Recommended Definition of Treatment-Emergent Adverse Events in Clinical Trials

Revision History

Version	Date	Summary
1.0		Initial version

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1: Overview: Purpose of this document

This document provides recommendations for better standardizing the treatment-emergent adverse event (TEAE) definition in clinical trials to reduce variability in implementation.

2: Scope:

This document defines treatment-emergent events in Phase 1 to 4 clinical trials and integrated summary documents across therapeutic areas. The recommendations described herein were based on the authors' collective experiences and a survey conducted by the PHUSE Treatment-Emergent Definition Recommendations project team [2] to solicit input from respondents on various TEAE scenarios for a simple clinical study design. The survey results are summarized in Appendix 1.

While "treatment-emergent" in clinical trials is commonly associated with adverse event analyses, the recommendations are generalizable to other safety data such as laboratory values or vital signs. For simplicity, the term "TEAE" will denote such events within this document.

The following concepts are considered out of scope; however, some aspects of the recommendations may apply:

- Methods for analyzing treatment-emergent events. See PHUSE [1] for an extensive discussion of appropriate analysis methods.
- Complex study designs such as randomized withdrawal, crossover, and open-label extension studies.
- Other types of medical research other than Phase 1 to 4 clinical trials (e.g. observational studies).
- The time interval included for treatment-emergent assessment after stopping treatment (sometimes referred to as the ascertainment window). See Section 10.7 of PHUSE [1] for considerations when defining the time interval.
- Derivation of specific SDTM / ADaM variables (e.g. TEAE start date).

3: Definitions:

Acronyms

Term	Definition
ADaM	Analysis Data Model
AE	Adverse event

FDA	Food and Drug Administration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
SDTM	Study Data Tabulation Model
TEAE	Treatment-emergent adverse event

4: Problem Statement:

While there is a general alignment across industry and regulators that a TEAE is an event following the first dose of treatment that is either new or a worsening of an existing event, there are differences in this definition across sources (see Table 1) that can lead to inefficiencies in defining and interpreting TEAEs between therapeutic areas and between industry and regulators. This ultimately limits the ability to consistently implement and fully leverage shared tools and analyses.

Table 1: Differences in Treatment Emergent Definitions by Source

Source	Definition
ICH E9 Statistical Principles for Clinical Trials [3]	An event that emerges during treatment having been absent pre-treatment or worsens relative to the pre-treatment state.
US FDA Clinical Reviewer Guideline [4]	In general, what are included are treatment emergent signs and symptoms (i.e., signs and symptoms not present at baseline, or not present at the severity seen on treatment).
US FDA Oncology Center of Excellence / Office of Oncologic Drugs [5]	New or worsening events occurring in the safety population at or after the first drug treatment up to and including 30 days after the last dose of the study drug or the day re start of subsequent therapy (whichever comes first). AEs starting more than 30 days after last dose of study drug that were determined by the sponsor to be related to the study drug should also be considered TEAEs.
PHUSE Analysis and Displays Associated with Adverse Events: Focus on Adverse Events in Phase 2-4 Clinical Trials and Integrated Summary Documents [1]	An event that is not present at baseline, or not present at the severity seen on treatment.
PHUSE Analysis and Displays Associated with Safety Topics of Interest: Focus on Phase II to IV Clinical Trials [6]	An AE following the first administration of the intervention that is either new or a worsening of an existing AE.

In addition to inconsistencies in the definitions, there are other challenges in defining treatment emergence from our experience. Some of these include:

- Historical precedence, e.g., "This is how we've always done it."
- Differences across therapeutic areas, e.g., defining TEAEs in vaccine trials vs oncology trials.
- Different timeframes for defining worsening in the event severity, e.g., using the worst severity before the first dose or the severity at the time of the first dose?
- The variability in AE collection methods also introduces additional variation in interpreting treatment emergence. See PHUSE [7] for a discussion on AE collection topics.

While it is noted that removing all sources of variability is impossible, this white paper is intended to provide recommendations that will provide a uniform context for classifying AEs as treatment-emergent. We hope future collaborations, such as an ICH initiative, will foster further improvement and standardization.

5: Background:

The PHUSE Best Practices for Data Collection Initiatives project team conducted a survey [8] to study the variation in the collection and definition of TEAEs in clinical studies. It noted the need to pursue additional research to harmonize industry practices.

The Treatment-Emergent Definition Recommendations project team was formed to further study TEAE definition inconsistencies and develop recommendations to reduce implementation variability. The project team conducted an additional survey to solicit input from industry and regulatory respondents on 13 TEAE scenarios for a simple study design.

The onset, recurrence, and severity of the AEs varied across the scenarios and respondents were asked if the scenario should be considered as a TEAE for an intervention period summary table. No TEAE definition was provided, as the project team intended to use the results to inform these recommendations. In each scenario, it was assumed that each event corresponded to an occurrence of the same medical concept. Respondents were also asked to ignore how AEs were collected at their organizations and rather focus on whether they thought the scenario was a TEAE or not. Further details about the survey assumptions are provided in Appendix 1.

6: Recommendations:

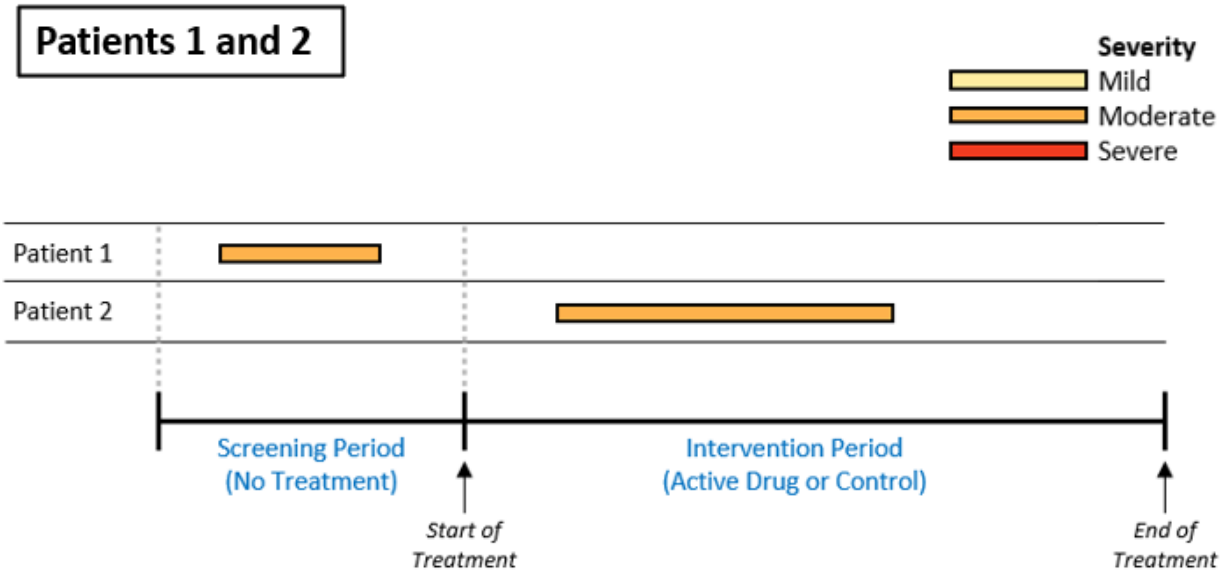
Our analysis of the survey responses (Appendix 1) confirms that respondents were not aligned on the

definition and/or implementation of treatment-emergent status. Several key areas of discordance were:

- How to define TEAEs in the presence of screening events.
- How to define TEAEs when the event severity decreased after the start of treatment.
- How to define TEAEs when there was a gap in time between the screening event and its re-emergence after the start of treatment.

To allow for a more consistent approach to characterizing TEAEs, we ask readers to consider the following recommendations for each scenario provided in the survey.

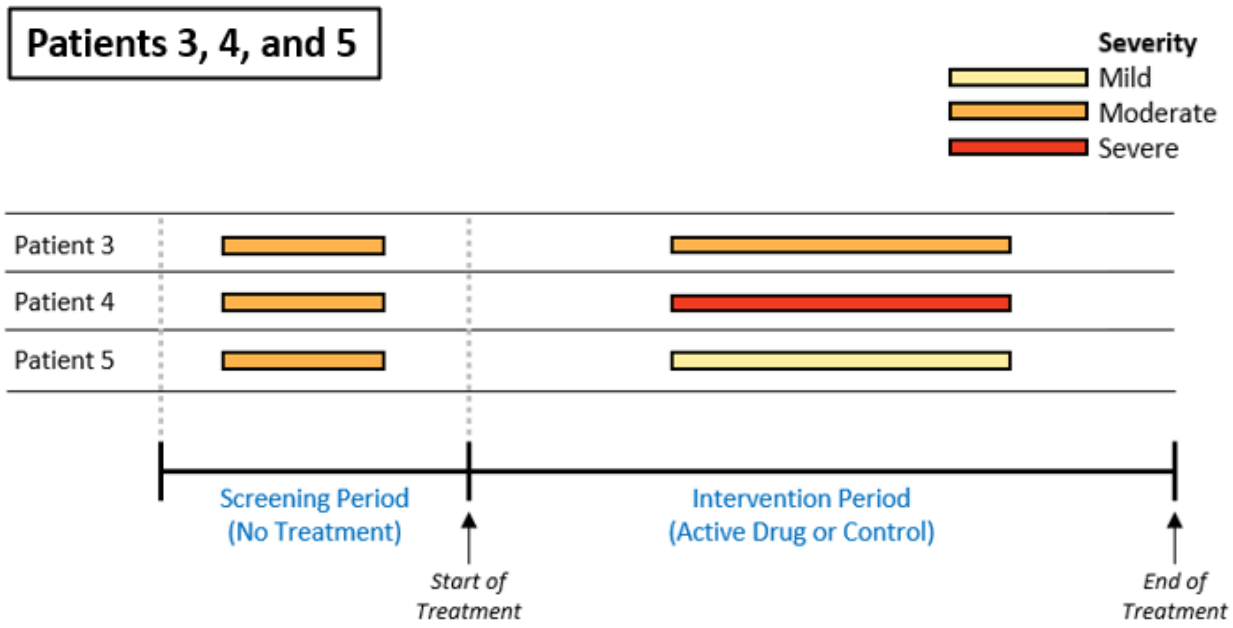
Scenario 1: When an event ends entirely before or entirely after the start of treatment:



Patient	Recommendation for Intervention Period Summary Table	Rationale for Recommendation
Patient 1	Not TEAE[a]	The event started and ended before the start of treatment.
Patient 2	TEAE[a]	The event started after the start of treatment.

[a] Complete alignment on recommendation within project team.

Scenario 2: When an event starts and ends before the start of treatment and an event with the same or similar description occurs after the start of treatment:

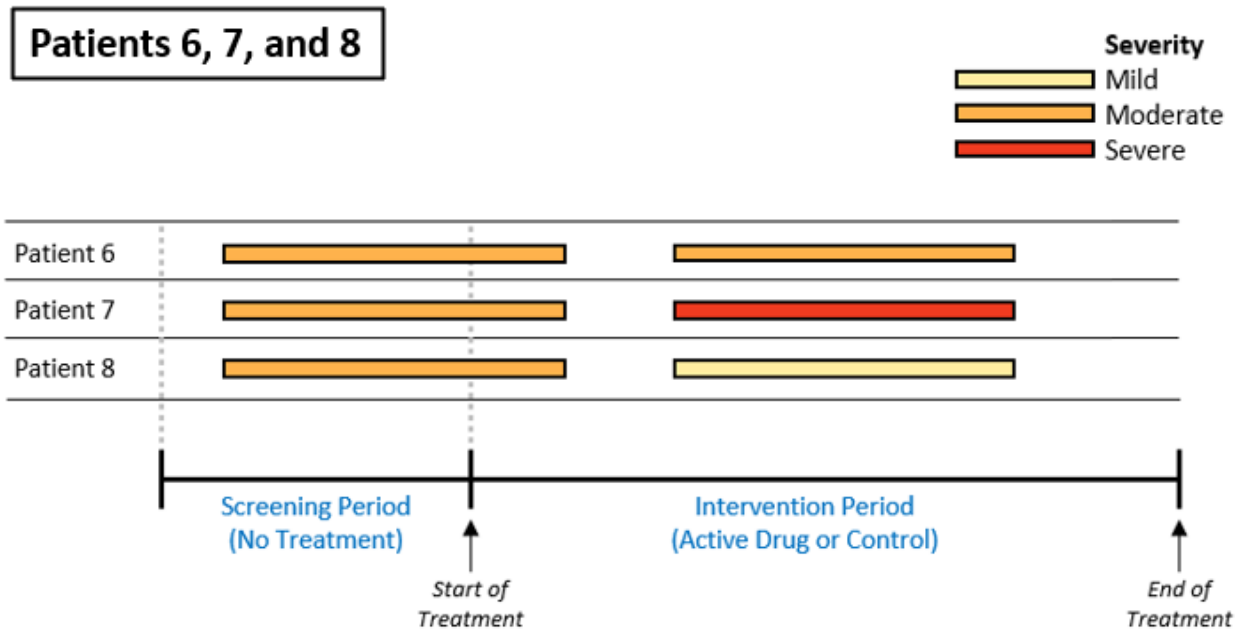


Patient	Recommendation for Intervention Period Summary Table	Rationale for Recommendation
Patient 3	TEAE[a]	While the survey was intended to elicit opinions assuming the event was the same, the reality is that most AE collection systems do not include a way to distinguish whether these are recurrences of the same event or different events. Therefore, for an event that ends before the start of treatment and an event with the same or similar description occurs after the start of treatment, we believe it is more appropriate to consider the later event as a new event.
Patient 4	TEAE[b]	
Patient 5	TEAE[a]	

[a] Difficult to gain complete alignment on recommendation within project team.

[b] Complete alignment on recommendation within project team.

Scenario 3: When an event starts before the start of treatment and ends after the start of treatment, and an event with the same or similar description occurs later:

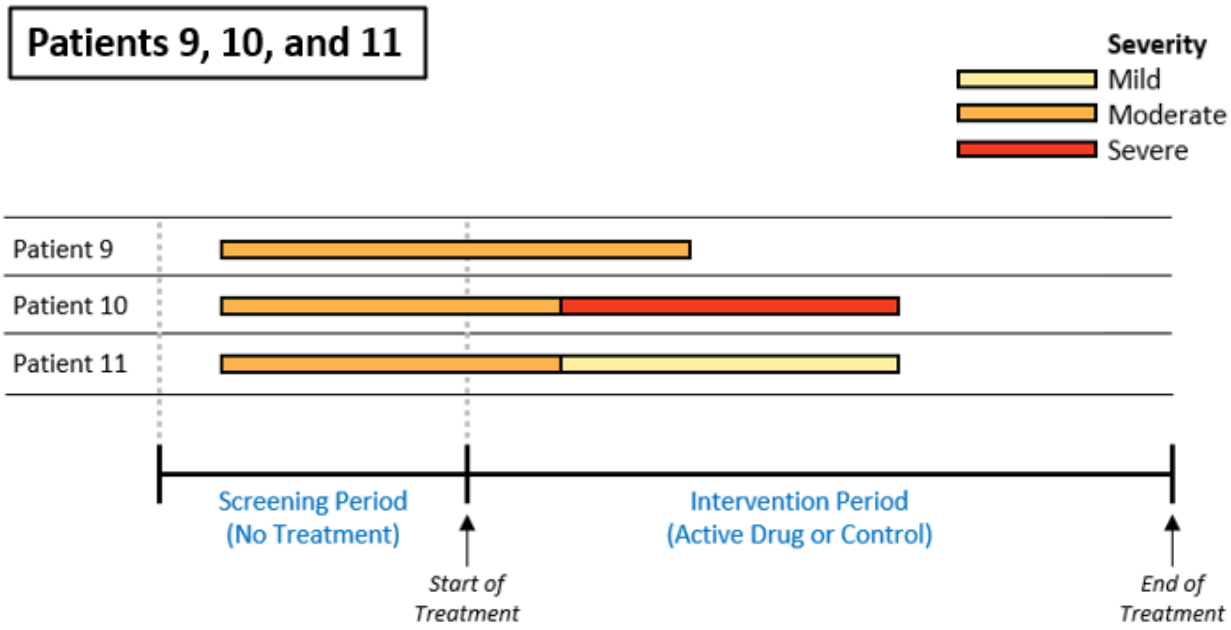


Patient	Recommendation for Intervention Period Summary Table	Rationale for Recommendation
Patient 6	TEAE[a]	While the survey was intended to elicit opinions assuming the event was the same, the reality is that most AE collection systems do not include a way to distinguish whether these are recurrences of the same event or different events. Therefore, for an event that starts before the start of treatment and ends after the start of treatment, and an event with the same or similar description starts later, we believe it is more appropriate to consider the later event as a new event.
Patient 7	TEAE[b]	
Patient 8	TEAE[a]	

[a] Difficult to gain complete alignment on recommendation within project team.

[b] Complete alignment on recommendation within project team.

Scenario 4: When an event starts before the start of treatment and ends after the start of treatment:

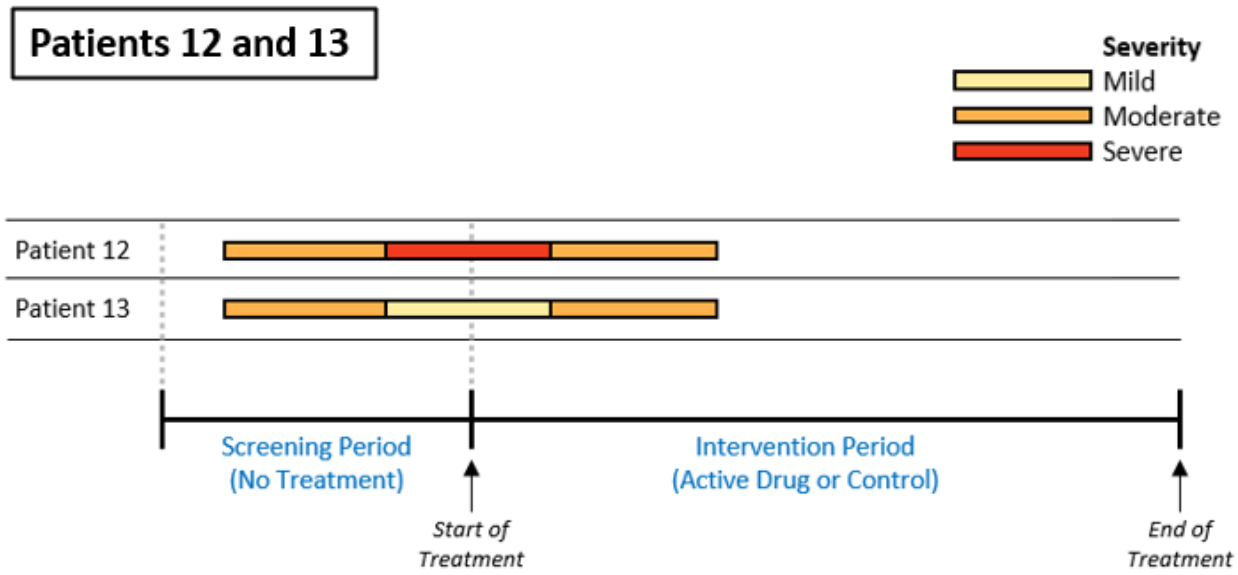


Patient	Recommendation for Intervention Period Summary Table	Rationale for Recommendation
Patient 9	Not TEAE[a]	The severity did not increase after the start of treatment.
Patient 10	TEAE[a]	The severity increased after the start of treatment.
Patient 11	Not TEAE[b]	The severity did not increase after the start of treatment.

[a] Complete alignment on recommendation within project team.

[b] Complete alignment on recommendation within project team. If AE collection guidelines require a separate database entry for the decrease in event severity, then programming instructions need to be clear that this record should not be a TEAE.

Scenario 5: When an event starts before the start of treatment, changes severity, and ends after the start of treatment:



Patient	Recommendation for Intervention Period Summary Table	Rationale for Recommendation
Patient 12	Not TEAE[a]	The severity did not increase after the start of treatment.
Patient 13	TEAE[b]	The severity increased after the start of treatment.

[a] Complete alignment on recommendation within project team.

[b] Difficult to gain complete alignment on recommendation within project team.

Summary

If stakeholders can align on the definition and application of treatment-emergent events, this will enable greater consistency in the understanding of safety profiles and promote improved exchangeability across drug classes, therapeutic indications, and safety organizations. To that end, we provide this summary of our recommendations:

For an event that ends entirely before or entirely after the start of treatment:

- Screening events should not be treatment-emergent.

- Events starting after the start of treatment should be treatment-emergent.

For an event that starts before the start of treatment and ends before or after the start of treatment, and an event with the same or similar description occurs later:

- Events starting after the start of treatment, irrespective of event severity or the presence of the same event during screening, should be treatment-emergent.
- The stop date of the screening event should have no impact on the treatment-emergent determination.

For an event that starts before the start of treatment and ends after the start of treatment:

- Events that increase in severity after the start of treatment should be treatment-emergent.
- Events that remain at the same severity or lessen in severity after the start of treatment should not be treatment-emergent.

Proposed TEAE definition:

A TEAE is an adverse event that starts or worsens in severity during a pre-defined treatment period(s).

The start time for the treatment period is typically the date/time of the first dose of treatment. The end time of the treatment period can vary depending on the study design, half-life of the investigational product, introduction of rescue medication, etc. [1]. In some cases, multiple ways of defining the end time are warranted (for example, using both on-treatment and treatment policy approaches) [9].

The treatment-emergent definition and the associated definition(s) for the treatment period(s) should be well-documented in key documents (e.g. Protocols, Statistical Analysis Plans, Program Safety Analysis Plans, and Aggregate Safety Analysis Plans) and consistently implemented across a drug development program as appropriate.

We believe the treatment-period definition(s) could be study-, molecule-, or indication-specific and is best defined separately from the treatment-emergent definition (see Section 10.7 in [1]). Further, the treatment-period definition depends on the analysis purpose, e.g. on-treatment analysis vs on-study analysis, where the timeframe will vary based on the safety question being addressed.

7: Disclaimer:

The opinions expressed in this document are those of the authors. They should not be construed to

represent the opinions of PHUSE members, respective companies/organizations, or the Regulator's views or policies. The content in this document should not be interpreted as a data standard and/or information required by Regulatory Authorities.

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10: References:

[1] PHUSE (2017). Analysis and displays associated with adverse events: Focus on adverse events in phase 2-4 clinical trials and integrated summary documents. Available from: https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Standard+Analyses+and+Code+Sharing/Analyses+and+Displays+Associated+with+Adverse+Events+Focus+on+Adverse+Events+in+Phase+2-4+Clinical+Trials+and+Integrated+Summary.pdf

[2] Palo W, Davis T, Haddad J (2023). Final results from a TEAE scenario survey by the PHUSE treatment emergence definition project team. Presented at PHUSE Computational Science Symposium. Available from: https://phuse.s3.eu-central-1.amazonaws.com/Archive/2023/CSS/US/Silver%20Spring/POS_PP09.pdf

[3] International Conference on Harmonization (1998). ICH topic E9 statistical principles for clinical trials. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf

[4] US Food and Drug Administration Center for Drug Evaluation and Research (2005). Conducting a clinical safety review of a new product application and preparing a report of the review. Available from: https://fda.report/media/71665/Conducting-a-Clinical-Safety-Review-of-a-New-Product-Application-and-Preparing-a-Report-on-the-Review.pdf

[5] US Food and Drug Administration (2021). FDA Oncology Center of Excellence (OCE) / Office of Oncologic Drugs (OOD) standard safety data requests v1.3. Available from: https://www.fda.gov/media/133252/download

[6] PHUSE (2021). Analysis and displays associated with safety topics of interest: Focus on phase II to IV clinical trials and integrated summary documents. Available from: https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Safety+Analytics/Analysis+and+Displays+Associated+with+Safety+Topics+of+Interest-+Focus+on+Phase+II+to+IV+Clinical+Trials.pdf

[7] PHUSE (2024). Adverse event collection recommendations. Available from: xxxx

[8] PHUSE (2020). Adverse event collection and treatment emergent. Available from: https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Safety+Analytics/Adverse+Event+Collection+and+Treatment+Emergence.pdf

[9] Duke Margolis-FDA Workshop: Advancing Premarket Safety Analytics (2022). Available from: https://healthpolicy.duke.edu/events/advancing-premarket-safety-analytics

11: Appendices:

Appendix 1: Survey Results for Treatment Emergent Scenarios

Background

Potential respondents were solicited through PHUSE communication channels and co-author networks to participate in the survey to gather their input on various TEAE scenarios. The survey was developed and implemented via SurveyMonkey, and responses were collected during two periods (August to September 2021 and November 2021 to February 2022) to gather input from as wide an array of respondents as possible.

Instructions

The following instructions were included in the survey:

Thank you for taking the time to complete this survey. Your input will help us to better harmonize industry practices.

*Please review each patient's event scenario and indicate whether **you think** the patient has a TEAE for an intervention period summary table. A TE definition will not be provided since we will use the survey results to inform our TE definition for this study design.*

Consider the following while completing the survey:

Study design:

- *This is a basic, two-period, two-treatment study*
- *Screening period*
  - *Patients undergo typical study screening assessments and receive no study treatment*
- *Intervention period*
  - *Patients receive a single study treatment (either active drug or control)*
  - *Patients take their study treatment throughout the entire period as planned per the protocol and there are no dosing modifications during this period*
  - *Patients complete the study once this period is over and there is no safety follow-up period afterwards*

Adverse events:

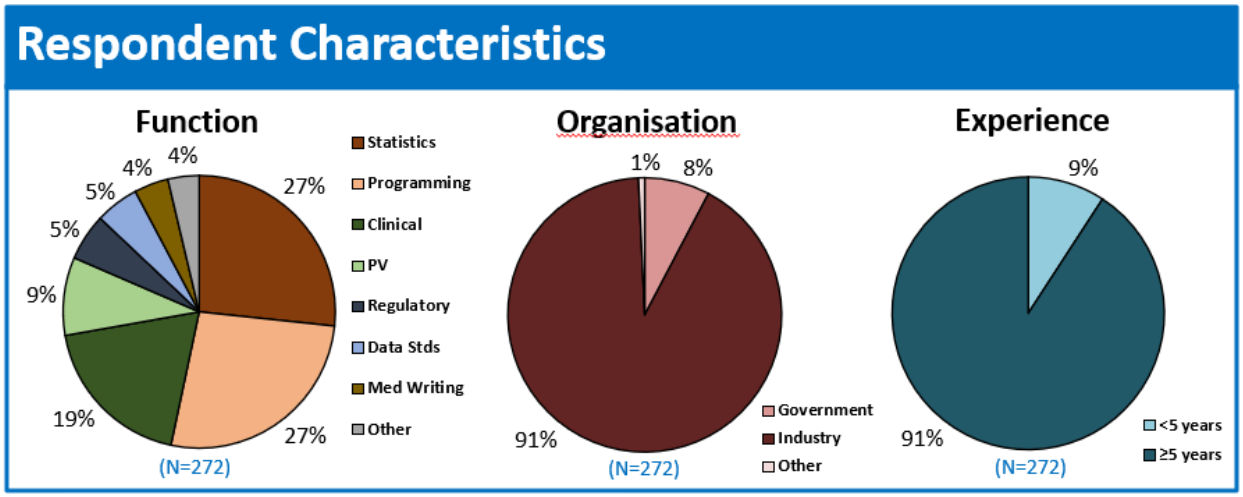
- *Each scenario represents the reported adverse event(s) for a single patient, with color coding signifying the event severity*
- *The onset, recurrence, and severity of the events can vary over time, however, changes in drug relatedness or regulatory seriousness (e.g. from non-serious to serious and vice versa) are out of scope*
- *Everything is known about the events (e.g. each event has a start and stop date and severity is always known across time)*
- *Each event is the same medical concept, and it occurs continuously from start to stop*
- *Please do not consider how you currently collect AE data at your organization; just focus on whether you think the patient has a TEAE or not.*

Respondent Characteristics

A total of 273 respondents answered at least 1 survey question. Respondent characteristics are provided in Figure 1 and illustrate that slightly over half of respondents were statisticians or statistical programmers, about a quarter were from clinical or pharmacovigilance functions, and the remaining

were from other functions. Nearly all respondents were from industry and nearly all had at least 5 years of experience.

Figure 1: Respondent Characteristics



Results by Treatment Emergent Scenario

The response to the survey scenarios was high (Figure 2), as all respondents provided input to all but 4 of the 13 scenarios. The scenarios with missing responses were skipped by 1 respondent each.

Respondents were asked to review each patient scenario and indicate whether they thought the patient had a TEAE for an intervention period summary table. Analysis of their responses revealed the following:

<u>For an event that ends entirely before or entirely after the start of treatment (Patients 1 and 2)</u>:

- There was near unanimous agreement (>99%) that screening events were not treatment-emergent (Patient 1).
- There was near unanimous agreement (>99%) that events starting after the start of treatment were treatment-emergent (Patient 2).

<u>For an event that starts before the start of treatment and ends before or after the start of treatment, and an event with the same or similar description occurs later (Patients 3 through 8)</u>:

- Approximately 2/3 of respondents (63-70%) agreed that an event recurring at the same or lower severity than screening was treatment-emergent, while approximately 1/3 decided these events were not treatment-emergent (Patients 3, 5, 6, and 8). Clearly there was discordance in

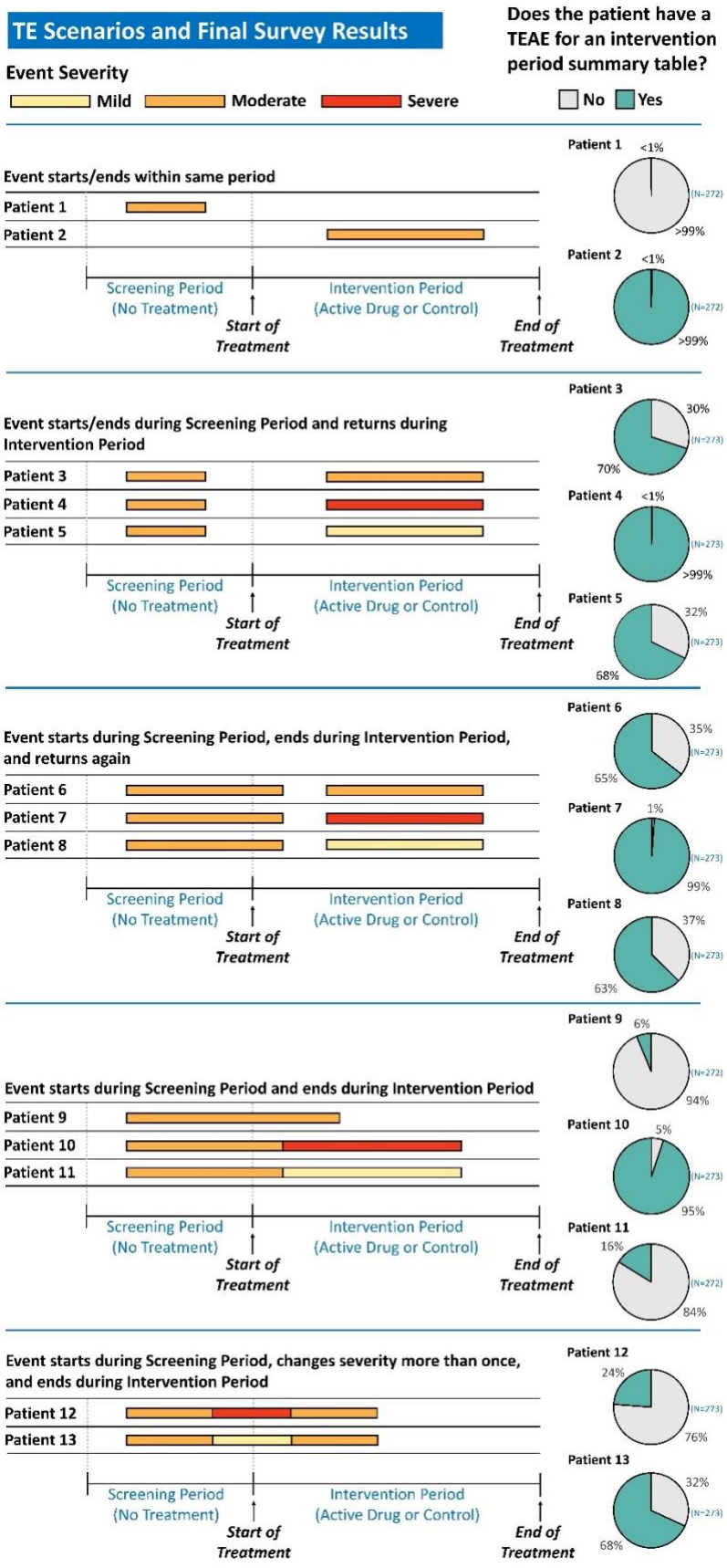
responses for these scenarios.

- There was near unanimous agreement (≥99%) that an event recurring at a higher severity than screening was treatment-emergent (Patients 4 and 7).
- The consistency in the results across these 6 scenarios when the event severity is the same (i.e., Patient 3 vs. 6, Patient 4 vs. 7, and Patient 5 vs. 8) indicates that the stop date of the screening event did not influence the treatment-emergent determinations.

<u>For an event that starts before the start of treatment and ends after the start of treatment (Patients 9 through 13)</u>:

- There was near unanimous agreement (94%) that screening events that continue after the start of treatment and maintain the same severity were not treatment-emergent (Patient 9).
- There was near unanimous agreement (95%) that screening events that continue after the start of treatment then increase in severity were treatment-emergent (Patient 10).
- A high percentage of respondents (84%) agree that screening events that continue after the start of treatment then decrease in severity were not treatment-emergent (Patient 11).
- The scenarios for Patients 9, 10, and 11 are similar to Patients 3 and 6, 4 and 7, and 5 and 8, respectively, with regards to the event severity profile. The difference between the scenarios is whether there is a time gap between the events.
    - The results highlight that the presence of a time gap mattered to respondents if the severity stayed the same or decreased after the start of treatment; they were more likely to define these events as treatment-emergent in the presence of a gap (for example, 70% for Patient 3 and 65% for Patient 6 (gap present), but only 6% for Patient 9 (no gap)).
    - Similar trends were noted if the severity decreased after the start of treatment: 68% for Patient 5 and 63% for Patient 8 (gap present), but only 16% for Patient 11 (no gap).
    - The presence of a time gap between events had little effect on the treatment-emergent determination when the severity increased after the start of treatment, as nearly all respondents considered these scenarios as treatment-emergent: Patient 4 (>99%) and Patient 7 (99%; gap present) vs. Patient 10 (95%; no gap).
- The scenarios for Patients 12 and 13 are more complex given the severity changes during screening and after the start of treatment. Approximately 3/4 of respondents (76%) determined Patient 12 was not treatment-emergent, while a similar percentage (68%) defined Patient 13 as treatment-emergent.

Figure 2: Results by Scenario

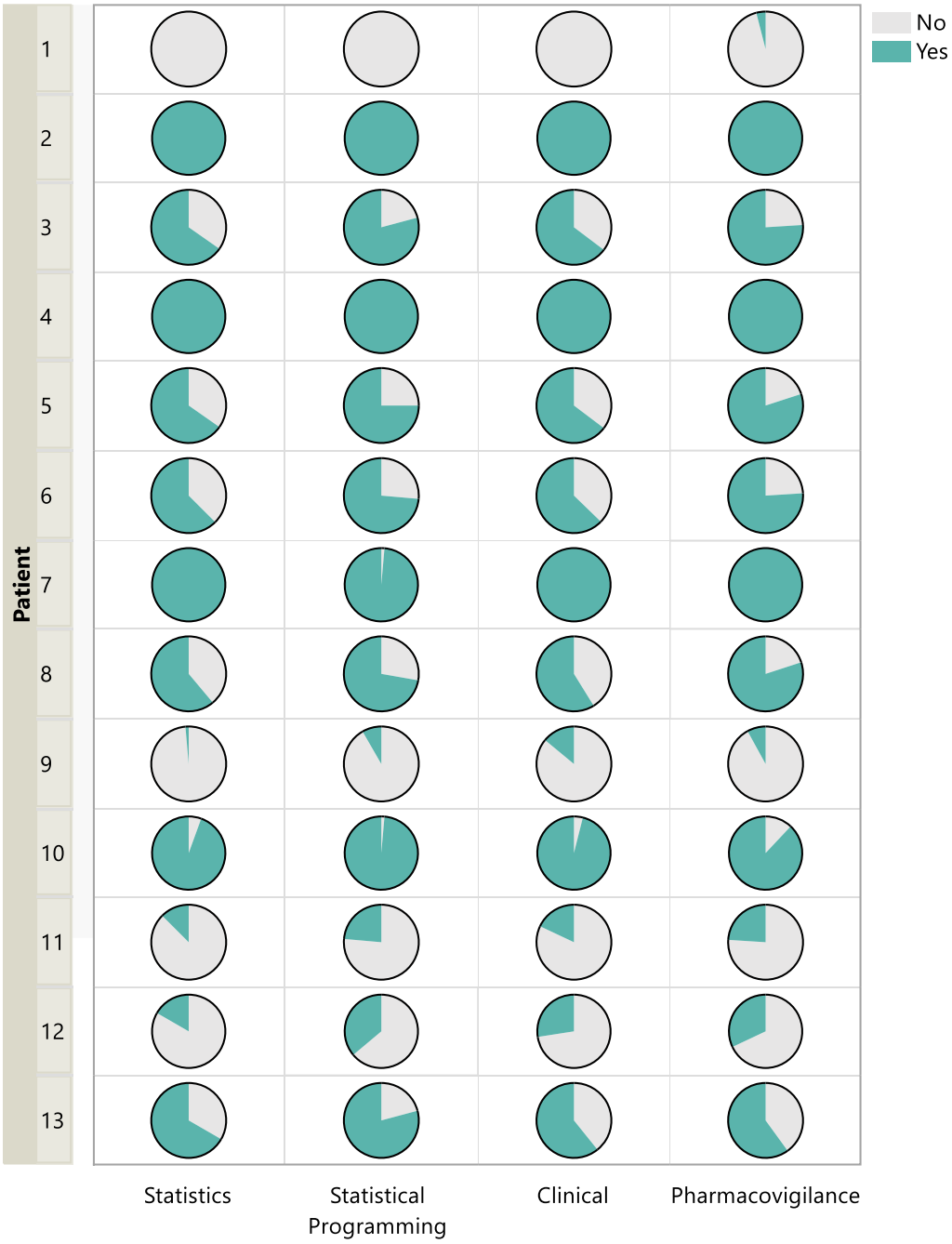

TE Scenarios and Final Survey Results
Event Severity
Mild
Moderate
Severe
Does the patient have a TEAE for an intervention period summary table?
No
Yes
Event starts/ends within same period
Patient 1
Patient 2
Screening Period (No Treatment)
Intervention Period (Active Drug or Control)
Start of Treatment
End of Treatment
Patient 1 <1% >99% (N=272)
Patient 2 <1% >99% (N=272)
Event starts/ends during Screening Period and returns during Intervention Period
Patient 3
Patient 4
Patient 5
Patient 3 30% 70% (N=273)
Patient 4 <1% >99% (N=273)
Patient 5 32% 68% (N=273)
Event starts during Screening Period, ends during Intervention Period, and returns again
Patient 6
Patient 7
Patient 8
Patient 6 35% 65% (N=273)
Patient 7 1% 99% (N=273)
Patient 8 37% 63% (N=273)
Event starts during Screening Period and ends during Intervention Period
Patient 9
Patient 10
Patient 11
Patient 9 6% 94% (N=272)
Patient 10 5% 95% (N=273)
Patient 11 16% 84% (N=272)
Event starts during Screening Period, changes severity more than once, and ends during Intervention Period
Patient 12
Patient 13
Patient 12 24% 76% (N=273)
Patient 13 32% 68% (N=273)

Note: Slight changes have been made to the survey scenario wording in the above visual compared to the white paper text. The intent of the survey was unchanged with these edits.

Results by Treatment Emergent Scenario and Respondent Characteristics

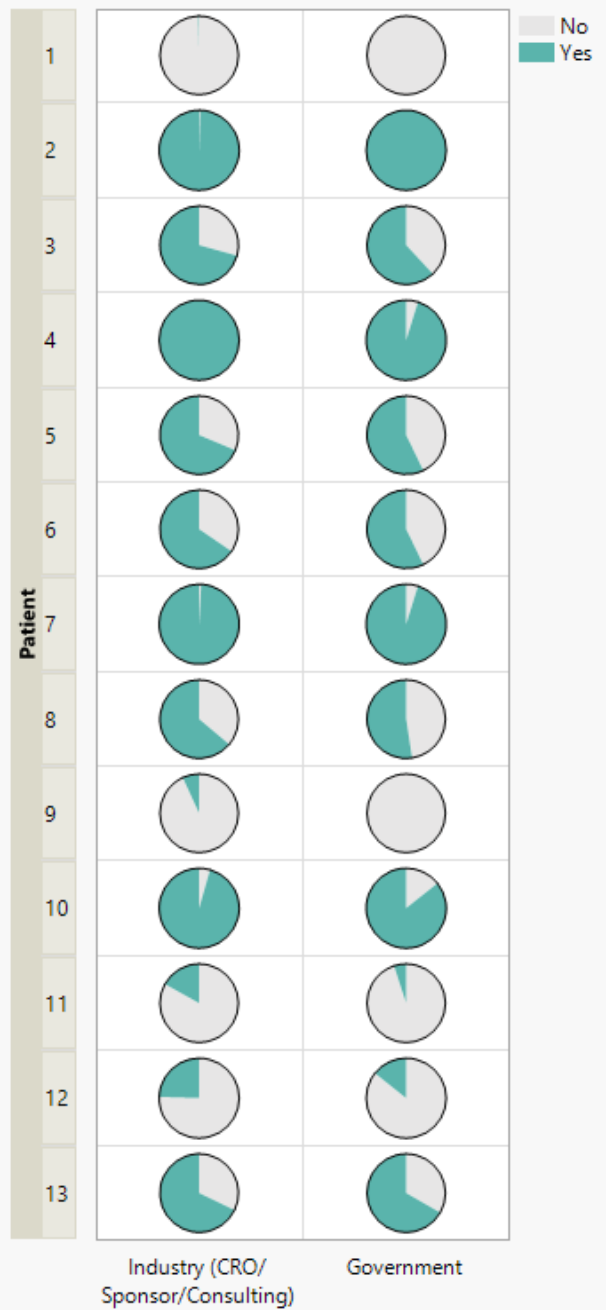
No meaningful differences were noted in responses when accounting for functional areas (Figure 3), organisational areas (Figure 4), or years of experience (Figure 5), as the results were generally consistent across the subgroups in each scenario.

Figure 3: Results by Functional Area



Note: The shaded areas represent the percentage for each response category. The number of respondents across the scenarios was 72 for Statistics, 72 for Statistical Programming, 51 for Clinical, and 25 for Pharmacovigilance. Results for other functional areas are excluded due to small sample sizes.

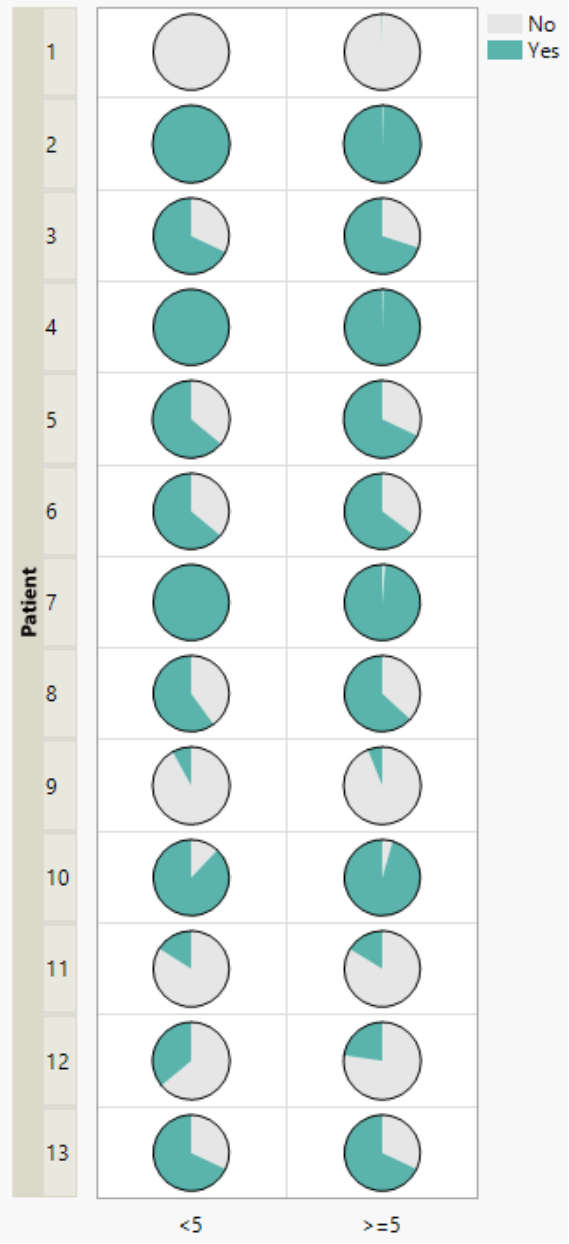
Figure 4: Results by Organisational Area



Note: The shaded areas represent the percentage for each response category. The number of

respondents across the scenarios was 249 for Industry and 21 for Government. Results for other organizational areas are excluded due to small sample sizes.

Figure 5: Results by Years of Experience



Note: The shaded areas represent the percentage for each response category. The number of respondents across the scenarios was 25 for respondents with <5 years of experience and 247 for respondents with ≥5 years of experience.