Interim monitoring for futility in clinical trials with co-primary endpoints

Koko Asakura1, Toshimitsu Hamasaki1*, Scott R Evans2

1National Cerebral and Cardiovascular Center, 2George Washington University

*Department of Data Science, National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-0873, Japan, email: toshi.hamasaki@ncvc.go.jp

A motivating case example

Tarenflurbil trial (Green RC et. al. JAMA 2009;302:2557-2564)
- Population: patients with mild Alzheimer’s disease
- Endpoints: change in ADAS-Cog, ADCS-ADL (co-primary)
- Evaluation of treatment effects: BOTH of the two endpoints

Issues raised by such examples with co-primary endpoints:
- Large and impractical sample size
- E.g. Tarenflurbil trial: 689 patients for a single endpoint
- No opportunity to evaluate the accuracy of the design assumptions
- Interim evaluation for futility could aid in go/no-go decision making

Approaches for evaluating futility

Fundamental approaches do not provide information regarding effect sizes (i.e., clinical relevance).

Predicted intervals (PIs) provide quantitative assessment of the effect and potential improvement in precision with trial continuation, increasing sample size and so on.

Repeating the process of generating future data allows for assessment of the sampling variations in the predicted point estimates.

An Illustration: settings

Tarenflurbil trial
- Sample size: 804 patients per intervention group
- 1-sided test, α = 0.025, 1 - β = 0.96
- Standardized effect size: 0.2 for both endpoints

Possible suggestions by each approach

Use of prediction in conjunction with other approaches is recommended.
A conservative decision would be recommended when there is a difference of opinion as to early stopping in the DMC.

Summary & Discussion

Advantages
- Provides information regarding effect sizes
- Not increase a planned sample size
- Provides flexible decision-making

Disadvantages
- Decision could depend on decision makers
- Depends on prior distribution or assumed effect sizes
- Not provide information regarding effect sizes

GS: Simple decision-making
- Requires larger planned sample size
- Not provide information regarding effect sizes

PD: Provides information regarding effect sizes
- Not increase a planned sample size
- Provides flexible decision-making