

Background

The Statistical Data Analysis Center (SDAC) at the University of Wisconsin performs interim analyses of evolving clinical trial data for review by independent data monitoring committees (DMCs). Our focus is on endpoint trials, many of which involve the adjudication of clinical events by an endpoint classification committee (EC).

At any given point during a trial, events which have taken place will fall into one of the following categories:

- completed the adjudication process
- currently under review by the EC
- reported, but not yet sent for review
- occurred, but not yet reported.

In order to make interim recommendations to the trial Executive Committee and/or Sponsor, the DMC may be interested in:

- the *process* of event reporting and adjudication
 - timeliness of initial notification
 - identification of delays (in collection of dossier information, review by EC)
- reported event type vs. final adjudication
- projected date for reaching event target.

Example

Consider a trial of a new treatment for cardiovascular disease. Events to be adjudicated include death, MI, angina, revascularization, hospitalization for CHF, and stroke. The primary endpoint is the composite of CHD mortality, non-fatal MI and unstable angina, with the target number (combined treatment and placebo events) of 850.

Event Reporting and Tracking

Events may be reported by the site or identified via review of SAEs. It is important to collect temporal data both to track individual cases and summarize the process.

Key data elements for tracking:

- *unique event identifier*
- subject ID
- reported event type
- date of event occurrence
- date event initially reported
- date dossier sent to EC.

Event Adjudication

Data usually include confirmation of the event type (using protocol-specified criteria) and event date, along with possible subclassification (e.g. cause of death).

Adjudication results *must* be linkable to reported events via a unique event identifier. Since event type and date may change on review, they cannot be used for linking.

Key data elements for adjudication:

- *unique event identifier*
- subject ID
- result of adjudication
 - event type (e.g. death, MI, stroke, non-event)
 - subclassification (e.g. cause of death)
 - adjudicated date of event occurrence
- date of final adjudication.

Analysis Dataset

Merging reported and adjudicated events produces an analysis dataset with the following structure (dates abbreviated for space):

Uniq Evnt ID	Subj Rand Num	Date Event Date	Date Initl Reprt	Event Type PerPI	Date Sent to EC	Date Final Adjud	Adjud Event Type	Sub Cate- gory	Curr Stat
0001	3506	Nov01	Dec01	CHF	Jun02	Sep02	CHF	.	Adj
0002	4321	Nov01	Jan02	MI	Jun02	Sep02	MI	.	Adj
0003	3333	Jan02	Mar02	MI	Jun02	Sep02	Ang	.	Adj
0004	0071	Apr02	Apr02	Death	Aug02	Sep02	Death	CHD	Adj
0005	4861	Aug02	Sep02	Stroke	Oct02	Dec02	Stroke	Isch	Adj
0006	4861	Dec02	Feb03	MI	Sep03	.	.	.	EC
0007	2215	Jun03	Aug03	Ang	Sep03	Dec03	NonEv	.	Adj
0008	2215	Oct02	Nov03	Revsc	Jan04	.	.	.	EC
0009	2215	Dec03	Dec03	Death	Rpt

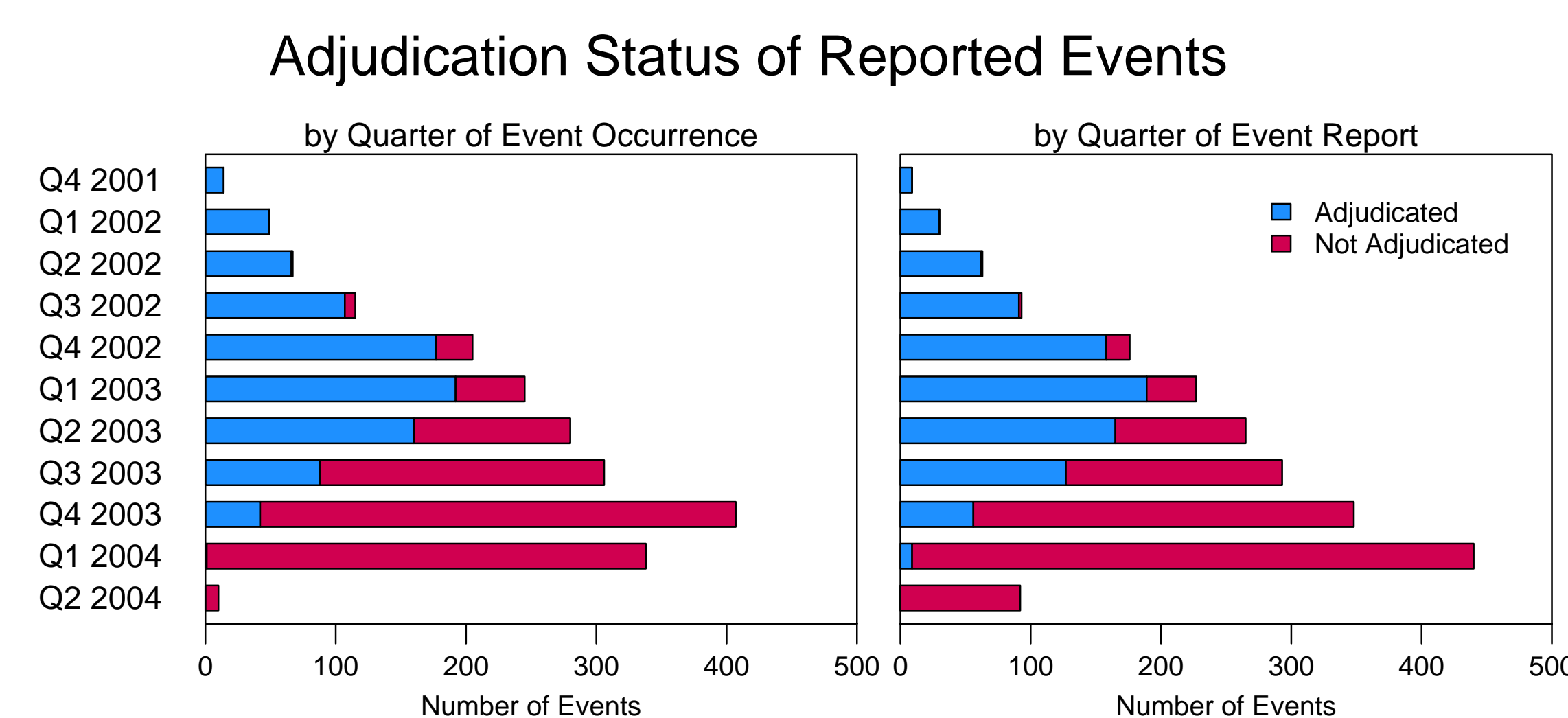
Since tracking data may not be subject to rigorous QC, we recommend paying special attention to issues of internal consistency (e.g. date sequences).

Special Challenges

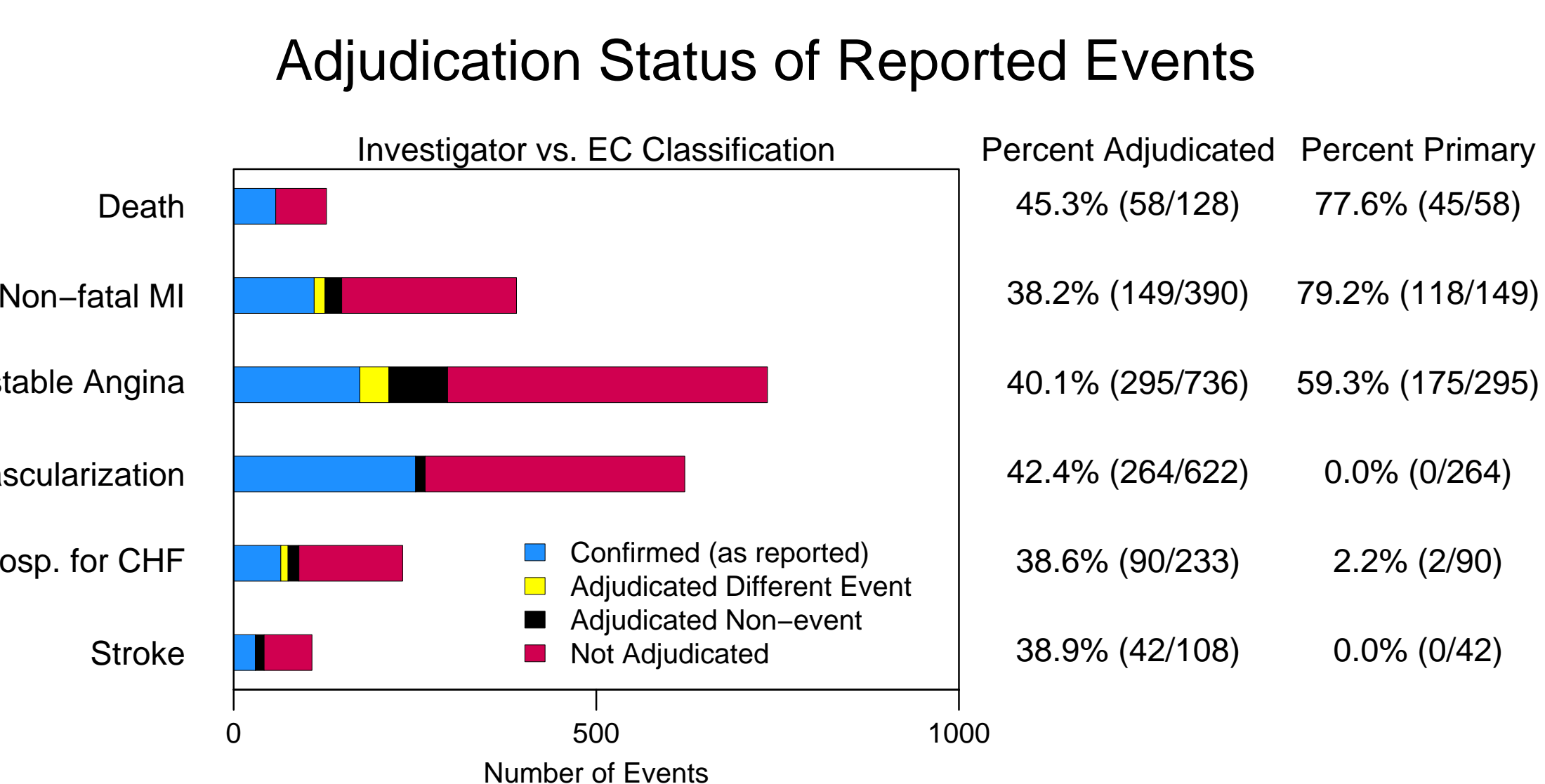
- events falling into multiple categories (e.g., fatal MIs)
- events “discovered” during adjudication process
- events “split” by the EC (revasc, MI).

Descriptive Summaries

The following panel provides a visual display of reported events as function of calendar time, as well as the proportion of events which have been fully adjudicated. Note that the decrease in number of events during the most recent periods are likely to represent reporting delay, rather than a change in rate of event occurrence.



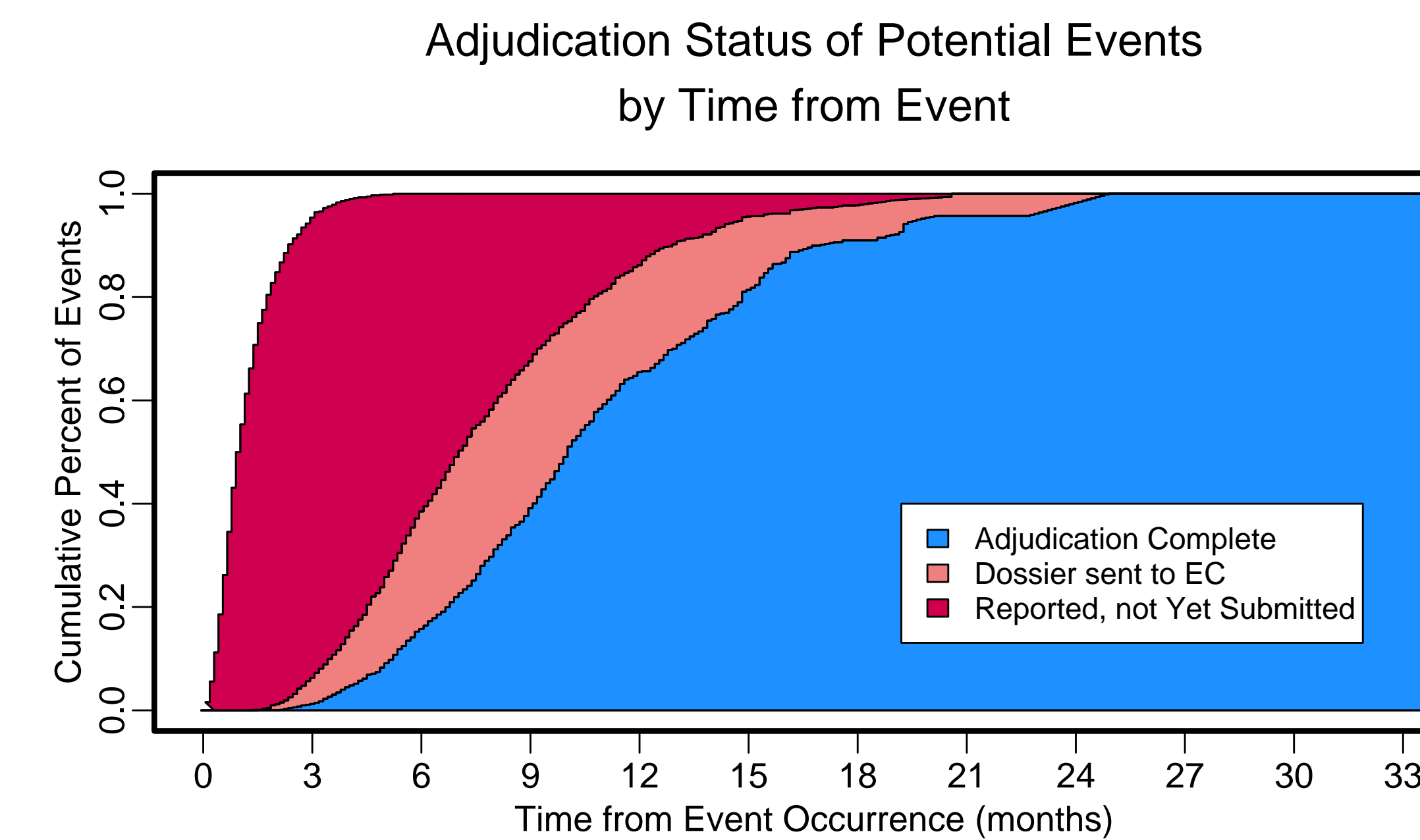
The following panel categorizes events by investigator-reported event type, indicating adjudication status and overall result (same or different type as reported, or a non-event). The right-hand columns display the percent of *reported* events which have been adjudicated, and the the percent of *adjudicated* events qualifying as “primary.” While all deaths are adjudicated as study events, only some are primary (CHD mortality). Two events reported as CHF hospitalization ended up as primary events (adjudicated to MI).



Estimating Delays in Event Reporting/Adjudication

Naive estimates of delay distributions will be incorrect because:

- Event reporting is right truncated – that is, events with longer reporting delays are less likely to be observed.
- Adjudication delays are right censored – that is, adjudication is less likely to be complete for more recent events.



From this figure, we can see, for example, that the median time from event occurrence to event report is about one month, and median time from event occurrence to completed adjudication is about ten months.

Event Reporting Delays: The distribution function for truncated data may be computed using the following truncated data estimator:

Let T be the calendar time of the current analysis. For the i th event, let

- t_i be the time of the i th event
- r_i be the reporting time of the i th event
- a_i be the adjudication time of the i th event
- $R_i = r_i - t_i$ reporting delay for the i th event
- $A_i = a_i - t_i$ time from event to adjudication for the i th event

For the j th distinct reporting delay time let

- $d_j = \#\{i | R_i = R_j\}$
- $Y_j = \#\{i | R_i \leq R_j < T - t_i\}$

$$Pr\{\text{Reporting delay} \leq t\} = \prod_{j | R_j > t} \left(1 - \frac{d_j}{Y_j}\right)$$

Adjudication Delays: Use Kaplan-Meier estimate for right censored data.

For the k th distinct adjudication delay time let

- $d_k = \#\{i | A_i = A_k\}$
- $Y_k = \#\{i | A_i \geq A_k \text{ or unadjudicated and } T_i - t_i \geq A_k\}$

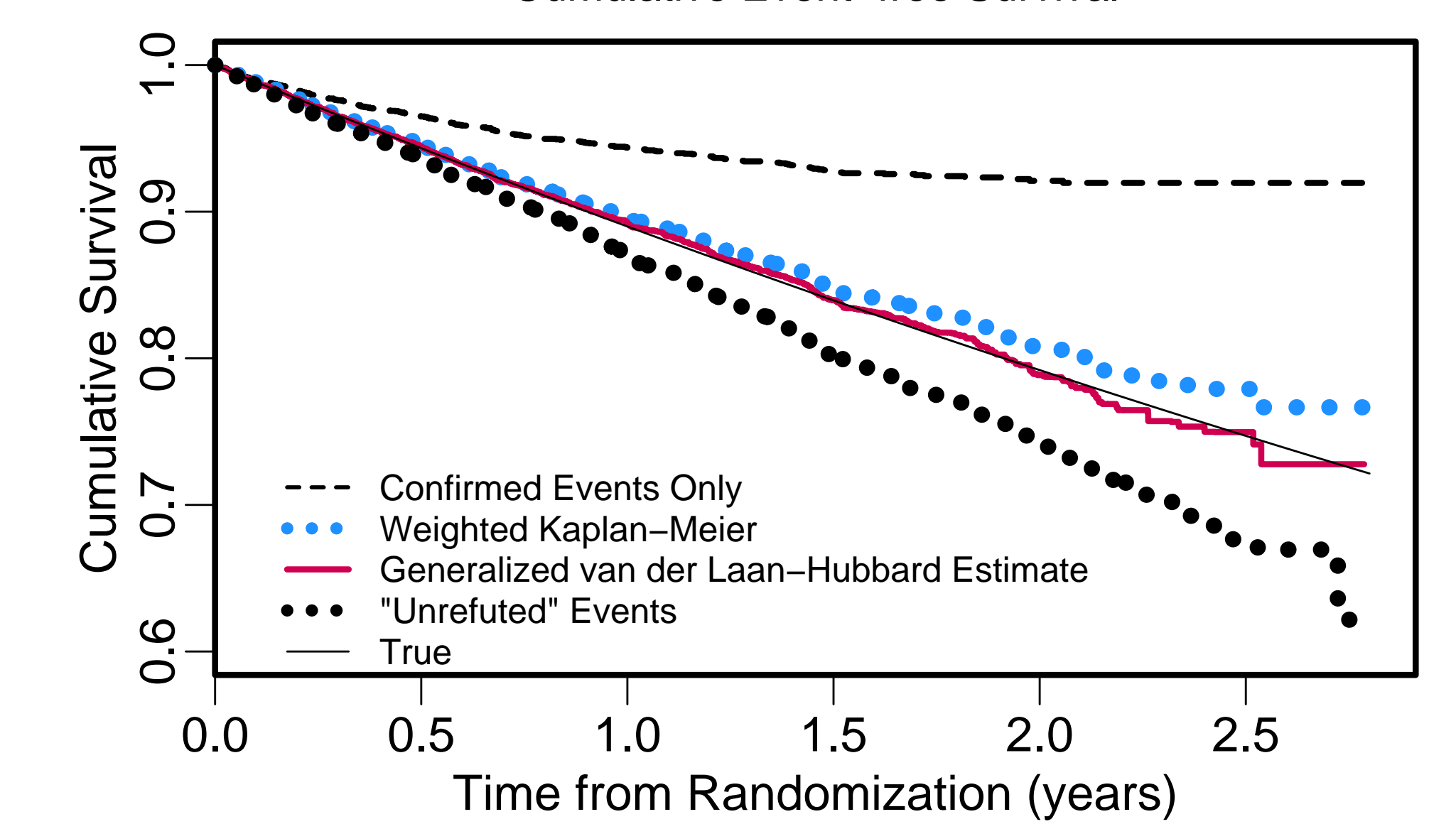
$$Pr\{\text{Adjudication delay} \leq t\} = 1 - \prod_{k | A_k \leq t} \left(1 - \frac{d_k}{Y_k}\right)$$

Implications for Data Analysis

Time-to-event analyses which do not account for delays in adjudication and event reporting may be incorrect. Below are four analyses of aggregate event-free survival for the composite primary endpoint:

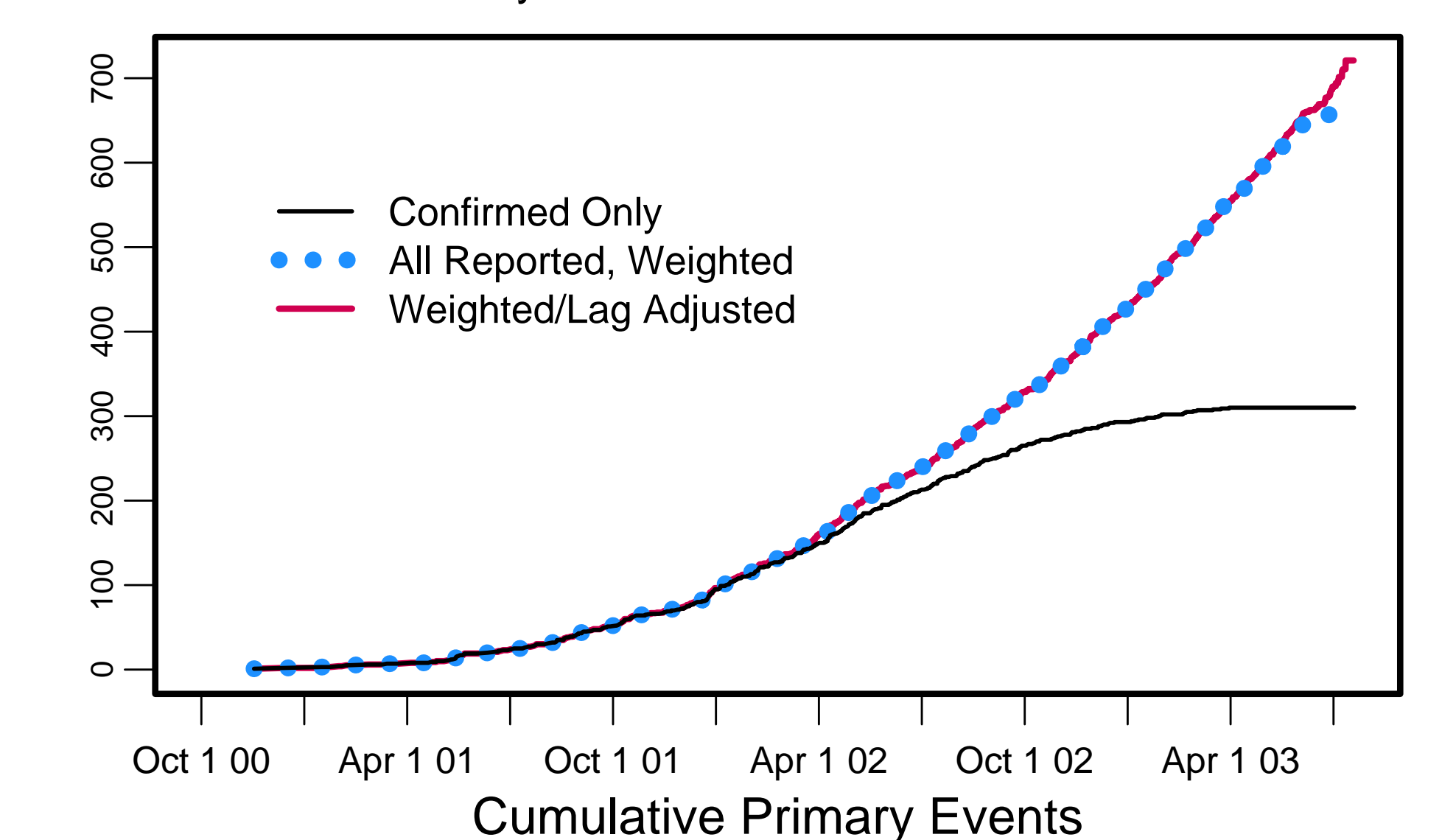
- confirmed primary events only
- all “unrefuted” events (confirmed + unadjudicated)
- weighted Kaplan-Meier using all reported events (Cook 2000, Cook and Kosorok 2004)
- van der Lann and Hubbard estimator generalized to data with incomplete adjudication (van der Laan and Hubbard 1998).

Primary Composite Endpoint



It is often useful, especially for event-driven trials, to understand the rate of accumulation of primary events. This information can be used to project when specified target numbers of events will be reached.

Cumulative Primary Events



References

- Cook, T. D. (2000). Adjusting survival analysis for the presence of non-adjudicated study events, *Controlled Clinical Trials* 21(3): 208–222.
- Cook, T. D. and Kosorok, M. R. (2004). Analysis of time-to-event data with incomplete event adjudication., *JASA*.
- van der Laan, M. J. and Hubbard, A. E. (1998). Locally efficient estimation of the survival distribution with right-censored data and covariates when collection of data is delayed, *Biometrika* 85: 771–783.

All figures are based on simulated data.