Decision making in Multi-Regional Clinical Trials using Predictive Probability of Success (PPoS)

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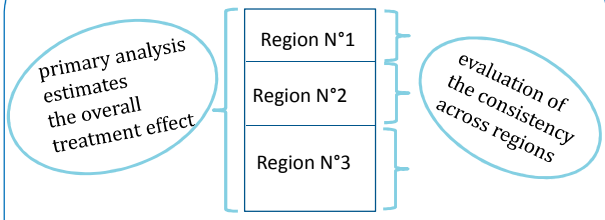
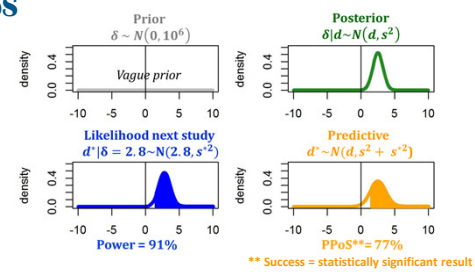
Background

MRCT



- Widely conducted for regulatory submissions
- Reduce the time lag of launch in key markets
- Improve patient access to new treatments

PPoS



- Based on observed results from previous studies
- Increasing interest to support decision making

Method

Objective Predict the success of a future MRCT given observed results in different regions in past trial(s), with a success defined as:

$$\underbrace{\hat{\Delta}_f > z_\alpha s_f}_{\text{Statistical significance on the overall treatment effect}} \cap \underbrace{\hat{\Delta}_{fj} > 0 \; \forall \, j = 1, \dots, J}_{\text{Positive treatment effect estimate for all regions (consistency)}}$$

Notations:
- Δ: true overall treatment effect
- $\hat{\Delta}$: estimate of the treatment effect, s its standard error
- Indexes:
  - $j = 1, \dots, J$ the region
  - J the number of regions
  - *prior:* vague prior
  - *p:* posterior distribution
  - *f*: future trial

Information coming from past study

$\forall j = 1, \dots, J$: $\hat{\Delta}_j \sim N(\Delta_j, s_j^2)$

$\Delta_j \sim N(\Delta, \tau^2)$ τ^2 is the between-region variance

Random (fixed, if $\tau^2 = 0$) effect meta-analysis to estimate the overall treatment effect:

$$\hat{\Delta} = \frac{\sum_{i=1}^{J} \frac{\hat{\Delta}_j}{s_j^2 + \tau^2}}{\sum_{i=1}^{J} \frac{1}{s_j^2 + \tau^2}} \quad ; \quad s^2 = \frac{1}{\sum_{i=1}^{J} \frac{1}{s_j^2 + \tau^2}}$$

Posterior distributions

Bayesian analyses using vague priors :

$\forall j = 1, \dots, J$:

$\Delta_j \sim N(\hat{\Delta}_{pj}, s_{pj}^2)$ for the treatment effect in each region

$\Delta \sim N(\hat{\Delta}_p, s_p^2)$ for the overall treatment effect

$$\hat{\Delta}_{pj} = \frac{s_{prior}^2}{s_{prior}^2 + s_j^2}\hat{\Delta}_j + \frac{s_j^2}{s_{prior}^2 + s_j^2}\Delta_{prior} \quad ; \quad s_{pj}^2 = \frac{s_{prior}^2 s_j^2}{s_{prior}^2 + s_j^2}$$

$$\hat{\Delta}_p = \frac{s_{prior}^2}{s_{prior}^2 + s^2}\hat{\Delta} + \frac{s^2}{s_{prior}^2 + s^2}\Delta_{prior} \quad ; \quad s_p^2 = \frac{s_{prior}^2 s^2}{s_{prior}^2 + s^2}$$

Predictive distributions and PPoS for the future study

$\forall j = 1, \dots, J$: $\hat{\Delta}_{fj} \sim N(\hat{\Delta}_{pj}, s_{pj}^2 + s_{fj}^2)$; $\hat{\Delta}_f \sim N(\hat{\Delta}_p, s_p^2 + s_f^2)$

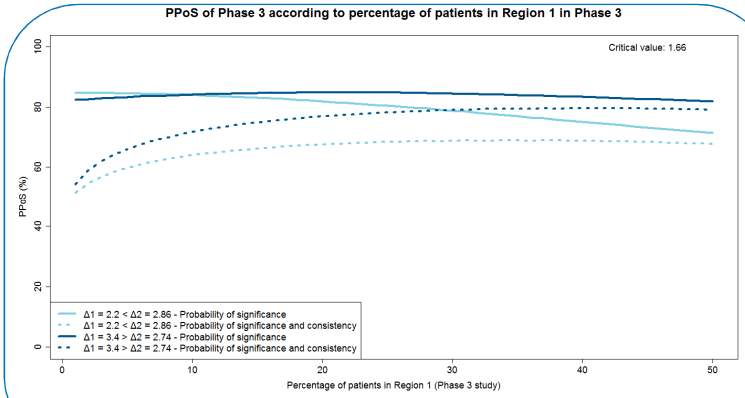
$$\boldsymbol{PPoS = P\left[\left(\hat{\Delta}_f > z_\alpha s_f\right) \cap \left(\hat{\Delta}_{fj} > 0 \quad \forall \, j = 1, \dots, J\right)\right]}$$

Application (hypothetical case-study)

MRCT with 2 regions

Prediction of success of a future phase 3 MRCT given results from a phase 2 MRCT

- Hypotheses for dose-ranging phase 2 study:
  N=125 per arm
  N_1: 10% of overall sample size
  $\hat{\Delta}$ = 2.8
  SD= 6 in each region and overall
- Hypotheses for phase 3 study:
  N= 100 per arm
  SD= 6 in each region and overall
- Hypothesis of no between-region variance ($\tau^2 = 0$)



- Probabilities are driven by treatment effect size in each region in ph2 study
- Probability of significance and consistency increase with the number of patient in Region1

Perspectives

Assess results in case of:
- consistency not achieve in phase 2 study
- between-region variability ($\tau^2 \neq 0$)

- Scenarios of different hypotheses for phase 3 study (on clinical hypotheses, on definition of consistency…)