Paper ET12

Interactive Visualization of Pooled Clinical Trial Safety Data

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Abstract

Pooling safety data in clinical trials is essential not only for regulatory submissions but also for ongoing safety assessments. Interactive visualizations of pooled data are particularly valuable for graphically reviewing key elements such as baseline demographic characteristics, treatment exposure, adverse events (AEs), Serious AEs (SAEs), AEs of special interest (AESIs), and other clinical safety measures. Visualizing pooled data already submitted to health authorities offers the added benefit of assessing safety signals in label-specific populations, with options to filter by specific studies and patients.

An interactive web interface enhances the visualization of pooled clinical safety data and offers significant benefits such as being open source with a reproducible solution. The interactive platform allows data exploration and molecule-specific customizations. By improving the efficiency of data review and making safety insights readily accessible to both technical and non-technical stakeholders, this approach ultimately supports more informed, data-driven decision-making.

1. Introduction

Pooling safety data from clinical trials is a cornerstone of regulatory submissions and safety signal detection in drug development. By integrating datasets across diverse studies, stakeholders gain comprehensive insights into patient safety, treatment risks, and adverse events.

Interactive data visualization tools, such as those built on the Shiny framework, offer transformative potential for analyzing pooled safety data. This paper presents the development and implementation of an interactive visualization platform designed to streamline safety data review and enhance stakeholder engagement.

2. General

2.1 Data Pooling Approach

Clinical data from multiple clinical trials are pooled into the Integrated Clinical Safety Database (ICSD) that is molecule-specific. The studies included in the database were selected based on their relevance to molecule-specific populations as reference populations for the molecule's safety profile. The primary focus is usually on the safety-evaluable population, which includes all patients who have received at least one dose of study drug. Data curation and integration focuses on key variables, including demographic characteristics, treatment exposure, adverse events (AEs), serious adverse events (SAEs), molecule-specific AEs of special interest (AESIs), and other clinical safety outcomes. By harmonizing these data across studies, the platform ensures a comprehensive and cohesive view of safety metrics, supporting both exploratory analysis and safety signal detection.

2.2 Visualization Framework

The visualization platform was developed using the {teal} R-Shiny framework, an open-source tool designed for interactive and reproducible data exploration via web browser. The platform incorporates several key features to enhance usability and customization, such as molecule-specific adjustments, filtering options for studies and patients, and drill-down capabilities that allow users to explore granular details of the data. These features make the platform highly adaptable for diverse safety data review needs while ensuring that both technical and non-technical stakeholders can easily engage with the visualizations.

3. Results

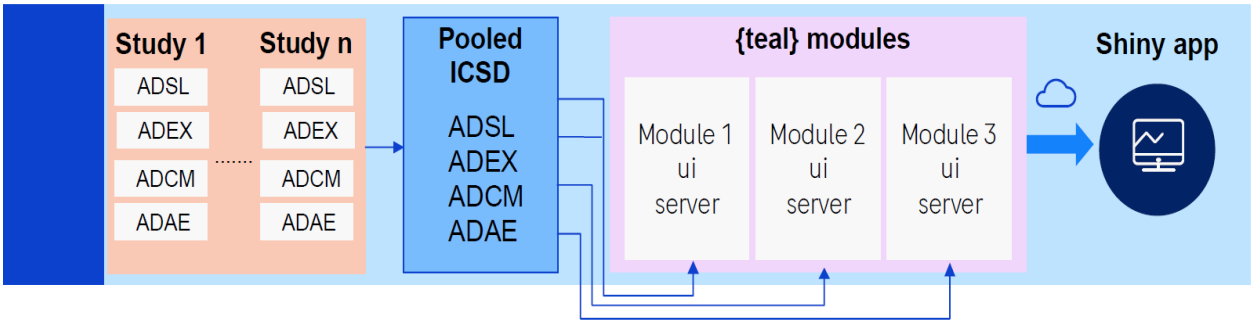
3.1 Platform Overview

The ICSD exploratory visualization tool supports safety data exploration with key features. The source data pooled from multiple studies follows Analysis Data Model (ADaM) structure. After study-level ADaM datasets are pooled into the ICSD database, the integrated population group variables are derived from ICSD. Specifically, the population could refer to the US Package Insert (USPI), Core Data Sheet (CDS), Summary of Product Characteristics (SmPC), or Risk Management Plan (RMP) pooled populations. These populations are regulatory-specific, tied to corresponding population sizes and spanning different studies.

Figure 1 illustrates the data flow, beginning with individual study-level ADaM datasets (ADSL, ADEX, ADCM, and ADAE) being consolidated into the Integrated Clinical Safety Database.

This pooled data serves as the foundation for the visualization framework. The {teal} modules, each incorporating the user interface (UI) and server components, process and integrate the data. The finalized pooled ICSD is then published as a web-based Shiny app on our internal servers, enabling interactive exploration of safety data. This structured workflow ensures an efficient, scalable, and user-friendly approach to safety data visualization.

Figure 1 Data Flow: From ADaM Datasets to Interactive Safety Database Visualization



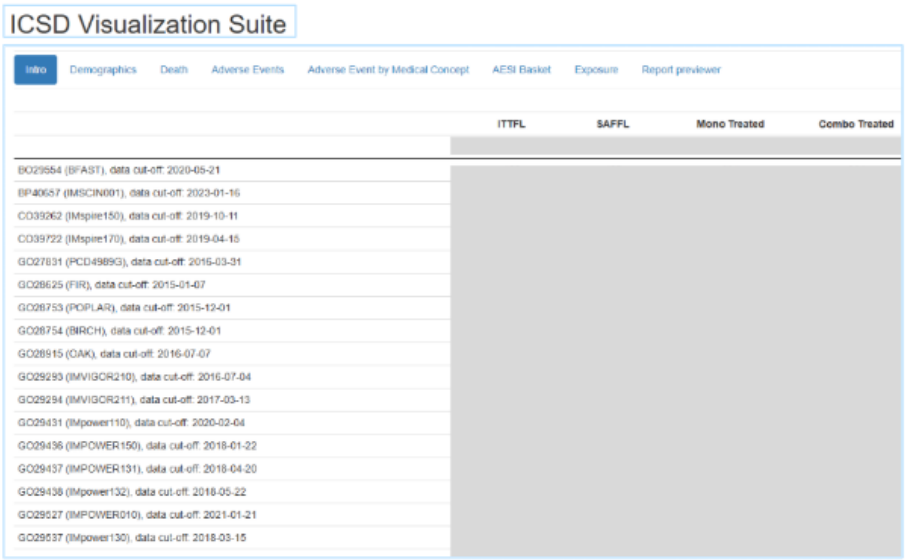
3.2 Key Visualizations

Figure 2 contains general information regarding the clinical trial(s) in the pooled visualization. Populations specified in the interactive visualization for this paper's illustration are defined as follows:

- **Molecule-Specific Monotherapy Population:** All safety-evaluable patients enrolled in the study who receive a single study drug.
- **Molecule-Specific Combination Therapy Population:** All safety-evaluable patients enrolled in the study who receive multiple drugs together to enhance efficacy.
- **Molecule- and Indication-Specific:** All safety-evaluable and grouped by tumor type indication

Figure 2 Introductory page listing the available clinical trials in the pool

List of studies and associated clinical cut-off dates of the studies included in the ICSD pool



The Filtering panel of the teal app restricts to the label-based populations or other characteristics in the pooled subject-level data in ADSL. The user's existing knowledge of label-specific populations is helpful for targeted analyses. Filtering enables the safety analyses of the pool to be "among" a particular subset - such as the SmPC Combination therapy population, the USPI population, etc.

For pooled analyses, the Encodings panel of the teal app drives the comparison of interest by selecting the "by variable" groupings. Comparators might be Study 1 vs. Study 2, or Combo Pool vs. Mono Pool, or multi-level indication by immunogenicity status, which is one of the presentation groupings used in the EU Risk Management Plan.

In Figure 3, the Demographics tab provides summarized variables that allow for rapid assessment of baseline characteristics and different disease characteristics.

Figure 3 Baseline Demographics

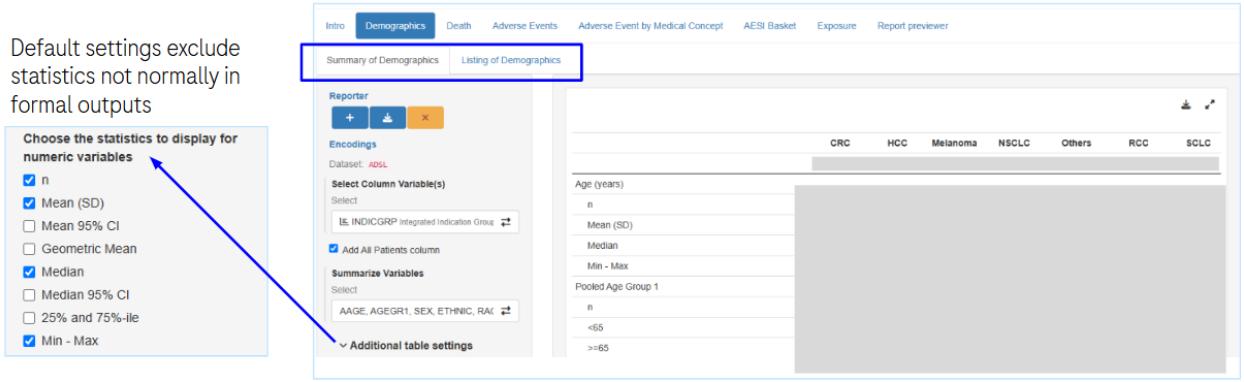


Figure 4 provides an example of the total number of doses administered and the overall treatment duration. The visualization can also incorporate dose intensity by filtering the relevant derived variables from the Exposure Analysis (ADEX) ADaM dataset.

Figure 4 Treatment Exposure

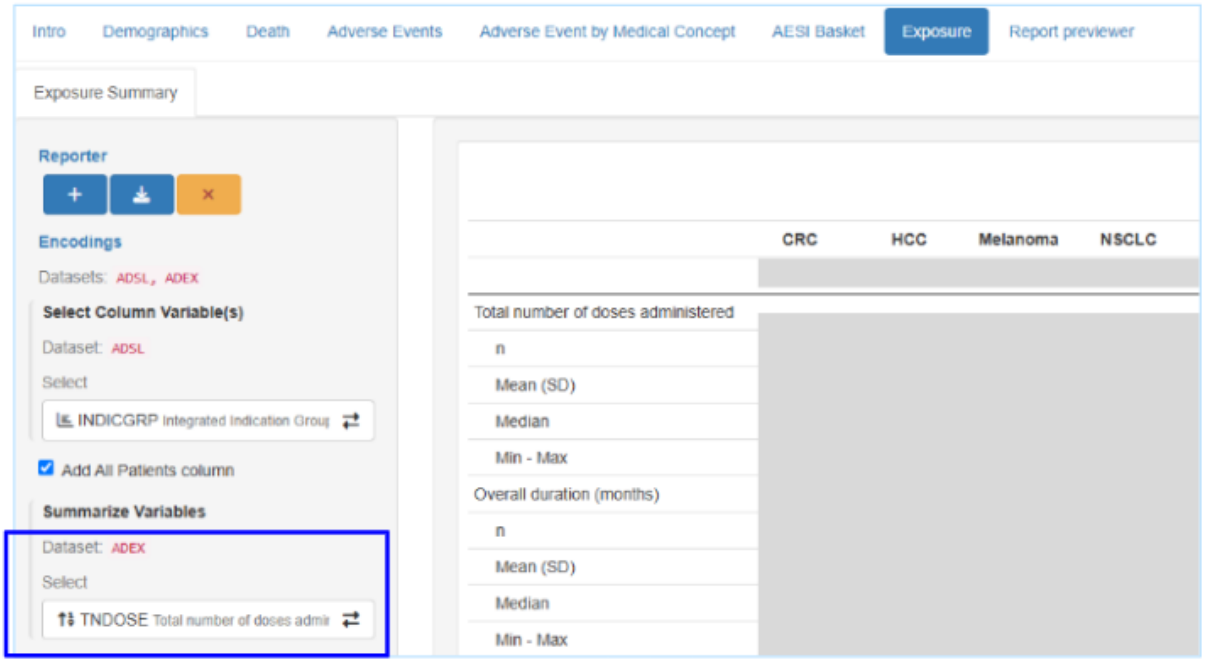
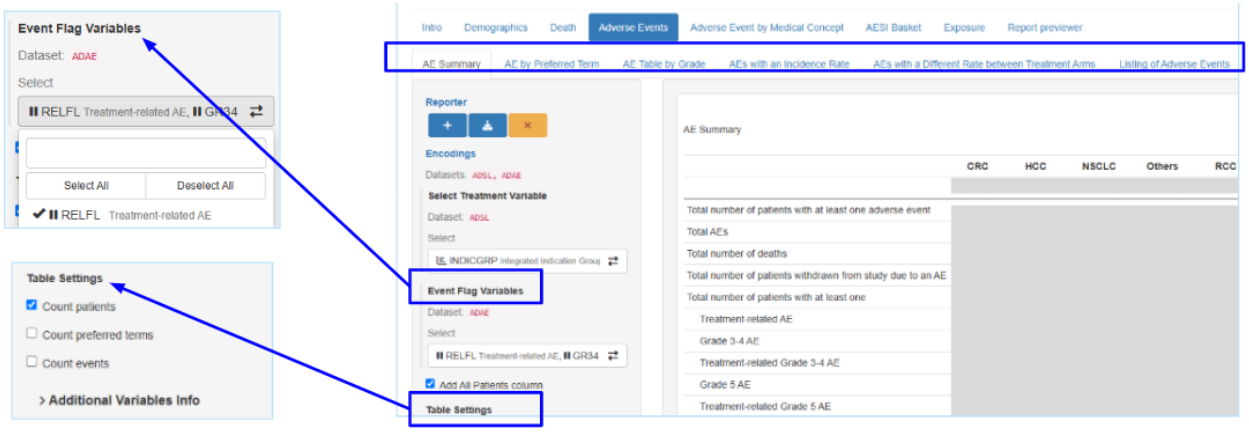


Figure 5 shows an overview of AEs. The visualizations are also presented by NCI CTCAE grades, incidence rate and preferred terms. By utilizing different filters, the table could be expanded to include SAEs, AEs leading to discontinuation, etc. All AE tables are restricted to treatment-emergent adverse events (TEAEs) as a default setting to ease stakeholder use and avoid discrepant tabulation approaches.

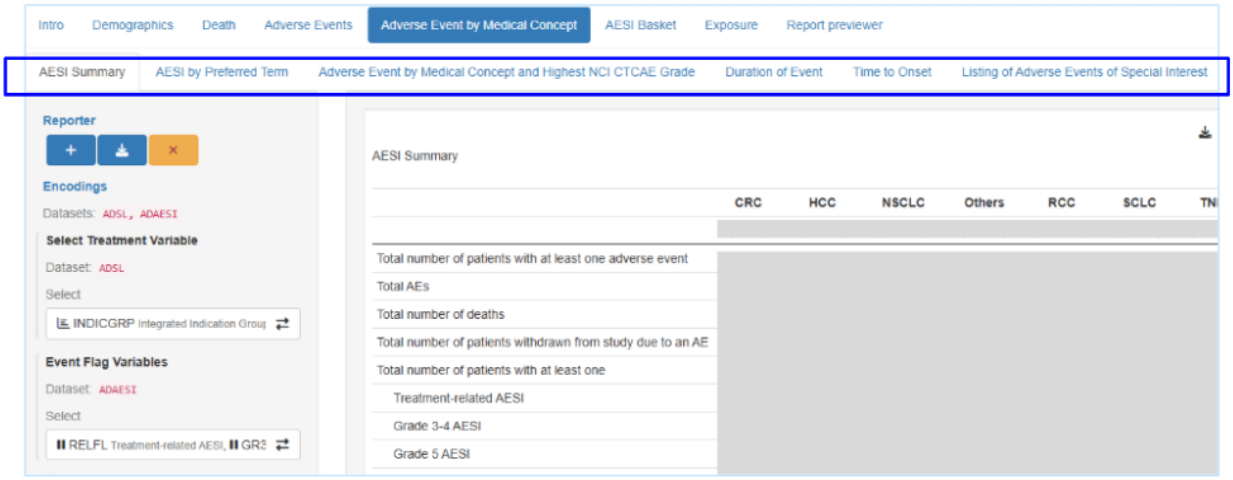
The MedDRA dictionary is updated biannually, with new versions released in March and September. Each update incorporates revisions to terms and hierarchical structures to align with the latest regulatory standards. This means the pooled safety visualization should use the latest version of MedDRA.

Figure 5 Adverse Events Analyses



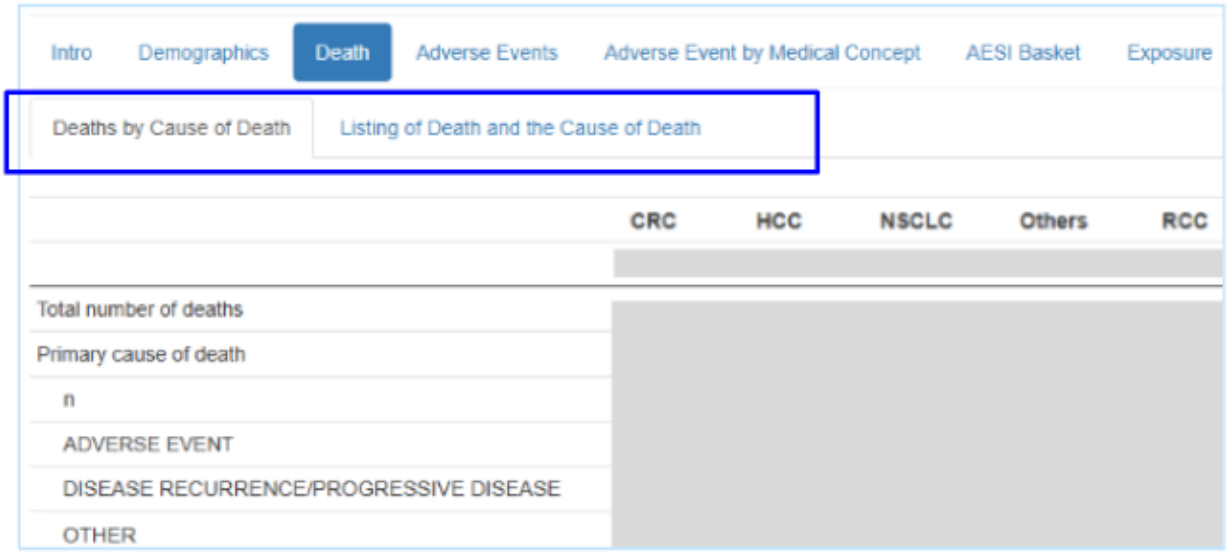
Protocol-specified AESIs are a critical component of safety profiles included in the pooled visualization. In addition to an overview of AESIs, the visualization also presents AESIs by NCI CTCAE grade, duration of AESIs, and time to first AESI onset.

Figure 6 AESIs



The Death Summary in Figure 7 shows an example of the total number of deaths and the primary cause of death. A detailed listing of deaths allows for drilling down to individual patient-level information.

Figure 7 Deaths



4. Discussion

The transition from static outputs to an interactive platform has significantly improved data accessibility and usability, fostering collaboration between technical data science

teams and broader stakeholders. However, certain limitations remain. With more studies being added for additional insights, there are maintenance needs required for the curation of pooled datasets. The semiannual MedDRA upversion offers timely insights of the reference populations of interest, but it also demands app re-deployment and add to the resourcing considerations. Regular updates, visualization refinements, and end-user training are necessary to ensure its continued effectiveness. Additionally, the tool is designed primarily for internal safety reviews and is not intended for direct regulatory submissions. There are also other comprehensive sources of safety data leveraged by Safety Scientists who are working on safety signal detection. Some of the overhead includes the ability to frame the visualization in the context of other available safety reporting tools. Looking ahead, future enhancements may focus on optimizing performance for handling large datasets, and expanding the visualization to cover more combination therapies and the inclusion of more dynamic pooling strategies in which a different pivotal study is included for comparison with an existing reference population. These improvements will further enhance the tool's efficiency and applicability in clinical safety assessments.

5. Conclusion

The ICSD visualization platform demonstrates the power of interactive tools in enhancing safety data review. By enabling molecule-specific customization and fostering accessibility for diverse stakeholders, this approach aligns with the broader goal of data-driven decision-making in clinical safety assessments. As the platform evolves, its foundational principles of transparency, reproducibility, and user-centered design will continue to guide its impact on the safety data landscape.

References

- Chendi Liao and Dony Unardi, TEAL: Enabling Comprehensive Interactive Data Analysis and Exploration in R with an Open Sourced Scalable Shiny Framework, PHUSE US Connect 2023. https://phuse.s3.eu-central-1.amazonaws.com/Archive/2023/Connect/US/Florida/PRE_OS15.pdf
- Teal: Interactive Exploratory Data Analysis with Shiny Web-Applications https://insightsengineering.github.io/teal/latest-tag/