Design and testing for clinical trials faced with misclassified causes-of-death

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Problem description

Interest in cause-specific mortality

- this is what is affected by exposure

Fallable cause-of-death assessment

- death certificates
- clinical trials
- ...

$\Rightarrow$ verbal autopsy: sensitivity as low as 50%

$\Rightarrow$ cause-specific survival analysis gives biased estimate and power loss

Options:

- all-cause analysis
- correct for the risk of misclassification
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Motivating study: Jaffar et al., *I.J.E.* 2003

- Impact of a vaccine on mortality from airway infections in Gambian children
- Phase III randomized, placebo controlled trial
- Need for ‘post-mortem questionnaires’ or ‘verbal autopsy’
- 2 CODs:
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Misclassification of causes

- Sensitivity = 0.4
- Specificity = 0.9
- Power: 87% ↓ to 25%
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- misclassification of causes
  
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Problem description

Power for a naive cause-specific logrank test

sensitivity \(= 0.4\)

specificity \(= 0.9\)

\(\downarrow\)

power \(= 25\%\)
Problem description

Power for a naive cause-specific logrank test

sensitivity = 0.4
specificity = 0.9
\[\downarrow\]
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All-cause logrank: 23%!
Impact on design: choice of primary outcome

Cutts et al., *Lancet* 2005

cause-specific mortality: power loss
⇒
all-cause mortality: sample size
⇒
primary endpoint: radiological pneumonia (!)

⇒ ITT-result: significant reduction
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Cutts et al., *Lancet* 2005

cause-specific mortality: power loss

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primary endpoint: radiological pneumonia (!)

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misclassification determines design and analysis!
Our approach

- keep CS mortality as focus
- acknowledge the misclassification rates
- adapt the analysis (and design)

→

- recover power
- reduce bias

→

- enough to tip the balance?
Design assumptions

- 2 sets of covariates $Z$ (works on dfd) and $X$ (works on doc)
- observation time $T$
- failure indicator $\delta$: 0=censored, 1=failure
- true cause-of-death $COD_{true}$: doc or dfd
  $\Rightarrow$ observed COD = $COD_{obs}$

$\Rightarrow$ observed data: $(Z, X, T, \delta, COD_{obs})$
Design assumptions

Assumptions: similar to Goetghebeur and Ryan, *Biometrika* 1995

- misclassification probabilities may depend on the true COD: $p_0(t)$ and $p_1(t)$
- failure patterns from proportional cause-specific hazards:
  \[
  h_{dfd}(t; \mathbf{Z}(t)) = e^{\phi^T \mathbf{Z}(t)} h_{dfd}(t)
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  \[
  h_{doc}(t; \mathbf{X}(t)) = e^{\rho^T \mathbf{X}(t)} h_{doc}(t)
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\[ h_{doc}(t) = h_{dfd}(t) e^{-\xi} \]
Partial likelihood

\[ L = \prod_{i=1}^{n} \left( \frac{\sum_{j=1}^{n} Y_j(t) \left[ e^{-\xi} e^{\rho^T X_i(t)} (1 - p_0(t)) + e^{\phi^T Z_i(t)} p_1(t) \right]}{\sum_{j=1}^{n} Y_j(t) \left[ e^{-\xi} e^{\rho^T X_j(t)} (1 - p_0(t)) + e^{\phi^T Z_j(t)} p_1(t) \right]} \right)^{dN_{i0}(t)} \]

no misclassification:

\[ L = \prod_{i:COD_{true,i}=d} \frac{e^{\phi^T Z_i(t)}}{\sum_{j \in R_i} e^{\phi^T Z_j(t)}} \]
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condition on type of event:

\[P(i \text{ has event of type } j \text{ at } t_i \mid \text{someone in risk set has event of type } j \text{ at } t_i)\]

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Problem description

Design assumptions

Likelihood inference

Case study

Discussion

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Misclassification in cause-specific survival analysis
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Estimating equations: \[ \left( \frac{\partial L}{\partial \phi}, \frac{\partial L}{\partial \rho}, \frac{\partial L^*}{\partial \xi} \right) = 0 \]

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Misclassification in cause-specific survival analysis

9/17
Case study: Jaffar et al., *I.J.E.* 2003

Testing one binary $Z$, no $X$

Score statistic:

$$\frac{T^n}{\sqrt{V^n}} = \frac{\sum_{i=1}^{\delta_i} w_i(t_i, COD_{obs,i})(Z_i - \bar{Z}_i)}{\sqrt{\sum_{i=1}^{\delta_i} w_i^2(t_i, COD_{obs,i}) \left[ \left( \sum_{j \in R_i} Z_j^2 / n_i \right) - \bar{Z}_i^2 \right]}}$$

with:

$$w_i(\xi, p_0(t_i), p_1(t_i)) = \begin{cases} 
COD_{obs,i} = doc : 1 \text{ - negative predictive value} \\
COD_{obs,i} = dfd : \text{positive predictive value}
\end{cases}$$

under $H_0$: \[\hat{\xi} = -\log \left( \frac{O_1 p_1 - O_0 (1 - p_1)}{O_0 p_0 - O_1 (1 - p_0)} \right)\]
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Testing one binary $Z$, no $X$

Asymptotic relative (Pitman) efficiencies: $\text{are}(1, 2) = \lim_{\phi \to \infty} \frac{n_{\phi, 2}}{n_{\phi, 1}}$

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$\Rightarrow$ Sample size for 80% power?

- naive: 123,516
- corrected: 87,600
- all-cause: 128,824
### Case study: Jaffar et al., *I.J.E.* 2003

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Estimating one binary $Z$, no $X$

$\phi$ estimation:
- less bias
- less precision
Case study: Cutts et al., *the Lancet*, 2005

- 17,433 individuals, equally divided over genders and treatments
- 917 deaths, of which 186 ALRI

One binary treatment

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⇒ how strong is the 'double signal'? ⇒ Cox model!
Case study: Cutts et al., *the Lancet*, 2005

One binary treatment, influencing both causes

cause-of-interest: \( e^\hat{\phi} = 0.889 \) (p-value 0.67)

competing risk: \( e^\hat{\rho} = -0.853 \) (p-value 0.27)

⇒ indicates structure beyond logrank assumption

⇒ Cox model potentially offers added value
Discussion

Constant relative baseline cause-specific hazards?

- simple approximation for design purposes
- not necessary: e.g. piecewise constant hazard ratios are simple alternative

Knowledge of misclassification probabilities

- $p_0$ and $p_1$ not always available
  - $\Rightarrow$ pilot study with gold standard: estimate $p_0$ and $p_1$
  - $\Rightarrow$ then continue with routine diagnosis

- Details to be worked out:
  - size of the pilot sample
  - further use of the pilot data
What to remember

- misclassification occurs routinely
- it leads to loss of power and bias
- under some assumptions a corrected inference can lead to
  - much smaller needed sample sizes
  - more meaningful inference

choice of primary endpoint can be affected:
- back to mortality rather than morbidity endpoint
- cause-specific analysis becomes more attractive!
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Acknowledgements

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