Student Scholar Poster Abstracts

Improved Power in Crossover Designs Through Linear Combinations of Baselines

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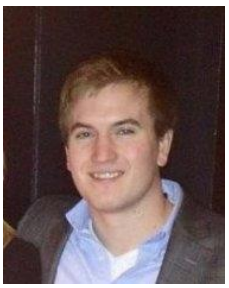

In a crossover design, including period-specific baselines as covariates in an analysis of covariance (ANCOVA) is known to increase the precision of the estimated treatment effect. The potential efficiency gain depends on the joint covariance structure of the baselines and post-treatment responses, as well as the metric used to incorporate the baselines. Here we examine improvements in power that can be achieved by choosing an optimal linear combination of baselines (LCB) that minimizes the variance of the ANCOVA-based estimate of the treatment effect. Our work is relevant to balanced designs with up to four periods, specifically the 2x2, 3x3 and 4x4; with a natural extension to incomplete block designs, such as the 2-period 3-treatment design. Since the optimal LCB is a function of the covariance structure, which in practice is unknown, we propose an adaptive method in which first a suitable covariance structure for the given dataset is selected via AICC values, and then the corresponding optimal LCB is used in the ANCOVA. Relative to previously published methods, the proposed method leads to sizable gains in power, while maintaining the nominal type I error rate.

Investigation on Combining Phase II PoC Trial with Dose Finding Trial

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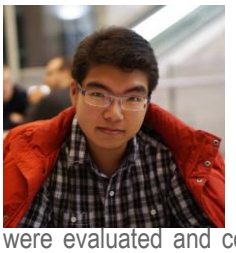

In this project we explore a seamless Phase IIa/IIb dose-finding design that provides better balance between efficiency of the development and the risk of large upfront investment. In the 1st stage of the trial, patients will be allocated to highest dose versus placebo. In the 2nd stage, patients will be allocated to multiple doses of interest according to pre-specified overall allocation ratio of the trial. A futility analysis will be conducted once the endpoints of the patients in the 1st stage are available. Allocating all patients to highest dose in active arm will minimize the sample size needed for earlier signal of Go/NoGo decision. Go/NoGo decision in futility analysis is to continue the expansion of full dose ranging or not. The impact of sample size, futility boundary and allocation ratio between stages and doses were evaluated and compared among various options. By reusing the PoC patient data in analysis, and providing option of stopping at interim, the design reduces the expected overall sample size and time needed for Phase II study while maintaining similar type I error and power. The impact on dose estimation behaviors was also explored.

A New Confidence Interval Based Design in Oncology Phase I Clinical Trials

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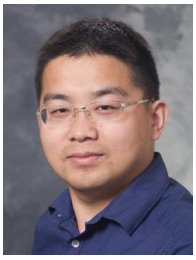

Recently, Bayesian optimal interval (BOIN) design (Liu and Yuan, 2015) was proposed for oncology Phase I trials. We identified two limitations of BOIN design. First, the next dose rule in BOIN design is only based on the information from the current dose that may not be reliable due to small sample size. Second, the inconclusive area in BOIN design remains the same even though information is accumulated throughout the trial. Motivated by a real clinical trial, we proposed an optimal confidence interval design to overcome these two limitations. The new design is based on the confidence interval for the dose-limiting toxicity (DLT) rate at the current dose that is constructed based on the power model. The confidence interval is compared with the target toxicity rate to determine the next dose. The coverage probability is considered as the design parameter that is optimized based on both accuracy and safety consideration. We conducted extensive simulations to explore the choice of the design parameter and the operating characteristics of the new design. Our simulation results showed that the new design compares favorably with BOIN, CRM, BLRM and 3+3 design.

Approximate Confidence Distribution Computing

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Approximate Bayesian computing (ABC) is a likelihood-free method that has grown increasingly popular since early applications in population genetics. However, the theoretical justification for inference based on this method has yet to be fully developed especially pertaining to the use of non-sufficient summary statistics. We introduce a more general computational technique; approximate confidence distribution computing (ACC) to overcome two defects of the ABC method, namely, lack of guardian for the selection of prior and lack of theory supporting the use of non-sufficient summary statistics. Inference based on ACC is justified (even if reliant upon a non-sufficient summary statistic) by establishing correct frequentist coverage properties using the theory of confidence distributions. Furthermore, the ACC method is very broadly applicable; the ABC algorithm can be viewed as a special case of an ACC method without damaging the integrity of ACC based inference. We supplement the theory with examples that illustrate the applications of ACC and provide some simulation results. We also demonstrate that a well-tended ACC algorithm can be more computationally efficient than ABC methods.

Rare Variant Association Test for Ordinal Traits

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In many genetic epidemiology studies, clinical assessments are recorded using either categorical or more precisely ordinal data. For example, doctors may record intellectual or motor disability as normal, mild, moderate, or severe. Moreover, critical information may be lost if we reduce our data to a simply binary trait, e.g., normal and not normal. Over the past decade, group tests have been widely developed to detect the association of rare genetic variants in sequencing studies. However, most statistical procedures are designed for either continuous or binary outcomes. In this poster, we present a computational very efficient score-based test to investigate the association of a set of rare variants and ordinal traits. Through simulation, we evaluated the performance of our method. The proposed statistic obtains an accurate type I error rate, and it has higher power than many comparable binary trail methods. As a score-based test, our method can quickly calculate p-values, and so can easily be applied to genome-wide data sets of many hundreds of individuals. We apply this methodology to an epilepsy exon sequencing study to show the practical relevance of this approach.