

Precision of estimating the sample size needed to power clinical trials: What is the effect of risk-based monitoring?

Yavorsky C², Meares K¹, McNamara C¹, DiClemente G¹, Burger F³
 Cronos CCS:Lambertville, NJ¹, Berkeley, CA², Buenos Aires, Argentina³

Introduction

Determining the optimal sample size is a critical step in the design of a proposed clinical trial. Sample size calculations for clinical trials typically follow one of the following three approaches:

- Specify the desired width of a confidence interval and determine the sample size; or
- Bayesian approach that adjusts utility function; or
- Analyzing the power of a test of hypothesis.

Enrolling too many subjects in a trial can be expensive and prolong the length of the trial. Likewise, if the study is not adequately powered, the statistical and clinical outcomes become questionable and may expose the subject to a potentially harmful treatment without enhancing knowledge. The current study proposes a novel method to sample size computation and utilizes a Bayesian approach that requires consideration of scientific goals, incorporating pilot data, study design, estimate of subject withdrawals, and estimate of data removed following risk based monitoring (RBM). Unlike current methods of sample size computation, Bayesian methods take into account the uncertainty of parameter estimates.

Objectives

- To re-estimate sample size given observed error and with or without dropouts in a retrospective analysis of PANSS data.

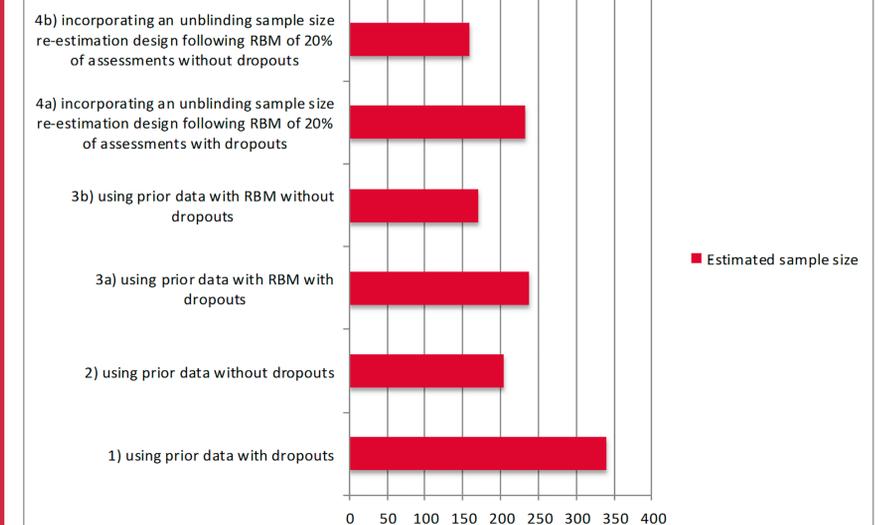
Methods

Data were evaluated retrospectively from a large multicenter randomized controlled trial for patients with schizophrenia. Power was calculated using the PAS software suite. Approximately 140 Site Raters participated in the study. A risk based monitoring paradigm was deployed to review psychometric and clinical scoring inconsistencies in PANSS data for within scale, within visit, across visits, within rater, and across raters. In addition to an automated data driven algorithm review, a an expert clinical review was conducted. Power and Effect Size computations utilizing both a Frequentist and Bayesian approach were completed for 4 groups as follows: 1) using prior data without dropouts, 2) using prior data with dropouts, 3) using prior data with RBM (with and without dropouts), 4) incorporating an unblinding sample size re-estimation design following RBM of 20% of assessments.

Results

- Of the 2,361 PANSS assessments reviewed, 28.46% (n = 672) were “flagged” following RBM and clinical review, and 62.73% (n = 1481) had minimal discrepancies “passed” with the remaining 8.81% (n= 208) no discrepancies) 1) using prior data without dropouts (as in common in schizophrenia trials), a total of 204 subjects were estimated, 2) using prior data with dropouts, a total of 340 subjects is needed as per the initial study, 3) a. using RBM dataset with 40% drop out rates, 238 subjects are needed and b. using prior data with RBM dataset without 40% drop out rates, 170 subjects are needed, 4) incorporating an unblinding sample size re-estimation design, a. 223 subjects with 40% dropout and b. 159 subjects are needed without the 40% dropout rate.

Estimated sample size



Conclusion

In all cases utilizing RBM, the sample size needed for hypothesis testing was reduced from the original by at least 30%, with the unblinding sample size re-estimation following RBM showing the most significant reduction in the number of subjects needed. Inadequately sized studies often results in investigator's unrealistic assumptions about the effectiveness of study treatment. Using an adequate sample size with high quality data collection through RBM could result in more reliable results, more timely trials and fewer resources.

References

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