Censoring and censoring mechanisms in light of the estimand framework

Stefan Englert

Tuesday, 14th June 2022, PSI

Censoring Sub-team

- Estimands in Oncology working group founded a Censoring Mechanisms Sub-team to clarify applicability of estimands guidance in time-to-event cancer trials.
- Members:
  - Jonathan Siegel
  - Lynda Grinsted
  - Feng Liu
  - Hans-Jochen Weber
  - Stefan Englert
  - Michelle Casey
- This presentation summarizes the views of the sub-team regarding censoring and censoring mechanisms in light of the estimand framework

Background: One size does not fit all

- In past, methods in pharmaceutical oncology time-to-event clinical trials have been **highly standardized**
  - A small set of methods, such as Kaplan-Meir, Cox, and log-rank tests, have been used across the board.
  - Underlying assumptions, such as non-informativity, have often gone unchallenged
  - Standardized censoring rules have been applied without regard to context or the underlying clinical question
- The estimands guidance focuses studies on addressing a clinically **meaningful, feasible research question**
  - It requires justifying assumptions and opens a wider range of tools.

Censoring Tables

Table C1. Example 1 for censoring scheme for PFS

Situation	Date of Progression or Censoring	Outcome
Incomplete or no baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Earliest of: • Date of progression assessment showing new lesion (if progression is based on new lesion); or • Date of last progression assessment	Progressed
No progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for undocumented progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for toxicity or other reason	Date of last progression with no documented progression	*Censored*
New anticancer treatment started	Date of last progression assessment with documented nonprogression before start of new treatment	*Censored*
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last progression assessment with documented nonprogression	*Censored*

Source: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics, https://www.fda.gov/media/116860/download

Censoring Tables

Table C1. Example 1 for censoring scheme for PFS

Situation	Date of Progression or Censoring	Outcome
Incomplete or no baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Earliest of: • Date of progression assessment showing new lesion (if progression is based on new lesion); or • Date of last progression assessment	Progressed
No progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for undocumented progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for toxicity or other reason	Date of last progression with no documented progression	*Censored*
New anticancer treatment started	Date of last progression assessment with documented nonprogression before start of new treatment	*Censored*
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last progression assessment with documented nonprogression	*Censored*

Censoring to address a missing data problem

Source: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics, https://www.fda.gov/media/116860/download

Censoring Tables

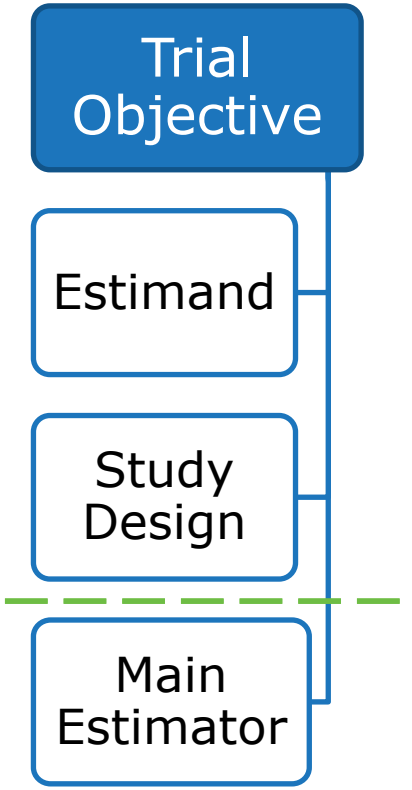
Table C1. Example 1 for censoring scheme for PFS

Situation	Date of Progression or Censoring	Outcome
Incomplete or no baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Earliest of: • Date of progression assessment showing new lesion (if progression is based on new lesion); or • Date of last progression assessment	Progressed
No progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for undocumented progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for toxicity or other reason	Date of last progression with no documented progression	*Censored*
New anticancer treatment started	Date of last progression assessment with documented nonprogression before start of new treatment	*Censored*
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last progression assessment with documented nonprogression	*Censored*

Censoring to address an Intercurrent Event

Source: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics, https://www.fda.gov/media/116860/download

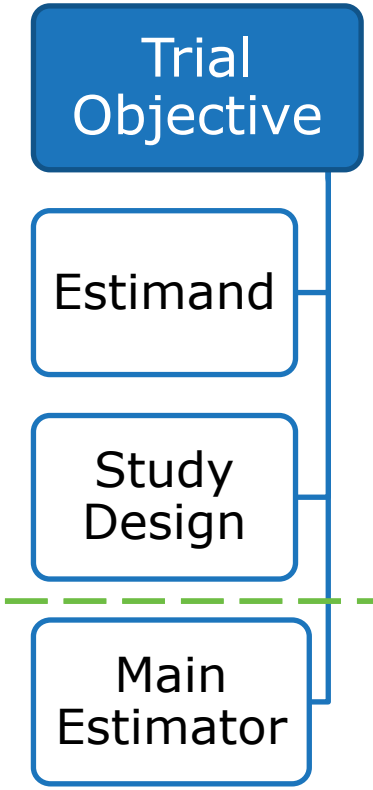
Two concepts of censoring



Censoring to address an Intercurrent Event

Censoring to address a missing data problem

Noumenal and phenomenal censoring



Censoring to address an Intercurrent Event

- **Noumenal censoring** is intentional, systematic censoring done as part of the study design
  - Noumenal censoring is a property of the estimand
  - Noumenally censored data lie outside the frame of inference (actual or hypothetical) to which the analysis is inferring.

Censoring to address a missing data problem

- **Phenomenal censoring** is censoring that occurs in an individual patient incidental to trial conduct
  - Things like individual decisions to withdraw from the trial
  - Phenomenal censoring is a property of the estimator
  - It does not change the frame of inference

Impact to Estimands and Sensitivity Analysis

- As noumenal censoring is a property of the estimand, switching the noumenal censored event to a progression outcome, will result in a different estimand
- Censoring tables with different outcome definitions for the same situation are not sensitivity analysis per ICH E9 (R1), but supplementary analysis
- This thinking and more narrow definition of sensitivity analyses per ICH E9 (R1) is (currently) not reflected in most clinical trial endpoint guidances

Example:

> The sensitivity analysis in Table D2 uses a conservative approach by assigning the dates of discontinuation, change of treatment, or missed visit as an event date.

Source: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics, https://www.fda.gov/media/116860/download

What strategy should be assigned to or is implied to noumenal censored intercurrent events?

Reminder: 5 Strategies for Intercurrent Events

Irrespective of	Include in Outcome	Scenario in which event does not occur	Prior to occurrence	As part of target population definition
• Outcome after intercurrent event is still of interest • Data should be collected after intercurrent event	• Define composite endpoint including the intercurrent event • Intercurrent event is informative for effect of interest	• A scenario is envisaged in which the intercurrent event would not occur	• Scientific question is about what happened prior to the intercurrent event • Outcome after intercurrent event is considered irrelevant	• Population is defined by those in whom the intercurrent event would or would not occur
Treatment Policy	**Composite**	**Hypothetical**	**While on Treatment**	**Principal Stratum**

4 Candidate Strategies for Censoring

Irrespective of	Include in Outcome	Scenario in which event does not occur	Prior to occurrence
• Outcome after intercurrent event is still of interest • Data should be collected after intercurrent event	• Define composite endpoint including the intercurrent event • Intercurrent event is informative for effect of interest	• A scenario is envisaged in which the intercurrent event would not occur	• Scientific question is about what happened prior to the intercurrent event • Outcome after intercurrent event is considered irrelevant
Treatment Policy	**Composite**	**Hypothetical**	**While on Treatment**

Is censoring a composite strategy?

Include in Outcome

- Define composite endpoint including the intercurrent event
- Intercurrent event is informative for effect of interest

Composite

- No, outcome is event.
- Method to avoid censoring / alternative to censoring.
- Done.

Is censoring a hypothetical strategy?

Scenario in which event does not occur

- A scenario is envisaged in which the intercurrent event would not occur

Hypothetical

- ⊕ The statistical assumption underlying censoring is that patients that are censored have the same hazard of experiencing an event as those not censored.
- ⊕ Using censoring to implement this strategy assumes the intercurrent event is non-informative, i.e., does not change future risks.
- ⊖ Most events that end assessments in cancer trials have at least some potential for being informative
- ⊖ The scenario envisioned is not about 'where the intercurrent event would not occur'

Is censoring a while on treatment strategy?

Prior to occurrence

- Scientific question is about what happened prior to the intercurrent event
- Outcome after intercurrent event is considered irrelevant

While on Treatment

⊕ Data are included up to the censoring event and outcomes after intercurrent event are considered irrelevant

⊖ The statistical assumption underlying censoring is that patients that are censored have the same (future) hazard of experiencing an event as those not censored.

⊖ Scientific inference goes beyond what happened prior to the intercurrent event

⊜ We believe this makes sense only when there is strong reason to believe a systematically censoring event is non-informative. An independent-causes while on treatment strategy (Unkel, 2019) is then possible.

Is censoring a treatment policy strategy?

Irrespective of

- Outcome after intercurrent event is still of interest
- Data should be collected after intercurrent event

Treatment Policy

- The treatment policy strategy comes closest to the "ITT" approach associated with Fleming (2009) and others.

  It has accordingly gotten the most attention from regulators and is considered the 'default'
- The scientific question is not concerned with the outcome from randomization to the event of interest, through and beyond the intercurrent event.
- Censoring applied to, for example, subsequent therapy, can be said to 'model' a treatment policy strategy: i.e., what would have happened if no subsequent therapy was initiated, and the planned treatment policy was followed

What is censoring?

- The Estimand in Oncology Censoring sub-team **considers** noumenal censoring as a **simple hypothetical strategy**
  - This interpretation was supported by some health authorities
  - Other health authorities are skeptical regarding hypothetical strategies, especially for licensure, but have recommended censoring as a 'catch-all-approach'
- The Estimand in Oncology Censoring sub-team **recommends** to describe the censoring approach as such, **not assigning it a strategy**
  - To avoid philosophical discussions not focused on the question of interest
  - Applicable, when a non-informative event is handled and no sensitivity/supportive analysis around this is planned
  - If censoring is used for a potentially informative event as a 'best fit', but suboptimal, strategy it may be better to describe it as one of possible hypothetical strategies.

Example

Strategy options to deal with intercurrent events and corresponding censoring approach for main endpoints in oncology

Endpoint	Intercurrent Event	Strategy for addressing intercurrent event	Censoring approach
PFS	Initiation of new anti-cancer therapy	Treatment policy, considering outcome after intercurrent event still of interest	Ignore
		Hypothetical strategy, to assess what would have happened if intercurrent event had not occurred	**Noumenal censoring** at the date of last progression assessment with no documented progression
		Composite strategy, considered informative about the event of interest	Event
All	Administrative censoring at the end of the trial do not define an intercurrent event and are assumed to not affect the inference		**Phenomenal censoring** at the date of last progression assessment with no documented progression

Recommendations & Summary

- Define trial-specific rules as well as consider when ‘noumenal’ and ‘phenomenal censoring’ is used.
- Design it from the beginning:
  Ensure that implementing the strategy, including the needed data collection, will be feasible in the study context aligned with protocol and visit schedule
- Alternative strategies to censoring should be considered.

Further reading:

Siegel, J.M., Grinsted, L., Liu, F., Weber, H.J., Englert, S., Casey, M. *Censoring and censoring mechanisms in oncology in light of the estimands framework* (2022). Submitted. | arxiv.

Thank you

Janssen-Cilag GmbH
Stefan Englert
senglert@its.jnj.com

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson


janssen
PHARMACEUTICAL COMPANIES OF
Johnson & Johnson