Adverse Event and Treatment Emergent Approaches in the Industry

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INTRODUCTION

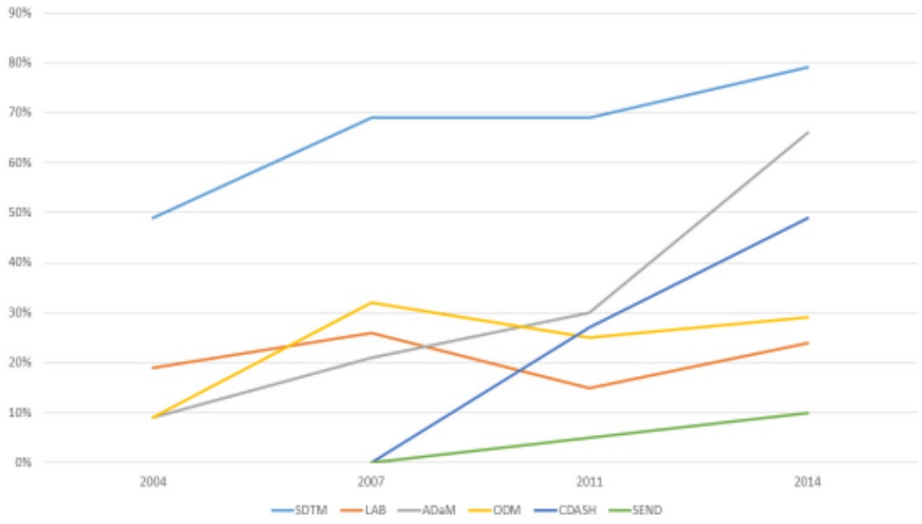
The Best Practices for Data Collection Instructions PHUSE Project Team conducted a survey to evaluate the different industry approaches for collecting adverse event data and how those data are evaluated for treatment emergence. The survey was conducted in conjunction with the Analysis and Display White Papers Project Team 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[1] (slide 29). While causality is typically not used to determine treatment emergence, the general variability in data reporting that Dr. Popat found demonstrates that collection of adverse event data varies greatly, and affects any subsequent analysis performed on that data.

Since regulatory authorities are requiring submission data standards, the Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) are being adopted more, as shown in Figure 1[2]. However, there is no requirement for data collection standards, so the Clinical Data Acquisition Standards Harmonization (CDASH) is not being adopted as quickly. In addition, the Clinical Data Interchange Standards Consortium (CDISC) does not prescribe the business rules around data collection and reporting, it only provides recommendations for completion guidelines of each field. Regulatory authorities try to fill this gap with non-binding guidance, but those recommendations are not required. Consequently, sponsors of clinical trials may be arriving at the same standardized data in different ways, which can make interpretation of those data more difficult.

FIGURE 1: TRENDS IN ADOPTION OF CDISC STANDARDS 2004-2014[2]



For example, in the Analysis and Displays Associated with Adverse Events white paper[3], it is stated, "variation in collection methods for AEs introduces additional variation in the eventual interpretation of treatment emergence." As stated in the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Statistical Principles for Clinical Trials Guideline (E9) a treatment emergent adverse event is "an event that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state.[4]" However, the execution of this definition can depend on the availability of some data.

Specific concerns were 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 attempted to answer these questions by gathering data to determine where data collection methods are most diverse.

METHODOLOGY

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.

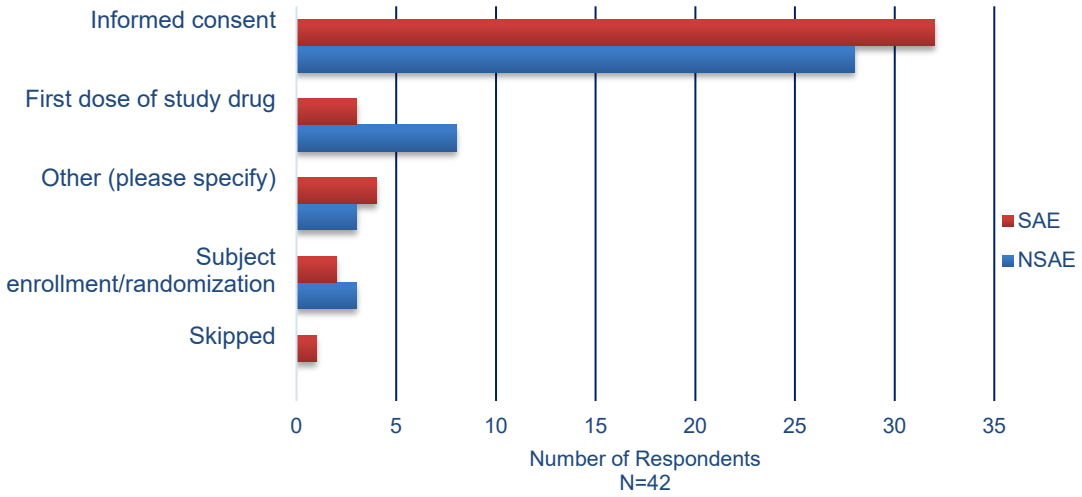
Since data managers are usually involved with collection and statisticians with treatment emergent (TE) determination, we encouraged the different functions to work together on the survey. More than half of the respondents (n=23) completed the survey through the first treatment emergent adverse event (TEAE) scenario, so this could have been difficult to accomplish.

The survey did not 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).

RESULTS

COLLECTING ADVERSE EVENT DATA IN THE CLINICAL DATABASE

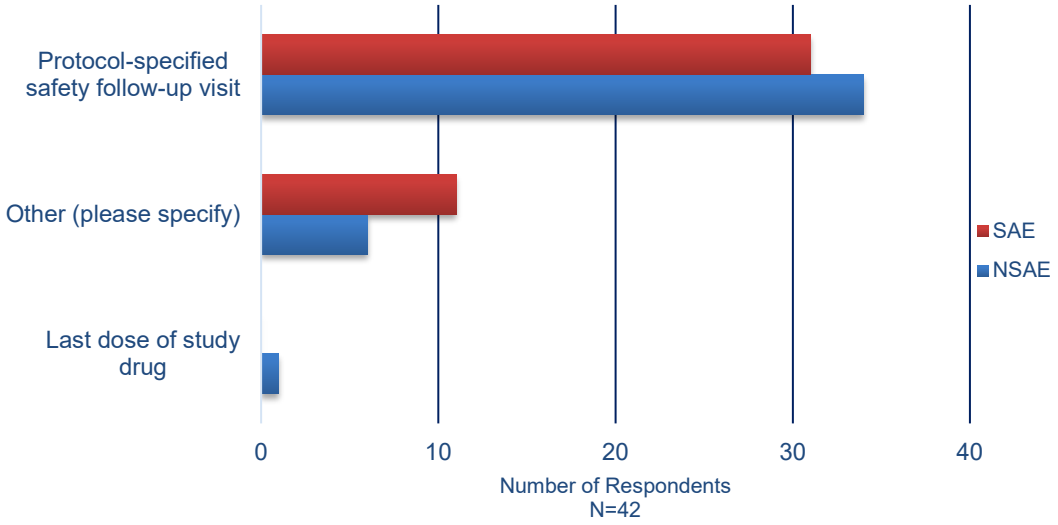
FIGURE 2: TRIGGER FOR START OF COLLECTION OF ADVERSE EVENTS IN THE CLINICAL DATABASE



In questions one and two of the survey (see Appendix A) we asked when does non-serious adverse event (NSAE) and serious adverse event (SAE) data collection start in the clinical database? The results show that there is a majority where collection of

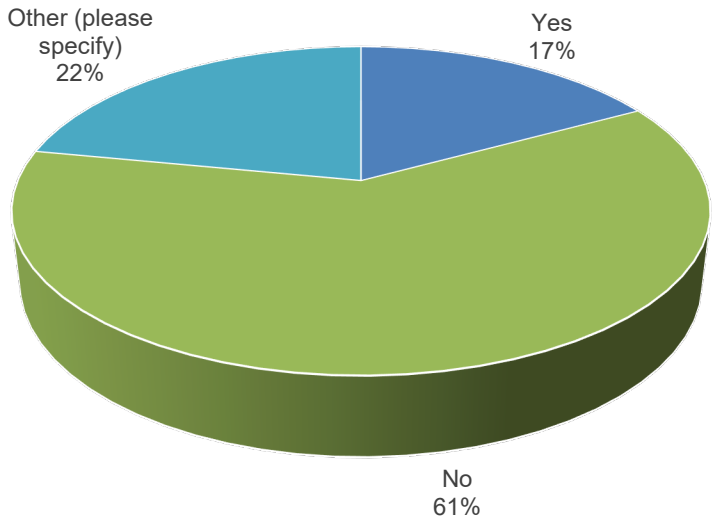
both SAEs and NSAEs start at informed consent, with slightly more responses of SAEs starting at informed consent and NSAEs starting at first dose of study drug.

FIGURE 3: TRIGGER FOR END OF COLLECTION OF ADVERSE EVENTS IN THE CLINICAL DATABASE



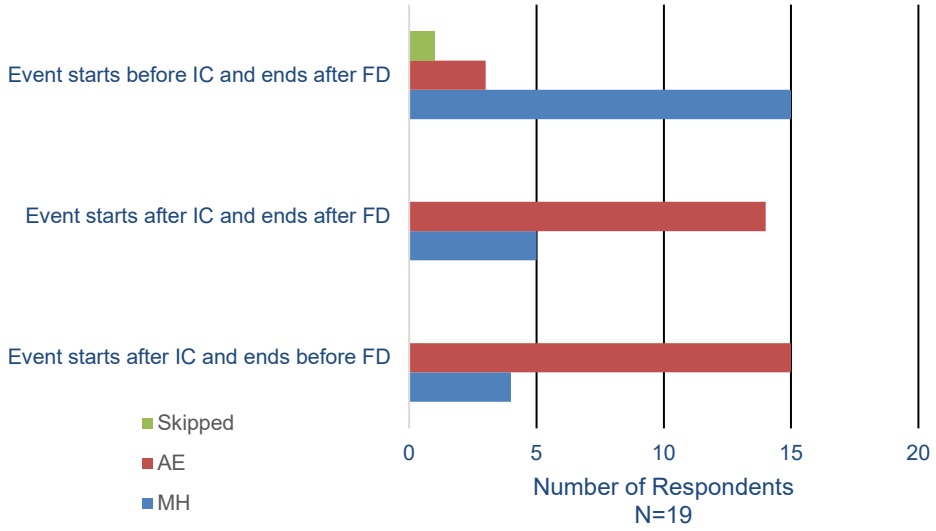
Questions three and four of the survey (see Appendix A) asked when does non-serious adverse event (NSAE) and serious adverse event (SAE) data collection stop in the clinical database? The results show that there is a majority where collection of both SAEs and NSAEs end at a protocol-specified safety follow-up visit, with slightly more responses of NSAEs ending at the protocol-specified safety follow-up. The comments from the high numbers of the 'Other' response indicate that SAEs may be collected in the clinical database for as long as the database is available, or for a specified period that may be unrelated to the safety follow-up visit.

FIGURE 4: SERIOUS ADVERSE EVENTS RECORDED IN THE CLINICAL DATABASE AFTER THE SUBJECT ENDS STUDY PARTICIPATION



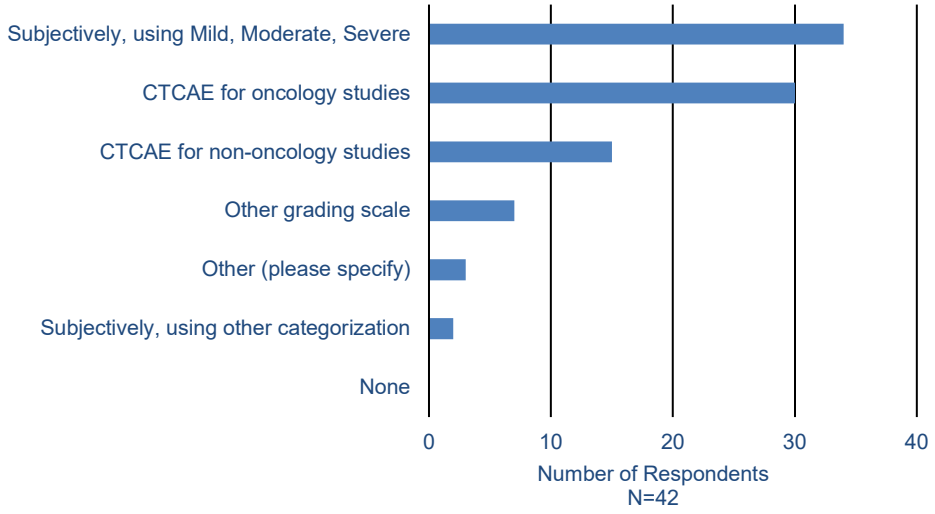
Question five (see Appendix A) asked respondents if an SAE is found after a subject is no longer participating in the study (after any follow-up period), is the SAE reported in the clinical database. The majority of respondents said it is not reported in the clinical database, but some of the responses of 'Other' indicated that if an SAE is reported in the clinical database, it would not be queried or removed and that it is based on the investigator's discretion.

FIGURE 5: WHEN IS AN EVENT RECORDED IN MEDICAL HISTORY VERSUS ADVERSE EVENT CRF



As noted in the Methodology section, fewer respondents answered questions later in the survey, so there are only 19 respondents to this question, but it confirms earlier questions about when adverse events are recorded in the clinical database. Most of the respondents enter an event that starts after informed consent (IC) on the adverse event case report form (CRF) and events that start before informed consent on the medical history CRF. Only one respondent noted that if an adverse event ends before the first dose (FD) then it would be recorded on the medical history CRF.

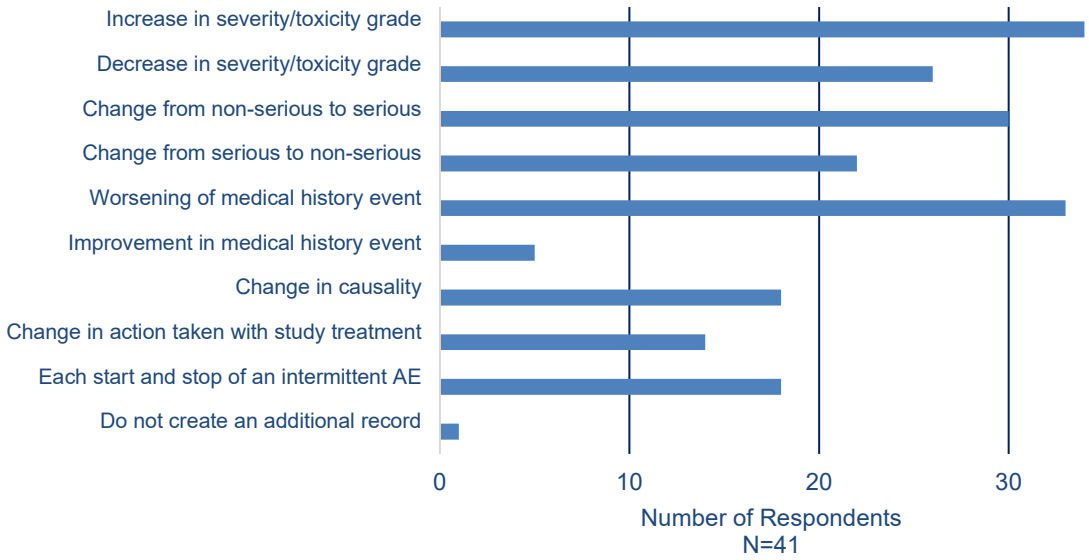
FIGURE 6: ADVERSE EVENT SEVERITY SCALE



The majority of respondents are using a subjective severity scale except for oncology studies which use the Common Terminology Criteria for Adverse Events (CTCAE) which is defined by the U.S. National Cancer Institute specifically for classifying adverse effects of drugs used in cancer therapy. Since we did not collect company name or therapeutic area, we do not know if the responses are based on oncology studies so these numbers could be skewed toward using the CTCAE scale. It is less common for the respondents to use CTCAE for non-oncology studies or another categorization or grading scale.

RECORDING CHANGES TO ADVERSE EVENTS

FIGURE 7: CREATION OF NEW RECORD TO COLLECT CHANGES TO AN ADVERSE EVENT



The most variability in adverse event collection seems to be how to record changes to an adverse event. Most respondents are creating new records for worsening of adverse events, such as increases in severity and/or toxicity grade, changes from non-serious to serious, and worsening of existing events (medical history events). However, fewer are recording changes when an adverse event improves (decreases in severity and/or toxicity grade, changes from serious to non-serious, and improvements in medical history events). In addition, fewer respondents, but still significant numbers are recording each change in the relationship to study drug (causality), actions taken with the study treatment and starts and stops of intermittent AEs.

TREATMENT EMERGENT DEFINITION

TABLE 1: SCENARIOS USED TO DETERMINE TREATMENT EMERGENT DEFINITIONS

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 (approximately 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.

The scenarios presented are a simplification of the actual scenarios provided in the survey, as the actual scenarios explored multiple patterns of an event changing over time (see Appendix A). It is possible that some subtlety has been lost in the simplification. Nevertheless, many answers did include comments that the response may depend on various things which are captured comments in the summary table, but not all comments have been included.

Finally, the survey focused on TE determination at the event level as opposed to a patient level, which may impact some analysis depending on the algorithm. In some cases, the results shown above may not translate, so we are presenting some assumptions and extrapolations in the summary statements above.

CONCLUSION

Although there was a majority response for some collection practices, the survey results indicate that adverse event data collection practices and especially treatment emergence definitions do indeed vary across the industry. As noted in the Analysis and Displays Associated with Adverse Events white paper[3], it seems that the variation in adverse event data collection practices partially affects the treatment emergence definition, but protocol definitions have a greater effect on treatment emergence definitions and the programming needed to calculate treatment emergence.

In addition to the impact that the variation in adverse event data collection has on the treatment emergence definition and programming, such variances also place additional burden on the sites to understand each sponsor's unique requirements which can further complicate data collection. This is especially true because the sites entering the data do not see the relationship between the entry of the data and the analysis. Therefore, it is critical that we be especially clear in our instructions on completing the case report form so that our analysis can be complete and accurate.

Not only does the variation in adverse event data collection impact the treatment emergence definition and site data entry, but regulatory authorities are also burdened by this variation. Even when data meet the standard submission and analysis models, variation in collection can cause the datapoints to vary greatly as noted in FDA Reviewer Dr. Vaishali Popat's presentation. So that even though standardized data improves the effort and speed of FDA reviews (slides 27-28)[1], the efficiencies are lost for any meta-analysis.

Should the data standards provide more definition for the collection methods in order to prevent these variabilities? The CDASH Implementation Guide states the purpose of CDASH "establishes a standard way to collect data in a similar way across studies and sponsors, so that data collection formats and structures provide clear traceability of submission data into the Study Data Tabulation Model (SDTM).[5]" To that end, version 2.1 of the CDASH Implementation Guide does have suggested Case Report Form Completion Instructions for standard adverse event collection variables, they do not cover the detailed collection practices that we surveyed. In fact, the CDASH Implementation Guide specifies that completion instructions for a CRF should provide references to protocol sections for the specifics of and/or limitations on the data to be reported. This supports our finding that some of the variability in data collection practices are based on variability in the protocol.

While it is difficult to handle every possible variability in study design, these results and concerns support a need for recommendations and best practices for adverse event data collection, including handling of some exceptions. Based on the findings of our research, we will pursue additional future efforts to further harmonize collection instructions and treatment emergence definitions.

REFERENCES

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APPENDIX A: TREATMENT EMERGENT SCENARIOS FROM THE ADVERSE EVENTS AND TREATMENT EMERGENT DEFINITION SURVEY

Q1. When does non-serious adverse event (NSAE) data collection in the clinical database start? (Choose one.)
Answer Choices
Informed consent
Subject enrollment/randomization
First dose of study drug
Other (please specify)

Q2. When does serious adverse event (SAE) collection in the clinical database start? (Choose one.)
Answer Choices
Informed consent
Subject enrollment/randomization
First dose of study drug
Other (please specify)

Q3. When does non-serious adverse event (NSAE) data collection in the clinical database stop? (Choose one.)
Answer Choices
Last dose of study drug
Protocol-specified safety follow-up visit
Other (please specify)

Q4. When does serious adverse event (SAE) collection in the clinical database stop? (Choose one.)
Answer Choices
Last dose of study drug
Protocol-specified safety follow-up visit
Other (please specify)

Q5. If an SAE is reported after a subject is no longer participating in the study (after any follow-up period), is the SAE reported in the clinical database?
Answer Choices
Yes
No
Other (please specify)

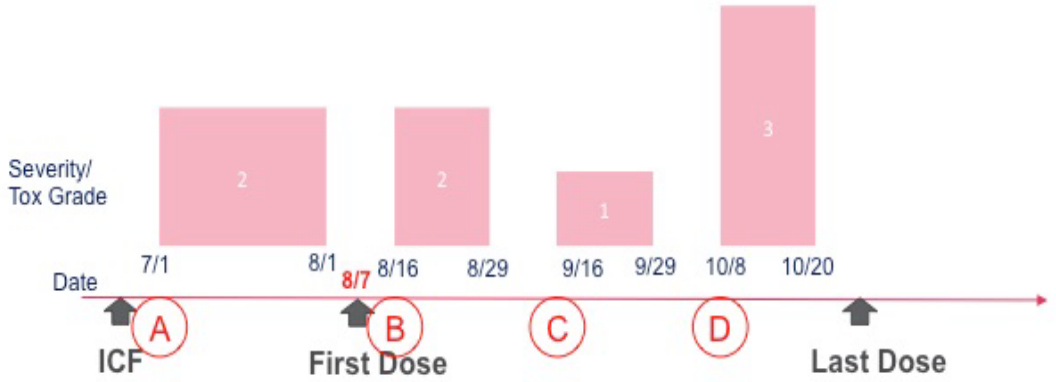
Q6. Are ongoing AEs followed until resolution after a subject is no longer in the study?
Answer Choices
Yes, all AEs
Yes, SAEs only
No
Other (please specify)

Q7. When is a new AE record created for previously entered events? (Check all that apply.)
Answer Choices
Increase in severity/toxicity grade
Decrease in severity/toxicity grade
Change from non-serious to serious
Change from serious to non-serious
Worsening of medical history (pre-existing) event
Improvement in medical history (pre-existing) event
Change in causality (relationship to study treatment)
Change in action taken with study treatment
Each start and stop of an intermittent AE
Do not create an additional record
New record is not created

Q8. How is severity of an AE categorized? (Check all that apply.)
Answer Choices
Subjectively, using Mild, Moderate, Severe
Subjectively, using other categorization
CTCAE for oncology studies
CTCAE for non-oncology studies
Other grading scale
None
Other (please specify)

Q9. Please use this comments box to provide any additional information.

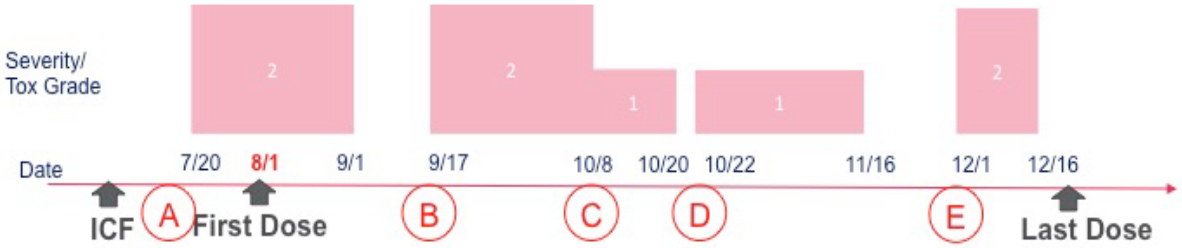
Q10. Scenario 1



For each of the points (A-D):

Question	On which CRF would this event be recorded?	What would be the start date for this record?	What would be the stop date for this record?	Would this be flagged as TEAE?
Answer Choices	AE MH Not recorded	7/1 8/1 8/16 8/29 9/16 9/29 10/8 10/20 Other	7/1 8/1 8/16 8/29 9/16 9/29 10/8 10/20 Other	Yes No

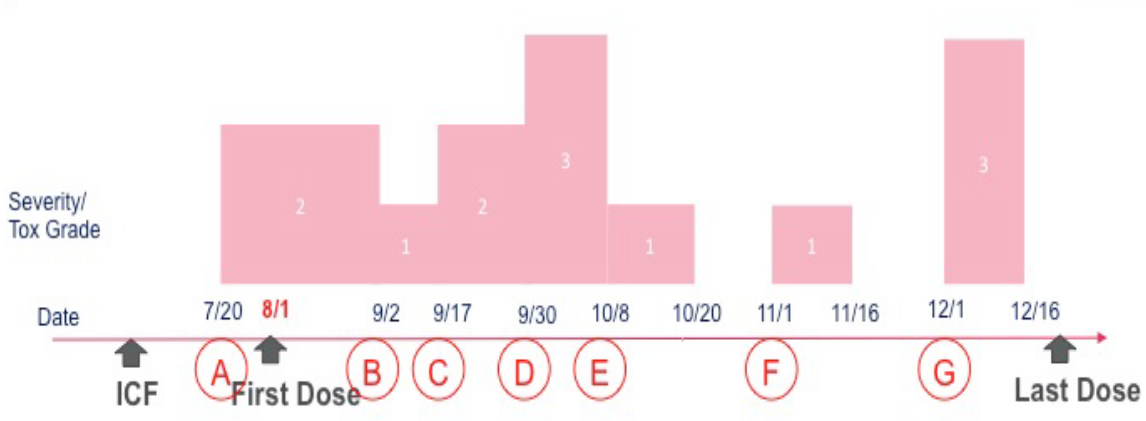
Q11. Scenario 2



For each of the points (A-E):

Question	On which CRF would this event be recorded?	What would be the start date for this record?	What would be the stop date for this record?	Would this be flagged as TEAE?
Answer Choices	AE MH Not recorded	7/20 8/1 9/1 9/17 10/8 10/20 11/16 12/1 12/16 Other	7/20 8/1 9/1 9/17 10/8 10/20 11/16 12/1 12/16 Other	Yes No

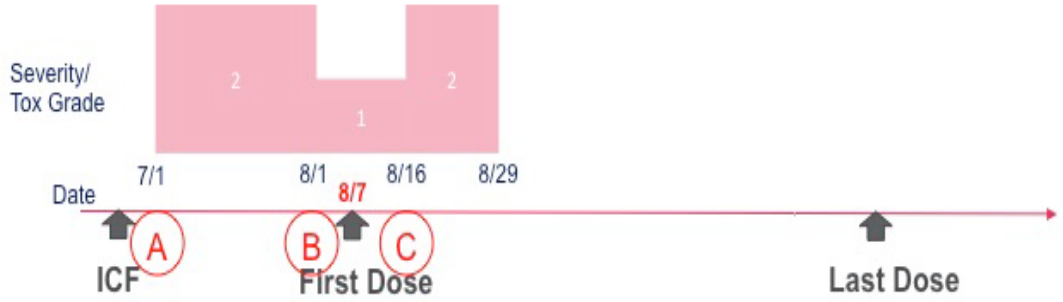
Q13. Scenario 3



For each of the points (A-G):

Question	On which CRF would this event be recorded?	What would be the start date for this record?	What would be the stop date for this record?	Would this be flagged as TEAE?
Answer Choices	AE MH Not recorded	7/20 8/1 9/2 9/17 9/30 10/8 10/20 11/1 11/16 12/1 12/16 Other	720 8/1 9/2 9/17 9/30 10/8 10/20 11/1 11/16 12/1 12/16 Other	Yes No

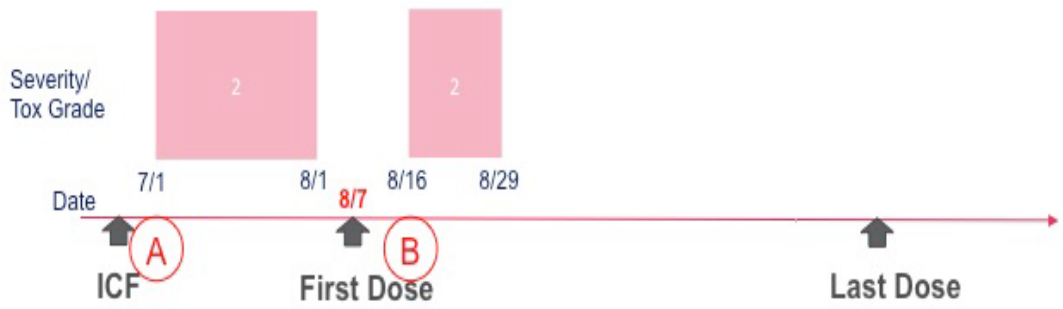
Q14. Scenario 4



For each of the points (A-C):

Question	On which CRF would this event be recorded?	What would be the start date for this record?	What would be the stop date for this record?	Would this be flagged as TEAE?
Answer Choices	AE MH Not recorded	7/1 8/1 8/16 8/29 Other	7/1 8/1 8/16 8/29 Other	Yes No

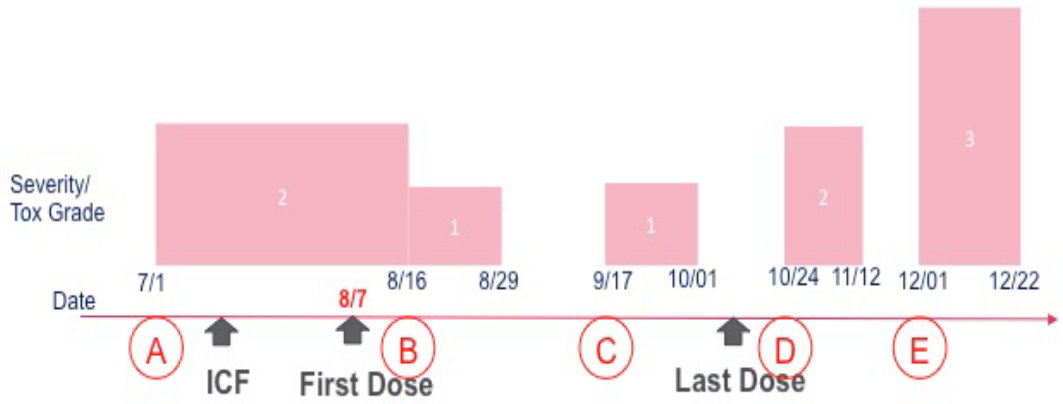
Q15. Scenario 5



For each of the points (A-B):

Question	On which CRF would this event be recorded?	What would be the start date for this record?	What would be the stop date for this record?	Would this be flagged as TEAE?
Answer Choices	AE MH Not recorded	7/1 8/1 8/16 8/29 Other	7/1 8/1 8/16 8/29 Other	Yes No

Q16. Scenario 6



For each of the points (A-E):

Question	On which CRF would this event be recorded?	What would be the start date for this record?	What would be the stop date for this record?	Would this be flagged as TEAE?
Answer Choices	AE MH Not recorded	7/1 8/7 8/16 8/29 9/17 10/1 10/24 11/12 12/01 12/22 Other	7/1 8/7 8/16 8/29 9/17 10/1 10/24 11/12 12/01 12/22 Other	Yes No