Monday 22 July 2024

15:30-17:00 Invited Session 3 (Main Room)

Innovative Complex Adaptive Designs for Confirmatory Clinical Trials with Multiple Primary Research Questions (Chairs: Babak Choodari-Oskooei and Ian White)

Pairwise and familywise error rate control in platform trials: Impact on sample size, trial timelines and analysis

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The operating characteristics of confirmatory randomised clinical trials are required to be controlled at prespecified levels. Traditionally, the overall type I error rate has been used to quantify the probability of false positive conclusions. It is often a key quantity of interest for both regulators and reviewers since it ensures the generalisability and reproducibility of trial results.

In platform trials and designs with a master protocol, there are two main measures of type I error rate: pairwise type I error rate; and familywise type I error rate. Recently, other performance measures such as the false discovery rate and “online” versions of these measures have been proposed for platform trials. However, there is no clear consensus in the statistical community about which of these quantities should be controlled in such trials. Further, the impact of the chosen measure on design and analysis of trials with master protocols have not been fully explored.

This talk provides an overview of the proposed performance measures and offers practical guidelines for selecting the most appropriate performance measure for the specific platform trial setting. Using the flagship STAMPEDE platform trial, it explores the impact of the chosen measure on the trial efficiency, i.e., sample size and timelines, as well as the analysis of the outcome measures.

The definitions of the false discovery rate, pairwise and familywise type I error rates as well as the concept of online error rates in trials with master protocol will be presented. We explain when each measure should be controlled at the pre-specified level, and what factors drive their values. We illustrate the degree of efficiency loss if an inappropriate measure of type I error rate is controlled. For online error rate control, the choice of method and the consideration of the order in which treatment arms enter the trial are crucial.

In platform trials, whenever possible, multiple distinct research questions should be addressed. This provides the rationale for targeting control of pairwise error rate. It is challenging to control the familywise error rate for all pairwise comparisons in a trial that adds new research arms. Either the number of new research arms should be limited, or in many situations a high price should be paid in terms of efficiency if new research arms are not added.

Keywords: platform trials; master protocols; familywise type I error rate (FWER); multi-arm multi-stage (MAMS) trials; adaptive designs, false discovery rate