Group sequential designs for recurrent events: new challenges and proposals

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Outline

1. Introduction group sequential designs
2. Comparison of group sequential designs for time-to-event and recurrent events
3. Group sequential designs for the negative binomial model
4. Group sequential designs for the LWYY model
Group sequential designs

• Accumulating data are analyzed repeatedly during the clinical trial
  – At each data look can be stopped for efficacy or futility
Illustration of group sequential designs

• Hypothesis testing problem $H_0: \beta \geq 0$ vs. $H_1: \beta < 0$

• Test statistic $Z_k$ at data look $k = 1, \ldots, 5$
Sequential designs for time-to-event vs. recurrent event

- Time-to-event outcomes: each patient contributes a new event to a single data look
Sequential designs for time-to-event vs. recurrent event

• Time-to-event outcomes: each patient contributes a new event to a single data look

• Recurrent events: each patient can contribute a new event to more than one data look

• Challenges in group sequential designs with recurrent events
  – In comparison to time-to-event endpoints, the correlation of test statistics from different data looks can be higher in the case of recurrent events
  – Event-driven trials could be driven by few subjects with large number of events
Notation and terminology for standard group sequential designs

• Parameter of interest $\beta$, e.g., log hazard ratio (time-to-event model) or log rate ratio (recurrent event model)

• $Z$-statistic at data look $k = 1, \ldots, K$

$$Z_k = \frac{\hat{\beta}_k}{SE(\hat{\beta}_k)}$$

• Information level at data look $k$: $I_k = \frac{1}{SE(\hat{\beta}_k)^2} = \frac{1}{Var(\hat{\beta}_k)}$

• Information fraction at look $k$: $w_k = I_k/I_{Max}$
  – Maximum information $I_{Max}$

• Information fraction is commonly used to determine the calendar time of a data look
Standard group sequential theory is based on canonical joint distribution

• Canonical joint distribution is assumed when calculation of stopping boundaries, sample size, and maximum information

• Canonical joint distribution
  – \((Z_1, \ldots, Z_k)\) follows a multivariate normal distribution
  – \(E[Z_k] = \beta \sqrt{J_k}\)
  – \(Var[Z_k] = 1\)
  – \(Cov[Z_{k_1}, Z_{k_2}] = \sqrt{J_{k_1}/J_{k_2}}, \quad k_1 \leq k_2\)
Group sequential designs for time-to-event outcomes

• Canonical joint distribution holds for common time-to-event models and tests such as the Cox model and the log-rank test

• Information for time-to-event endpoint (Log-rank test)
  – $d_k$: number of accumulated events at data look $k$
  – Information (Schoenfeld, 1981): $I_k \approx \frac{d_k}{4}$
  – Information fraction: $w_k = \frac{d_k}{d_{Max}}$
Group sequential designs for negative binomial outcomes: Canonical joint distribution

• Focus on two-arm study with maximum likelihood based analysis

• Canonical joint distribution holds asymptotically for the negative binomial model (Mütze et al., 2018a)

➢ Standard group sequential software (e.g., EAST, R package gsDesign, SAS proc seqdesign) can be used to calculate stopping boundaries
Group sequential designs for negative binomial outcomes: Information

• Information at data look $k$:

$$J_k = \frac{1}{\frac{1}{I_{1k}} + \frac{1}{I_{2k}}}$$

with Fisher information $I_{ik} = \sum_{j=1}^{n_i} \frac{t_{ijk} \mu_i}{1 + \phi t_{ijk} \mu_i}$

• Information and information fraction at a data look depend on individual follow-up times $t_{ijk}$, sample size $n_i$, rates $\mu_i$, and the overdispersion parameter $\phi$

➢ The number of events is not the same as the information for designs with negative binomial outcomes
Planning of group sequential designs with negative binomial outcomes

• Goal: Calculate maximum information and sample size
  – Not implemented in EAST, R package gsDesign, SAS proc seqdesign

• R package gscounts, available on CRAN, implements planning of trials with negative binomial outcomes

• Example
  – One-sided significance level $\alpha = 2.5\%$
  – Power $1 - \beta = 80\%$
  – Maximum number of looks $K = 3$
  – Information fraction of look $w_1 = \frac{1}{3}, w_2 = \frac{2}{3}, w_3 = 1$
From maximum information to sample size using gscounts

• Determining the sample requires assumption on
  – the rates,
  – the overdispersion parameter,
  – trial duration,
  – and minimum follow-up

```
design_gsnb(rate1=0.0875, rate2=0.125, dispersion=5, ratio_H0=1, power=0.8, sig_level=0.025, timing=c(1/3, 2/3, 1), esf=obrien, study_period=4, accrual_period=1.25, random_ratio=1)
```
From maximum information to sample size using *gscounts* (cont’d)
Group sequential designs for the LWYY model

• Canonical joint distribution does not hold (asymptotically) in the LWYY model (Mütze et al, 2018b) for overdispersed recurrent events

• If standard group sequential stopping boundaries are applied, no asymptotic type I error rate control guaranteed
  – Group sequential test becomes asymptotically conservative

• Studied performance of standard stopping boundaries for LWYY model in simulation study
  – No practically relevant deviation of type I error rate from target level
Practical aspects of group sequential designs for the LWYY model

• Stopping boundaries from standard software packages can be used in practice

• Maximum information can be planned using canonical joint distribution

• Calculating sample size from maximum information is possible but not trivial; has not yet been implemented in R package gscounts
Discussion

• In practice, standard group sequential boundaries can be used in designs with common recurrent event models

• Number of events is not the same as the information level in recurrent event trials
  – Actual information level should be used to monitor trials, see Friede et al. (2018, submitted) for blinded information monitoring procedure

• Information level and information fraction depend on individual follow-up times, sample size, rates, and the overdispersion parameter

• R package *gscounts* can be used for planning purposes of designs with negative binomial outcomes
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References


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