Evaluation of sample size and power for multi-arm survival trials allowing for non-proportional hazards, loss to follow-up and cross-over

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Outline

(1) Introduction
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(3) Extensions
(4) Performance of the method
(5) Final remarks
1 Introduction

- Logrank test commonly used in analysis of phase III clinical trials with survival time outcome
- Sequential accrual followed by period of follow-up
- Administrative censoring
- Multiple arms
- Loss to follow-up and cross-over
- Schoenfeld (1983):
  - two survival distributions under logrank test, administrative censoring
- Lachin & Foulkes (1986):
  - loss to follow-up using exponential distribution

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2 The general method

- $H_0 : \ln \left\{ \frac{\lambda_2}{\lambda_1} \right\} = 0$
- $H_1 : \ln \left\{ \frac{\lambda_2}{\lambda_1} \right\} \neq 0$
- Logrank statistic
  \[
  U = \sum_{j=1}^{m} \left[ \text{observed}(events) - \text{expected}(events) \right]
  \]
- Variance $V$
- Test statistic $Q = U^2/V \sim \chi_1^2$
2 The general method

- Under $H_1$ non-centrality parameter

$$\tau = n \left( \ln^2 \left\{ \frac{\lambda_2}{\lambda_1} \right\} \right) p(1 - p) \psi$$

- Assume local alternatives

- Total sample size required

$$n = \frac{(z_{1-\alpha/2} + z_\beta)^2}{\left( \ln^2 \left\{ \frac{\lambda_2}{\lambda_1} \right\} \right) \psi p(1 - p)}$$
3 Extensions

- General framework: total trial time split into periods of equal length
  ⇒ examine number of patients at risk and occurrence of events in all groups separately for each period
- Length of periods depend on knowledge available about patient behaviour at start of trial
- Allows to take into account:
  - staggered patient entry
  - loss to follow-up
  - cross-over
  - non-proportional hazards
3.1 Staggered patient entry and loss to follow-up

- $T$ as the total number of periods in a trial
- Accrual over periods 0 to $R$
- Accrual piecewise truncated exponential or uniform
- Point mass at zero
- Survivor function of loss to follow-up and of failure times
- Survivor functions piecewise exponentials
- Probabilities of failure and loss to follow-up over duration of trial
  \[ \Rightarrow \text{probability } \psi \text{ of not being censored} \]
3.2 Multi-arm trials

- $n$ patients randomised to one of $K$ treatments
- $K$ treatments to be compared globally, i.e.

\[ H_0 : \lambda_1(t) = \lambda_2(t) = \ldots = \lambda_K(t) \]

\[ H_1 : \lambda_k(t) \neq \lambda_{k-1}(t) \text{ for at least one } k \]

- Test statistic under $H_0$

\[ Q = U'(V(0))^{-1}U \sim \chi^2_{K-1} \]

- Under $H_1$ non-centrality parameter

\[ \tau = nE(U|H_1)'(V(0))^{-1}E(U|H_1) \]

- Important since heuristic approach does not take into account multiple comparisons during analysis
3.3 Cross-over

- A patient who changes from designated treatment group into another but remains available for follow-up
- $C$ as time at which cross-over occurs
- Hazard function $\nu_i(t)$ of cross-over
- Calculate proportion of non-compliant patients
- Readjust $n$
4 Performance of the method

- Assess overall performance of sample size calculations as implemented in STATA 8
- Compare with software of similar scope, i.e. SIZE developed by Joanna Shih based on Lakatos (1988)
- Lakatos: loss to follow-up and withdrawal from allocated treatment under nonstationary Markov model
- Different states:
  - adhere to treatment
  - lost to follow-up
  - cross-over
  - experience event
4.1 Simulation results

- Performed in STATA 8
- 2 years accrual, 2 years follow-up
- Median survival 1 year
- Equal allocation
- Uniform accrual and exponential survival
- 90% power and 5% significance level
- 5000 simulated trials
- Standard error 0.4%, i.e. CI from 89.2 to 90.8% power
- Adjusted and unadjusted sample size calculation run
- Analysed under intention to treat

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### 4.1.1 Loss to follow-up

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* sample size adjusted for loss to follow-up

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### 4.1.2 Non-proportional hazards

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* sample size adjusted for non-proportional hazards

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### 4.1.3 Cross-over

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* sample size adjusted for cross-over

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4.2 Relationship between power and sample size

HR1 = 0.7, HR2 = 0.8, accrual = 2, follow-up = 2
proportion lost to follow-up = 30% in both arms
cross-over = 30% from both arms
4.3 Trial example: Optima

- Trial currently run in UK, Canada and USA
- Management of patients with HIV infection and failure of 1st and 2nd line HAART
- 4.5 years accrual and 1 year follow-up
- Standard arm event rate in year 1 23%, 25% annual increase thereafter
- Cross-over from mega to standard 5% in year 1, 50% decrease every year thereafter
4.3 Trial example: Optima

- Drop-in from standard to mega ART 1% in year 1 (increasing by 10% thereafter)
- Hazard ratio 0.7
- Loss to follow-up at 5.5 years 5%
- Significance level 5% and power 80%
4.3 Trial example: Optima
4.3 Trial example: Optima

- For 80% power:
  - Adjusted sample size 825, 287 events
  - Unadjusted sample size 711, 250 events
- For 90% power:
  - Adjusted sample size 1105, 384 events
  - Unadjusted sample size 951, 334 events


5 Final remarks

- Adjustments for non-proportional hazards and cross-over substantial in terms of power

- Main differences with SIZE:
  - Sample size up to 5% higher with SIZE
  - Different loss to follow-up distributions in treatment arms
  - More than two treatment arms
  - Non-uniform accrual
  - User friendly interface
  - Convergence problems with SIZE (time)

- STATA program allows for distant alternatives from $H_0$ but only marginal improvements in accuracy

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5 Final remarks

equal allocation to both treatment arms, accrual = 2, follow-up = 2
solid lines give 95% CI around 90% power
5 References


Barthel et al.. A menu-driven facility for complex sample size calculation in randomized controlled trials with a survival or a binary outcome: update. The Stata Journal submitted.


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