

Adverse Event and Treatment Emergent Approaches in the Industry

Aimee Basile, Surface Oncology; Mary Nilsson, Lilly

PHUSE Best Practices for Data Collection Instructions and Analysis and Display White Papers Project Teams

INTRODUCTION

The Best Practices for Data Collection Instructions PHUSE Working Group conducted a survey to evaluate the different industry approaches for collecting adverse event data and how those data are evaluated for treatment emergence. The survey was conducted in conjunction with the Analysis and Display White Papers Working Group which published a white paper on the Analysis and Displays Associated with Adverse Events. In that paper there were many questions raised about the variations in collection and definition of adverse event data that would support the analysis and displays the team developed. Here, we present the findings of our survey and how the variation, if any, would influence the standardization of analysis and displays associated with adverse events. Based on the results we will develop a future white paper with recommendations for next steps in developing best practices for adverse event data collection and treatment emergence calculations.

OBJECTIVES

By conducting this survey, we hoped to determine how differently adverse events (AE) data are collected for various studies. There are several sources that call into question the consistency of AE data collection. For example, in a 2019 presentation FDA Reviewer Dr. Vaishali Popat stated that she found 329 ways to represent AE causality in standardized data (slide 29)¹.

Also, in the Analysis and Displays Associated with Adverse Events white paper², it is stated, “variation in collection methods for AEs introduces additional variation in the eventual interpretation of treatment emergence.”

Specific concerns raised in that paper as to whether the following types of AEs are consistently collected:

- Events that start after informed consent but before treatment initiation
- Events that start before treatment initiation and worsen in severity/relatedness/seriousness after treatment initiation
- Events that start before treatment initiation but improve after treatment initiation
- Specific timing of serious events
- Serious events after study completion
- Intermittent events

We aimed to collect data to support the assumptions and anecdotes that data collection methods are diverse.

REFERENCES

1. Popat, Vaishali. (2019) FDA Analysis Data Standards presentation [PowerPoint slides]. Retrieved from https://healthpolicy.duke.edu/sites/default/files/atoms/files/ads_master_slide_deck.pdf
2. PHUSE Analysis & Display White Papers Project Team. (2017). *Analysis and Displays Associated with Adverse Events: Focus on Adverse Events in Phase 2-4 Clinical Trials and Integrated Summary Documents* (Doc ID: WP-003) Version 1.0. Retrieved from <https://www.phusewiki.org/docs/WorkingGroups/New%20Template%20Deliverables/Standard%20Analyses%20&%20Code%20Sharing/Analysis%20and%20Displays%20Associated%20with%20Adverse%20Events.pdf>

METHODS

We designed a two-part survey, first to capture how AEs are collected in the clinical database, and second, to capture how treatment emergence is determined given certain scenarios. We asked that each response was based on a certain study or therapeutic area for the sponsor due to variations depending on the study type or indication.

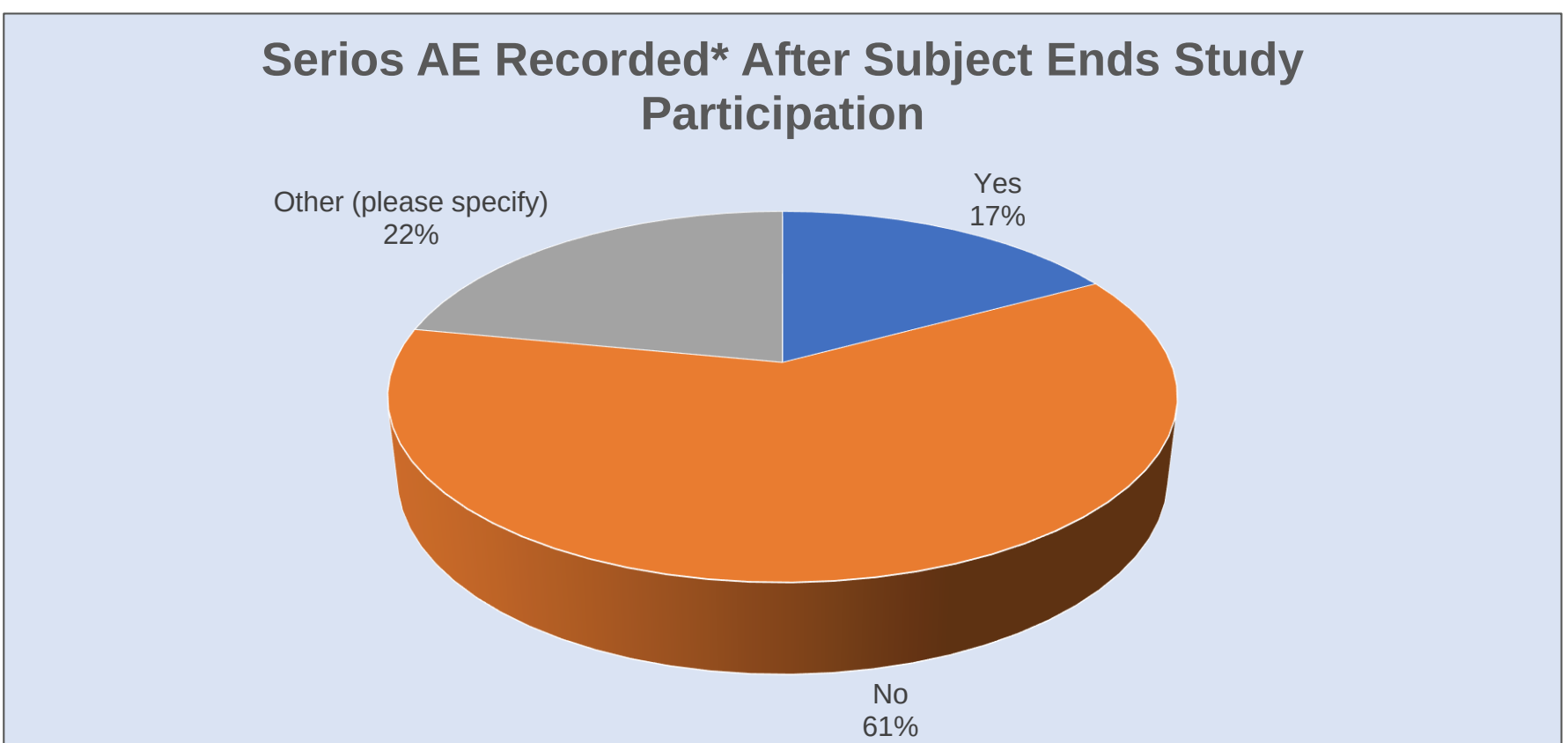
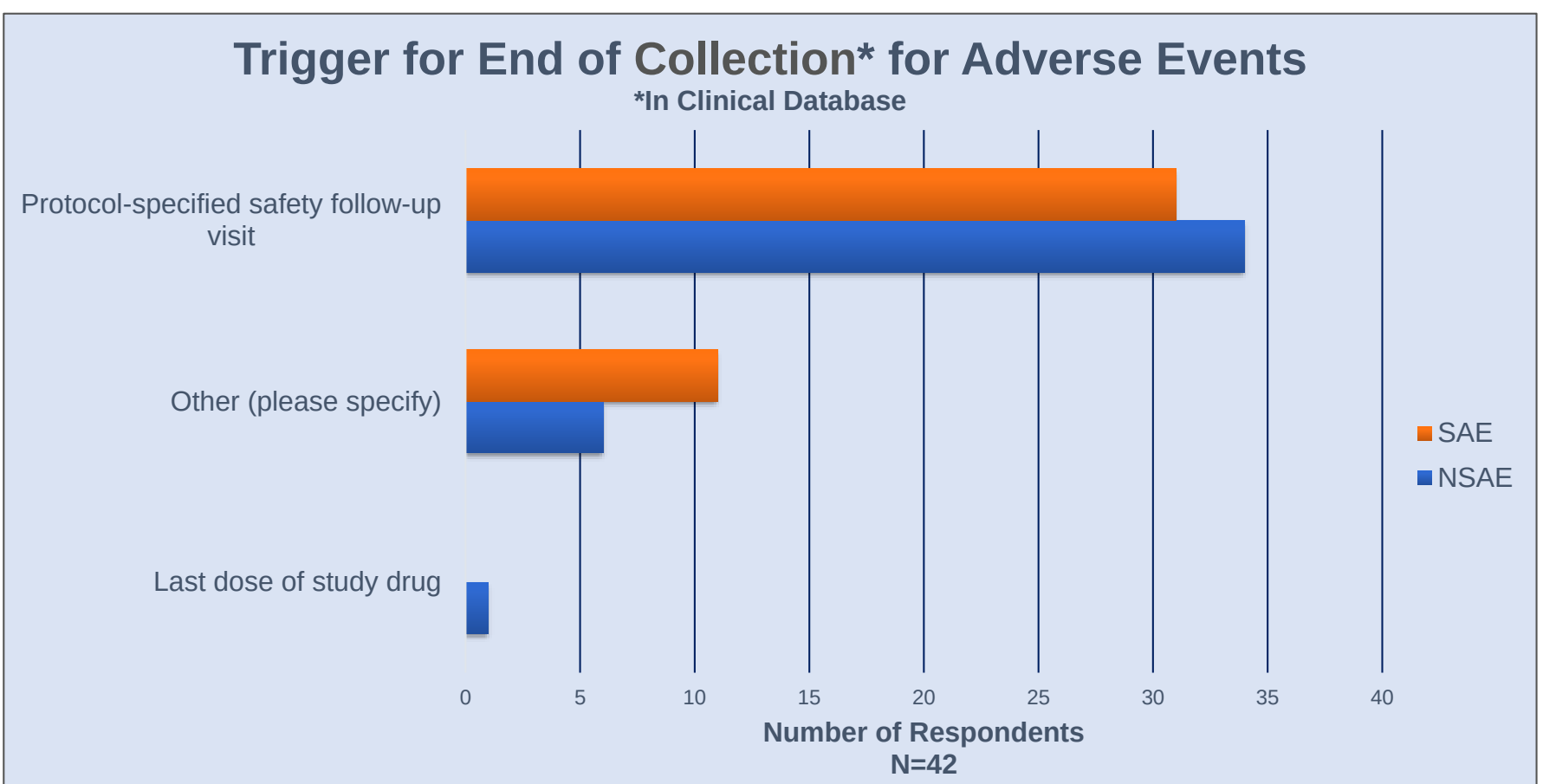
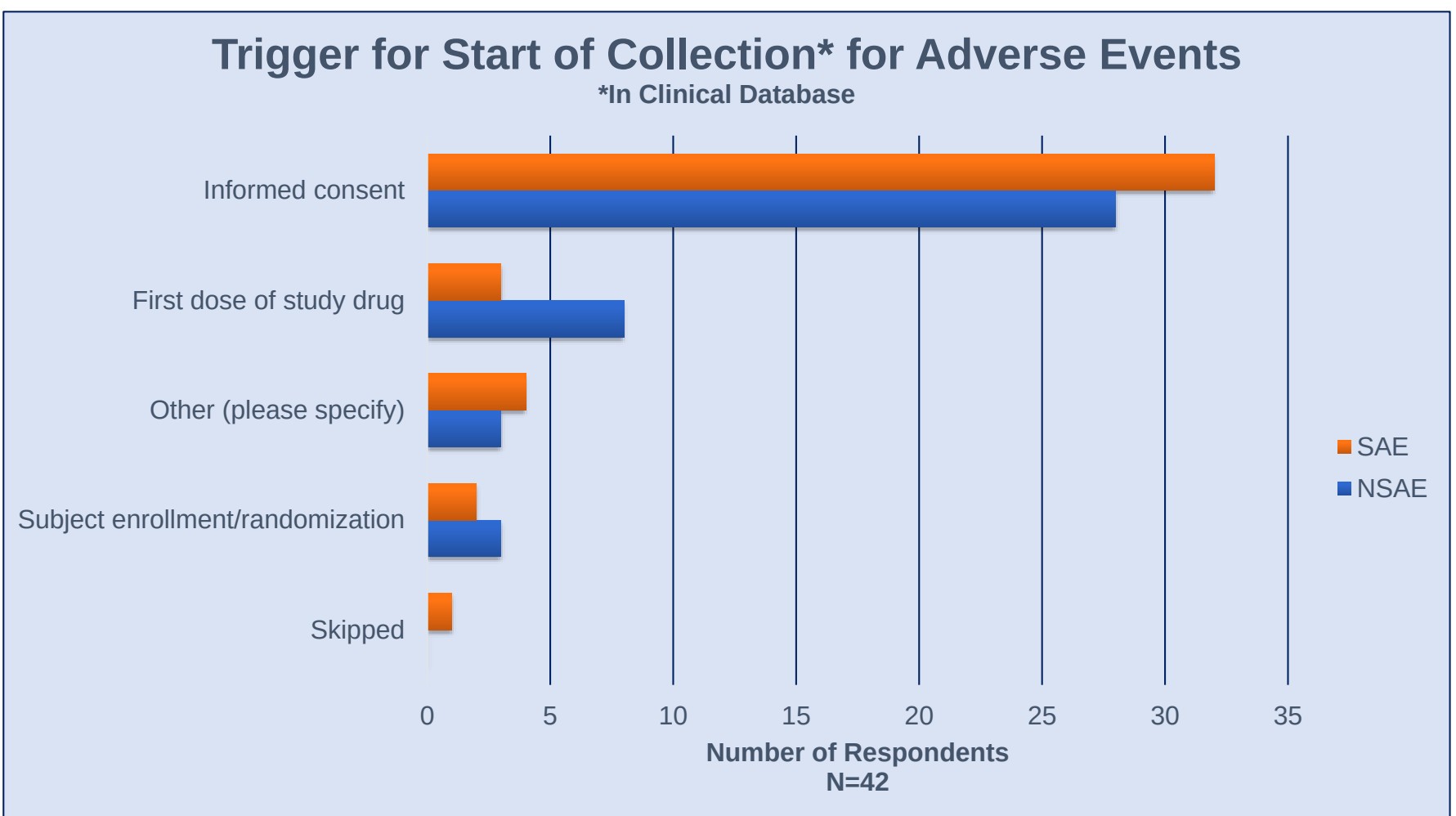
The survey was sent to PHUSE members and industry groups via social media. There were 42 respondents. Due to privacy concerns we did not ask for the company name so it is difficult to know if the 42 respondents are from 42 different sponsors/CROs.

Since data managers are usually involved with collection and statisticians with treatment emergent (TE) determination, we encouraged the different functions to work together on the survey. Many respondents completed the survey through the first treatment emergent adverse event (TEAE) scenario, so this could have been difficult to accomplish.

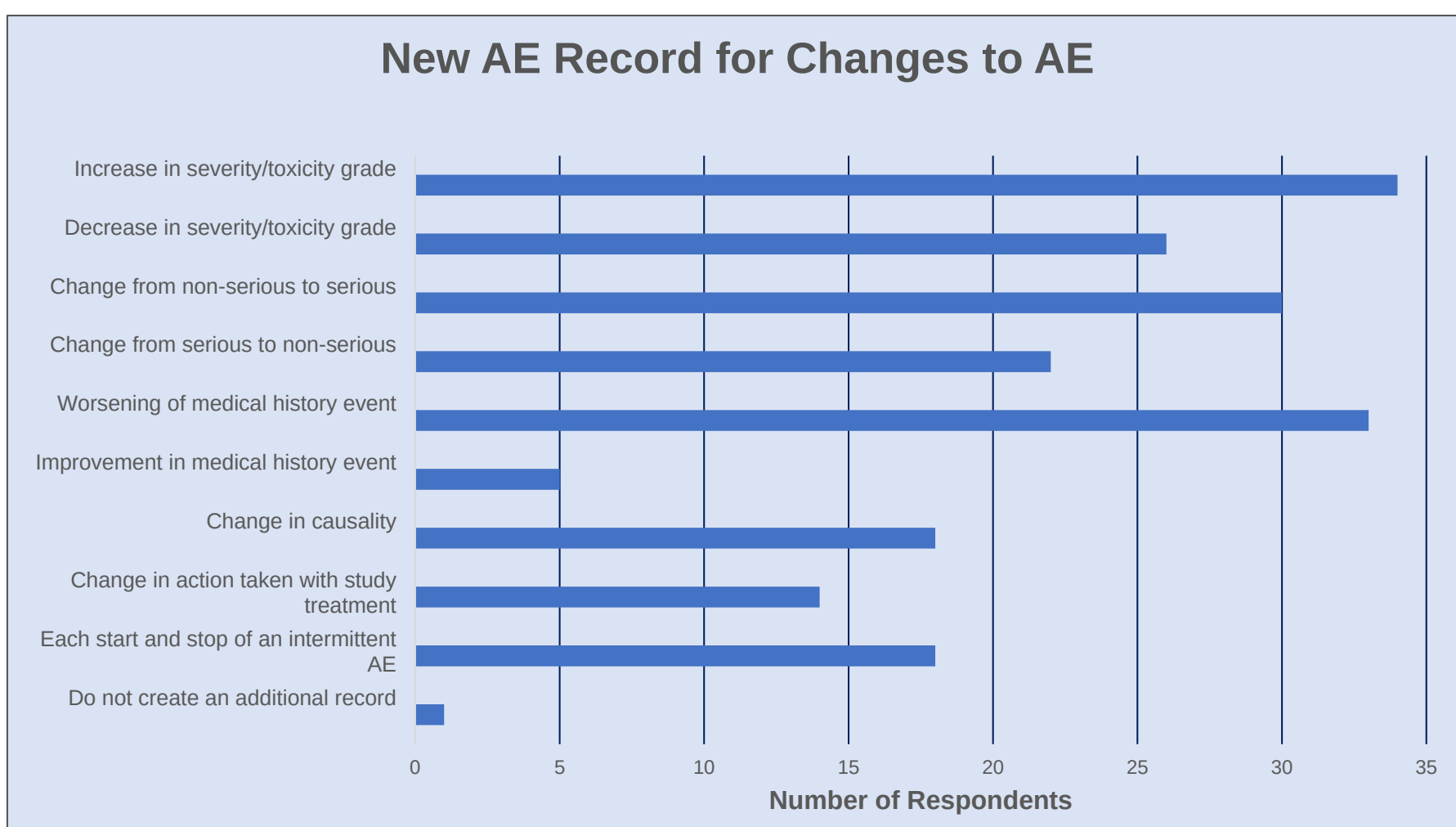
The survey didn’t capture all potential sources of variation for TE determination in order to keep the survey from becoming too complex. The focus was on changes in severity and didn’t include changes in seriousness and relatedness. Also, the survey did not include complex study designs (e.g., randomized withdrawal designs, designs with a maintenance or extension period following a treatment period).

How Much Variation is There Really?

Collecting Adverse Event Data in Clinical Database



Recording Changes to Adverse Events



Medical History vs. Adverse Event Form Collection

Scenario	Counts
Event starts after Informed Consent (IC) and ends before First Dose (FD)	MH = 4 AE = 15
Event starts after IC and ends after FD	MH = 5 AE = 14
Event starts before IC and ends after FD	MH = 15 AE = 3

Treatment Emergent Definition

Scenario	Counts	Comments
Event did not occur between IC and FD, the event started during treatment	NA	We did not survey this scenario; we assume all will consider this TE; most events will likely fall in this category
Event started between IC and FD, continued into treatment and eventually the severity increased in severity during treatment	TE = 17 Not TE = 0	Conceptually, there should be no debate that this is TE; survey results support this
Event started and stopped between IC and FD; the event came back during treatment with a higher severity	TE = 19 Not TE = 0	Conceptually, there should be no debate that this is TE; survey results support this
Event started between IC and FD, continued into treatment and shortly after FD, the severity decreased	TE = 4 Not TE = 7	For those with TE = yes, likely due to entering events when the severity changes (increases or decreases), then defining TE as having an event start date after FD
Event started and stopped between IC and FD; the event came back during treatment with the same severity	TE = 14 Not TE = 3	
Event started and stopped between IC and FD; the event came back during treatment with a lower severity	TE = 18 Not TE = 2	
Event started after IC and decreased in severity before FD, and increased back to the original severity during treatment (without stopping between severity changes)	TE = 7 Not TE = 5	
Event started before IC and ended during treatment; the event came back shortly after last dose (approx 20 days) at the same severity	TE = 8 Not TE = 7	Several responded that how events are counted after treatment ends depends on the protocol.
Event started before IC and ended during treatment; the event came back a couple months after Last Dose at a higher severity	TE = 5 Not TE = 9	Several responded that how events are counted after treatment ends depends on the protocol.

TE DEFINITION NOTES

- The scenarios at left are a simplification of the actual scenarios provided in the survey, as the actual scenarios explored multiple patterns of an event changing over time. It’s possible that we missed some subtlety in the simplification.
- Not all comments are included here.
- More respondents completed the survey through the first TEAE scenario which explains why there are some differences in the numbers across the scenarios.
- The survey focused on TE determination at the event level as opposed to a patient level for a particular analysis. In some cases, the results may not translate so we are making some assumptions and extrapolations in the summary statements.

CONCLUSIONS

- The survey results indicate that adverse event data collection practices and treatment emergence definitions do indeed vary across the industry, although there was a majority response for some collection practices.
- Based on comments, it seems that the variation in adverse event data collection practices partially affects the treatment emergence definition, but protocol definitions have a greater affect on treatment emergence definitions.
- In addition to the impact that the variation in adverse event data collection has on the treatment emergence definition, such variances also place additional burden on the sites to understand each sponsor’s unique requirements which can further complicate data collection.
- While the CDASH Implementation Guide v2.1 does have Case Report Form Completion Instructions for standard adverse event collection variables, they do not cover the detailed collection practices that we surveyed.
- These results and concerns support additional future efforts to further harmonize collection instructions and treatment emergence definitions.

CONTACT

Aimee Basile: abasile@surfaceoncology.com

Mary Nilsson: nilsson_mary_e@lilly.com