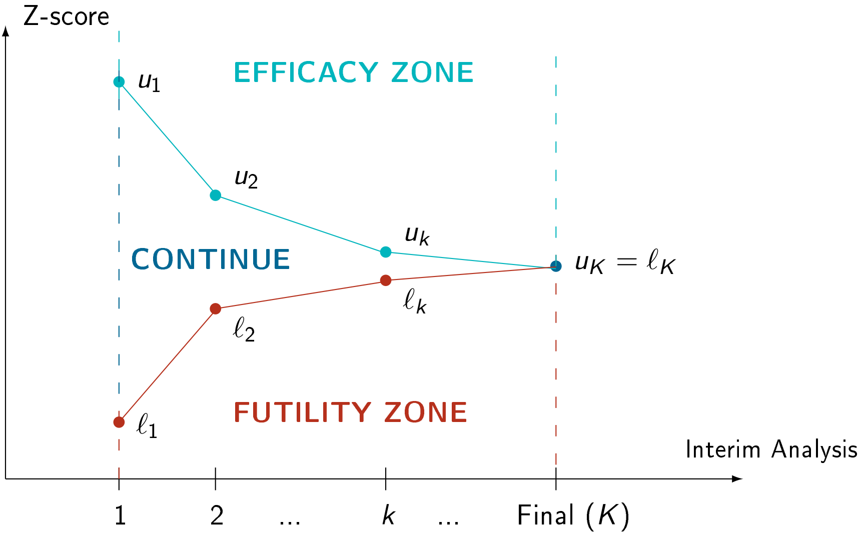
Adaptive designs
a) Group Sequential Design

A group sequential design follows the following diagram :



IA^* : Interim Analysis

- z_k : z-score at interim k
- u_k : efficacy boundary at interim k
- ℓ_k : futility boundary at interim k

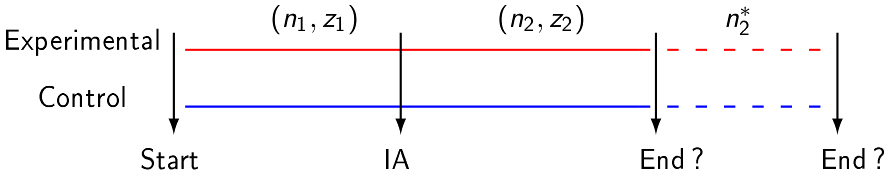

Z-score
EFFICACY ZONE
u_1
u_2
u_k
CONTINUE
$u_K = \ell_K$
ℓ_k
ℓ_2
FUTILITY ZONE
ℓ_1
Interim Analysis
1
2
...
k
...
Final (K)

Design : $k = 1$, interim analysis at $N_1 = 72$ subjects

Efficacy boundaries		Effect	Stopping probability	
$k = 1$ ($N_1 = 72$)	Final ($N_2 = 144$)	θ	$k = 1$ ($N_1 = 72$)	Final ($N_2 = 144$)
2.963	1.96	7	0.163	0.637

Futility boundaries		Effect	Stopping probability	
$k = 1$ ($N_1 = 72$)	Final ($N_2 = 144$)	θ	$k = 1$ ($N_1 = 72$)	Final ($N_2 = 144$)
0.506	1.96	7	0.07	0.13

Design that allows an increasing of the sample size based on the results of interim analysis



Should we increase the sample size to $n_2^* > n_2$?

Metha and Pocock method : Principle

Increase in sample size based on **Conditional Power** at interim

Conditional Power

Probability of rejecting null hypothesis based on the results obtained at interim

$$\text{CP} = 1 - \Phi\left(\frac{z_\alpha\sqrt{n_2} - z_1\sqrt{n_1}}{\sqrt{n_2 - n_1}} - \frac{z_1\sqrt{n_2 - n_1}}{\sqrt{n_1}}\right)$$

Increasing rules based on conditional power

(1) **Non-favorable zone** : $\boxed{CP < CP_{low}}$

Decision : Continue with n_2

(2) **Promising zone** : $\boxed{CP_{low} < CP < CP_{max}}$

Decision : Increasing the sample-size to reach a power of CP_{max}

(2) **Favorable zone** : $\boxed{CP \geqslant CP_{max}}$

Decision : Continue with n_2

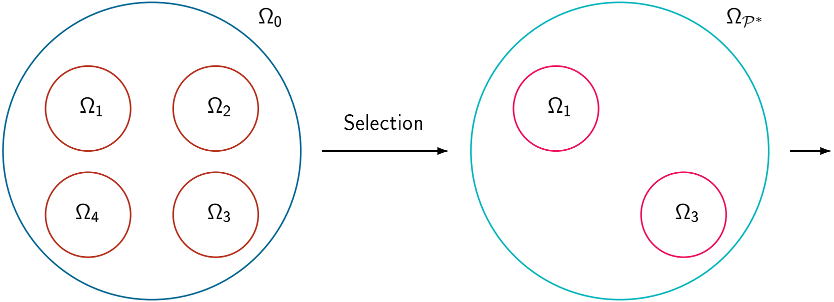
Effect	Boundaries (associated θ)			
7	CP_{fut}	CP_{low}	CP_{max}	CP_{eff}
	0.05 (1.99)	0.31 (4.02)	0.80 (6.38)	0.99 (8.22)
	Probabilities (%)			
	Stop (Futility)	Stop (Efficacy)	Increment	No increment
	7.8	13.3	23.2	55.6
	Average re-estimated sample-size		Probability of success (%)	
	150		85	

- $\mathbb{P}(CP < CP_{min}) \simeq 12.2\,\%$
- $\mathbb{P}(CP \geqslant CP_{max}) \simeq 43.4\,\%$

Adaptive designs

c) Enrichment Design

Group Sequential Enrichment Design (Magnusson & Turnbull, 2013)



$$n_I = \sum_{j=1}^{4} n_{j,1} \xrightarrow[\text{Enrichment}]{\text{Enrollement in } \Omega_1 \text{ and } \Omega_3} n_{II} = n_{1,2} + n_{3,2} > n_I$$

c) Enrichment Design

Sub-sample	Probability of selection (%)
Ω_1 $\Omega_1 \cup \Omega_2$ $\emptyset$	62.4 37.5 0.1
Probability of rejecting at leat one subset (%)	Probability of not rejecting $H_{0,(\Omega_1 \cup \Omega_2)}$ (%)
0.98	0.024
Average sample-size	
245	
Probability of rejecting at leat one subset (by stages) (%)	
$(k = 1)$	$(k = 2)$
76.7	20.9
Probability of not rejecting null hypothesis (by stages) (%)	
$(k = 1)$	$(k = 2)$
0.1	2.3

Conclusion

- Adaptive designs $\Rightarrow$ deal with uncertainty
- Simulations $\Rightarrow$ determining charasteristics that permit decision making

Conclusion

This works represents :

- About 400 hours of understanding complex mathematical theories
- About 21 hours of explanations
- More than 40 statistical articles, presentations and books
- An R clinical platform of 17 algorithms
- 2400 code lines
- More than 26 unsuccessful tests
- Development on continuous, binary and survival outcome

Thank you for your attention !

« *Do not worry about your difficulties in Mathematics. I can assure you mine are still greater* »

Albert Einstein