Analyzing Recurrent Adverse Events from RCTs

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Background

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- 70–80% of all information collected in RCTs is safety-related (Gong et al. 2014)
- Adverse Events (AEs) are routinely collected as time-to-event variables
- Analyses are usually restricted to displaying raw rates of events or tests of 2x2-tables
  $\rightarrow$ especially problematic if treatment durations differ
- Why not use **survival methods** to analyse AE data?
- But: AE data is complex!
  - recurrent events
  - competing risks (e.g. death, disease progression, …)
  - …

Statistical Framework

Statistical Framework

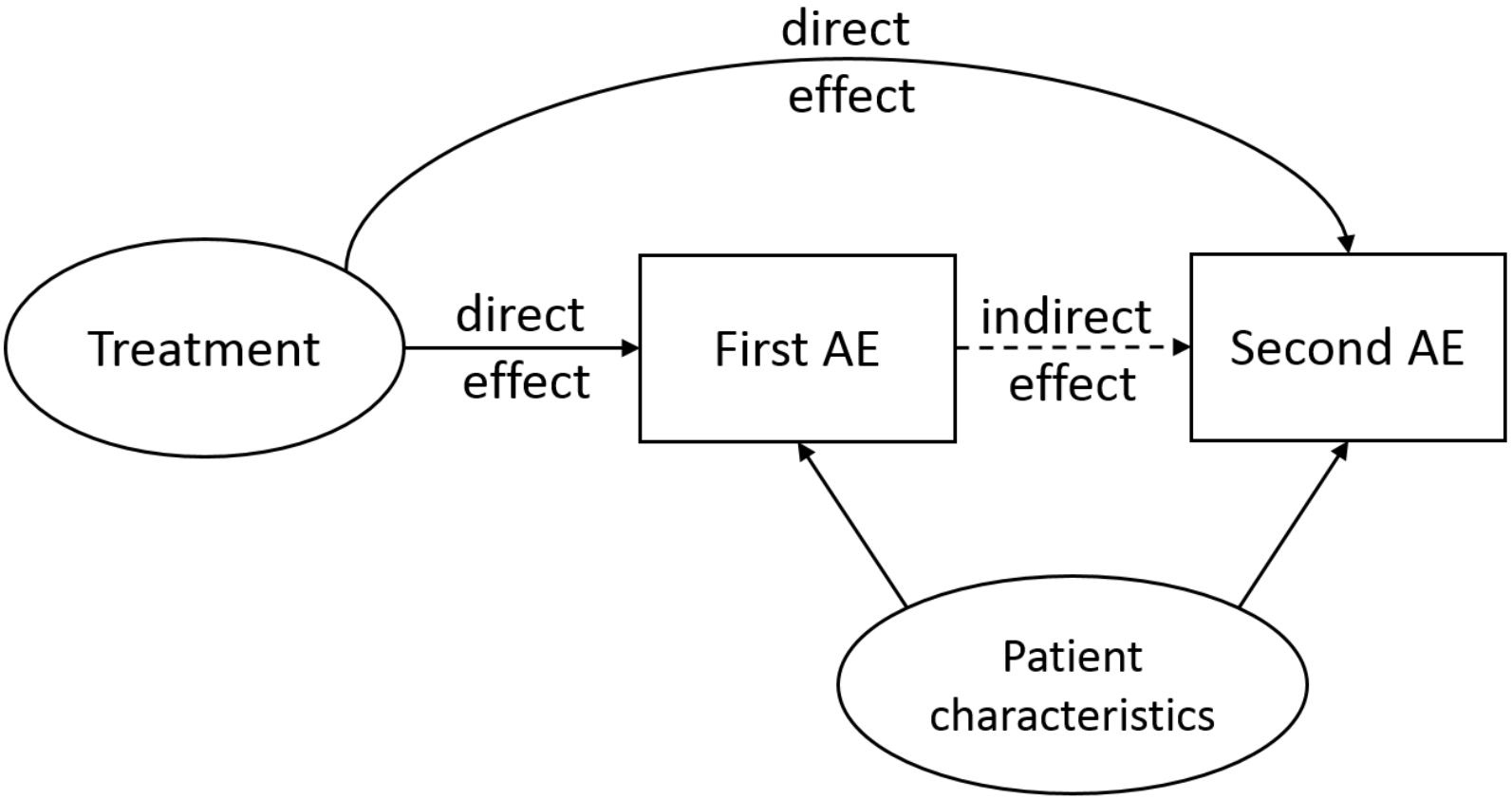
- In some trials, we may be interested in AEs
- Survival analysis methods provide ways to analyse recurrenct events
- But: modelling of recurrent events raises additional questions
  - When are events recurrent, when ongoing?
  - What matters? Time to onset or event duration?
  - What **statistical quantity** is of interest?
- Here: focus on as endpoint (no incorporation of event duration)

Statistical Framework

- Modelling of AE data can be made (almost) arbitratily complex
  - Joint models of primary and safety endpoints
  - Multi-state models incorporating competing events
  - …
- Here: focus on two approaches

1. Modelling a counting process (Andersen-Gill model)
2. Modelling state transitions (simple Multi-state model)

Statistical Framework



Counting process model

- Extension of the Cox model to counting processes
- Cox model:

$$\lambda(t|z_i) = \lambda_0(t)\exp(z_i'\beta),$$

$$L(\beta) = \prod_{i=1}^{n}\left[\frac{\exp(z_i'\beta)}{\sum_{j\in R_j}\exp(z_j'\beta)}\right]^{\gamma_i}$$

- Andersen and Gill (1982):

$$L(\beta) = \prod_{i=1}^{n}\prod_{k=1}^{K}\left[\frac{\exp(z_i'\beta)}{\sum_{j\in R_j}\exp(z_j'\beta)}\right]^{\gamma_{ik}}$$

- R_j: all individuals still under risk at T_{ik}.

Counting process model

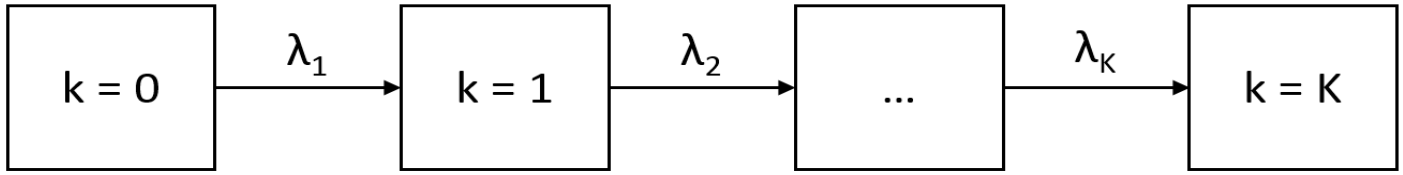
- ML estimate of β is unbiased also for counting processes
- But: events of single individuals likely to be correlated
  $\rightarrow$ model individual effects via a frailty term ω

$$\lambda(t|z_i, \omega_i) = \lambda_0(t) \exp(z_i'\beta + \omega_i),$$

  or use cluster-robust standard errors
- Usual model checks can be employed

Multi-state Model

- Alternative: model **conditional** probabilities:

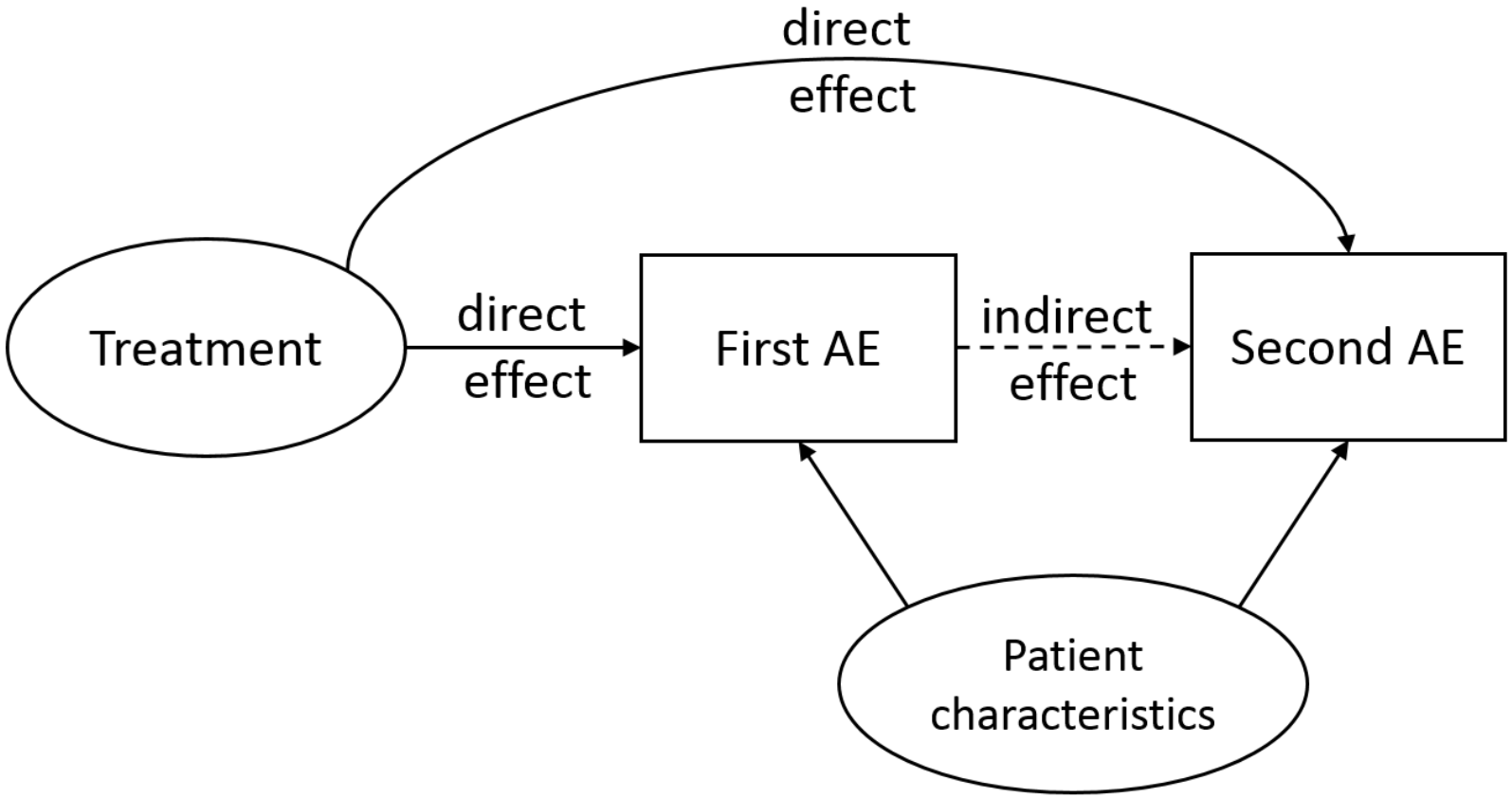


- Almost the same (partial) likelihood:

$$L(\beta) = \prod_{i=1}^{n} \prod_{k=1}^{K} \left[\frac{\exp(z_i' \beta)}{\sum_{j \in R_j} \exp(z_j' \beta)} \right]^{\gamma_{ik}}$$

- R_j: all individuals still under risk at T_{ik} and in state $k-1$
- β can vary by state: β_k
- Conditining on k is bound to strict assumptions

Multi-state Model



- Partial solution: model patient characteristics via a frailty term

Simulation

Simulation Design

- Experimental ($Z = 1$) and control group ($Z = 0$), with $n = 370$ for both
- Exponentially distributed gap times T_{ij} and censoring times
- (Direct) treatment effect $\exp(\beta) = 1.5$
- Two scenarios:
  - event risk is independent of k_i
  - event risk increases with k_i
- Two further scenarios:
  - event risk depends only on z_i
  - event risk also depends on ω_i, $\omega \sim N(0, 0.4^2)$

Simulation Results

	Event Risk independent of k_i			Event Risk increases with k_i		
No unmeasured heterogeneity ($\omega = 0$)	True total effect	=	0.4	True total effect	=	0.474
	True direct effect	=	0.4	True direct effect	=	0.4
	AG model	=	0.403 (95.2%)	AG model	=	0.472 (94.2%)
	Multi-state model	=	0.403 (96.0%)	Multi-state model	=	0.401 (93.2%)
	Multi-state RE model	=	0.403 (96.4%)	Multi-state RE model	=	0.401 (93.8%)
Unmeasured heterogeneity ($\omega \sim N(0, 0.4^2)$)	True total effect	=	0.4	True total effect	=	0.482
	True direct effect	=	0.4	True direct effect	=	0.4
	AG model	=	0.401 (95.7%)	AG model	=	0.481 (94.2%)
	Multi-state model	=	0.339 (81.0%)	Multi-state model	=	0.321 (69.8%)
	Multi-state RE model	=	0.396 (94.5%)	Multi-state RE model	=	0.389 (94.3%)

Application Example

Application Example

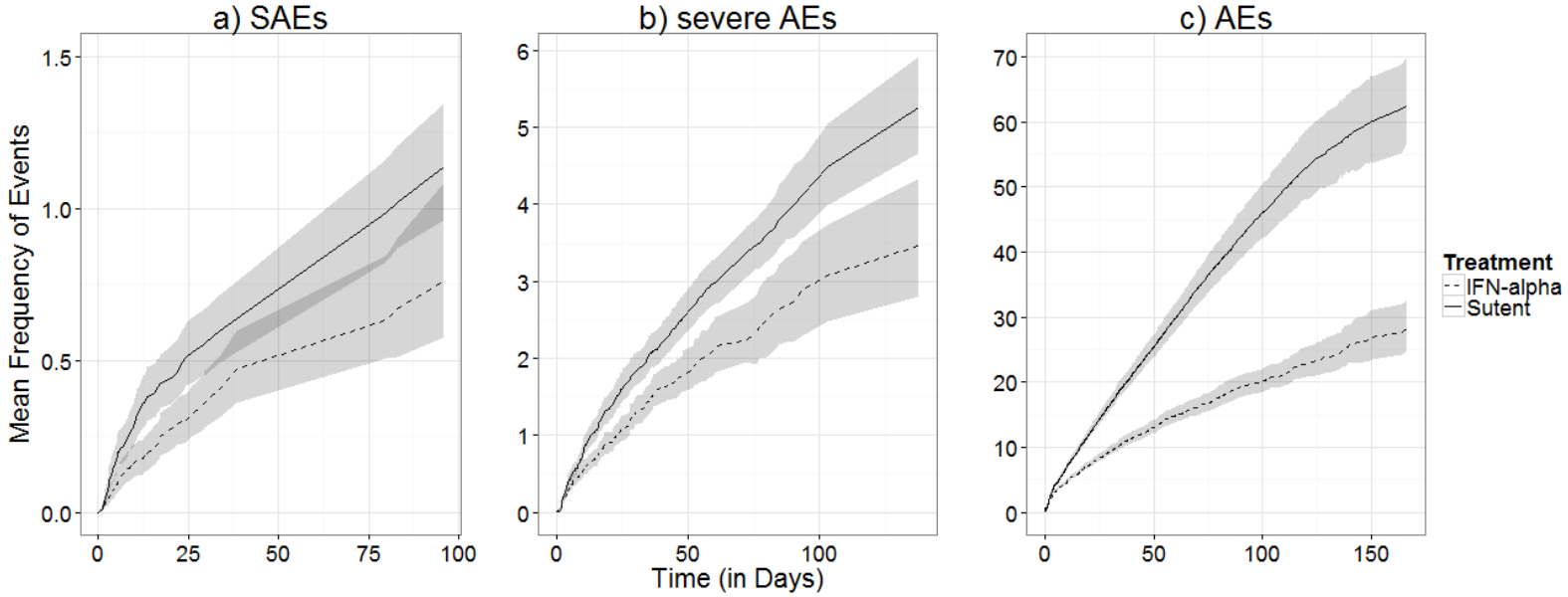
Application: Phase III study for firstline treatment of metastatic renal cell carcinoma (Motzer et al. 2009, Hengelbrock et al. 2016)

Median treatment duration: 11 (experimental) vs. 4 months (control group)

Endpoint	Proportion of patients with at least one event	Cox model	AG model	Multi-state model	Multi-state RE model
Severe AEs	83.2% vs. 60.0%	1.34 [1.13; 1.60]	1.41 [1.20; 1.66]	1.18 [1.04; 1.34]	1.19 [0.95; 1.48]
Serious AEs	45.3% vs. 25.8%	1.30 [1.00; 1.70]	1.43 [1.09; 1.88]	1.17 [1.94; 1.45]	1.24 [1.06; 1.44]

Application Example

- Drawback: Hazard ratios provide no evidence on **event incidence**
- One approach for counting process models: plug in an estimator for the cumulative baseline hazard (e.g. Breslow's estimator):



Discussion

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- In some trials (with comparable treatment durations), simple descriptive listings of AEs may be preferred over complex modelling
- Especially if duration times vary heavily, survival methods are more appropriate
- The analysis of recurrent events adds complexity but can provide more informative estimators
- Hazard-based models are still valid if competing risks are present. Care is needed if the incidence of events is estimated
- The definition of is not always straightforward (sensitivity analyses?)

References

Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. The Annals of Statistics 1982; 10(4):1100–1120.

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