Endpoint and Time-to-Event Analyses in Interim Clinical Trial Reports

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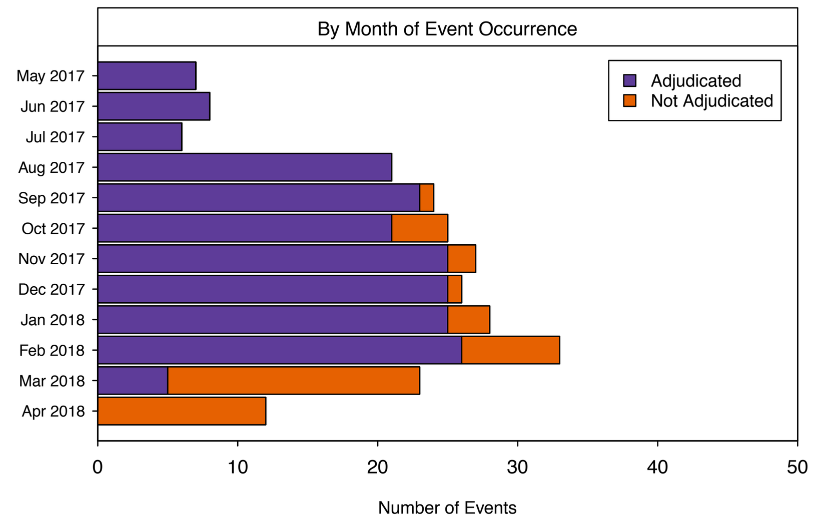
A clinical trial is designed to answer a primary question, with a pre-specified analysis of the primary endpoint. Upon completion of a trial, full information is available to answer the question. For clinical trials in which data reviews occur before completion, issues arise that are unique to interim reporting. Data monitoring committees (DMCs) need to be aware of these issues and how they affect patient safety.

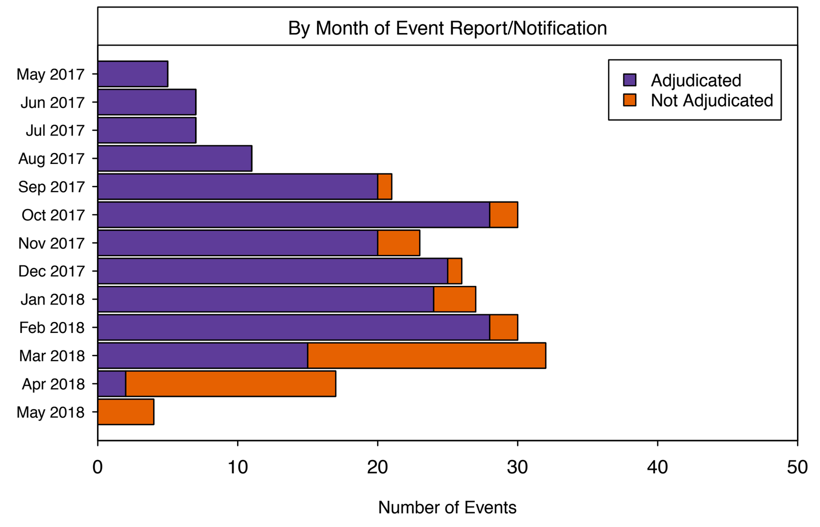
A typical endpoint may be mortality, a disease-related event such as stroke, or a composite endpoint. In many studies, an adjudication committee (AC) formally classifies potential endpoint events reported by trial investigators. During a trial not all events have been adjudicated; thus "unrefuted" or best-available information must be used for analysis, combining adjudication results with reported events.

Interim clinical trial data can be missing, inconsistent, or incomplete. Procedures are needed to handle situations such as conflicting, partial, or missing dates; a single event reported as multiple events; censoring for time-to-event analyses; and other analysis concerns. We discuss some of our best practices for presenting useful and coherent analyses to facilitate efficient review of interim endpoint analyses, presenting sample displays commonly used in our reporting.

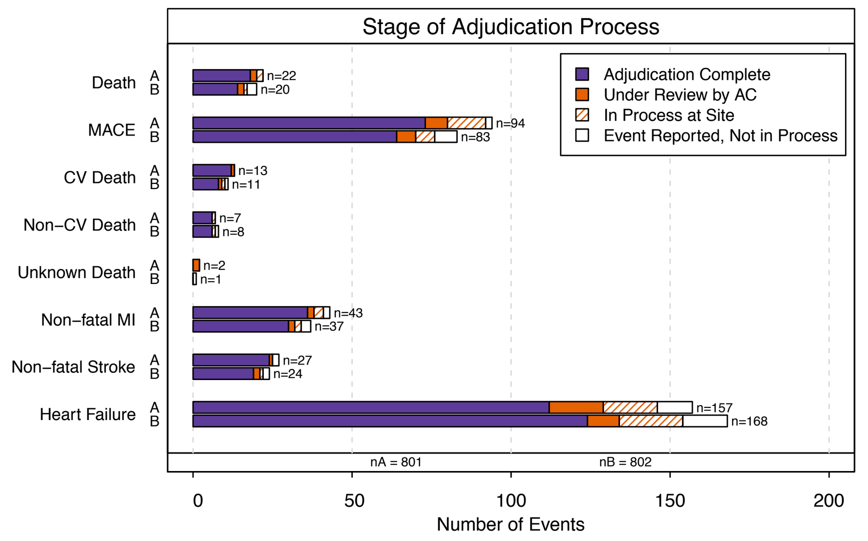
Adjudication Status

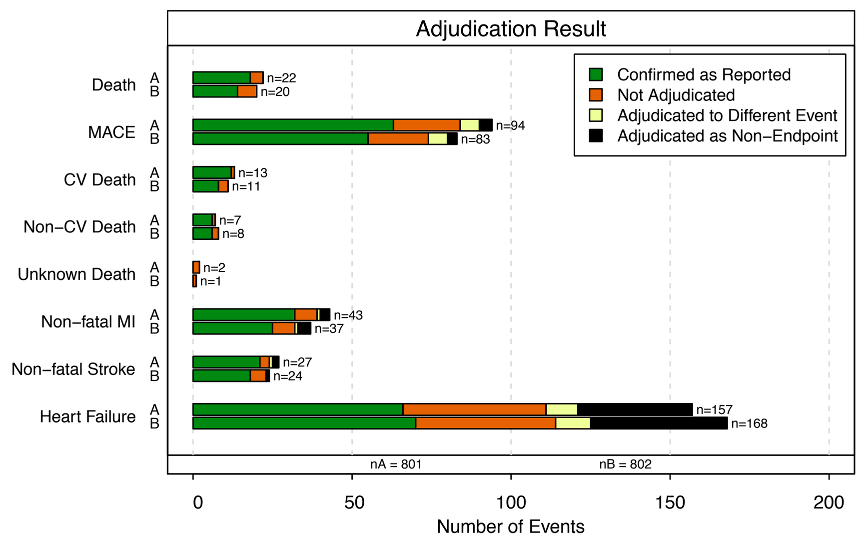
Adjudication Status by Month





Adjudication by Reported Event Type





Adjudication Status

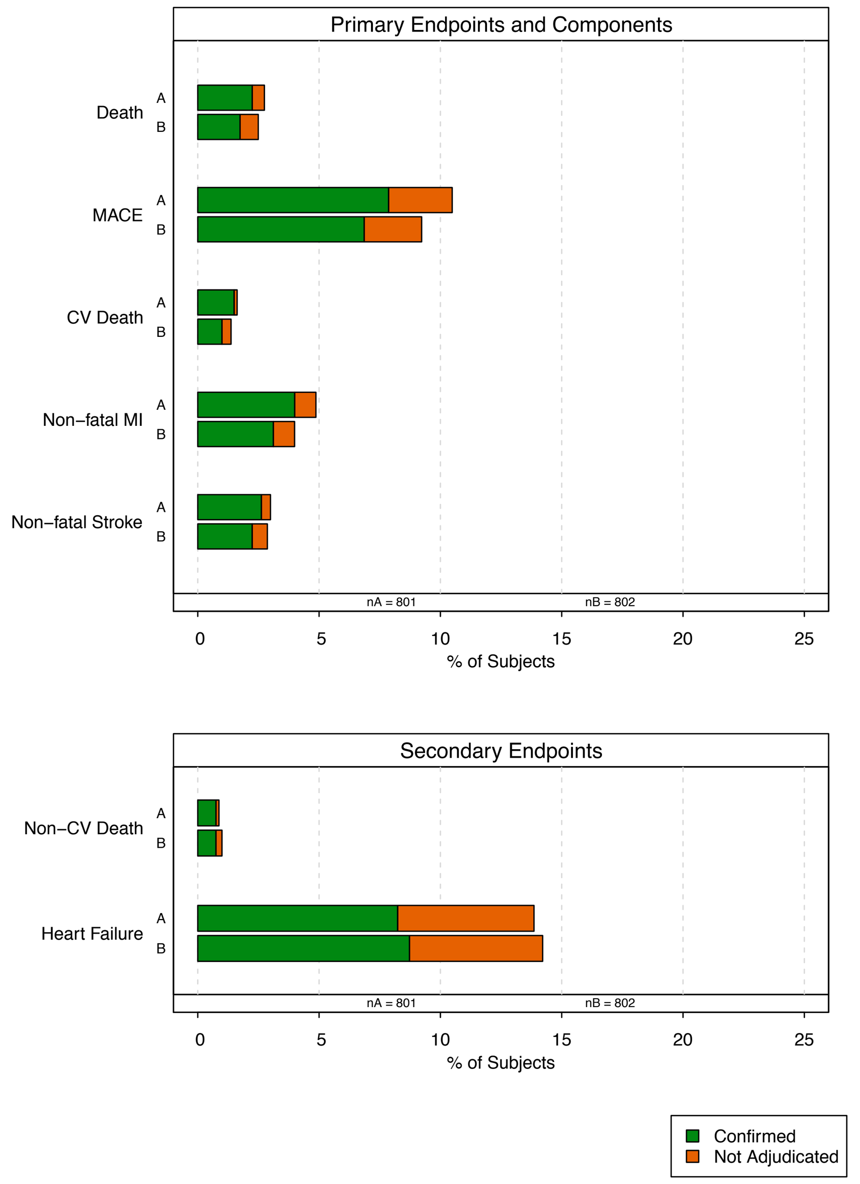
To provide a high-level overview of the adjudication process, we begin with a graphic showing adjudication status by month of event occurrence and event report. These graphics allow the DMC to assess whether events are being reported by the site and adjudicated by the AC in a timely manner.

For more detail on the status of individual event types, we present, for each event type as well as composite endpoints, the result of adjudication. If detailed information is available, we present the stage in the adjudication process.

Note that these graphics display information for each event, including multiple events for a given subject.

Adjudication Results

Primary and Secondary Endpoints (Unrefuted)



Investigator-to-Adjudicator Concordance Table of Events

Deaths

Investigator-Reported Clinical Endpoint	*Total Reported*	Adjudication Result			
		Pending adjudication	CV death	Non-CV death	Death from unknown cause
CV death	24	4	20	0	0
Non-CV death	15	3	0	12	0
Death from unknown cause	3	3	0	0	0
OVERALL	**42**	**10**	**20**	**12**	**0**

Other Events

Investigator-Reported Clinical Endpoint	*Total Reported*	Adjudication Result					
		Pending adjudication	Non-fatal MI	Non-fatal Stroke	Heart Failure	Other Event	Not an endpoint
Non-fatal MI	80	14	57	0	2	0	7
Non-fatal Stroke	51	8	1	39	0	0	3
Heart Failure	325	89	6	0	136	15	79
OVERALL	**456**	**111**	**64**	**39**	**138**	**15**	**89**

Adjudication Results

Because DMCs are reviewing interim trial data and adjudication is generally incomplete at any given data review, an analysis showing best-available ("unrefuted") results for events of interest is presented. This display shows the percent of subjects with at least one occurrence of each event of interest; events are counted if they were adjudicated as such or if they were reported by an investigator and were not yet adjudicated.

In cases where detailed information is available on event subtypes, a table showing concordance of investigator reported event type and adjudicated event type is useful to show exactly how events are classified upon adjudication.

SDAC Software Overview

The SDAC report system combines the capabilities of SAS, R, and LaTeX.

- SAS
  - Used to preprocess, restructure, and summarize data
  - Efficient manipulation and handling of large data sets
- R
  - Flexible statistical software, easily customizable
  - Can build complex graphics and data displays
  - Functions written to perform repetitive tasks
- LaTeX
  - Document preparation software for technical or scientific writing
  - Used to format text, listings and tables, and report compilation

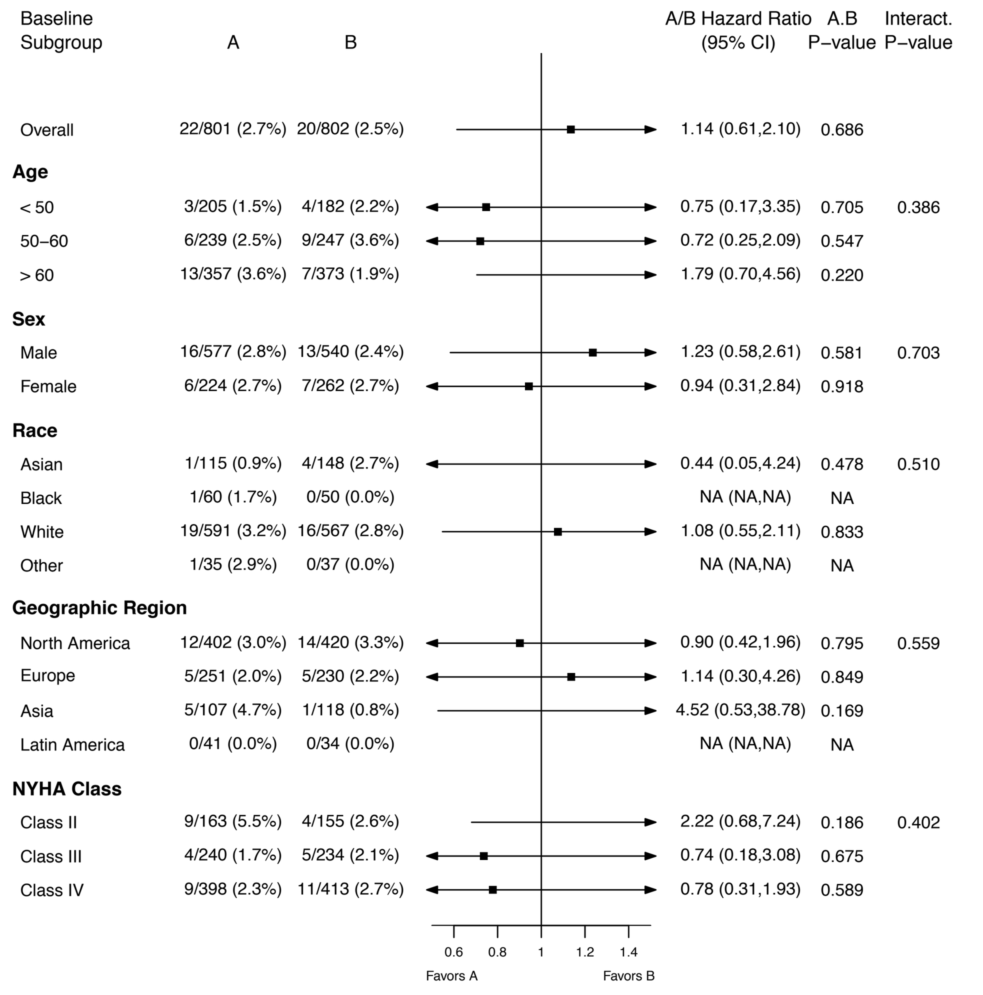
For More Information…

For more information about SDAC, including a sample DMC report, visit our website at:

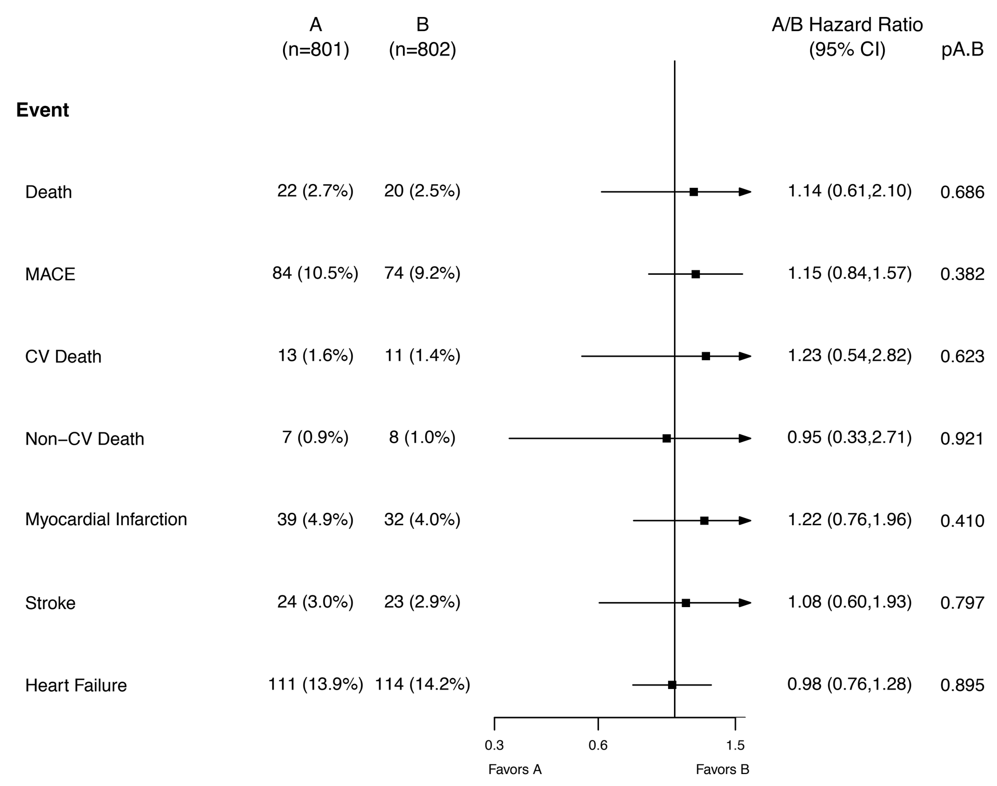
https://www.biostat.wisc.edu/content/sdac-sample-dmc-reports

Endpoint Analyses

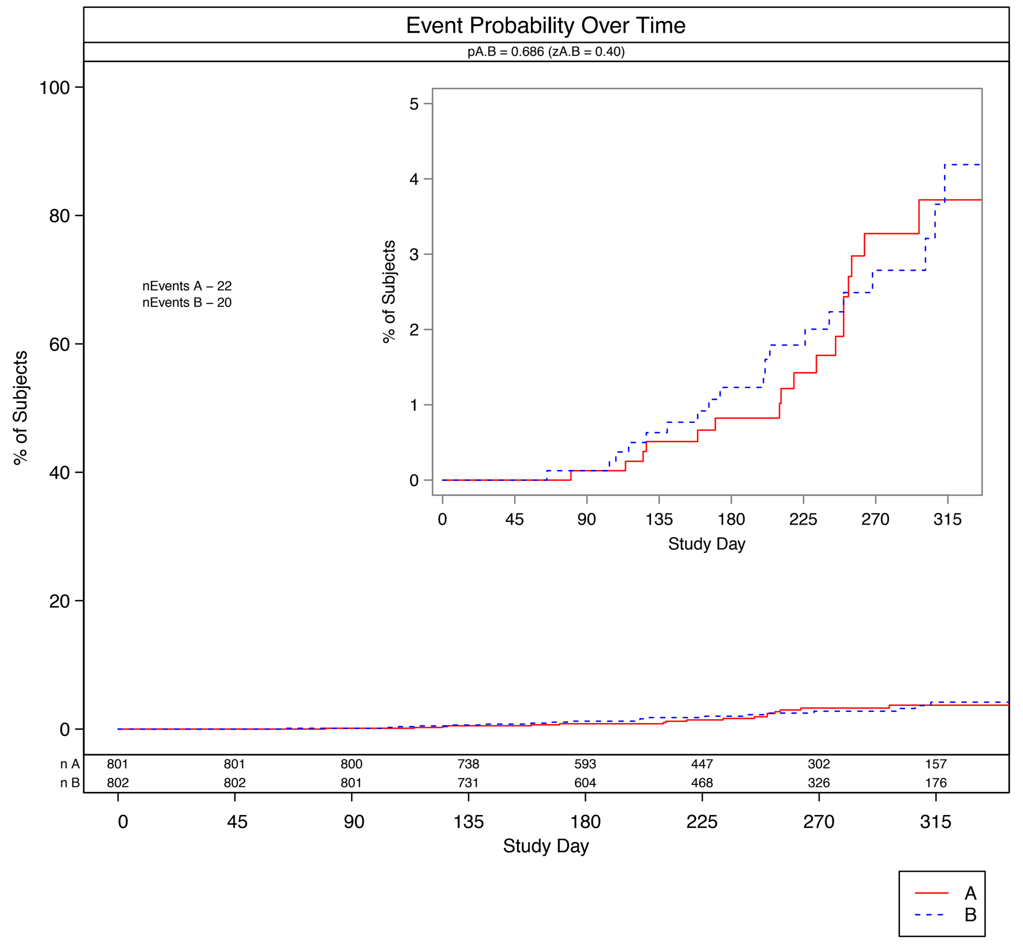
Hazard Ratios for Unrefuted All–Cause Mortality



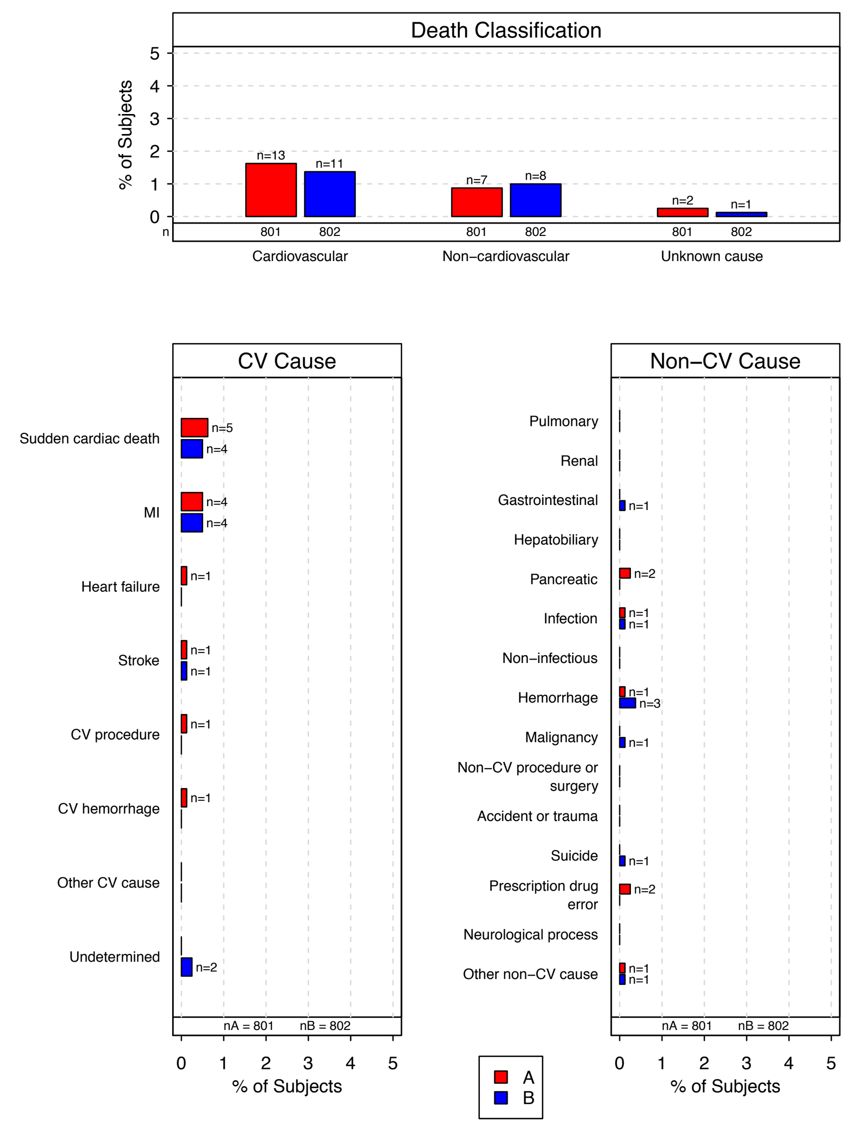
Hazard Ratios for Unrefuted Endpoint Events



Time to Death (All–Cause Mortality, Unrefuted)



Cause of Death



Endpoint Analyses

Plots of hazard ratios show, at a glance, which events occur more commonly in each treatment group. For primary and secondary endpoints, a similar display with more detail may show hazard ratios by baseline subgroups.

Kaplan-Meier curves display the cumulative probability of an event of interest as a function of time since randomization. For subjects with no event, follow-up time is censored at the earliest time a subject would no longer be expected to contribute data; this may be the earliest of study completion or withdrawal, data cut-off date, and death (for non-fatal endpoints). Kaplan-Meier curves are often presented in parallel for confirmed and unrefuted events.

In trials where death is an endpoint of interest, and detailed causes of death are available, a figure showing cause of death is included. These displays usually summarize unrefuted information, showing adjudicated cause if known or else using investigator-reported cause.