Predictive Probability of Success (PPoS)
Application to an interim analysis

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1 – Introduction

Sponsors in drug development are more and more interested in prediction of upcoming event (e.g. the success of a clinical study). This kind of prediction can be used to make early decision. In this poster, we focus on the predictive probability, which takes into account both expected value and uncertainty from available information to predict an event of interest.
The available information can be gathered from different sources. Usually, it comes from previous clinical studies (involving the same treatments, same protocol, same population, ...). This information can be used to predict a new (or ongoing) study, assuming that further patients' response will be similar to previous ones. In some case, one can also include information from an interim analysis. If the interim analysis is unblinded, the observed patients can be easily used to update treatment effect estimation. If the interim analysis is blinded, one has to carefully define the information that can be used. We will focus in this poster on an example of blinded interim analysis of a two-arms randomized clinical trial.
For this example, our event of interest is the success of the clinical study (i.e. observing a significant difference between two treatment response). This is usually named (predictive) Probability of Success, PPoS or PoS.

2 – PPoS: General case

The main objective of the PoS, compared to the Power, is to take into account the uncertainty about the parameters required for the success prediction. The general process to calculate a PoS is quite simple:

1) Define the success: $Success(\theta) = P(positive\ study|\theta)$
2) Define available information: Prior or Posterior distribution of θ given observed data Y^p
3) Expected probability of success given the parameters distribution: $PoS(Y^p) = E(Success(\theta)|\ Y^p)$

$$= \int_\Theta Sucess(\theta)[\theta|Y^p]d\theta$$

The expectation can be approximated by Monte Carlo method:
$PoS(Y^p) \approx \frac{1}{K}\sum_{i=1}^{K} Success\left(\theta^{(i)}\right)$, where $\theta^{(i)}$ are simulated according to the distribution $[\theta|Y^p]$ representing the available information. Other approximation methods can be used, but Monte Carlo method is very convenient for multiple integrations and quite easy to use.

3 – Study design

We focus on a two-arms randomized clinical trial. The patient's response to treatment is a binary endpoint (reaching a predefined clinical target without a serious adverse event). The patient's positive response is equal to 1, 0 if negative response. We want to compare a new treatment and an active control. We include 1800 patients in each group. A blinded interim analysis is performed when 900 patients are observed in each treatment group. Thus each group is composed by two cohorts of 900 patients. The design is expressed as followed:

$$y_{ij} = \#\ of\ positive\ responses\ in\ group\ i\ and\ cohort\ j \qquad y_{ij} \sim Binom(n_{ij}, p_i)$$

$$n_{ij} = \#\ of\ patients\ in\ group\ i\ and\ cohort\ j = 900 \qquad \hat{p}_1 = \frac{y_{11} + y_{12}}{n_{11} + n_{12}}$$

$$p_i = probability\ of\ positive\ response\ in\ group\ i \qquad \hat{p}_2 = \frac{y_{21} + y_{22}}{n_{21} + n_{22}}$$

At the end of the study, we plan a X^2 statistical test based on the following hypotheses: $H_0: p_1 = p_2 = 0{,}45$ versus $H_1: p_1 = 0{,}5\ \&\ p_2 = 0{,}45$.

3 – Available information and updated probabilities of event (p_1 & p_2)

We performed a similar study with the same population, treatment and endpoint. We observed, for Group 1, **200 positive responses among 400 patients**, and for Group 2, **180 positive responses among 400 patients**. This information can be used through a Beta prior distribution using the numbers of positive and negative responses. We also got tow pieces of information from the interim analysis: the pooled number of positive responses $\boldsymbol{y_{pool} = 727}$ and the inequality $\boldsymbol{\hat{p}_1 - \hat{p}_2 < a = 0{,}06}$ (we get this inequality from an overwhelming efficacy stopping rule that didn't occur). This information can be expressed through the following likelihood function (it's also used for conditional distributions of response rates estimators): $\left[y_{pool}, \hat{p}_1 - \hat{p}_2 < a \middle| p_1, p_2\right] = \sum_{i=0}^{\left\lfloor\left(a + \frac{y_{pool}}{n_{21}}\right)\frac{n_{11}n_{21}}{n_{11}+n_{21}}\right\rfloor} \binom{n_{11}}{i} p_1^i (1-p_i)^{n_{11}-i} \binom{n_{21}}{y_{pool}-i} p_2^i (1-p_2)^{n_{21}-y_{pool}+i}$

Using a Bayesian inference algorithm (here a Sampling-resampling algorithm), we get the following posterior distributions:

Parameter	Mean	SD	CI 95%
p_1	0,441	0,017	[0,41 ; 0,47]
p_2	0,41	0,017	[0,38 ; 0,44]
$p_1 - p_2$	0,031	0,027	[-0,03 ; 0,08]

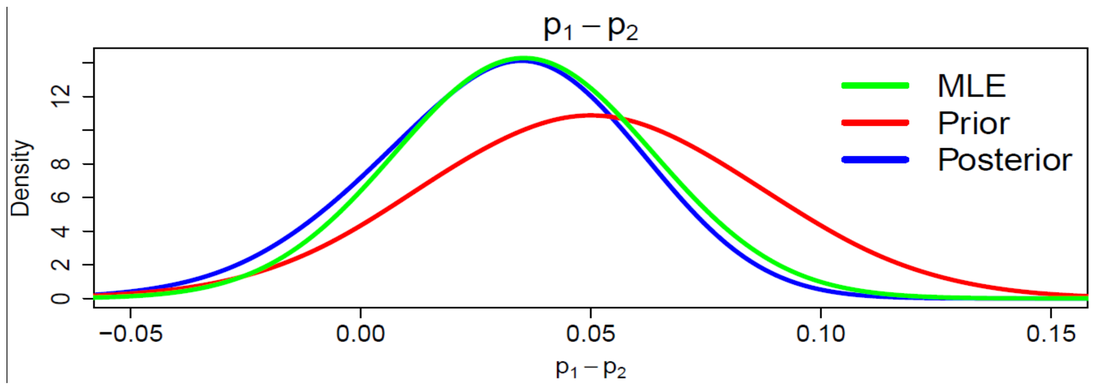

Figure 1: Prior and posterior distributions of $p_1 - p_2$ using the available information. The MLE curve corresponds to the frequentist inference pooling both prior information and interim blinded information.

3 – PPoS and Conditional Power

We initially calculate a Power equal to 76,2% and a PPoS equal to 62,2%. With the updated distributions of p_1 and p_2, we get a conditional Power equal to 59,1% and an updated PPoS equal to 36,6%. This large decrease is due to two factors: 1) the global response rate is decreased leading to a lower statistical power, 2) the unapplied overwhelming efficacy stopping brings a string information about the difference $p_1 - p_2$ (supposed to be 0,05, but estimated at 0,031).

4 – Conclusion

The PPoS main advantage, compared to statistical Power, is to take into account the uncertainty. Moreover, it is very convenient to take into account various sources of information. The main conclusion is one can include any observation, as soon as its information can be formalized. The second conclusion is a strong decision rule (here the overwhelming efficacy stopping rule) brings a strong information (whatever the decision is) that can be used.