Package SSDDA : Sample Size Determination and Data Analysis in the context of continuous co-primary endpoints in clinical trials.

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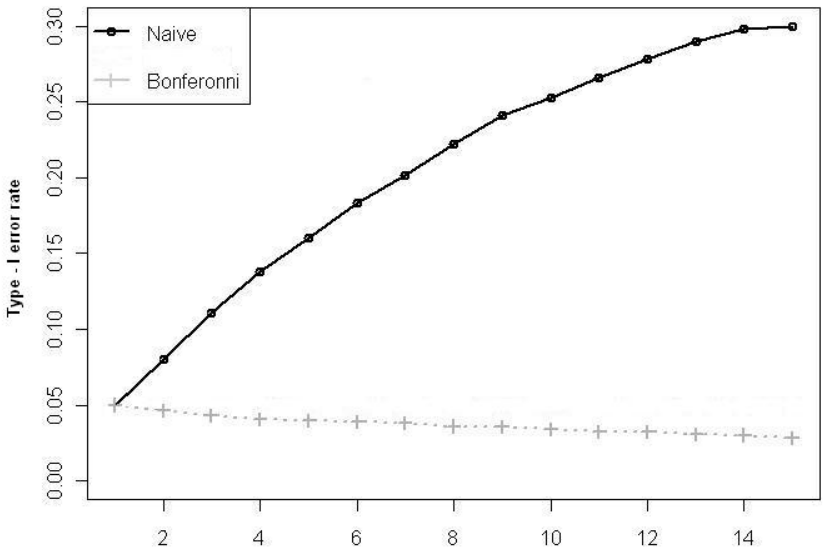
Clinical Context

- The use of **multiple endpoints** to characterize product **safety and efficacy** measures is an increasingly common feature in recent clinical trials;
- Usually, these endpoints are divided into **one** primary endpoint and several secondary endpoints;
- Nevertheless, when we observed a **multi factorial effect** it is necessary to use some **multiple primary endpoint** or a **composite endpoint**.

Multiple Testing Context

Underlying problem

Multiple Co-primary endpoints implies multiple testing problem.



Multiple Testing Context

Table : Possible scenarios for m Tests

Null Hypotheses	Not Rejected	Rejected	Total
True	U	V	m_0
False	T	S	$m - m_0$
Total	W	R	m

In confirmatory context, during data analysis statistician use FWER control:

$$Type - I\ FWER = \mathbb{P}(V \geq 1).$$

$$Type - II\ FWER = \mathbb{P}(T \geq 1).$$

Multiple Testing Context

Type-I error rate Control:

$$Type - I\ gFWER \quad = \quad \mathbb{P}(V \geq q),\ 1 \leq q \leq m.$$

Romano et al.(2005, 2006) developed some procedures which control the gFWER for single step and stepwise procedures. These procedures generalize the Bonferroni, Holm and Hochberg procedures.

The choice of the sample size computation procedure depends on primary endpoint definition.

Primary endpoint definition

- At least one win: At least one test significant among the m;
- At least r win: At least r tests significants among the m,$(1 \leq r \leq m)$;
- All must win: All the m tests significants.

Multiple Testing Context

Table : Control of error rate for different scenarios

Primary Endpoint	Type-I Error rate	Power
At least 1	Classical MCP	Disjunctive Power
At least r	Classical MCP	R-Power
All	No Correction (Offen et al. (2011))	Conjunctive Power

Type-II error rate and Power Control:

$$\begin{aligned} \text{Disjunctive Power} &= \mathbb{P}(S \geq 1), S : (\text{Reject of } \mathcal{H}_0^k | \mathcal{H}_0^k \text{ is false}), \\ \text{r Power} &= \mathbb{P}(S \geq r),\ 1 \leq r \leq (m - m_0), \\ \text{Conjunctive Power} &= \mathbb{P}(S = (m - m_0)). \end{aligned}$$

R functions

1. bonferroni.1m.ssc();
2. global.1m.ssc()[1];
3. global.1m.analysis()[1];
4. indiv.1m.ssc()[1];
5. indiv.1m.analysis()[1];
6. indiv.rm.ssc().

[1] Lafaye de Micheaux, P., Liquet, B., Marque, S., Riou,J. (2013) Power and sample size determination in clinical trials with multiple primary continuous correlated endpoints. *Journal of Biopharmaceutical Statistics,* accepted for publication the 10/21/2012.

Reminders

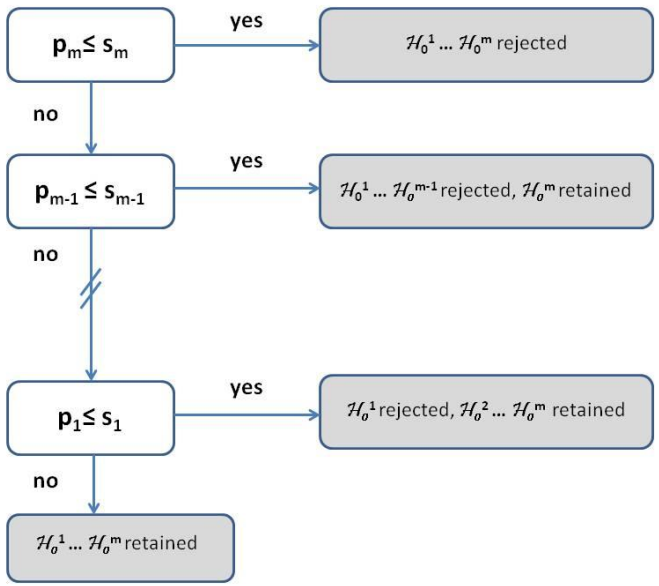
- *m* co-primary endpoints;
- Success of the trial is defined if at least *r* co-primary endpoints are significant;
- r-Power and gFWER control;
- Single step and StepWise methods.

Step up methods

We focus this presentation on Step up methods. Nevertheless, the methodology is available for all Single step and StepWise methods.

Step up methods Principle

1. Sort the p_{values}: $p_1 \leq p_2 \leq \ldots \leq p_m$ corresponding respectively to $\mathcal{H}_0^1, \mathcal{H}_0^2, \ldots, \mathcal{H}_0^m$;
2. Algorithm:



Step up r-Power Formula

$$1-\beta^{u}_{r,m}=\pi^{u}_{r,m}=\sum_{p=0}^{m-r}\mathbb{P}\left[\left(\bigcap_{k=1}^{p}(T_{k:m}<u_k)\right)\cap(T_{(p+1):m}\geq u_{p+1})\right]$$

where the u_k's are critical values for step-up procedures.

This formula depends on order statistics. We need to use the Margolin and Maurer Theorem in order to obtain a power formula which depends on joint distribution of statistics.

Sample Size Computation

Step up methods

The developed formula depends only on the joint distribution and the sample size, and if the joint distribution is known the sample size computation is possible.

So, we decided to focus our work on continuous endpoints.

Data

Indiv	Group	Primary Endpoints				
		1	...	k	...	m
1	0	X^0_{11}	...	X^0_{1k}	...	X^0_{1m}
⋮	⋮	⋮	⋱	⋮	⋱	⋮
i	0	X^0_{i1}	...	X^0_{ik}	...	X^0_{im}
⋮	⋮	⋮	⋱	⋮	⋱	⋮
n	0	X^0_{n1}	...	X^0_{nk}	...	X^0_{nm}
n+1	1	$X^1_{(n+1)\ 1}$	...	$X^1_{(n+1)k}$	...	$X^1_{(n+1)\ m}$
⋮	⋮	⋮	⋱	⋮	⋱	⋮
i	1	X^1_{i1}	...	X^1_{ik}	...	X^1_{im}
⋮	⋮	⋮	⋱	⋮	⋱	⋮
2n	1	$X^1_{(2n)1}$	...	$X^1_{(2n)k}$	...	$X^1_{(2n)m}$

t-test

- Assumptions: $\mathbb{E}[X_{ik}^0] = \mu_0^k$, $\mathbb{E}[X_{ik}^1] = \mu_1^k$, $\mathbb{V}[X_{ik}^0] = \mathbb{V}[X_{ik}^1] = \sigma_k^2$.
- Hypotheses:

$$\mathcal{H}_0^k : \delta^k = \mu_0^k - \mu_1^k \leq d^k; \text{ versus } \mathcal{H}_1^k : \delta^k = \mu_0^k - \mu_1^k > d^k.$$

- Student t-Statistics: $T_k = \frac{\bar{X}_k^0 - \bar{X}_k^1 - d^k}{\sqrt{\widehat{\mathbb{V}}(\bar{X}_k^0 - \bar{X}_k^1 - d^k)}} \sim t_{\nu df, 1-\alpha}$, where $\nu = 2n - 2$;
- $\mathbf{T} = (T_1, \ldots, T_m)^T$ follows a non-central Type-II multivariate Student distribution with f degrees of freedom;
- The analytical form of this distribution is unknown, but can be estimated by a non-central Type-I multivariate Student distribution (Hasler & Hothorn (2011)) ($\mathrm{pmvt}()$ under R software).

Context: ANRS 114 Pneumovac Trial

- Endpoints used in this application for the evaluation of immunogenicity in the Vaccine trials are means of log-transformed antibody concentrations for each serotype;
- Data come from ANRS 114 Pneumovac Trial, where the multivalent vaccines yields a response on 7 serotypes;
- We used data from Pedrono et al (2009);
- Covariance matrices are supposed to be the same between groups;
- The analysis will be performed using seven individual superiority Student t-statistics;
- **What is the required sample size for confirmatory trial with different decision rules (r)?**

R code

```
library(SSDDA)

# Parameters definitions
delta <- c(0.55,0.34,0.38,0.20,0.70,0.38,0.86)

var <- c(0.3520^2,0.6219^2,0.5427^2,0.6075^2,0.6277^2,0.5527^2,0.8066^2)

cov <- matrix(1,ncol=7,nrow=7)
cov[1,2:7] <- cov[2:7,1] <- c(0.1341692,0.1373891,0.07480123,0.1401267,0.1280336,0.1614103)
cov[2,3:7] <- cov[3:7,2] <- c(0.2874531,0.18451960,0.3156895,0.2954996,0.3963837)
cov[3,4:7] <- cov[4:7,3] <- c(0.19903400,0.2736123,0.2369907,0.3423579)
cov[4,5:7] <- cov[5:7,4] <- c(0.1915028,0.1558958,0.2376056)
cov[5,6:7] <- cov[6:7,5] <- c(0.2642217,0.3969920)
cov[6,7] <- cov[7,6] <- c(0.3352029)

diag(cov) <- var
```

R code

```
#Sample size Computation

n3su <- Indiv.rm.ssc(method="Hoch",r=3,m=7,muC=delta,muT=rep(0,7), sigmaC=cov,
sigmaT=cov,delta=rep(0,7),power=0.8,alpha=0.05,interval=c(10,2000),g=1)
n5su <- Indiv.rm.ssc(method="Hoch",r=5,m=7,muC=delta,muT=rep(0,7),sigmaC=cov,
sigmaT=cov,delta=rep(0,7),power=0.8,alpha=0.05,interval=c(10,2000),g=1)
```

Results

Table : Sample Size Computation for various definitions of immunogenicity:

	$r = 3$	$r = 5$
Bonferroni	22	51
Holm	21	41
Hochberg	20	40

Conclusion

- The SSDDA package provides some sample size computation methods in the context of continuous primary endpoints;
- Package SSDDA for sample size and power computation is nearly available.