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Subject-Level, Dose-Stratified Swimmer Plots for Comparative Adverse Event Time-Course Assessment in Clinical Trials Using SAS® PROC TEMPLATE

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ABSTRACT

Background: Subject-level adverse event (AE) data are critical for clinical safety assessment in new drug applications. However, standard summary tables and listings provide limited visibility into AE time course, including onset, duration, recurrence, and resolution(etc.), and can hinder intuitive comparisons between active treatment and control arms.

Methods: We describe a reproducible swimmer-plot methodology implemented with SAS® ODS Graphics using PROC TEMPLATE to visualize AE trajectories at the individual participant level while incorporating treatment arm and dose exposure. Each participant is represented by a horizontal timeline spanning their treatment duration, with grouping by placebo and dose-stratified treatment cohorts. AE episodes are displayed as time-stamped intervals, allowing the representation of multiple occurrences per participant. Event-level attributes (e.g., severity grade, seriousness, duration, resolution status) can be encoded with symbols, line properties, and annotations to support clear clinical interpretation.

Results: The resulting displays facilitate rapid review of a specific AE event and the heterogeneity across participants and enable visual assessment of arm- and dose-related patterns in timing (early vs. late onset), persistence (short-lived vs. prolonged), recurrence, and outcome (discontinuation vs. ongoing). This subject-level perspective complements conventional outputs and supports efficient safety signal evaluation and clear communication in clinical and regulatory review.

Conclusion: Patient-level, dose-aware swimmer plots generated with PROC TEMPLATE provide a robust, publication-quality visualization approach that enhances comparative AE time-course assessment for new drug development and regulatory approval submissions.

Keywords: subject-level data; adverse events; treatment comparison; swimmer plot; PROC TEMPLATE

INTRODUCTION

Understanding the trajectory of adverse events (AEs)including their time to onset, duration, and longitudinal patterns—is essential for accurately characterizing a drug’s safety profile throughout clinical development and in new drug applications (NDAs). Time-course evaluation helps identify whether AEs occur early, late, cumulatively, or intermittently, an aspect that is increasingly recognized as a major gap in traditional AE reporting systems, which focus primarily on frequency and grade rather than temporal dynamics. Francis et al. (2025) highlight that conventional AE tables systematically underestimate chronic and persistent toxicities because they fail to capture timing, duration, and trajectory, which are crucial for understanding the real-world tolerability of modern therapies administered over extended periods. Studying AE trajectories also helps distinguish drug-related toxicities from background disease manifestations or placebo effects, supporting more accurate causality assessment —particularly important for immune-mediated or cumulative toxicities, where onset may be delayed or progressive. Moreover, temporal analysis informs dose selection and optimization, as increasing AE incidence or severity over time may signal exposure-related toxicity requiring dose adjustment or modified treatment schedules. FDA safety assessment frameworks emphasize that understanding how toxicities evolve over time is fundamental to designing appropriate monitoring schedules, anticipating risk periods, and evaluating the reversibility or persistence of AEs, all of which influence clinical decision-making and regulatory assessment. Duration and timing also significantly affect patient burden and the likelihood of treatment discontinuation, even when AEs are low-grade; Zhang et al. (2024) underscore that persistent symptomatic AEs may meaningfully impact adherence, emphasizing the need for duration-based analysis rather than severity alone. For NDAs, regulators increasingly require safety evaluations incorporating temporal trends to support benefit–risk conclusions, identify high-risk periods in different populations (e.g., pediatric vs. adult), and develop evidence-based risk-mitigation strategies and product labeling. Thus, incorporating AE trajectory analysis is not only scientifically necessary but also operationally essential for modern drug development.

Traditional summary AE tables and listings provide only static counts and severity grades, which obscure the timing, duration, and longitudinal trajectory of adverse events. As Francis et al. (2025) emphasize, conventional tabular reporting fails to capture when AEs begin, how long they persist, or whether they worsen or recur, leading to systematic underestimation of cumulative and chronic toxicity in modern therapies. Similarly, Zhang et al. (2024) highlight that AE duration—not just frequency—significantly affects patient burden and treatment discontinuation, yet this information is not captured in traditional listings. FDA safety assessment guidance further notes that understanding temporal patterns is essential for accurate tolerability assessment, risk mitigation, and regulatory decision-making, none of which can be adequately supported by tables alone. Consequently, graphical displays, such as swimmer plots or AE trajectory figures, are increasingly required to vividly illustrate the time course of AEs at the subject level.

Visualization of adverse event (AE) trajectories at the subject level helps reviewers understand onset, duration, recurrence, and resolution patterns that are not readily apparent from aggregate tables. Swimmer plots—horizontal timelines for each subject with overlays for events—are widely used in oncology and safety reviews. Leveraging SAS® Graph Template Language (GTL) in PROC TEMPLATE offers fine-grained control, layered composition, and publication-quality output without heavy reliance on annotations. This paper focuses on a safety use case involving a specific adverse event, vomiting, and illustrates a GTL-based approach to render treatment exposure, follow-up, and multiple AE episodes with clear legends and encodings.

DATA AND METHODS

We assume that CDISC ADaM structures: ADSL (subject-level) and ADAE (adverse events) provide the needed information to produce the swimmer plot for presentation by the sponsor or other stakeholders, such as follow-up duration, duration of each AE episode, the start and end days for each AE episode.

In this paper, we created a dummy dataset in Excel format. For simplicity, the dataset includes three arms, placebo, low-dose and high-dose groups, and only three subjects in each treatment group as Table 1 showed. The dataset contains the subject ID, duration of follow-up in days, relative study day for each AE episode along with episode duration, the subject's end of study status, etc., as listed in Table 1. Further information, such as the severity of each episode and whether the AE resolved or required additional treatment, can be derived based on sponsor requirements.

Table 1: variables in dummy data

Variable in the dummy data	SAS Variable Format	label
SUBJID	$CHAR20	Subject ID
TR1GRP1	$CHAR20	Treatment group
FUDSRT	Numeric 8.	Follow-up start relative day
FUDDAY	Numeric 8.	Follow-up end relative day
START1	Numeric 8	AE start relative day
END1	Numeric 8	AE End relative day
AEDUR	Numeric 8	AE episode duration in days
EOSSTT	$CHAR20	End of treatment subject status

Tracy, et al (2024) detailed how to use PROC SGPLOT to construct interactive HTML swimmer plots that delineate patient trajectories across diverse studies, such as adverse events and efficacy endpoints. Here Proc template is applied using HIGHLOWPLOT to draw horizontal bands for follow-up and episode spans, and SCATTERPLOT layers for start/end markers as mentioned by Huang et al. (2016). The data are reshaped to index repeated AE episodes per subject (e.g., start1–start3, end1–end3). Legends are composed of discretelegend/keylegend, and design choices (bar width, line patterns, caps) follow prior recommendations to improve readability and consistency across pages. In this implementation, we use the highcap statement to show the status of each subject in the clinical trials, for example, a FilledArrow symbol is used for the status of "Ongoing", and no symbol for "Completed" and "Discontinued". A portion of the sample code is shown below.

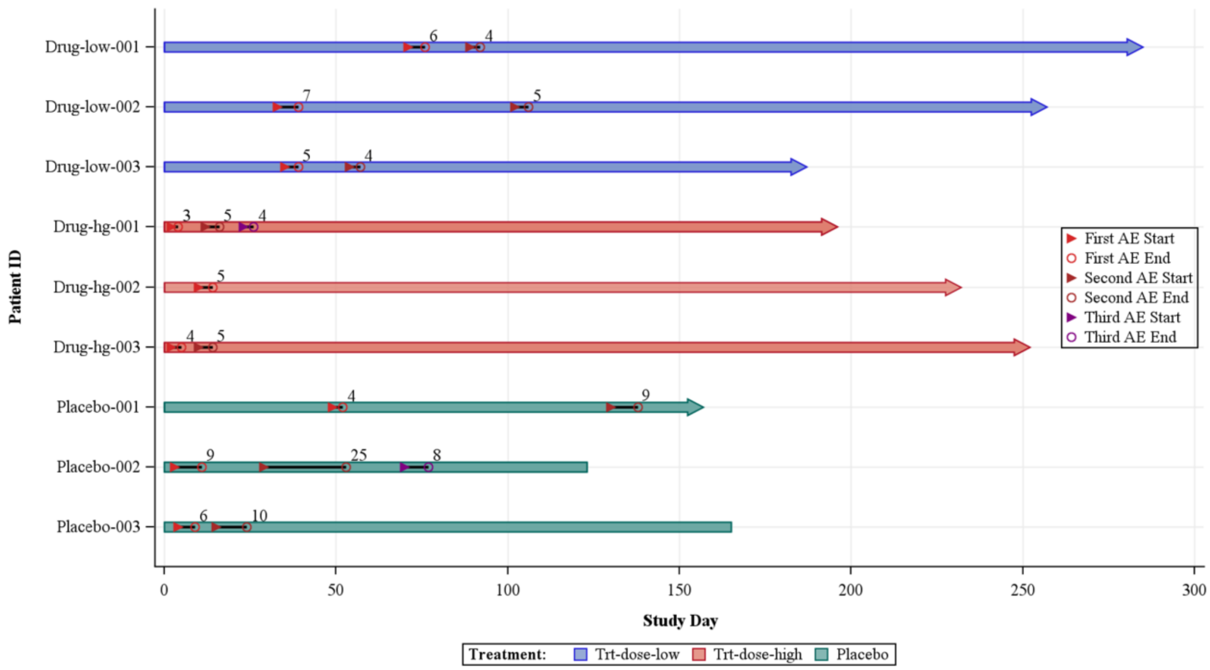
```
Part of sampel codes
proc template;
      define statgraph swimmer;
      dynamic xlabel ylabel maxdur;
      begingraph / designwidth=9in designheight=6in attrpriority=color;
       layout overlay / walldisplay=none
                    xaxisopts=(griddisplay=on
                          linearopts=(includeranges=(0-300) viewmin=0 viewmax=300)
                          display=(line ticks tickvalues label) label=xlabel)
                    yaxisopts=(griddisplay=on reverse=true
                          display=(line ticks tickvalues label) label=ylabel);
  /* Follow-up band */
 highlowplot y=subjid2 low=fudsrt high=fudday /group=tr1grp1 type=bar
      barwidth=0.95 lineattrs=(thickness=5) highcap=highcap name='followup';

  /* AE duration */
 highlowplot y=subjid2 low=astdy high=aendty /group=tr1grp1 type=line
   lineattrs=(color=black thickness=2) name='ae_span';

  /* Episode markers */
 scatterplot x=start1 y=subjid2 / markerattrs=(symbol=trianglefilled size=7
   color=blue) name='start1' legendlabel='First AE Start';

 scatterplot x=end1   y=subjid2 / markerattrs=(symbol=circle size=7 color=blue)
   datalabel=aedur datalabelposition=top name='end1' legendlabel='First AE End';

 /* Add a legend inside the graph */
             discretelegend "low_marker" "high_marker" "First AE Start" "First AE End"
     "Second AE Start" "Second AE End" "Third AE Start" "Third AE End" /
                    across=1
                    location=inside valign=center halign=right
                    titleattrs=(size=10 weight=bold)
                    valueattrs=(size=9);

             /* Outside Legend */
             discretelegend "followup_band"  /
                    location=outside valign=bottom halign=center
                    title="Treatment: "
                    titleattrs=(weight=bold);

             endlayout;
      endgraph;
      end;
run;
```

RESULTS

The swimmer plot displays per-subject follow-up with arrows for ongoing status and superimposed AE episodes labeled by duration. Visual inspection supports rapid identification of early versus late onset, recurrence patterns, and whether episodes resolved before the end of follow-up, as well as differences in AE episodes across placebo and treatment arms. The technique also scales multidose settings through the use of color grouping based on dose levels.

From the sample Figure 1, with a brief review, we can easily derive three impressions. (1) adverse events occur in both the placebo and treatment groups; (2) within the treatment groups, AE episodes occur earlier in the high-dose group than in the low-dose group; and (3) subjects in the placebo group appear more likely to discontinue treatment, which may suggest that they do not perceive sufficient benefit and therefore choose not to remain in the trial.

Figure 1: Swimmer plot: vomiting episode



DISCUSSION

Compared with conventional tables, swimmer plots highlight heterogeneity across subjects and dose cohorts. The GTL route allows: (1) clear visualization of the time course of a specific AE for safety review; (2) clear identification of AE episode differences within and across groups, providing reviewers with insights to seek additional information or conduct further analyses; (3) the status of a subject with a specific AE, as mentioned by Almond (2019). Practical refinements such as buffer offsets for caps/markers and bar width tuning improve aesthetics without misrepresenting clinical meaning when transparently documented. Extensions include encoding severity grade or seriousness with shapes/colors and splitting treatment versus follow-up segments with distinct patterns. Additional summary tables for AE frequency, event counts, or incidence rates may also complement the visualization.

CONCLUSION

Using PROC TEMPLATE with GTL, we present a reproducible method to create dose-aware swimmer plots for safety events such as "Vomiting." The approach is compatible with standard ADaM inputs and yields publication-quality figures suitable for professional journal publications and regulatory submissions.

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CONTACT INFORMATION <HEADING 1>

Your comments and questions are valued and encouraged. Source dummy data and sample code will be provided upon request. Contact the author at:

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