Comparison of Time-To-First-Event and Recurrent Event Methods in Multiple Sclerosis Trials

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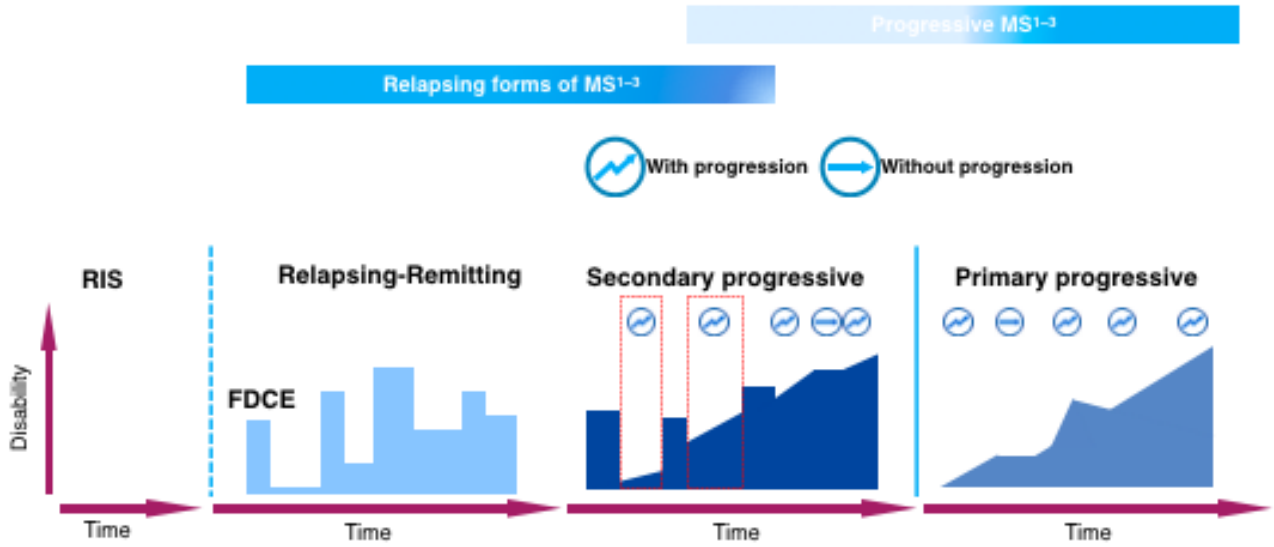
Outline

1. Introduction to MS and the ORATORIO trial in PPMS
2. Recurrent event methods in RCTs
3. Recurrent event analyses of the ORATORIO trial
4. Simulation studies
   - Generic simulation study
   - MS-specific simulation study
5. Conclusions

Multiple sclerosis (MS) disease course - 2013 consensus

- MS is a chronic, inflammatory and degenerative demyelinating disease of the human central nervous system
- Basic clinical phenomena of MS: relapses and disability progression
- Different disease courses: relapsing-remitting, secondary progressive and the primary progressive MS (RRMS, SPMS and PPMS)



FDCE, First Demyelinating Clinical Episode; RIS, radiologically isolated syndrome

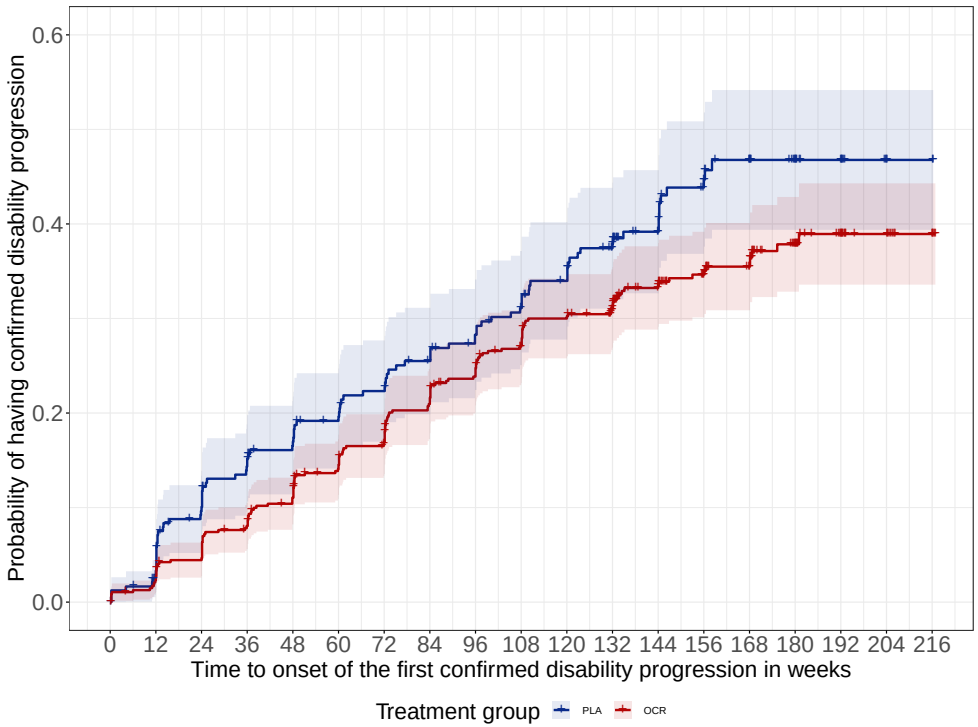
$\Longrightarrow$ Potential for recurrent event analyses in PPMS?

ORATORIO: Roche's pivotal study of ocrelizumab in PPMS

- Phase III trial
- $n = 732$ subjects, $2:1$ randomization ocrelizumab versus placebo
- **Primary endpoint:** Time from randomization to the **first** 12-week confirmed disability progression (CDP12)
  - Definition based on longitudinal assessments of Expanded Disability Status Scale (EDSS)
  - Events must be initial disability progression (IDP) which are confirmed (CDP12)
    - ★ IDP: increase in EDSS by ≥ 1.0 points (if baseline EDSS ≤ 5.5) or ≥ 0.5 points (if baseline EDSS > 5.5)
    - ★ CDP12: increase sustained for at least 12 weeks

Time-to-first-event analysis of the ORATORIO trial

Cox proportional hazards model and log-rank test:



	OCR (N=488)	PLA (N=244)
Patients included in analysis	487 (100.0 %)	244 (100.0 %)
Patients with first CDP12 event (%)	160 (32.9 %)	96 (39.3 %)
Time-to-first-event analysis		
p-value (log-rank)	0.0321	
HR (95% CI)	0.76 [0.59, 0.98]	

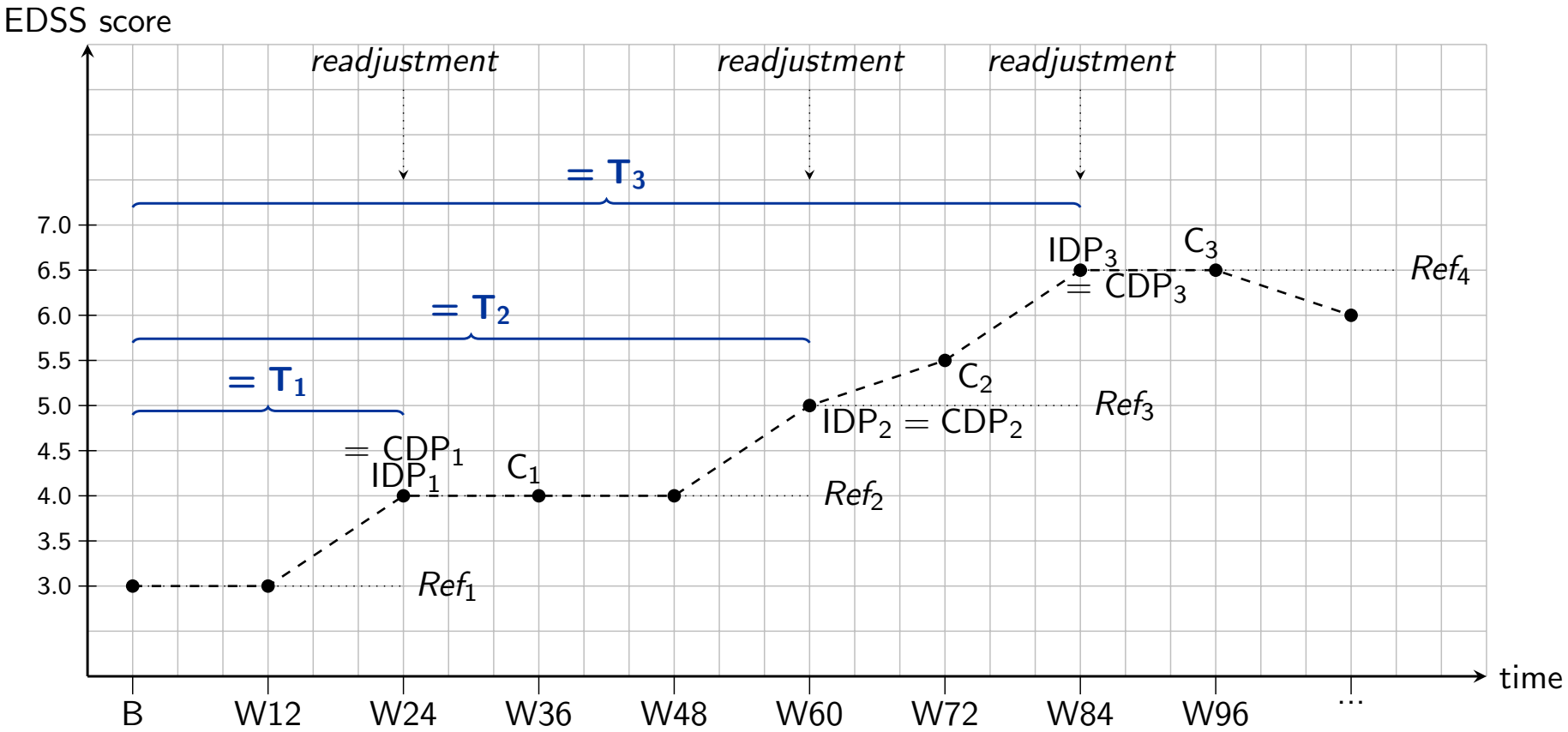
Recurrent event definition

Event	Definition
First CDP12 event	increase in EDSS score of ≥ 1.0 (if baseline EDSS ≤ 5.5) or ≥ 0.5 points (if baseline EDSS > 5.5) from the **baseline** EDSS score, confirmed for at least 12 weeks (CDP12)
Repeated CDP12 event	increase in EDSS score of ≥ 1.0 (if reference EDSS ≤ 5.5) or ≥ 0.5 points (if reference EDSS > 5.5) from a **reference** EDSS score, confirmed for at least 12 weeks (CDP12)

Reference EDSS score:

- Readjustment of reference EDSS level after each event
- Definition:
  - First CDP12 event: baseline EDSS score
  - j^{th} CDP12 event: EDSS score at IDP of $(j-1)^{th}$ CDP12 event

Recurrent event definition for a stylized subject



$IDP_j = j^{th}$ initial disability progression, C_j = confirmation of IDP_j, $CDP_j = j^{th}$ confirmed disability progression (event)
Ref_j = reference EDSS score for j^{th} CDP, T_j = time to onset of the j^{th} CDP

- Reference EDSS level readjusted after each event
- CDP definition looks into the future (as for the established time-to-first CDP definition)

Recurrent event methods

Model	Description
Negative binomial (NB)	- Parametric rate-based model - Given gamma frailty, underlying recurrent event process is Poisson - Random effect induces dependency between recurrent events - Constant event rates over time - Effect measure: RR
Lin-Wei-Yang-Ying (LWYY)	- Semiparametric rate-based model - Allows arbitrary dependence structure between recurrent events - Baseline rate function unspecified - Effect measure: RR
Andersen-Gill (AG)	- Semiparametric intensity-based model - Extension of Cox proportional hazards model - Dependence structure among recurrent events must be fully specified, (e.g., via conditioning on the past, internal time-varying covariates) - Baseline intensity function unspecified - If only adjusted for baseline covariates, underlying recurrent event process is Poisson with unspecified baseline intensity function - Effect measure: HR

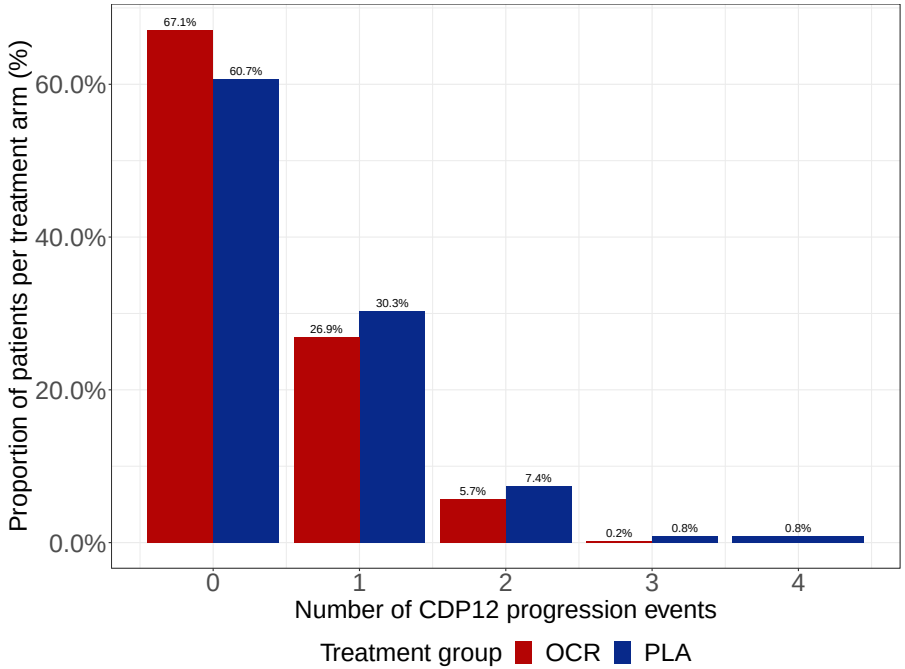
$\Longrightarrow$ All methods (NB, LWYY and AG model) estimate the 'overall' treatment effect!

Rate-based vs Intensity-based Modelling

- Conditional intensity-based model – requires full specification of the past history (event, censoring, internal/external covariate, etc.)
  - Recurrent events are conditionally uncorrelated given the past history
  - Very sensitive to model misspecification
- Marginal rate-based model – conditions only on a part of the underlying process history
  - Allows for dependence structure between recurrent events
- If the past information is incomplete, a rate function rather than a intensity function is targeted.
- The rate function can be interpreted as the average intensity function at time t across all possible histories.
- Roughly speaking: LWYY=AG with robust SE

Recurrent event analyses of the ORATORIO trial

Number of CDP12 events during double-blind treatment period:

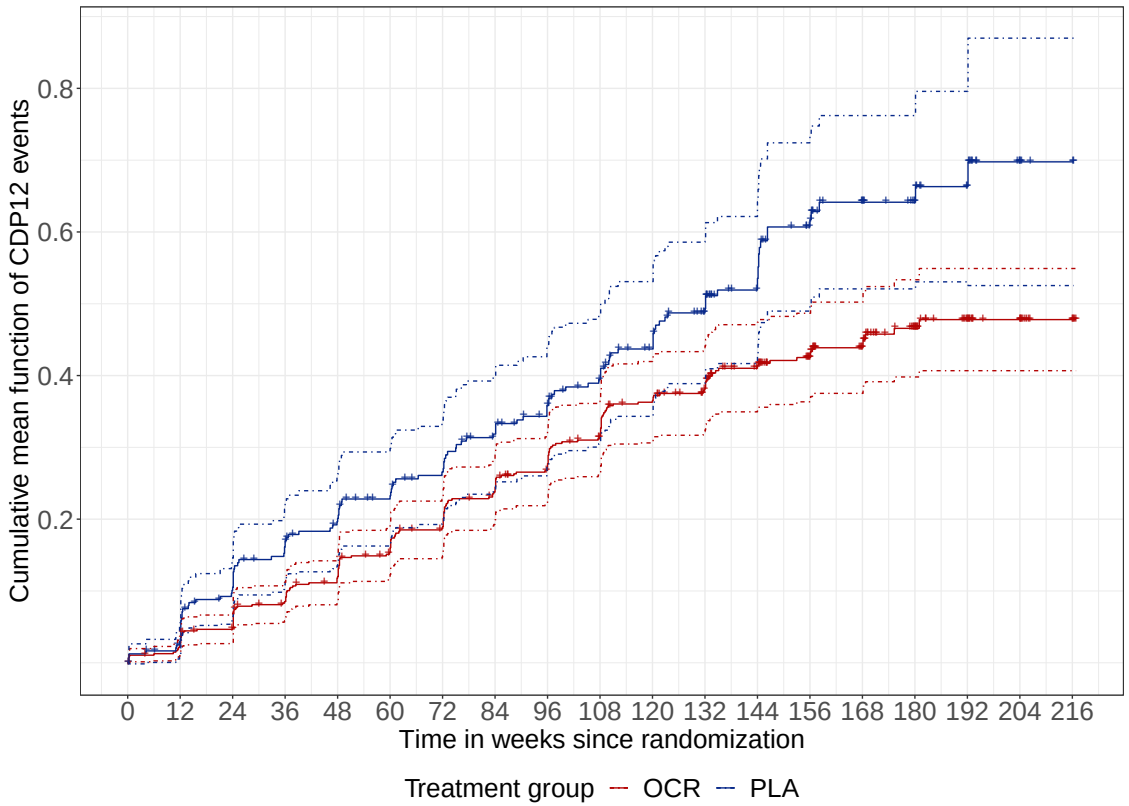


Treatment group	No. of first CDP12 events	No. of repeated CDP12 events
PLA (N=244)	96	124
OCR (N=488)	160	190
Total	256	314

$\Longrightarrow$ 58/314 (18%) CDP12 events not used in the primary time-to-first-event analysis

Recurrent event analyses of the ORATORIO trial

Cumulative mean function of CDP12 events:



- OCR or PLA patients experience on average 0.37 (95% CI $[0.31, 0.43]$) or 0.46 (95% CI $[0.36, 0.56]$) 12-week CDPs over the first 120 weeks of the double-blind treatment period

Recurrent event analyses of the ORATORIO trial

	Model	# CDP12 events included	Treatment effect
Time-to-first-event	Cox	256	HR 0.76 [0.59, 0.98], p=0.03
Recurrent event	NB	314	RR 0.71 [0.57, 0.91], p=0.005
	LWYY		RR 0.72 [0.57, 0.92], p=0.007
	AG		HR 0.72 [0.58, 0.91], p=0.005

- Smaller p-values observed for the recurrent event analyses

$\Longrightarrow$ Do all recurrent event analyses protect type I error? How much power can be gained?

$\Longrightarrow$ Investigate this in two simulation studies:

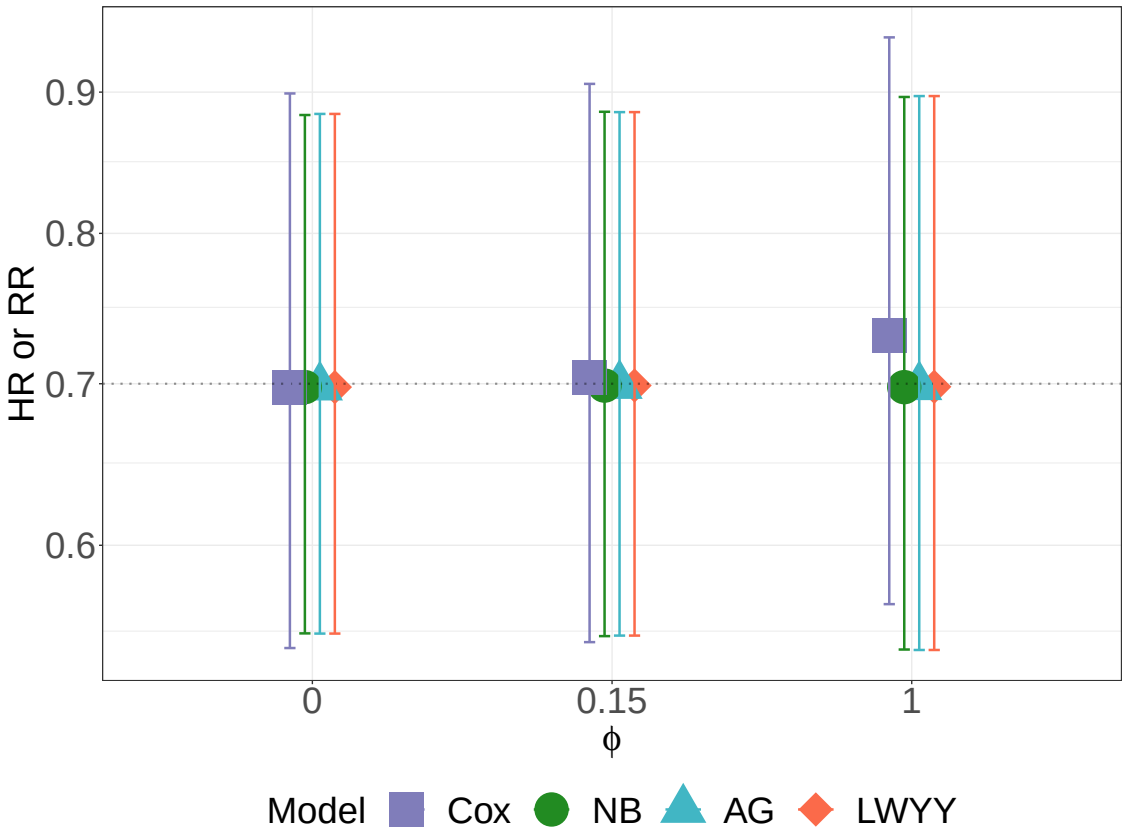
- Generic simulation study
- MS-specific simulation study

Generic simulation study - simulation setup

- Recurrent event data simulated according to a (mixed) non-homogeneous Poisson process
- Baseline intensity function of Weibull form (slightly decreasing event rates over time, as in ORATORIO data)
- Heterogeneity simulated with gamma frailty with variance ϕ:
  - homogeneous ($\phi = 0.0$), moderate ($\phi = 0.15$) and large ($\phi = 1.0$) heterogeneity
- Treatment effect: HR = 1.0 (no effect) or HR=0.7
- $n = 1000$ subjects (1:1 randomization) recruited uniformly over 1 year
- Trial continues until 246 first CDP12 events observed
  - 80% power for time to first CDP12 analysis with HR=0.7
- N = 10000 simulation runs

Generic simulation study - simulation results

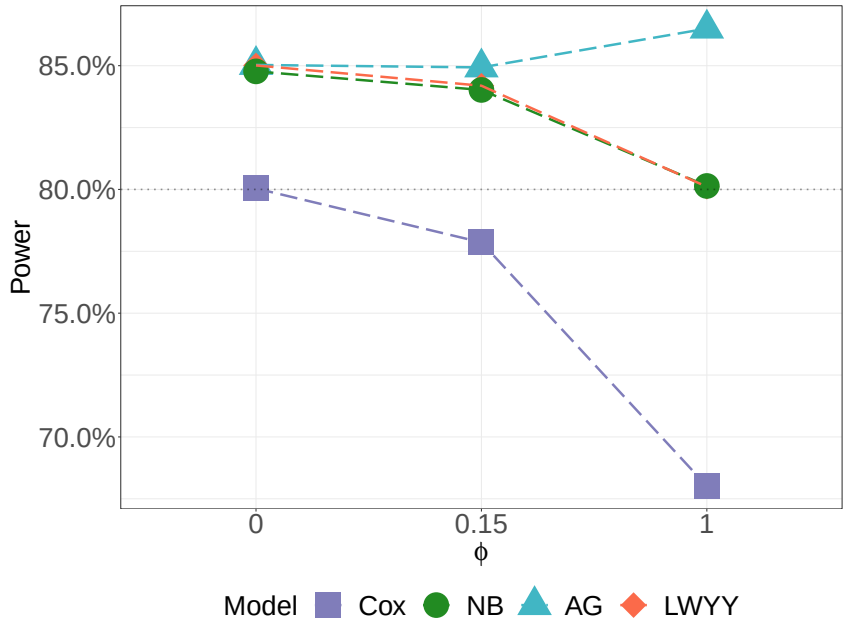
Treatment effect estimation:

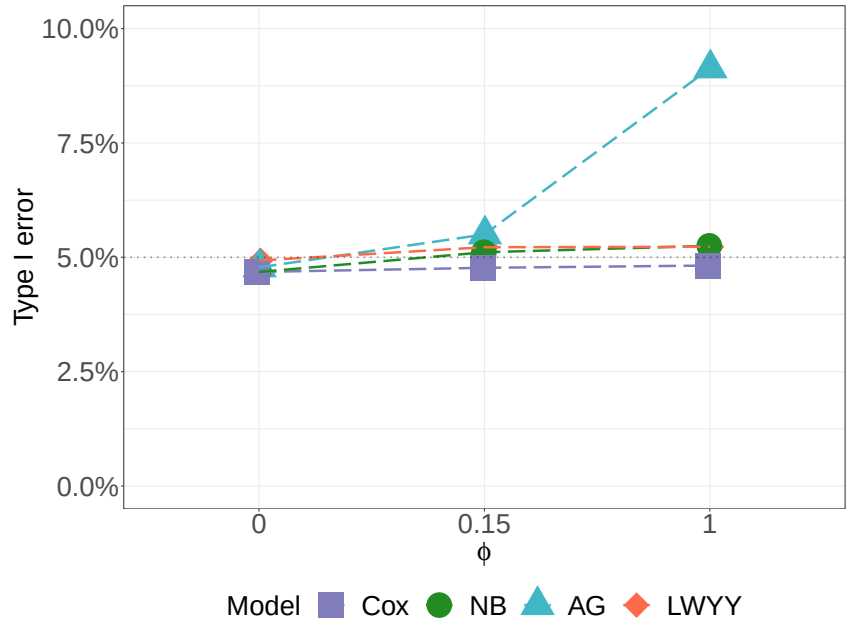


- Selection effects in time-to-first-event approach
- Recurrent event methods provide unbiased treatment effect estimates in presence of heterogeneity

Generic simulation study - simulation results

Power and type I error:



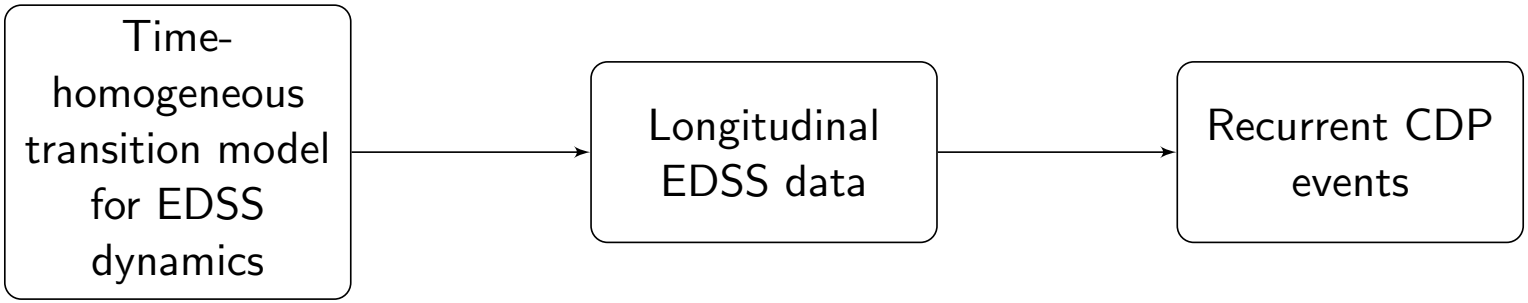


$\Longrightarrow$ Recurrent event approaches outperform time-to-first-event approach in terms of statistical power!

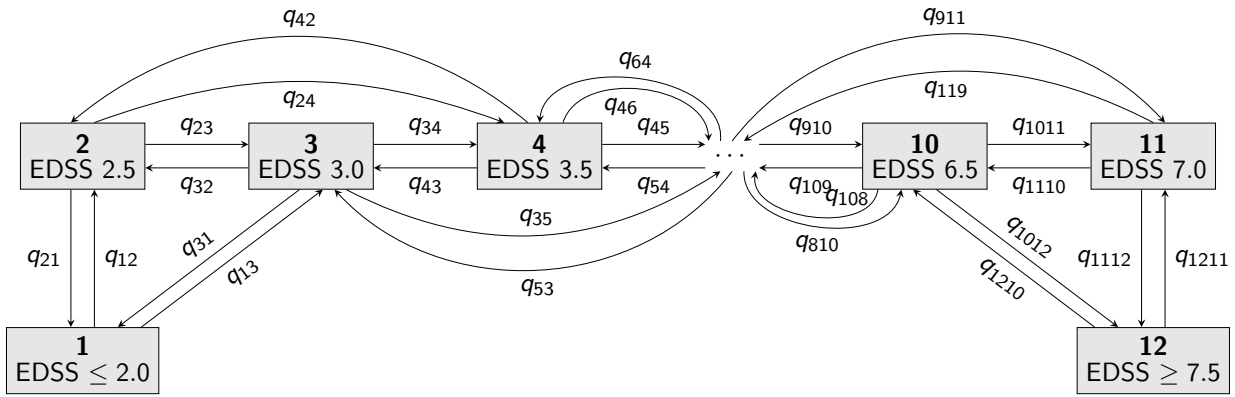
$\Longrightarrow$ Type I error inflated for the AG model in presence of heterogeneity

MS-specific simulation study - simulation setup

- Idea:



- Simulation of longitudinal ordinal EDSS measurements based on a time-homogeneous multistate model (transition intensities chosen according to ORATORIO data)

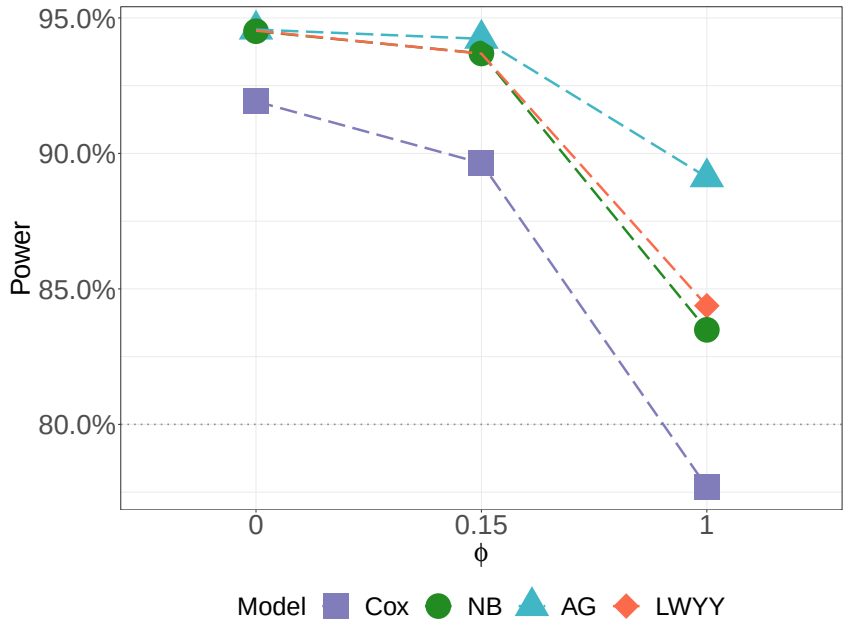


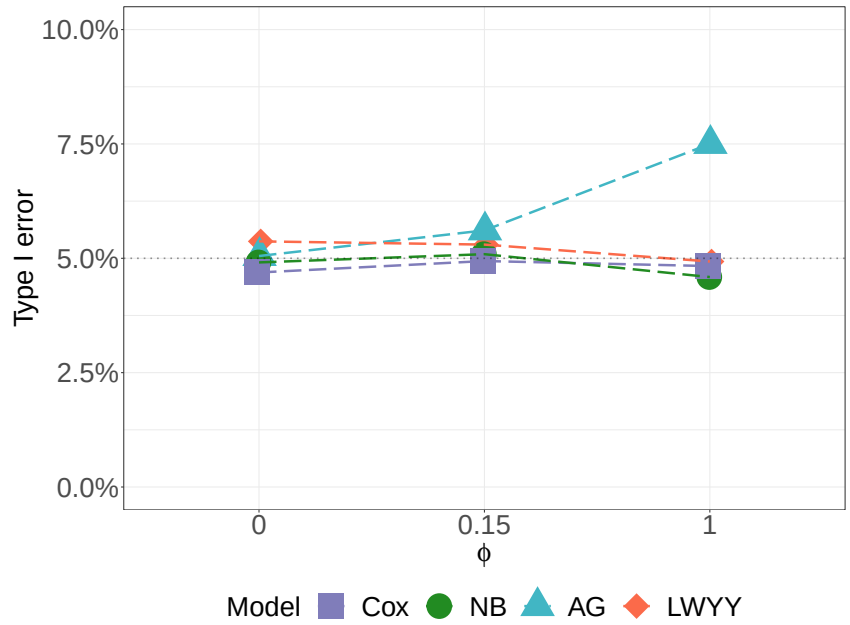
MS-specific simulation study - simulation setup

- Treatment effect and heterogeneity simulated on upper diagonal (= EDSS worsenings) of the EDSS transition intensity matrix
  - Treatment effect sizes: HR = 1.0 (no effect) or HR = 0.7
  - Gamma frailty with variance ϕ: homogeneous ($\phi = 0.0$), moderate ($\phi = 0.15$) and large ($\phi = 1.0$) heterogeneity
- Recurrent CDP endpoint derived based on simulated EDSS data
  - Simulated treatment effect sizes on transition intensity do not translate 1 : 1 to effect sizes for recurrent events
- n = 1000 subjects recruited uniformly over 1 year, trial continues until 246 first CDP events observed
- 1:1 randomization
- N = 10000 simulation runs

MS-specific simulation study - simulation results

Power and type I error:





$\Longrightarrow$ Recurrent event approaches outperform time-to-first-event approach in terms of statistical power!

$\Longrightarrow$ Type I error inflated for the AG model in presence of heterogeneity

Conclusions

- Recurrent event analysis use all clinically relevant disability progression data and increase power but add complexity
- Sample size of a trial with a recurrent endpoint could be $10 - 20\%$ lower compared to a time-to-first-event endpoint in the PPMS setting
- Type I error inflated for the AG model in the presence of heterogeneity
- Comparable performance of the LWYY and NB models
- Semiparametric LWYY model is recommened as primary analysis in RCTs
- NB model already popular for the analysis of recurrent relapses in MS
- Extension: multitype recurrent event models (CDP, 9HPT and T25FW)