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# Predicting milestone events for time-to-event trials

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# Outline

1 Predicting Milestone Events

2 Predictive Distributions

3 (Mixture of) Piecewise Exponential (PWE) Models

4 Case Studies

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# Predicting Milestone Events

*Predicting the time to a pre-specified number of events*

- Prediction of landmark/milestone events in time-to-event trials
- That is, the time when the required number of events is reached for interim or final analysis
- These are important operational milestones for
  - data entry and cleaning
  - scheduling Data Monitoring Committee meetings
  - planning for submission

# Predicting Milestone Events

*Uncertain time-to-event, dropout, enrollment process*

- Prediction: a statement about future data
  - Note the difference to estimation (statement about parameters), which is much more common in statistics
- In time-to-event trials, the predicted time of the k-th event depends on
  - time-to-event process (uncertain)
  - dropout process (uncertain)
  - enrollment process (uncertain)
- Milestone event prediction must account for the uncertainties for each of the three processes

# Predicting Milestone Events

*Simulating  from the three processes*

**1) Patients not yet enrolled**

**simulate enrollment time** | **min (simulated event time, simulated dropout time)**

**2) Patients enrolled and still at risk**

Time to last TA before clinical cutoff | **min (simulated event time, simulated dropout time)**

**Calendar time**

→ **sort all calendar events times**

**select milestone event time**

'Event': progression or death
'Dropout': lost to follow-up, or withdrawal of consent

# Predicting Milestone Events
*Operational and statistical challenges*

- Statistical
  - Event and dropout rates are not only uncertain, they may also change over time
  - Blinding
    - unblinded interim data if independent statistician performs the prediction
    - otherwise, data are blinded, which further complicates predictions
- Operational
  - Data entry lags
  - Change in enrollment process
  - Low complicance in scheduled assessments

# Predicting Milestone Events
*Some literature*

- Bagiella and Heitjan (2001)
  - Methods with constant enrollment, event, and dropout rate (exponential case)
- Donavan (2006)
  - Extension of Bagiella and Heitjan's method for blinded data
- Ying and Heitjan (2008)
  - Weibull distribution for the event and dropout process
  - Future enrollment is based on sampling from past arrival times
- Ying (2004)
  - Nonparametric model using the Kaplan-Meier method to estimate the distribution of the event and dropout process

# Predictive Distributions

*At least two sources of uncertainty*

- Predicting future data
  - Data (statistical) model for current data Y and future data Y*

$$pr( Y \mid \theta ), \qquad pr( Y^* \mid \theta )$$

  - Note: same parameter for Y and Y*. This may not always be realistic.
- Predictive distribution of future data given current data

$$pr( Y^* \mid Y )$$

- Note: two sources of uncertainty
  - Sampling uncertainty even if $\theta$ were known: $pr(Y^*|\theta)$
  - Parameter uncertainty: $\theta$ is uncertain although informed by Y, $pr(\theta| Y)$
  - Probability calculus: $pr( Y^*|Y) = \int pr(Y^*,\theta \mid Y)d\theta = \int pr(Y^*| \theta)\times pr(\theta|Y)d\theta$



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# Predictive Distributions

*Exponential data (constant hazard)*

- $Y=(Y_1,...,Y_n)$ exponential data with hazard $\theta$
- Distribution pr(Y*|Y) for a future exponential event time Y*
  - Prior: $\theta \sim$ *Gamma(a,b)*
  - Posterior is closed-form: $\theta \mid Y \sim$ *Gamma*(a+r,b+S)
    - $S = \Sigma Y_j$ total exposure time
    - r = number of events
    - a = prior number of events, b = prior exposure time:
      for a weakly informative prior use small values for a and b
  - The predictive distribution pr(Y*|Y) is closed-form:
    a *Gamma-Exponential* (Pareto type-II, Lomax) distribution
  - It can also be obtained by simulation:
    - simulate $\theta$ from Gamma(a+r,b+S)
    - for $\theta$ then simulate Y* from Exponential($\theta$)



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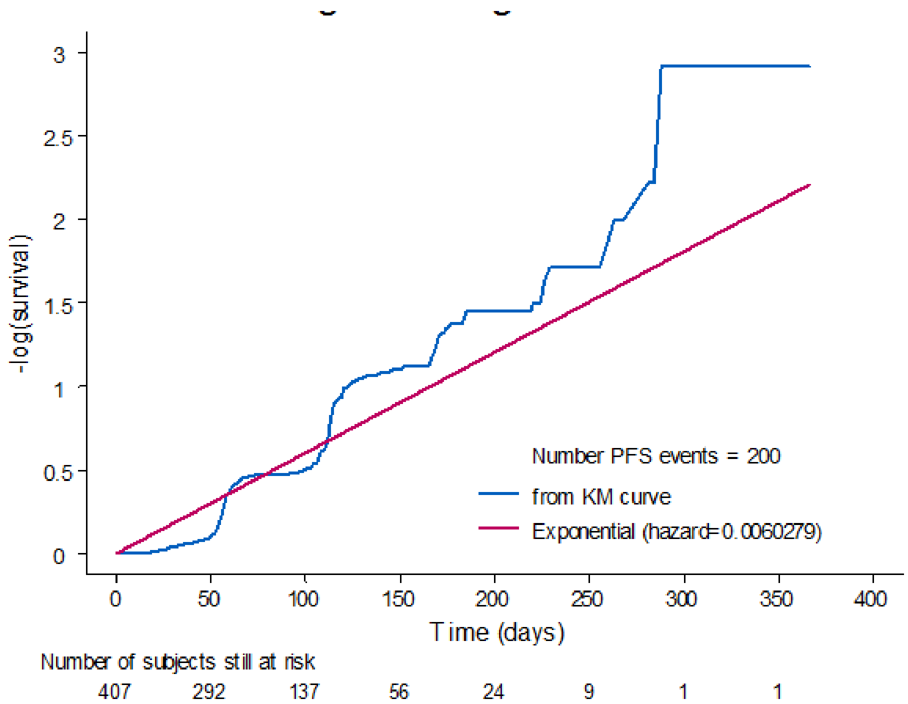
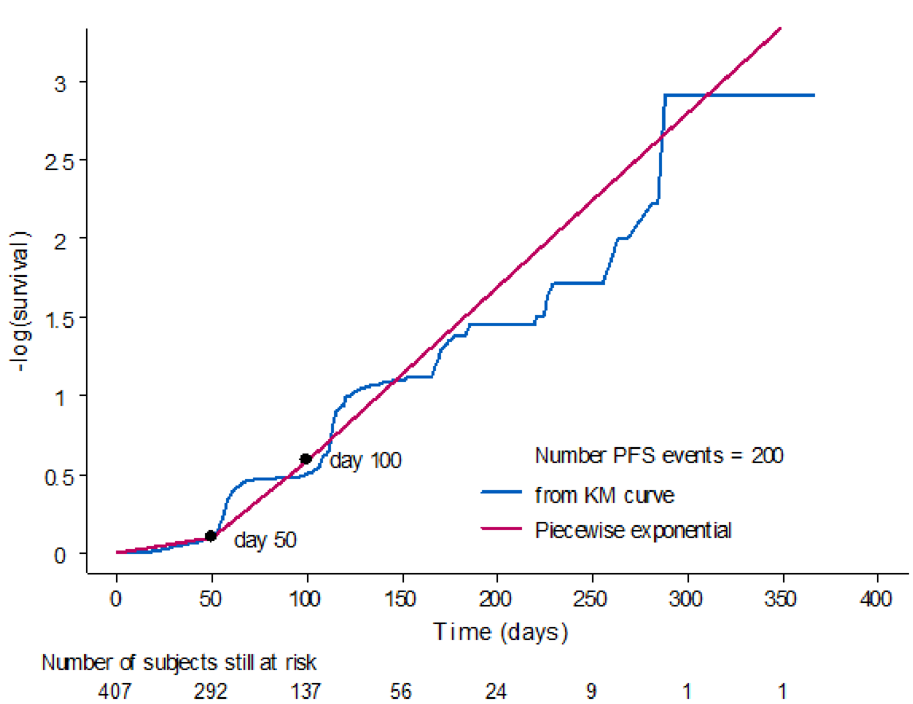
# Piewewise Exponential Distributions
*Beyond constant hazards*

- Exponential model for events and dropout often too restrictive
- Extension 1: piecewise exponential (PWE) models
  - PWE models are much more flexible
  - Calculus is easily extendable to PWE models:
    simply do the conjugate analysis for each interval with the respective number of events and exposure times
  - For milestone event prediction: we select the number of intervals and interval boundaries pragmatically
    - 1-4 intervals
    - each interval must have a reasonable large number of events (at least 30)
    - interval selection: based on visual comparisons of observed data and fitted negative-log survival curve (straight lines)

# Piecewise Exponential Distributions
*Interval finding: example*

- An example for choice of PWE intervals (event process)
  - exponential vs. PWE fit (after 200 events)
  - cutoffs at 50 and 100 days (3 intervals)



# Mixtures of PWE Models

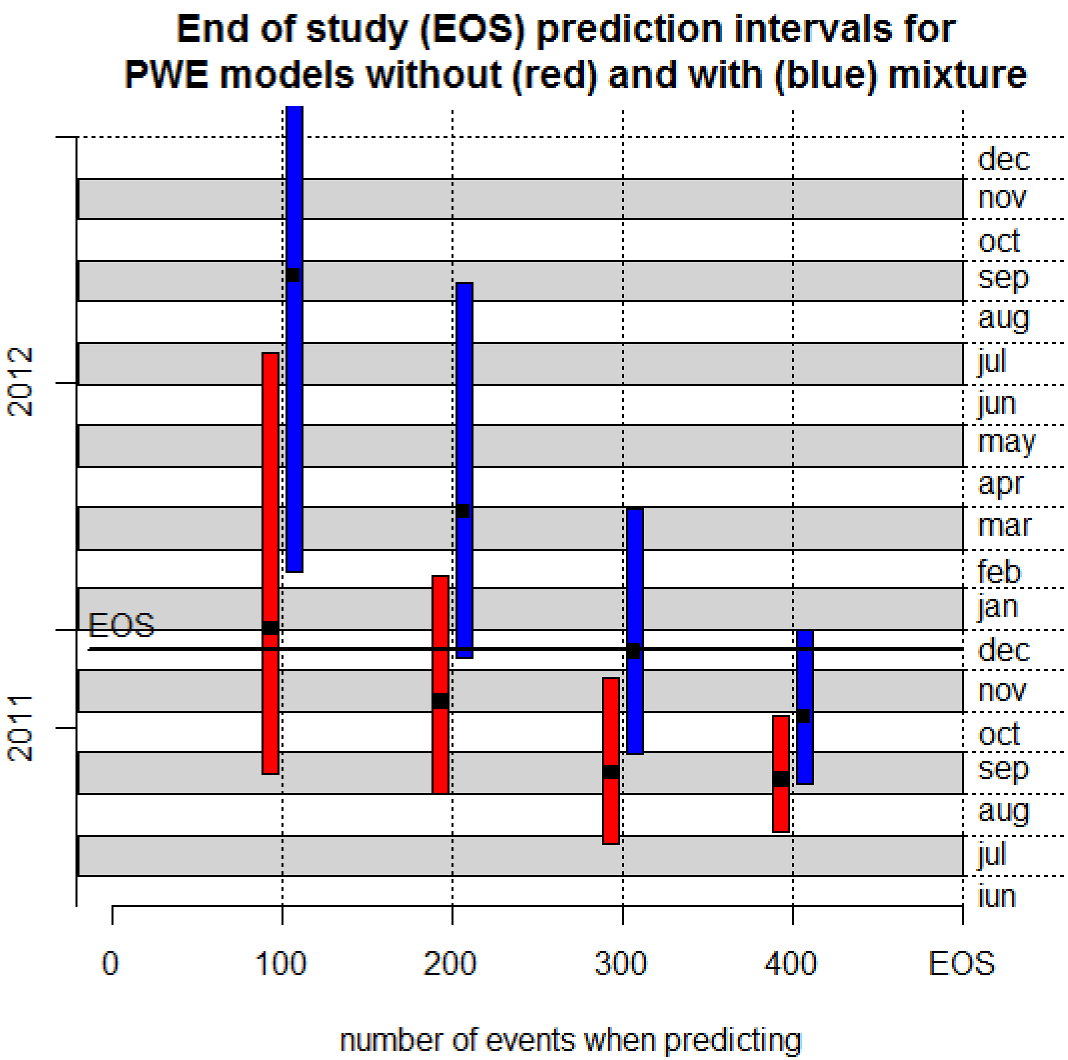
*Robust models and sensitivity analyses*

- What if current event and dropout times are not fully representative of future data?
  - Future event times may come mainly from patients on the experimental treatment. For blinded data, the current pooled estimate for the event process may be misleading.
- Extension 2: a mixture of PWE models with two components
  - Component 1: with probability p, same hazards for current/future data
  - Component 2: with probability 1-p, they have different hazards
- Two examples
  - Robustness scenario: weakly-inf priors for hazards of 2$^{nd}$ component
  - Future process is thought to differ from current one: informative prior (or fixed value) for hazards of 2$^{nd}$ component
- The model choices must be sensible and require justification

# Case Studies

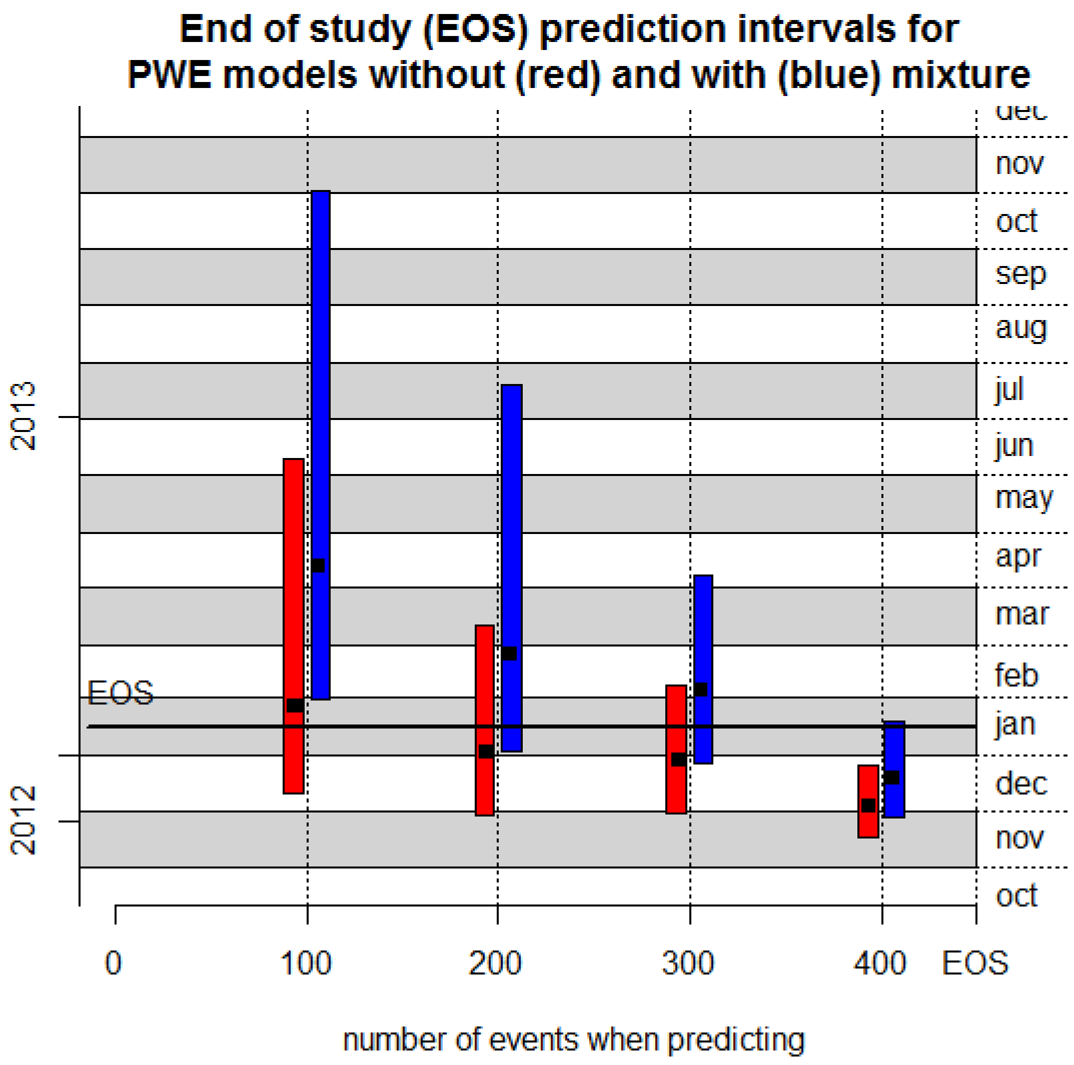
- Case study 1:
  - Phase III trial with a large treatment effect: estimated HR = 0.45
  - Final 500 events on December 15, 2011
  - Predictions made after 100, 200, 300 and 400 events: 18 to 6 months before final analysis
- Case study 2:
  - Phase III trial with “no” treatment effect: estimate HR = 0.9
  - Final 450 events on January 15, 2013
  - Predictions made after 100, 200, 300 and 400 events: 11 to 3 months before final analysis

# Case Study 1




- End of study (EOS): after 500 events, on 15 Dec 2011
- Predictions after 100, 200, 300, 400 events
- Blinded data
- Model 1: PWE
- Model 2: PWE with a 2nd mixture component
  - mixture weights 50-50.
  - 2nd component with a 1/3 hazard reduction
  - assumption: a treatment effect, so there will be more remaining patients on experimental trt.
- Conclusion: PWE works better earlier, mixture PWE model works better later in the trial.

# Case Study 2




- End of study (EOS): after 450 events, on 15 Jan 2013
- Predictions after 100, 200, 300, 400 events
- Blinded data
- Model 1: PWE
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# Conclusions

- Milestone event prediction is challenging
  - Simulations from 3 processes: time-to-event, dropout, and enrollment. They are uncertain and may change over time.
  - Accounting for sampling and parameter uncertainty is important.
  - Blinding: current data may not represent future data well.
- Mixture PWE model are flexible, but care is required
  - Selection of intervals
  - Sensible weights and parameters of the 2nd mixture component
  - Choice of sensitivity analyses (small number recommended)
  - Mixture model is only recommended later in the trial
- Communication of results:
  - a challenge that should not be underestimated
  - customers are used to overly precise (but often inaccurate) predictions