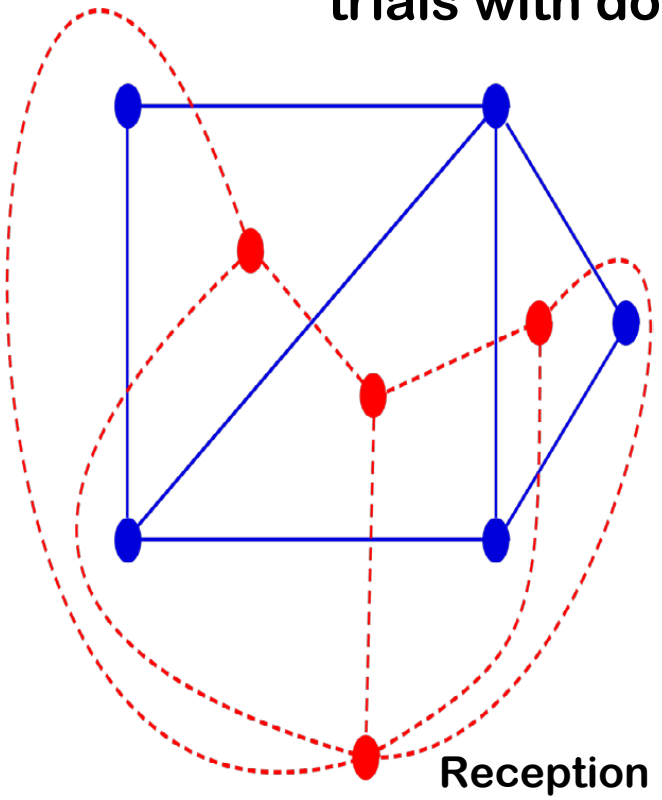
COLLOQUIUM

Title: A rank-based approach to improve the efficiency of inferential seamless phase 2/3 clinical trials with dose optimization



3-21-24

RONG FAN

PFIZER, INC.

Time: 3-4:00 pm

Place: Neckers 156

Reception immediately following in the Math Library.

Abstract: To accelerate clinical development, seamless 2/3 adaptive design is an attractive strategy to combine phase 2 dose selection with phase 3 confirmatory objectives. As the regulatory requirement for dose optimization in oncology drugs shifted from maximum tolerated dose to maximum effective dose, it's important to gather more data on multiple candidate doses to inform dose selection. A phase 3 dose may be selected based on phase 2 results and carried forward in phase 3 study. Data obtained from both phases will be combined in the final analysis. In many disease settings biomarker endpoints are utilized for dose selection as they are correlated with the clinical efficacy endpoints. As discussed in Li et al. (2015), the combined analysis may cause type I error inflation due to the correlation and dose selection. Sidak adjustment has been proposed to control the overall type I error by adjusting p-values in phase 2 when performing the combined p-value test. However, this adjustment could be overly conservative as it does not consider the underlying correlations among doses/endpoints. We propose an alternative approach utilizing biomarker rank-based ordered test statistics which takes the rank order of the selected dose and the correlation into consideration. If the correlation is unknown, we propose a rank-based Dunnett adjustment, which includes the traditional Dunnett adjustment as a special case. We show that the proposed method controls the overall type I error, and leads to a uniformly higher power than Sidak adjustment and the traditional Dunnett adjustment under all potential correlation scenarios discussed.

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