Statistical Methodology
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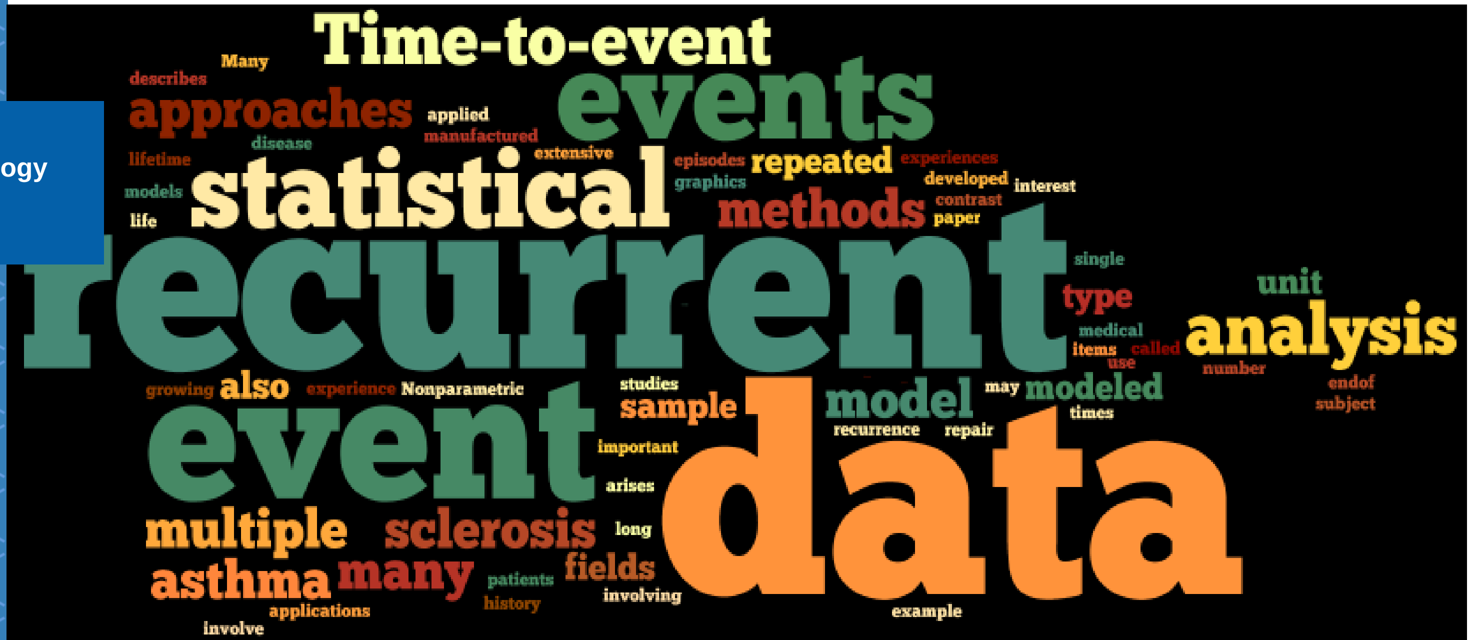

Group sequential designs for recurrent events: new challenges and proposals

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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

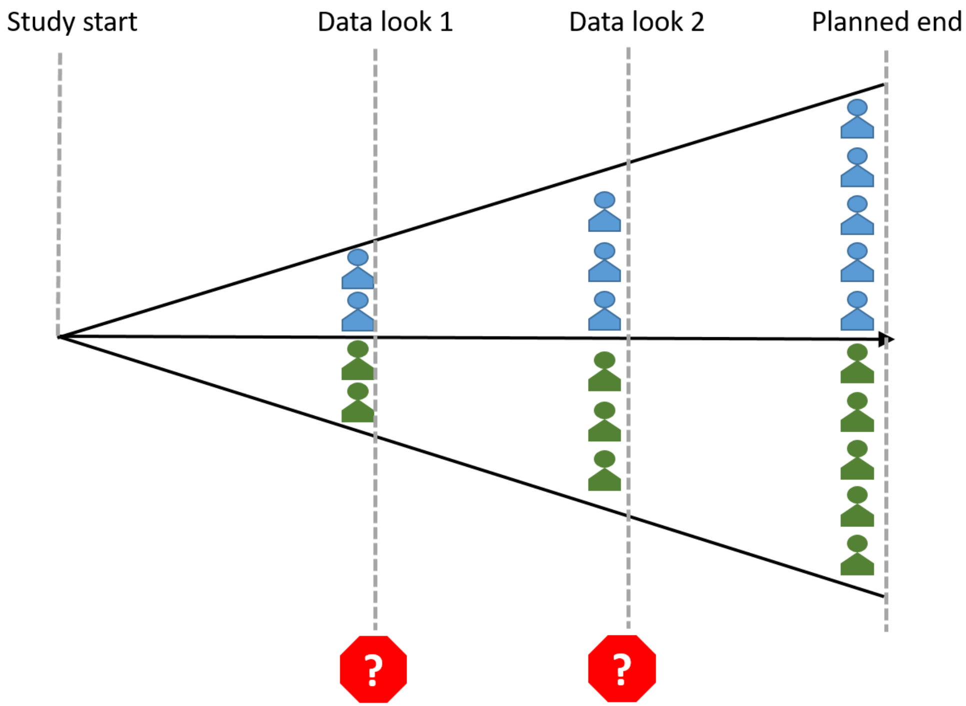
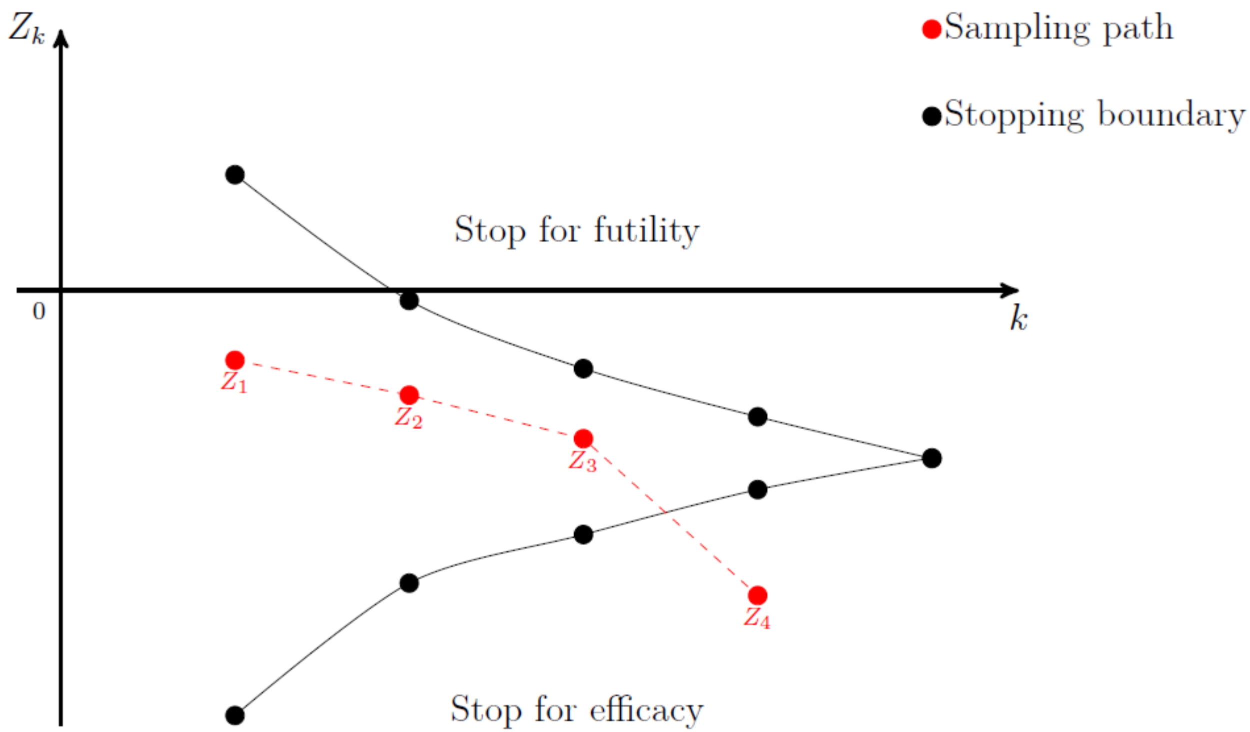


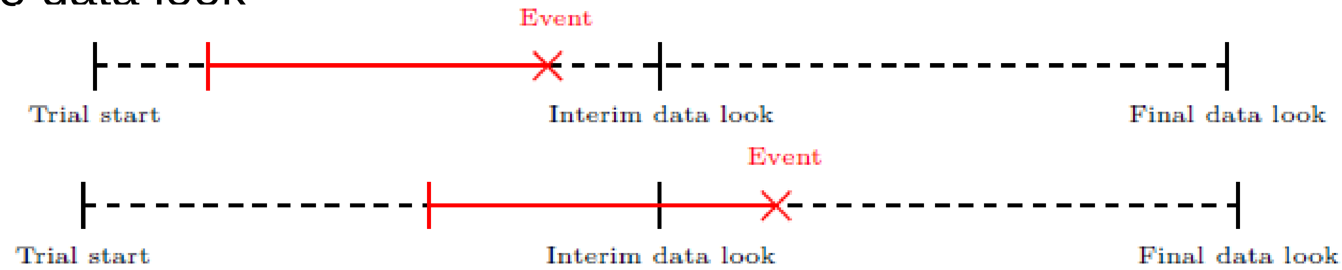
Illustration of group sequential designs

- 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



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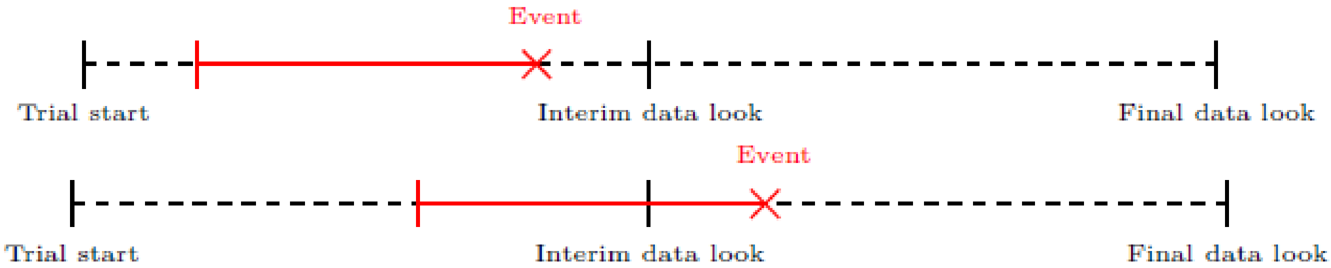
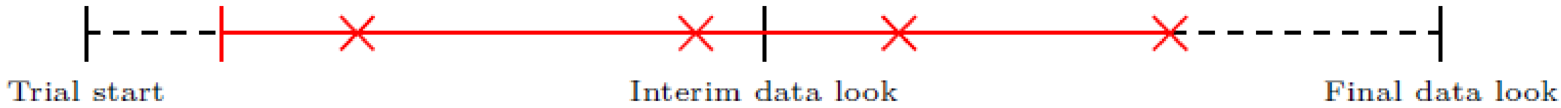


- Recurrent events: each patient can contribute a new event to more than one data look



- 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

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Notation and terminology for standard group sequential designs

- Parameter of interest β, e.g., log hazard ratio (time-to-event model) or log rate ratio (recurrent event model)
- Z-statistic at data look $k = 1, \dots, K$

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

- Information level at data look k: $\boldsymbol{\mathcal{I}}_k = \frac{1}{SE(\hat{\beta}_k)^2} = \frac{1}{Var(\hat{\beta}_k)}$
- Information fraction at look k: $\mathrm{w_k} = \boldsymbol{\mathcal{I}}_k / \boldsymbol{\mathcal{I}}_{Max}$
  - Maximum information $\boldsymbol{\mathcal{I}}_{Max}$
- Information fraction is commonly used to determine the calendar time of a data look

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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
  - $E[Z_k] = \beta\sqrt{\boldsymbol{\mathcal{I}}_{\mathrm{k}}}$
  - $Var[Z_k] = 1$
  - $Cov\left[Z_{k_1}, Z_{k_2}\right] = \sqrt{\boldsymbol{\mathcal{I}}_{\mathrm{k}_1}/\boldsymbol{\mathcal{I}}_{\mathrm{k}_2}}, \quad k_1 \leq k_2$

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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): $\mathcal{I}_k \approx \frac{d_k}{4}$
  - Information fraction: $w_k = \frac{d_k}{d_{Max}}$

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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

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Group sequential designs for negative binomial outcomes: Information

- Information at data look k:

$$\mathcal{I}_k = \frac{1}{\frac{1}{\mathrm{I}_{1k}} + \frac{1}{\mathrm{I}_{2k}}}$$

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

- Information and information fraction at a data look depend on individual follow-up times t_{ijk}, sample size n_i, rates μ_i, and the overdispersion parameter ϕ

➢ The number of events is not the same as the information for designs with negative binomial oucomes

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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 $w_1 = \frac{1}{3}, w_2 = \frac{2}{3}, w_3 = 1$

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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 trial with negative binomial outcomes

Distribution parameters
 Rate group 1:  0.0875
 Rate group 2:  0.125
 Dispersion parameter:  5
Hypothesis testing
 Rate ratio under null hypothesis:  1
 Rate ratio under alternative:  0.7
 Significance level:  0.025
 Power group sequential design:  0.8
 Power fixed design:  0.805
 Maximum information:  62.47
 Number of looks:  3
 Information times of looks:  0.3333, 0.6667, 1.0000
 Calendar times of looks:  1.195, 2.082, 4.000
Sample size and study duration
 Sample size group 1:  987
 Sample size group 2:  987
 Accrual period:  1.25
 Study duration:  4
```

```
Critical values and spending at each data look
                            +------- Efficacy -------+
   Look    Information time      Spending      Boundary
      1                0.33    0.00010351       -3.7103
      2                0.67     0.0059449       -2.5114
      3                   1      0.018952       -1.9930

Probabilities of stopping for efficacy, i.e. for rejecting H0
 Rate ratio        Look 1      Look 2     Look 3      Total
        1.0 0.0001035057 0.005944886 0.01895161 0.0250000
        0.7 0.0186487878 0.398800420 0.38255093 0.8000001

Expected information level
 Rate ratio      E[I]
        1.0 62.35806
        0.7 53.40283
```

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

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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*

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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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Thank you