Published in final edited form as:

Ther Innov Regul Sci. 2018 November ; 52(6): 696–700. doi:10.1177/2168479018754846.

The Safety Explorer Suite: Interactive Safety Monitoring for Clinical Trials

Jeremy Wildfire, MS¹, Ryan Bailey, MA¹, Rebecca Z. Krouse, MS¹, Spencer Childress, BS¹, Britt Sikora, MS¹, Nathan Bryant, BS¹, Shane Rosanbalm, MS¹, Emily Wilson, BS¹, and Jack G. Modell, MD¹

¹Rho, Chapel Hill, NC, USA

Abstract

Background—Frequent and thorough monitoring of patient safety is a requirement of clinical trials research. Safety data are traditionally reported in a tabular or listing format, which often translates into many pages of static displays. This poses the risk that clinically relevant signals will be obscured by the sheer volume of data reported. Interactive graphics enable the delivery of the vast scope of information found in traditional reports, but allow the user to interact with the charts in real time, focusing on signals of interest.

Methods—Clinical research staff, including biostatisticians, project managers, and a medical monitor were consulted to guide the development of a set of interactive data visualizations that enable key safety assessments for participants. The resulting “Safety Explorer” is a set of 6 interactive, web-based, open source tools designed to address the shortcomings of traditional, static reports for safety monitoring.

Results—The [Safety Explorer](#) is freely available on GitHub as individual JavaScript libraries: [Adverse Event Explorer](#), [Adverse Event Timelines](#), [Safety Histogram](#), [Safety Outlier Explorer](#), [Safety Results Over Time](#), and [Safety Shift Plot](#), or in a single combined framework: [Safety Explorer Suite](#). The suite can also be utilized through its R interface, the [safetyexploreR](#) package.

Conclusions—The Safety Explorer provides interactive charts that contain the same information available in standard displays, but the interactive interface allows for improved exploration of patterns and comparisons. Medical Monitors, Safety Review Boards, and Project Teams can use these tools to effectively track and analyze key safety variables and study endpoints.

Keywords

safety reporting; medical monitoring; interactive graphics; JavaScript; R

Corresponding author: Ryan Bailey, ORCID# 0000-0001-8223-5302, Rho, 6330 Quadrangle Drive, Chapel Hill, NC 27517; ryan_bailey@rhoworld.com; 919-408-8000.

Conflict of interest: The authors declare that they have no known conflicts related to the publication of this article.

Disclaimers: None

Introduction

Data visualizations and statistical graphics have a well-established history in the conduct of clinical trials, but traditional methods are focused on static displays of data. In recent years, web-based interactive graphics have increased in popularity and usage¹, including many innovative scientific data visualizations.^{2–4} The clinical research industry seems poised to tap into this trend, as companies like SAS[®] and Tableau now offer interactive online charting tools for clinical research and organizations such as PhUSE⁵ and CTSPedia⁶ encourage the application of innovative data visualization methods in clinical trials.

Statistical graphics are especially useful for safety oversight and risk-based monitoring.^{7–9} The appeal of these tools for clinical investigators comes from the need to constantly monitor data and quickly identify concerns while trials are in progress. Interactive monitoring tools offer a promising alternative to traditional reporting approaches, which are characterized by the tedious review of pages of text-based listings.^{7,10} Such methods are not merely inefficient, but also problematic, as the sheer volume of data reported threatens to obscure clinically relevant signals.

Interactive reports give researchers an intuitive and streamlined workflow for data analysis by combining a summary view of a given data domain with on-demand access to data listings for observations of special interest.¹¹ This approach can cover the broad scope of information found in traditional safety reports, while improving the signal-to-noise ratio and eliminating the need to sort through pages of static listings. Using these principals of interactive data visualization, we created the Safety Explorer, a set of open-source interactive graphics designed specifically for safety monitoring in clinical trials.

While other interactive data visualization tools for clinical research exist, they are generally packaged as add-ons to expensive clinical trial analytics environments and cannot be broadly shared or fully customized by the end-user (e.g., JMP[®] Clinical, SAS[®] Analytics, Tableau CLINTEL). The Safety Explorer suite is open source and freely available, so it can be implemented in any contemporary web browser with no specialized or proprietary software required.

Methods

Six interactive graphics were developed for the Safety Explorer suite: Adverse Event Explorer, Adverse Event Timelines, Safety Histogram, Safety Outlier Explorer, Safety Results Over Time, and Safety Shift Plot. Clinical project staff – principal investigators, medical monitors, biostatisticians, project managers, and data managers – were consulted to provide use cases and design feedback on the charts. The charts were created to monitor key safety metrics at both the population-wide and participant-specific level. This dual utility is necessary for effective safety monitoring, which tasks monitors with protecting the well-being of individual participants as well as assessing product or intervention safety among all trial participants.

All graphics were built in JavaScript using d3.js¹ and the Webcharts framework.¹² No other dependencies are required, so the charts can be easily implemented in a variety of web

environments and used in any modern web browser. The suite can also be utilized through its R interface with the `safetyexploreR` package, which implements the JavaScript libraries using the `htmlwidgets` framework.¹³ The resulting interactive graphics can be viewed in the RStudio viewer,¹⁴ embedded in an R Markdown document¹⁵ or Shiny application¹⁶, or output as a standalone webpage.

To encourage broad adoption of the tools, the data specifications were configured to match existing standards for common safety data domains. The charts use CDISC's Analysis Data Model (ADaM) standard¹⁷, which is the preferred, and soon to be mandated, standard for clinical data submission to the FDA.¹⁸ Since trials increasingly conform to CDISC standards, the Safety Explorer can be used on a broad set of studies with very little configuration required. However, while the Safety Explorer is designed around the ADaM standard, it is also designed to be adaptable; the charts can easily be configured to use other data conventions via simple run-time data mapping.

Results

The [Safety Explorer suite](#) consists of 6 custom interactive graphics and 2 helper libraries (Table 1). The 6 graphics libraries improve upon traditional static reports by adding simple user interface elements, including filters, dynamic searches, toggles for display options, and linked charts and listings. For example, the Adverse Event (AE) Explorer graphic provides group-level adverse event rates (Figure 1) while also allowing users to dynamically investigate adverse events data at a participant level (Figure 2). The adverse events table mirrors a familiar static AE summary^{19,20} when first initiated, showing AE rates categorized by system organ class and preferred term. Enhancements to the traditional report give the user the ability to drill down and examine details for comparisons of special interest. Interactive features include customizable filters and search capability, as well as the ability to select any row in order to display a detailed listing of the underlying raw data.

A second chart, the Safety Outlier Explorer, displays clinical results over time, allowing users to easily identify values that fall outside of expected ranges (Figure 3). An interactive control is provided to quickly display any measure of interest. Each line in the graph represents a single participant's results over the course of the study. Selecting an individual line generates a brief demographic overview of the participant along with a set of small charts showing the participant's results for all available measures and time points.

The 4 remaining charts consist of an AE timeline that provides a detailed participant-level view of AE activity and 3 additional views of key safety markers (i.e., Lab Results and Vital Signs). Fully functional examples are publicly [available online](#). The charts can be implemented individually or as a group using the `safety-explorer-suite` helper package or the `safetyexploreR` R package. In summary, the suite provides robust reporting capabilities for a typical longitudinal randomized clinical trial.

Discussion

Regardless of study phase or disease area, safety monitoring occurs during all stages of a clinical trial and must incorporate the principals of risk-based monitoring.²¹ For large or

complex trials, study monitors are charged with reviewing thousands of records, which are traditionally presented as many pages of tables or listings. Reporting this volume of data in text-based format across many different pages makes identifying clinically relevant signals difficult and time consuming. As such, the Safety Explorer is designed to be implemented at the beginning of a project and then used throughout the data pipeline.²² The simple design of the tools allows for frequent or real-time data updates across a variety of environments with minimal overhead, and its interactivity provides a powerful platform for exploratory data analysis with no specialized training required. Further, the *safetyexploreR* package enables R users to initiate the charts with a single line of R code, allowing analysts to use the tools as part of their standard workflow for data cleaning and data exploration.

Improving access to safety data and creating a streamlined workflow is a key step towards a robust risk-based monitoring plan, but, like any change to the traditional clinical trial workflow, it also creates new challenges. As with any standardized reporting tool, the Safety Explorer works best when the underlying data sets are stable, which can be a challenge early in clinical trials when analysis data sets may not be ready for use and case report form changes are more common. Further, the validation and regulatory framework differs for static statistical listings (typically, double programming) to interactive software (21 CFR Part 11).²³

Two key areas for further technical development of these tools are performance improvements for very large data sets, and incorporating more options for statistical testing. By running the current version of the Safety Explorer entirely through the web-browser, performance is determined by the end user's computing environment and options for statistical testing are limited. Both of these constraints could be mitigated by supporting server-side processing and statistical calculations; however, these efforts should be balanced against the need to maintain the generalizability and ease of use of the tools.

Following an open source development paradigm distinguishes the Safety Explorer from many comparable data visualization tools, which are proprietary and require the purchase of a license. Not only is Safety Explorer freely available, the source code is public and available for users to customize and enhance. We anticipate that clinical research software will increasingly move toward open source tools, driven by the ideals of transparency, public good, and open sharing, which are prevalent among the scientific and web development communities. Clinical trial research groups such as PhUSE and CTSPedia primarily focus on tools built using traditional statistical programming languages, but are open to other types of applications, and may serve as important forums for interactive, open source tools as they become more common. In the future, open software platforms like Apple Health Kit and Open mHealth²⁴ may improve the accessibility of data visualization tools for clinical trials operations and safety monitoring. However, given the current lack of open source options in the clinical trials domain, the Safety Explorer suite fills a void in this area.

Conclusions

We have used the Safety Explorer to support several clinical trials, and it has proven to be a valuable tool. Our web-based implementation makes deployment and use of the tools

simple. In addition, we ensure transparency, customizability and reproducibility by developing, documenting and updating the tools in a fully open manner and releasing them under the permissive MIT license. Full technical specifications, data guidelines, user requirements and more examples for all are available on the project's [home page](#) and all code is hosted on [GitHub](#).

Acknowledgments

None

Grant support: National Institute of Allergy and Infectious Diseases; Division of Allergy, Immunology, and Transplantation; Statistical and Clinical Coordinating Center; #UM2AI117870

References

1. Bostock MO. Vadm; Heer, Jeffrey D3 Data-Driven Documents. *IEEE Transactions on Visualization and Computer Graphics*. 2011; 17(12):2301–2309. [PubMed: 22034350]
2. Broman KW. R/qtlcharts: interactive graphics for quantitative trait locus mapping. *bioRxiv*. 2014
3. *Degust: RNA-seq exploration, analysis and visualisation* [computer program]. Version 3.1.02017
4. Su S, Law CW, Ah-Cann C, Asselin-Labat M-L, Blewitt M, Ritchie M. Glimma: interactive graphics for gene expression analysis. *bioRxiv*. 2017
5. PhUSE. Data Visualisations for Clinical Data. 2017. http://www.phusewiki.org/wiki/index.php?title=Data_Visualisations_for_Clinical_Data. Accessed December 8, 2017
6. Soukup M. FDA/Industry/Academia Safety Graphic Working Group Charter. 2011. <http://www.ctspedia.org/do/view/CTSpedia/SafetyGraphicsCharter>. Accessed December 8, 2017
7. Cooper C. Use of New Tools for Safety Analysis. 2017. <https://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm118818.pdf>. Accessed August 16, 2017
8. Herson J. Data and Safety Monitoring Committees in Clinical Trials. 2nd ed. New York: Chapman and Hall/CRC; 2016.
9. Zink RC. Risk-Based Monitoring and Fraud Detection in Clinical Trials Using JMP® and SAS®. SAS Institute; 2014.
10. O'Connell MPK. Interactive Clinical Data Review for Safety Assessment and Trial Operations Management. Paper presented at: PhUSE 2010 Conference Proceedings 2010; Berlin, Germany.
11. Shneiderman B. The eyes have it: A tasy by data type taxonomy for information visualizations. Paper presented at: Proceedings 1996 IEEE Symposium on Visual Languages 1996; Boulder, CO.
12. Bryant NW, Jeremy. Webcharts - A Web-based Charting Library for Custom Interactive Data Visualization. *Journal of Open Research Software*. 2016; 4(1)
13. *htmlwidgets: HTML Widgets for R* [computer program]. Version 0.92017
14. RStudio: Integrated Development for R [computer program]. Boston, MA: RStudio, Inc.; 2016.
15. rmarkdown: Dynamic Documents for R [computer program]. Version 1.62017
16. shiny: Web Application Framework for R [computer program]. Version 1.0.42017
17. CDISC. Analysis Data Model (AdAM). 2017. <https://www.cdisc.org/standards/foundational/adam>. Accessed August 16, 2017
18. Study Data Technical Conformance Guide. US Food and Drug Administration. 2017
19. Amit O, Heiberger RM, Lane PW. Graphical approaches to the analysis of safety data from clinical trials. *Pharmaceutical Statistics*. 2008; 7(1):20–35. [PubMed: 17323410]
20. Harrell FE. Principles of Graph Construction. Vanderbilt University School of Medicine, Department of Biostatistics; 2014. <http://biostat.mc.vanderbilt.edu/wiki/pub/Main/StatGraphCourse/graphscourse.pdf>. Accessed August 16, 2017
21. NIH Policy for Data and Safety Monitoring. National Institutes of Health. 1998.
22. Leek JTP, Roger D. Statistics: P values are just the tip of the iceberg. *Nature News*. 2015; 520(7549):612.

23. Electronic Records. Electronic Signatures. 1997; 21(pt. 11) CFR.
24. Estrin D, Sim I. Open mHealth Architecture: An Engine for Health Care Innovation. *Science*. 2010; 330(6005):759–760. [PubMed: 21051617]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Human Subjects

This article does not contain any studies with human or animal subjects performed by any of the authors.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.

Adverse Event Explorer: Summary View - The primary view of the Adverse Event Explorer shows the data ordered by prevalence from highest to lowest. The System Organ Class designation and nested Preferred Term are displayed in the Category column, with corresponding event rates for each of the 3 Groups (Placebo, Treatment A, Treatment B) and an aggregate Total in adjacent columns. The AE Rate by group column is a simple dot plot providing a quick visual display of differences between the groups. The Difference Between Groups column displays the magnitude of difference between each binary comparison of the Groups (e.g., Placebo vs. Treatment A, Placebo vs. Treatment B, Treatment A vs. Treatment B are each represented). Users can use the controls above the chart to dynamically transform the data in real time, including: filtering by prevalence, searching for terms of interest, and filtering by other criteria of interest (e.g., severity, outcome, site, treatment group, demographics).

[Return to the Summary View](#)

Details for 5 Stomach pain (Gastrointestinal disorders) records

ID	Site	Age	Sex	Race/Ethnicity	Treatment Arm	System Organ Class	Preferred Term	Start Day	End Day	Serious?	Severe?	Related to Treatment?	Outcome
01-0231		48	M	Black	Treatment A	Gastrointestinal disorders	Stomach pain	220	276	N	MILD	UNLIKELY RELATED	RESOLVED, RECOVERED
03-0253		53	F	Black	Treatment B	Gastrointestinal disorders	Stomach pain	293	342	N	SEVERE	PROBABLY RELATED	RECOVERED
04-0094		39	F	Hispanic	Placebo	Gastrointestinal disorders	Stomach pain	27	47	N	SEVERE	DEFINITELY RELATED	RESOLVED WITHOUT SEQUELAE
05-0235		49	M	Hispanic	Treatment A	Gastrointestinal disorders	Stomach pain	277	283	N	MILD	PROBABLY RELATED	RESOLVED WITH SEQUELAE
05-0305		23	F	Hispanic	Treatment A	Gastrointestinal disorders	Stomach pain	347	365	Y	MODERATE	POSSIBLY RELATED	RESOLVED, RECOVERED

Figure 2.

Adverse Event Explorer: Details View - Users can select a System Organ Class or Preferred Term from the Category column in the Summary View (Figure 1) and access this detailed event-level view for the corresponding adverse events. This allows users to instantly toggle between summary data and participant-level data.

Figure 3.

Outlier Explorer - This chart presents data for individual participants for a given measure across the various collection points in a trial (e.g., repeated lab tests). Each line in the chart represents a unique participant, allowing users to track changes over time and survey population-level trends. Selecting an individual participant's line toggles on a view of the other measures for that participant, providing a quick summary snapshot of all an individual's measures at one time. The "small multiple" charts of other measures also include shaded normal ranges to help the user see when values fall outside of the expected limits. Controls above the chart allow the user to change which measure is displayed and to change which values are displayed on the x-axis (e.g., study day vs. visit number.)

Table 1

Components of Safety Explorer Suite

Repository	Description	Links
aetable	Interactive graphic giving an overview of adverse event (AE) rates by group	Repository Documentation Example
ae-timeline	Interactive graphic showing the timeline of participant AEs	Repository Documentation Example
safety-outlier-explorer	Interactive graphic showing patterns of participant-level longitudinal safety markers.	Repository Documentation Example
safety-results-over-time	Interactive graphic showing population trends in longitudinal safety results.	Repository Documentation Example
safety-histogram	Interactive graphic showing the distribution of safety markers.	Repository Documentation Example
safety-shift-plot	Interactive graphic showing participant-level trends for longitudinal safety markers.	Repository Documentation Example
safety-explorer-suite	Helper library implementing all 6 graphics on a single page.	Repository Documentation Example
safetyexploreR	Helper library implementing all 6 graphics in R using htmlwidgets and Shiny.	Repository Documentation Example