Sample Size Re-estimation of Event-Driven Trials with Composite Events and Delayed Data Ascertainment

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Introduction

- Clinical trials with a time-to-event primary endpoint frequently have an *event-driven* sample size, i.e. number of expected primary events determines subject enrollment and length of follow-up

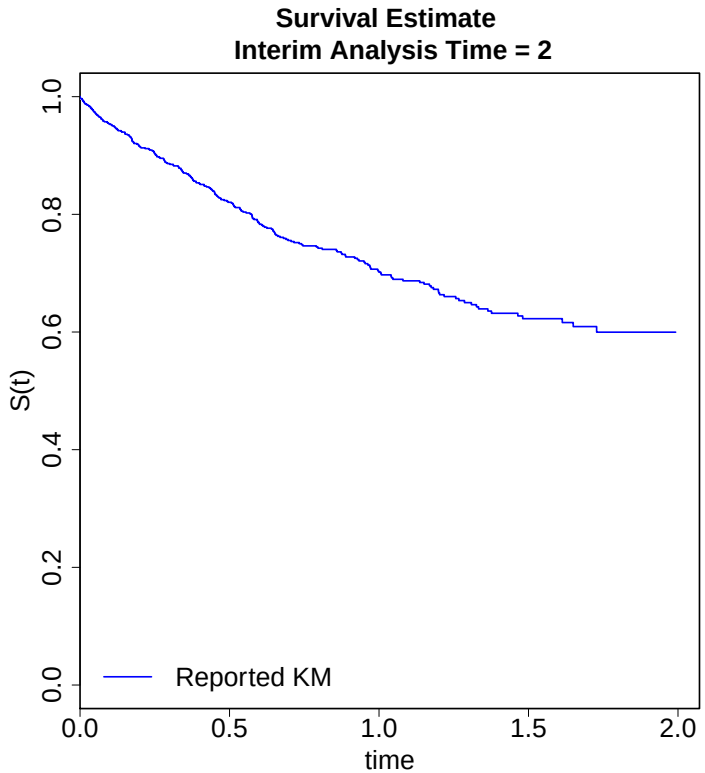
Primary Endpoint of interest

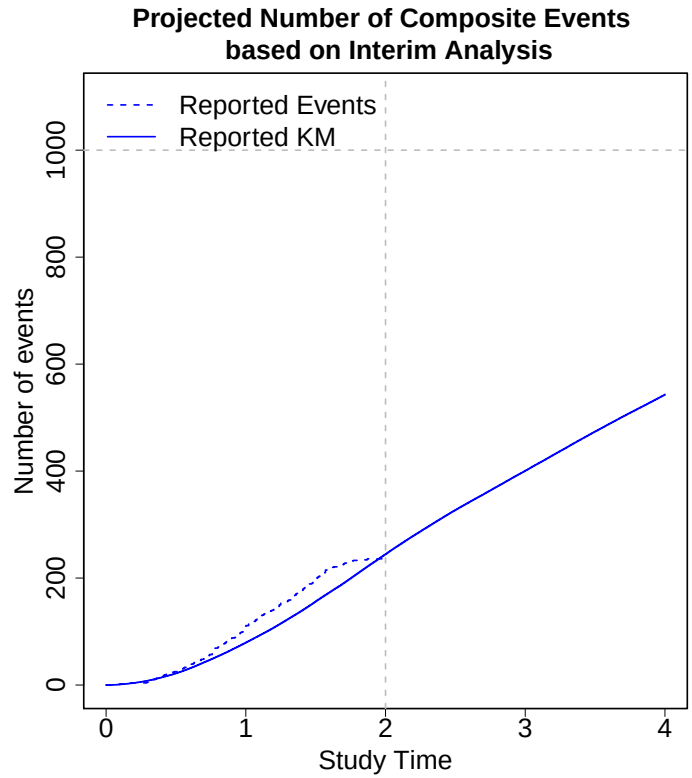
- Survival time to a single endpoint e.g. death
- Survival time to a *composite outcome*
  - More than one event type of interest - primary event constituents
  - Events may be recurrent, or of multiple types
  - E.g. first cardiovascular event - MI, stroke, CV death
  - Interested in time to *first* event in this set of primary event constituents
  - Note: events may be reported to the database out of order (non-monotone event reporting)

Introduction

- When designing a trial, event-rate estimated from historical data e.g. literature, Phase 2 trials
- During the course of a trial, if event rate is higher or lower than expected, enrollment and/or length of follow-up may need to be adjusted
- Use observed data at an interim time point

Observed Event Rate and Projected Number of Events





- E.g. 4 year trial, re-evaluate at year 2
- Enroll n = 1580, target number of events = 1000
- Based on observed projection, will fall short of target $\Rightarrow$ increase enrollment and/or follow-up time

Event reporting in clinical trials

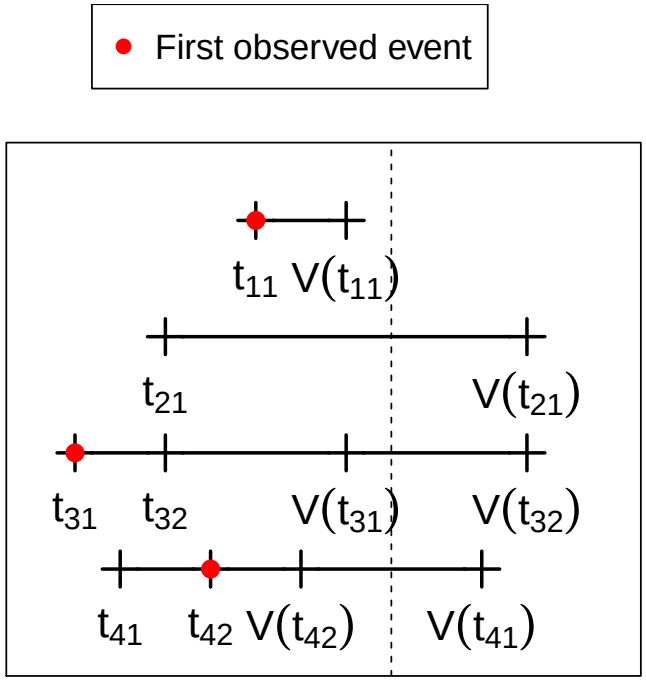
Subject has event

Event reporting in clinical trials

Event reporting in clinical trials

Issue with using observed data for event projection - not all events may be reported to the database at interim time point

Delay Illustration and Notation

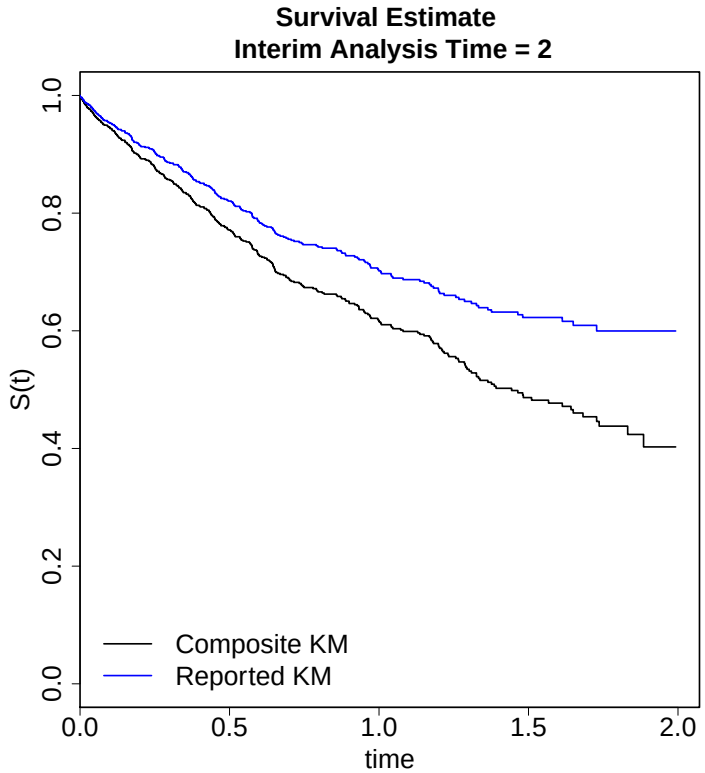


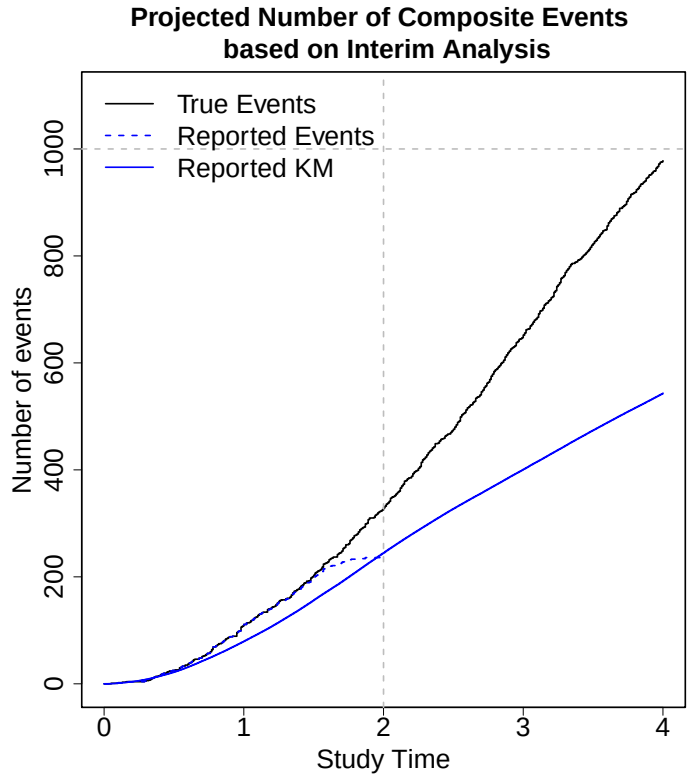
Subject	$N_i^*(C_i)$ Reported Events	$N_i^{**}(C_i)$ Unreported Events	$N^R(C_i)$ Total Events
1	1	0	1
2	0	1	1
3	1	1	2
4	1	1	2

t_{ij}	j^{th} event for subject i
C_i	Administrative censoring time for subject i
$V(t_{ij})$	reporting time of the event at t_{ij}
D_{ij}	$V(t_{ij}) - t_{ij}$ = delay time corresponding to the event at t_{ij}
$N_i^R(t)$	count of (possibly recurrent) primary event constituents in subject i at time less than or equal to t = sum of reported and unreported events = $N_i^*(t) + N_i^{**}(t)$

Non-Monotone Event Reporting: $t_{i1} < t_{i2} \not\Longrightarrow V(t_{i1}) < V(t_{i2})$

Observed Event Rate and Projected Number of Events compared with Actual Number of Events





- Events may be reported with delays up to 1.0 years
- True event rate higher than observed due to unreported at interim time point
- Observed: Must increase enrollment and/or follow-up time
- Truth: On target

Objective: Consistently estimate the survival function of the time to primary outcome (either a single event or composite outcome) in the context of delayed event ascertainment and non-monotone event reporting.

Inverse Probability of Censoring Weighted (IPCW) Estimator

Correct for unreported events at interim time point due to delayed reporting to the database

- IPCW estimator proposed by Robins and Rotnitzky (1992)
- Weight contribution of observed events to the survival estimate by the *probability of not being censored*

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- Event with large weight $\Rightarrow$ expect to see *more* events at time point but don't due to censoring

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- Note: Kaplan-Meier estimator can be written as an IPCW estimator

Example: Kaplan-Meier Estimator as IPCW estimator

- Observe $Y_i = \min(T_i, C_i)$, $\Delta_i = I(T_i \leq C_i)$
- KM estimator: $\hat{S}(t) = \prod_{s=0}^{t} \left(1 - \frac{\sum_i \Delta_i I(Y_i = s)}{\sum_i I(Y_i \geq s)}\right)$

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- Let $\bar{G}(t) = P(C \geq t)$
- $\bar{G}_n(t) =$ KM estimate reversing the roles of censoring and event times $= \bar{G}_n(t) = \prod_{s=0}^{t} \left(1 - \frac{\sum_i (1 - \Delta_i) I(Y_i = s)}{\sum_i I(Y_i \geq s)}\right)$

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Write KM estimator as IPCW estimator:

$$\begin{aligned} \tilde{S}(t) &= 1 - \frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i I(Y_i \leq t)}{\bar{G}_n(t)} \\ &= \hat{S}(t) \end{aligned}$$

Proposal: Weight contribution of first observed event by probability of not being censored when event is reported with delay i.e. censoring time is greater than event time plus delay time

Estimator

- Upweight based on probability of observing event that has been reported with delay

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$$
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\text{Delay distribution } H(d) &= P(D \leq d) \\
\text{Censoring distribution (with delay) } \bar{G}^*(s) &= P(C \geq s + D) \\
&= \int H(c - s) d\bar{G}(c)
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- Numerator (monotone event reporting): First observed event time per subject

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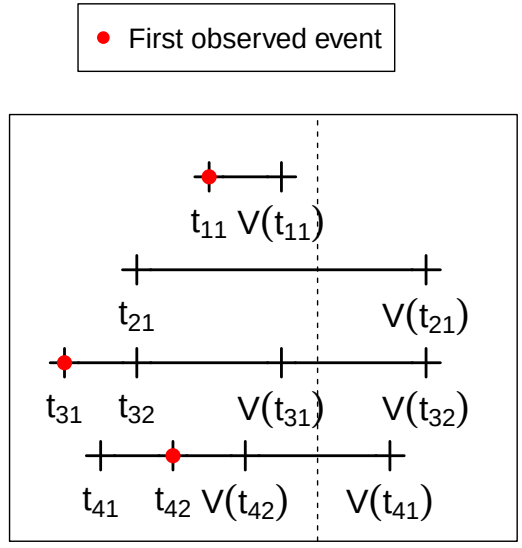
$$\hat{S}_{MON}(t) = 1 - \frac{1}{n} \sum_{i=1}^{n} \int_0^t \frac{I\{N_i^*(s-) = 0\} dN_i^*(s)}{\bar{G}_n^*(s)}.$$

Issue with Non-Monotone Reporting



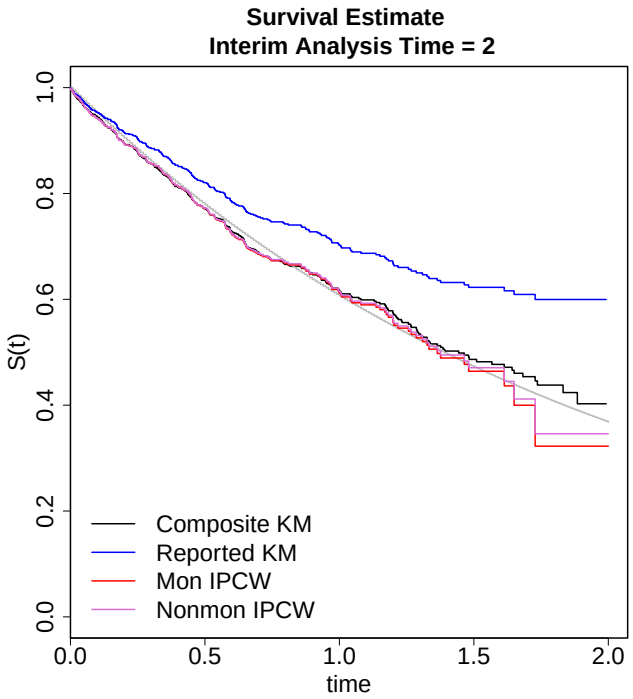
- Can't weight each observed event by probability that event is censored due to delay
- First observed event $\not\Longrightarrow$ first true event
- Solution: Also weight each first observed event by probability that there are no *unreported* events prior to it
- $w_i(s) = P(N_i^{**}(s-) = 0 \mid C_i, \{N^*(u), u < C_i\})$

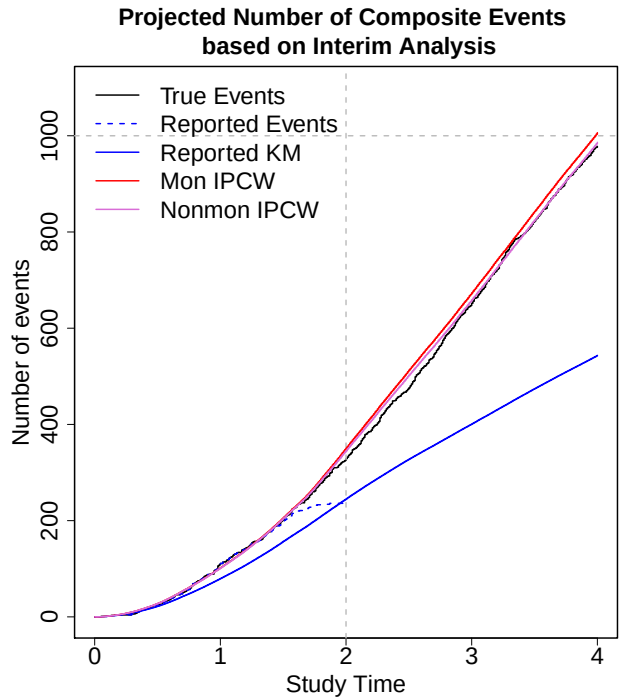
$$\hat{S}_{NM}(t) = 1 - \frac{1}{n}\sum_{i=1}^{n}\int_0^t \frac{\hat{w}_i(s) I\{N_i^*(s-) = 0\} dN_i^*(s)}{\bar{G}^*(s)}.$$

Trial planning

- Event-driven trials are designed presuming some event rate (e.g. based on event rate from phase 2 trial)
- Reassessment of sample-size and followup time based on survival estimates at interim analysis
- Simulated example: trial enrollment 3.5 years, followup for 6 months after enrollment of last subject, target number of events $= 1000$, exponential event rate $\mu = .5$
  $\Rightarrow n = 1580$
- Events may be reported out of order

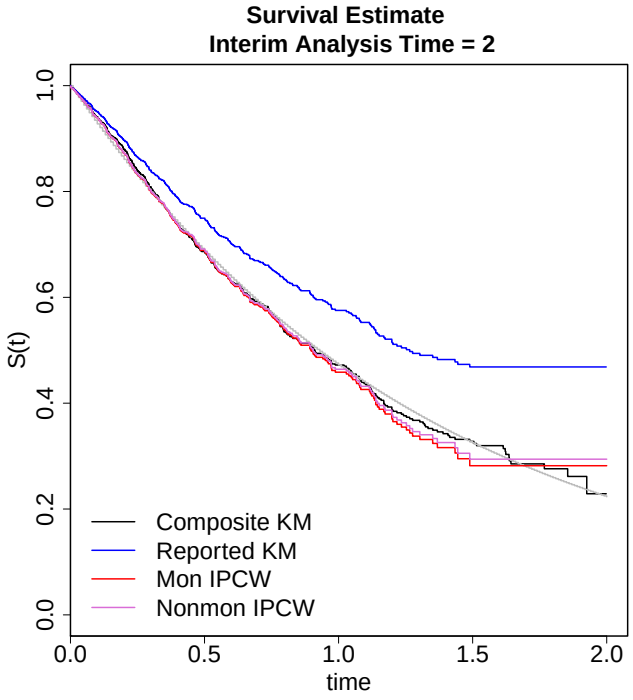
Trial running on time, long delays

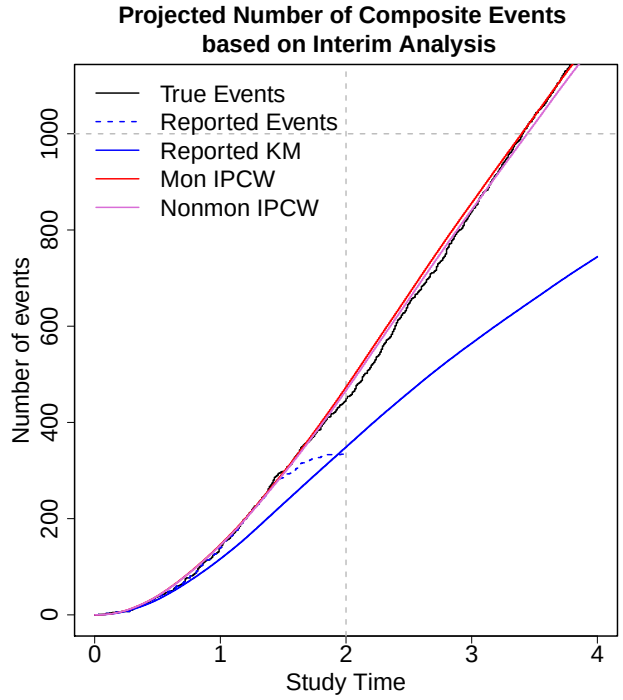




Based on interim projection using non-monotone IPCW estimator, trial on target for completion at year 4 $\Rightarrow$ no adjustment to enrollment or follow-up time needed

Event rates higher than planned





Based on interim projection using non-monotone IPCW estimator, trial on target for completion around 3 years, 5 months $\Rightarrow$ can shorten length of follow-up in trial

Conclusion

- Correct estimation of the survival function at the interim monitoring time of event-driven trials is crucial to adequately planning the future of the trial.
- If there are long delays between event occurrence and reporting to the database, this should be taken into account in the survival estimate and event projection

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- Note: May also need to adjust for non-monotone event reporting

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- If there are long delays between event occurrence and reporting to the database, this should be taken into account in the survival estimate and event projection
- Proposed solution: Correct for delayed event ascertainment using IPCW estimator
- Note: May also need to adjust for non-monotone event reporting
- Can use similar approach if event reporting is delayed, non-monotone, and event adjudication is required but incomplete at time of interim monitoring

Questions?