Adverse Event Collection
and Treatment Emergence
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Overview: Purpose of this document

This white paper presents the results of a survey to study the variation in the collection and treatment emergence definition of adverse event data. In addition, the paper examines how the variation, if any, would influence the standardisation of analysis and displays associated with adverse events.

The PHUSE Best Practices for Data Collection Instructions 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. The published paper raised questions about the variations in the collection and definition of adverse event data that would support the analysis and displays developed by the team. This publication presents the findings of the survey.

Scope

This paper summarises the results of a survey designed to capture how adverse events (AEs) are collected in the clinical database and how treatment emergence is determined given certain scenarios. Instructions were given to focus a set of responses on a certain Phase II to III study or therapeutic area since there can be variations based solely on study type or indication.

The survey was split into two parts – the first focussed on AE data collection, with eight multiple choice questions and one open question for additional comments. The second part was focussed on treatment emergent adverse event (TEAE) definition using six different scenarios to capture when AEs are considered treatment emergent (TE) and how the data would be recorded.

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

Since data collection involves data managers and treatment emergent determination involves statisticians, the survey instructed different functions to collaborate on the survey. However, some respondents only answered the data collection portion, and thus likely worked on the survey independently. Only 23 of 42 respondents completed one of the 6 TEAE scenarios.

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

Problem Statement

This survey was conducted to determine the variability of adverse event data collection and how those data are evaluated for treatment emergence. The survey was conducted in part to answer questions raised in the Analysis and Display White Papers project team white paper on the Analysis and Displays Associated with Adverse Events.

For example, the Analysis and Displays Associated with Adverse Events white paper (PHUSE, 2017) states “Variation in collection methods for AEs introduces additional variation in the eventual interpretation of treatment emergence.” The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Statistical Principles for Clinical Trials Guideline E9 (1998) defines a treatment emergent adverse event as “an event that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state” (p. 35). However, the execution of this definition can depend on the availability of certain data.

Specific concerns raised in the Analysis and Displays Associated with Adverse Events paper were 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

Other sources call into question the consistency of AE data collection. For instance, in a 2019 presentation, FDA Reviewer Dr Vaishali Popat stated that she found 329 ways to represent AE causality in standardised data (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 2016, when regulatory authorities began requiring submission data standards, adoption of the Clinical Data Interchange Standards Consortium's (CDISC) Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) has continued to increase. Even before the 2016 requirement, adoption of CDISC standards was on the rise, as shown in Figure 1 (CDISC, 2014).
However, the CDISC standards only provide standardised metadata for data in their life cycle from collection through analysis; they do not prescribe the business rules around data collection and reporting. The US Food and Drug Administration (FDA) publishes a Study Data Technical Conformance Guide (TCG) with data handling and business rules for standardised study data, but the TCG does not address the questions that were covered by this survey. Consequently, sponsors of clinical trials may be arriving at the same standardised data in different ways, which can make interpretation of those data more difficult.

The results presented are a first step to defining the variability of adverse event data collection and where data collection methods are most diverse.

Results

The results presented are in order of topic instead of the order of survey questions. For example, some of the questions in the TEAE section of the survey pertained to AE data collection practices and are presented under Collecting Adverse Event Data in the Clinical Database. Also note that each figure does not necessarily represent responses to one question; in some cases, responses have been combined.

COLLECTING ADVERSE EVENT DATA IN THE CLINICAL DATABASE

The first section of the survey focussed on how the adverse event data are collected in the clinical database, with the understanding that there may be differences in the collection of serious adverse events between the clinical and safety databases. Since the clinical database is used for the analysis and displays of clinical data, the focus was the data available in the clinical database.
In questions one and two of the survey, we asked when non-serious adverse event (NSAE) and serious adverse event (SAE) data collection start in the clinical database. The results show that a majority of both SAE and NSAE collection start at informed consent, with slightly more responses of SAEs starting at informed consent and NSAEs starting at first dose of study drug.

Questions three and four of the survey asked when 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.

We purposefully did not specify a time period for the safety follow-up visit as it depends on the study treatment and the study design. The protocol should specify this period based on the scientific understanding of the treatment.
Question five asked respondents if an SAE is found after a subject is no longer participating in the study (after any follow-up period), whether the SAE is 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 4: SERIOUS ADVERSE EVENTS RECORDED IN THE CLINICAL DATABASE AFTER THE SUBJECT ENDS STUDY PARTICIPATION

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

As noted in the Scope section, fewer respondents answered questions in the TEAE scenario part of the survey. There were 19 respondents to this question for each of the different scenarios, 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 in the comments that regardless of when a medical event occurs, if the event ends before the first dose (FD), then it would be recorded on the medical history CRF.
The majority of respondents used a subjective severity scale, except for oncology studies, which use the Common Terminology Criteria for Adverse Events (CTCAE), which is defined by the US National Cancer Institute (NCI) specifically for classifying adverse effects of drugs used in cancer therapy. Since company name or therapeutic area was not collected, it is unknown whether the responses are oncology studies; therefore, these numbers could be skewed towards using the CTCAE scale. It is less common for the respondents to use CTCAE for non-oncology studies or another categorisation or grading scale.

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

- 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 event
- Improvement in medical history event
- Change in causality
- Change in action taken with study treatment
- Each start and stop of an intermittent AE
- Do not create an additional record

Number of Respondents N=41
The most variability in adverse event collection seems to be how to record changes to an adverse event. Most respondents reported 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 respondents 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 EMERGENCE DEFINITIONS

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Counts</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event did not occur between IC and FD, the event started during treatment</td>
<td>NA</td>
<td>Survey did not contain this scenario, but it is likely that all sponsors consider this TE; most events will likely fall into this category</td>
</tr>
<tr>
<td>Event started between IC and FD, continued into treatment and eventually the severity increased during treatment</td>
<td>TE = 17 Not TE = 0</td>
<td>Conceptually, this is TE and survey results support this</td>
</tr>
<tr>
<td>Event started and stopped between IC and FD; the event came back during treatment with a higher severity</td>
<td>TE = 19 Not TE = 0</td>
<td>Conceptually, this is TE and survey results support this</td>
</tr>
<tr>
<td>Event started between IC and FD, continued into treatment and shortly after FD, the severity decreased</td>
<td>TE = 4 Not TE = 7</td>
<td>For those with TE = yes, this is likely due to creating a new record when the severity changes (increases or decreases), and defining TE as having an event start date after FD</td>
</tr>
<tr>
<td>Event started and stopped between IC and FD; the event came back during treatment with the same severity</td>
<td>TE = 14 Not TE = 3</td>
<td></td>
</tr>
<tr>
<td>Event started and stopped between IC and FD; the event came back during treatment with a lower severity</td>
<td>TE = 18 Not TE = 2</td>
<td></td>
</tr>
<tr>
<td>Event started after IC and decreased in severity before FD, and increased back to the original severity during treatment (without stopping between severity changes)</td>
<td>TE = 7 Not TE = 5</td>
<td></td>
</tr>
<tr>
<td>Event started before IC and ended during treatment; the event came back shortly after last dose (approximately 20 days) at the same severity</td>
<td>TE = 8 Not TE = 7</td>
<td>Several responded that the protocol defines how events are counted after the treatment ends</td>
</tr>
<tr>
<td>Event started before IC and ended during treatment; the event came back a couple months after Last Dose at a higher severity</td>
<td>TE = 5 Not TE = 9</td>
<td>Several responded that the protocol defines how events are counted after the treatment ends</td>
</tr>
</tbody>
</table>

Abbreviations: TE = Treatment Emergent; IC = Informed Consent; FD = First Dose

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 was 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; however, not all comments were included.

Finally, the survey focussed 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.

Recommendation

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 (PHUSE, 2017), it seems that the variation in adverse event data collection practices partially affects the treatment
Adverse Event Collection and Treatment Emergence

emergence definition, but protocol definitions have a greater
effect on treatment emergence definitions and the programming
needed to calculate treatment emergence. Variation also affects
the ability to produce some of the displays in the Adverse Events
white paper. For example, improvements in severity would be
needed for a display that shows AEs over time using colour to
show how severity changes over time (Section 18, Appendix B in
the PHUSE Adverse Events white paper).

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 an additional burden
on the sites to understand each sponsor’s unique requirements,
which further complicates 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 the instructions for completing the adverse event
case report form is especially clear so that the 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 met 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 (2019). Even though standardised data improves
the effort and speed of FDA reviews (slides 27–28), the
efficiencies are lost for any meta-analysis (Popat, 2019).

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
is to establish “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)” . To that end, version
2.1 of the CDASH Implementation Guide does suggest Case
Report Form Completion Instructions for standard adverse event
collection variables as examples; however, they do not cover
the detailed collection practices that were 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 is 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 certain exceptions. The goal
for any recommendations would be to reduce variability, but it
would be impossible, and perhaps inappropriate, to eliminate all
differences. Based on the findings of our research, the project
team will pursue additional future efforts to further harmonise
collection instructions and treatment emergence definitions.

Disclaimer

The opinions expressed in this document are those of the
authors and should not be construed to represent the opinions
of PHUSE members’ respective companies or organisations
or the FDA’s views or policies. The content in this document
should not be interpreted as a data standard and/or information
required by regulatory authorities.
References


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Acknowledgements

Additional contributors/reviewers (e.g. participated in discussions, provided review comments on portions of the content) include: Wendy Dobson, Kit Howard, Jane Lozano, Janet Low, Shannon Labout, Kim Musgrave, Melvin Munsaka, Todd Bazin, Jennifer Alf, Cathy Bezek, Nancy Brucken, Titania Dumas-Roberson, Shalini Dwivedi, Farhan Hameed, Lisa Houterloot, Jeannine Hughes, Aparna Kulkarni, Elizabeth Langevin, Pranab Mitra, Russell Newhouse, Charity Quick, Jennifer Showalter, Alec Vardy, Sharon Weller, Joanne Zhou. Apologies to contributors/reviewers that we may have missed.