BAYESIAN POWER CALCULATIONS: PROBABILITY OF SUCCESS AND PREDICTIVE POWER

PROBLEM - Uncertainty about treatment effects impede clinical trial design
SOLUTION - East® allows Bayesian calculations to formally address this uncertainty
BENEFITS - Ability to incorporate prior information leads to more accurate predictions of trial success

PROBLEM

Sample size and power calculations can be highly dependent on the assumed magnitude of the treatment effect. Sensitivity analysis is typically performed by checking calculations for a range of potential values. Indeed, East is ideally suited for performing sensitivity analysis of this kind.

This ad hoc approach to sensitivity analysis can be complemented by a Bayesian approach, which addresses uncertainty about the treatment effect in a more formal fashion. The assurance (O'Hagan et al., 2005), or probability of success, is a Bayesian version of power, which corresponds to the unconditional probability that the trial will yield a significant result. Specifically, it is the expectation of the power, averaged over a prior distribution for the unknown treatment effect. This prior distribution expresses the uncertainty about the treatment effect, before the trial began, in terms of the relative plausibility of different parameter values.

Depending on one's goals, a prior distribution can take one of many forms. It may be non-informative (e.g., uniform); it may represent the beliefs of an "enthusiastic" or "skeptical" stakeholder, or it may adopt a complex shape that represents diverse opinions from a group of experts.

The probability of success is an important consideration for your clinical trial at the design stage. Another Bayesian measure, known as predictive power (Lan et al., 2009) aids decision making at the interim monitoring stage. During the course of a trial, it is often helpful to calculate the conditional power: the probability of obtaining a significant result when the trial ends, given the current results. If the conditional power is low, the trial may stop early for futility, or there may be an opportunity to re-estimate and increase the sample size.

As with computing power in the design stage, the conditional power calculation depends on the assumed treatment effect, such as an estimate at the interim. However, empirical estimates may not be reliable. Thus, rather than assuming a single value for the treatment effect, one could calculate conditional power for several different values, and weigh them by the posterior distribution for the treatment effect.

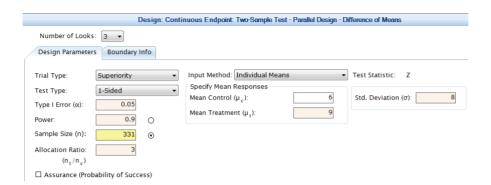> **"...ASSURANCE SHOULD BE A MAJOR CONSIDERATION WHEN DESIGNING A CONFIRMATORY TRIAL."**
>
> -Chuang-Stein, et al. (2011)

SOLUTION

Design: Continuous Endpoint: Two-Sample Test - Parallel Design - Difference of Means

Number of Looks: 3

Design Parameters | Boundary Info

Trial Type:	Superiority	Input Method: Individual Means	Test Statistic:	Z
Test Type:	1-Sided	Specify Mean Responses		
Type I Error (α):	0.05	Mean Control (μ_c): 6	Std. Deviation (σ):	8
Power:	0.9	Mean Treatment (μ_t): 9		
Sample Size (n):	331			
Allocation Ratio: (n_t/n_c)	3			

☐ Assurance (Probability of Success)

East offers the flexibility to use a standard parametric prior distribution, or a user-defined CSV file for more complex prior distributions. Bayesian measures, such as assurance and predictive power, are calculated from these priors.

Suppose we are designing a group sequential clinical trial for a weight loss treatment, with the inputs displayed above. In particular, note that we target 90% power to detect a treatment difference of 3 kg.

This calculation rests on the assumption that the magnitude of the treatment effect (3 kg) is known with certainty. A more realistic scenario is that the true treatment effect lies within

some range of possible values. The uncertainty about the treatment effect can be represented, for example, as a Normal distribution with mean 3, and standard deviation of 2. In this more realistic scenario, **East shows that the probability of success (72%) is lower than the desired 90% power.**

Once the trial is underway, the interim monitoring dashboard in East can compare the conditional power calculated at the estimated treatment effect, the predictive power based on a posterior distribution derived from a diffuse prior, and the Bayes predictive power based on a posterior distribution derived from the user-specified prior. The difference in these three estimate are striking and highlight the importance of incorporating prior beliefs into the decision making, especially for futility analysis

☑ Assurance (Probability of Success): 0.72
Prior Distribution for: δ   Distribution: Normal
Input Method: User Specified E(δ) and SD(δ)
User Specified
E(δ): 3
SD(δ): 2

CP	Predictive Power	Bayes Predictive Power	Post. Dist. Of δ	
			Mean	SD
0.84	0.719	0.488	1.218	0.661

BENEFITS

The Bayesian approach to statistical decision making is becoming increasingly accepted as a valuable way to manage uncertainty in clinical trial design and analysis. One key advantage is the ability to incorporate quantitative prior information to support calculations and decision making. In fact, any prior information about the treatment effect - whether gained from previous trials or from expert opinions - can be accounted for in a power calculation. As the industry standard software for clinical trial design, East continues to incorporate Bayesian and related methodologies to improve clinical success rates.

References

Chuang-Stein, C., Kirby, S., Hirsch, I., & Atkinson, G. (2011). The role of the minimum clinically important difference and its impact on designing a trial. Pharmaceutical Statistics, 10, 250-256.

Lan, K., Hu, P., & Proschan, M. (2009). A conditional power approach to the evaluation of predictive power. Statistics in Biopharmaceutical Research, 1, 131-136.

O'Hagan, A., Stevens, J.W., & Campbell, M.J. (2005). Assurance in clinical trial design. Pharmaceutical Statistics, 4, 187-201.