Journal of Biometrics & Biostatistics

Liu, J Biom Biostat 2016, 7:3
http://dx.doi.org/10.4172/2155-6180.1000311

Opinion Open Access

Statistical Methods in Trials with Sequential Parallel Design for Trials with High Placebo Response

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Rec date: June 06, 2016; **Acc date:** June 08, 2016; **Pub date:** June 15, 2016

Citation: Liu Y (2016) Statistical Methods in Trials with Sequential Parallel Design for Trials with High Placebo Response. J Biom Biostat 7: 311. doi: 10.4172/2155-6180.1000311

Introduction

Strong placebo response has been problematic in central nervous system (CNS) clinical trials, leading to a reduced drug effect and thus resulting in decrease in probability of finding an effective drug. The ideal situation is to have comparative data collected only from subjects who are placebo non-responders. Stringent trial procedures together with enrichment of placebo non-responders are some of the ways to decrease placebo response in clinical trials. Fava et al. (2003) proposed a SPD where subjects are only randomized during Period 1. Accordingly, some placebo non-responders in Period 1 continue on placebo in Period 2 and others switch to drug in Period 2; and subjects who are treated with drug in Period 1 would continue to receive drug in Period 2. Treatment sequences for all subjects are all pre-specified prior to trial start; and data from Period 2 for subjects who are on drug in both periods are for safety evaluations only. An estimator is proposed to assess drug effect in each period, and a combined estimator is also proposed to test superiority of investigational drug over placebo across periods.

Various papers have been published on this in recent 10 years, among which a paper by myself and coauthored in Contemporary clinical trials Communications entitled "On clinical trials with high placebo response rate" has drawn a lot of attentions in statistical community by comprehensively tangled this problem by proposing a test based on combined test statistic irrespective of randomization ratio and other design parameters; proper consistency test between two periods; and unbiased estimator for a SPD in the presence of placebo response.

Survival Analysis

When cause-specific mortality is considered, a reliable assessment of the cause of death is required. If the cause of death is not known, relative survival can be calculated. This is especially popular in cancer research. Mortality in the patients with a certain cancer is compared with the background mortality from the general population. The difference can be thought of as mortality due to the cancer. The pros and cons of relative survival estimates are open to debate. Some have proposed to also study conditional survival for patients already surviving for some years after diagnosis. These measures may sometimes be more meaningful for clinical management and prognosis than 5-year relative survival from time of diagnosis. Others have proposed that median survival times are better indicators of survival than 5-year relative survival rates, especially when survival times are short. Other than survival for cancer patients, time to relapse for subjects who have been stabilized by a treatment for a period of time is required for indication of maintenance effect by regulatory agencies. These trials are called randomized withdrawal trials, where subjects who have been stabilized with treatment for symptoms will either continue to be treated or switch to placebo in the double-blind phase in order to collect data of time to first relapse in the double-blind phase between treatment and placebo. Designs and analyses for survival trials; use biomarker(s) to enrich proper subpopulations; composite end point; recurrent events analyses; repeated and correlated events dealt with extension of cox regression; adaptive designs for survival data; and prediction of trial land mark in survival trials are all interesting topics for statisticians to tangle. I've done a couple of papers on issues in clinical trial with survival end points. sensitivity analyses for informative censoring in survival data; sample size increase during a survival trial when interim results are promising; prediction of the timing of events in clinical trials with survival endpoints; planning a comparative group sequential clinical trial with loss to follow-up and a period of continued observation; planning the duration of a survival group sequential trial with a fixed follow-up time for all subjects.