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

Alexandra Bühler, Qing Wang¹, Marcel Wolbers¹, Fabian Model¹, Jan Beyersmann²

¹ Roche, Biostatistics, Basel, Switzerland
² Ulm University, Institute of Statistics, Ulm, Germany

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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)

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 \( \geq 1.0 \) points (if baseline EDSS \( \leq 5.5 \)) or \( \geq 0.5 \) 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:

![Graph showing time to onset of first confirmed disability progression in weeks and probability of having confirmed disability progression for OCR and PLA groups.]

- **Patients included in analysis:**
  - OCR (N=488)
  - PLA (N=244)
- **Patients with first CDP12 event (%):**
  - OCR: 160 (32.9 %)
  - PLA: 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

<table>
<thead>
<tr>
<th>Event</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>First CDP12 event</td>
<td>increase in EDSS score of $\geq 1.0$ (if baseline EDSS $\leq 5.5$) or $\geq 0.5$ points (if baseline EDSS $&gt;5.5$) from the baseline EDSS score, confirmed for at least 12 weeks (CDP12)</td>
</tr>
<tr>
<td>Repeated CDP12 event</td>
<td>increase in EDSS score of $\geq 1.0$ (if reference EDSS $\leq 5.5$) or $\geq 0.5$ points (if reference EDSS $&gt;5.5$) from a reference EDSS score, confirmed for at least 12 weeks (CDP12)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Model</th>
<th>Description</th>
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</table>
| **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 |

⇒ 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:

![Bar chart showing number of CDP12 progression events per patient.]

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>No. of first CDP12 events</th>
<th>No. of repeated CDP12 events</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLA (N=244)</td>
<td>96</td>
<td>124</td>
</tr>
<tr>
<td>OCR (N=488)</td>
<td>160</td>
<td>190</td>
</tr>
<tr>
<td>Total</td>
<td>256</td>
<td>314</td>
</tr>
</tbody>
</table>

⇒ 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

<table>
<thead>
<tr>
<th>Time-to-first-event</th>
<th>Model</th>
<th># CDP12 events included</th>
<th>Treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cox</td>
<td>256</td>
<td>HR 0.76 [0.59, 0.98], p=0.03</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Recurrent event</th>
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<tbody>
<tr>
<td>Model</td>
<td>NB</td>
<td>RR 0.71 [0.57, 0.91], p=0.005</td>
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<tr>
<td></td>
<td>LWYY</td>
<td>RR 0.72 [0.57, 0.92], p=0.007</td>
<td></td>
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<tr>
<td></td>
<td>AG</td>
<td>HR 0.72 [0.58, 0.91], p=0.005</td>
<td></td>
</tr>
</tbody>
</table>

- Smaller p-values observed for the recurrent event analyses

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

⇒ 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 $\phi$:
  - 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:

⇒ Recurrent event approaches outperform time-to-first-event approach in terms of statistical power!
⇒ Type I error inflated for the AG model in presence of heterogeneity
MS-specific simulation study - simulation setup

- **Idea:**
  - Time-homogeneous transition model for EDSS dynamics 
  - Longitudinal EDSS data 
  - Recurrent CDP events 

- 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 $\phi$: 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
Recurrent event approaches outperform time-to-first-event approach in terms of statistical power!
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 recommended 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)