ASA Biopharmaceutical Section

Safety Working Group Quarterly Scientific Webinar

Interactive Adverse Event (AE) Volcano Plot for Monitoring Clinical Trial Safety

Speaker: Spencer Childress (Sr Manager of Biostatistics, Gilead Sciences)

Renal Explorer: Interactive Graphic for Exploring Kidney Function Data in Clinical Trials

Speakers: Preston Burns (Principal Data Scientist, Sarepta Therapeutics)
James Buchanan (President, Covilance LLC)

Interactive Safety Profile Shiny Application for Monitoring Clinical Trial Safety

Speaker: Natalia Andriychuk (Statistical Data Scientist, Pfizer)

Discussion

Discussants : Cynthia McShea (Senior Director, UCB Biosciences)
James Buchanan (President, Covilance LLC)

Interactive Safety Graphics Taskforce

ASA Biopharmaceutical Section

WS1: Interdisciplinary Safety Evaluation

Interactive safety graphics (ISG)

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Dilip Nalla
Richard Anziano

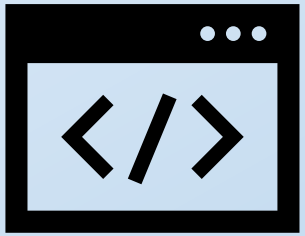
https://community.amstat.org/biop/workinggroups/safety-home

ISG Guiding Principles

https://safetygraphics.github.io/

Open Source

Highly Collaborative

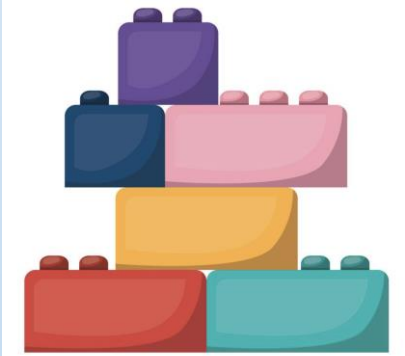


Interactive

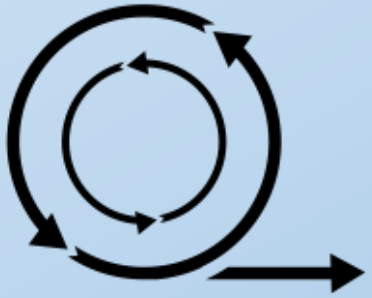
Easy to use

cdisc

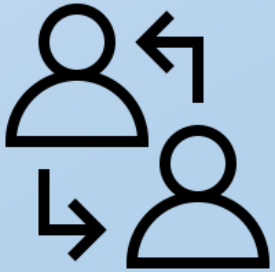
Data Standard Compliant



Extensible Data Model



Agile



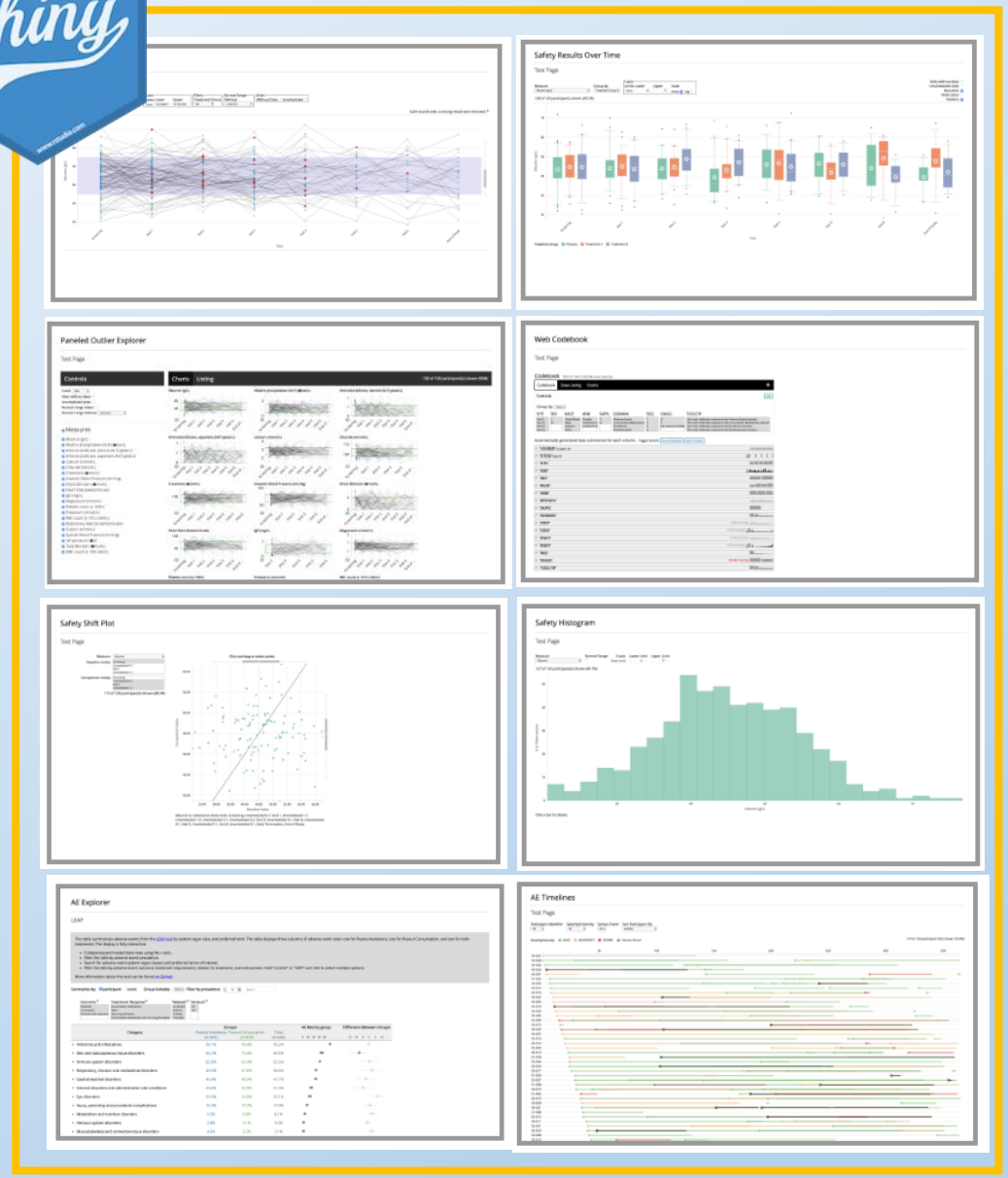
Engaging

Study Data

Chart Specs

Data + Chart Mappings

Web Application

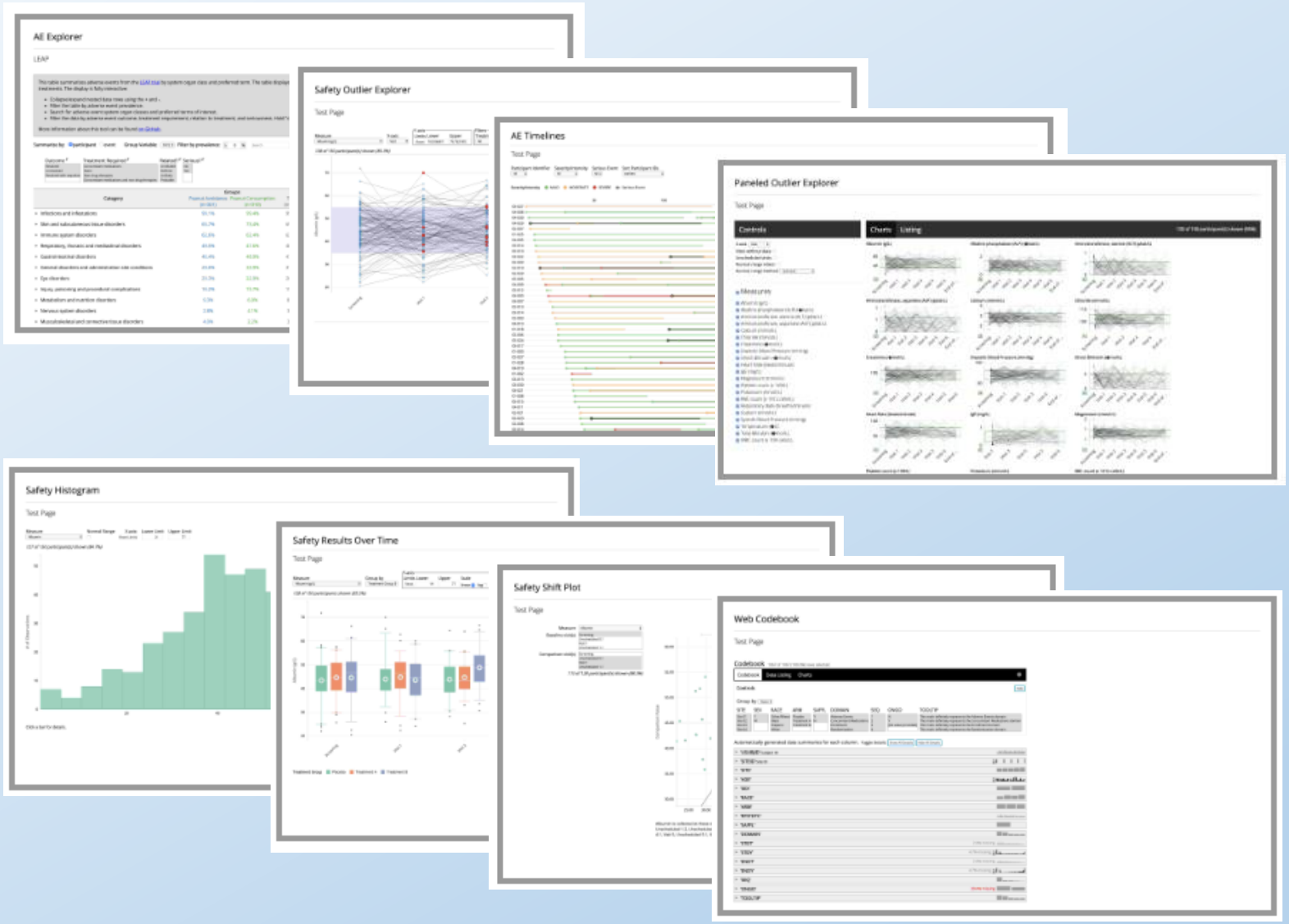


Stand-alone Reports

Chart Code

Application Code

Safety Explorer Suite



DIA

Original Research

Therapeutic Innovation & Regulatory Science
1-5

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The Safety Explorer Suite: Interactive Safety Monitoring for Clinical Trials

Jeremy Wildfire, MS[1], Ryan Bailey, MA[1], Rebecca Z. Krouse, MS[1], Spencer Childress, BS[1], Britt Sikora, MS[1], Nathan Bryant, BS[1], Shane Rosanbalm, MS[1], Emily Wilson, BS[1], and Jack G. Modell, MD[1]

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

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 usage,[1] 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 PhUSE[5] and CTSPedia[6] 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 principles 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

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Email: ryan_bailey@rhoworld.com

Hepatic Safety Explorer

↓ Raw Data

Messages (2) Clear

Caution: This graphic has been thoroughly tested, but is not validated.

Caution: 9 rows were removed.

Filters

254 of 254 participants shown.

Treatment
- Placebo
- Xanomeline High Dose
- Xanomeline Low Dose

Sex
- F
- M

Race
- AMERICAN INDIAN OR ALASKA
- BLACK OR AFRICAN AMERICA
- WHITE

Age group
- 65-80
- <65
- >80

R Ratio Range

Filter points based on R ratio [(ALT/ULN) / (ALP/ULN)]

0 - 4.4 Reset

Settings

Group

Grouping variable

TRTA

Display Type

Relative or absolute axes

Upper limit of normal adjusted (

Plot Style

Max Values ◉ By Study Day ○

X-axis Measure

Alanine Aminotransferase (U/L)

Alanine Aminotransferase (U/L) Reference Line

X-axis Reference Line

3

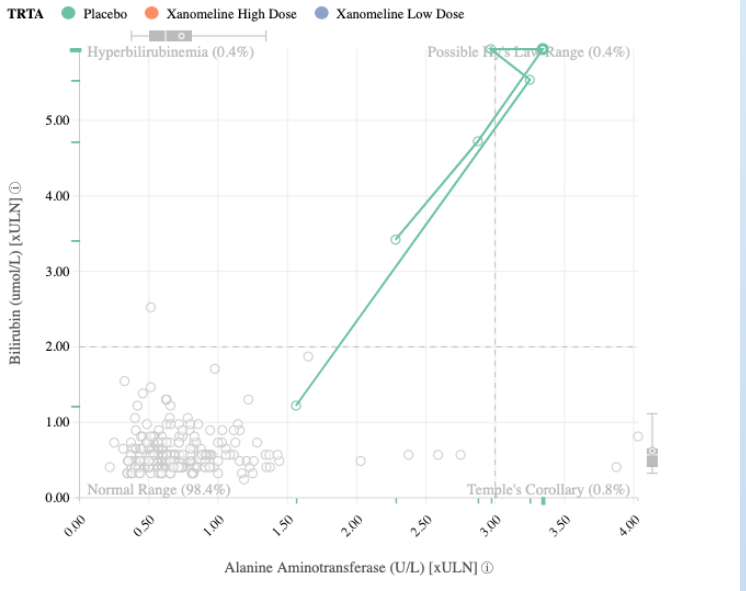
Bilirubin (umol/L) Reference Line

Y-axis Reference Line

2

Point Size

Parameter to set point radius



Use controls to update chart or click a point to see participant details.
Points where maximum Alanine Aminotransferase (U/L) and Bilirubin (umol/L) values were collected within 30 days are filled, others are empty.

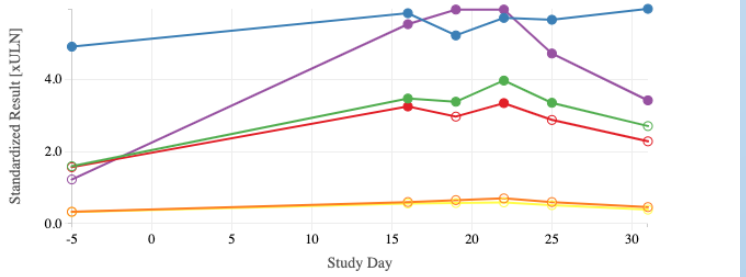
Participant Details

Subject Identifier	Treatment	Sex	Race	Age group	R Ratio
01-705-1186	Placebo	F	WHITE	>80	0.59

Standardized Lab Values by Study Day

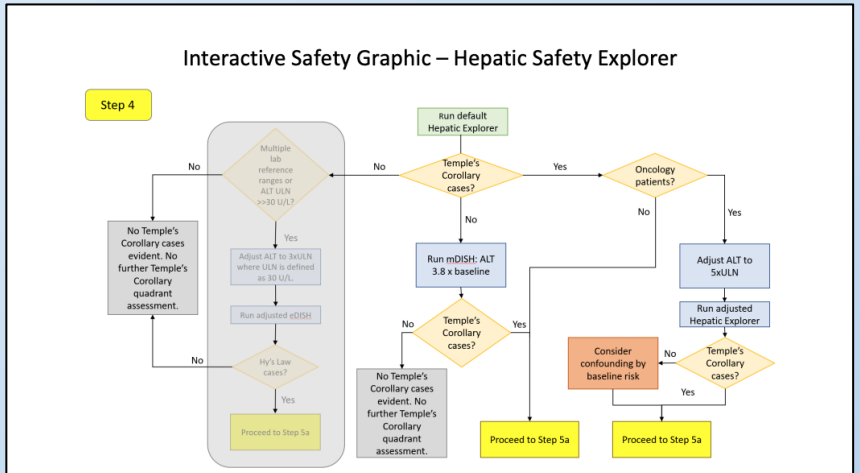
Select Labs
- Alanine Aminotransferase (U/L)
- Alkaline Phosphatase (U/L)
- Aspartate Aminotransferase (U/L)
- Bilirubin (umol/L)

Y-axis Display Type: Upper limit of normal adjusted (eDish)

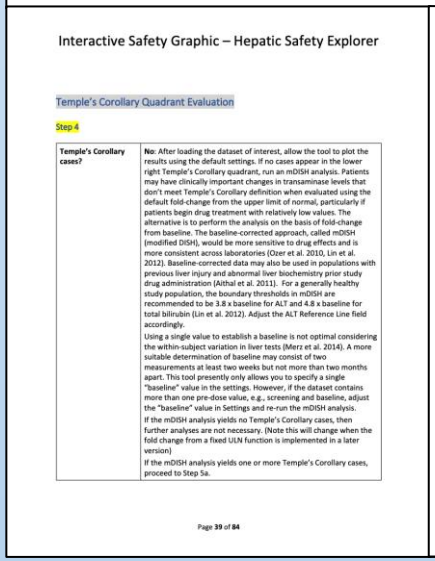


PARAM — Alanine Aminotransferase (U/L) — Alkaline Phosphatase (U/L) — Aspartate Aminotransferase (U/L)

Points are filled for values above the current reference value. Mouseover a line to see the reference line for that lab.



Note: The grayed-out portion is not available in Version 1.0 but is intended to be included in a later version.



Interactive Safety Graphic – Hepatic Safety Explorer

Temple's Corollary Quadrant Evaluation

Step 4

Temple's Corollary cases?	**No:** After loading the dataset of interest, allow the tool to plot the results using the default settings. If no cases appear in the lower right Temple's Corollary quadrant, run an mDISH analysis. Patients may have clinically important changes in transaminase levels that don't meet Temple's Corollary definition when evaluated using the default fold-change from the upper limit of normal, particularly if patients begin drug treatment with relatively low values. The alternative is to perform the analysis on the basis of fold-change from baseline. The baseline-corrected approach, called mDISH (modified DISH), would be more sensitive to drug effects and is more consistent across laboratories (Ozer et al. 2010, Lin et al. 2012). Baseline-corrected data may also be used in populations with previous liver injury and abnormal liver biochemistry prior study drug administration (Althal et al. 2011). For a generally healthy study population, the boundary thresholds in mDISH are recommended to be 3.8 x baseline for ALT and 4.8 x baseline for total bilirubin (Lin et al. 2012). Adjust the ALT Reference Line field accordingly. Using a single value to establish a baseline is not optimal considering the within-subject variation in liver tests (Merz et al. 2014). A more suitable determination of baseline may consist of two measurements at least two weeks but not more than two months apart. This tool presently only allows you to specify a single "baseline" value in the settings. However, if the dataset contains more than one pre-dose value, e.g., screening and baseline, adjust the "baseline" value in Settings and re-run the mDISH analysis. If the mDISH analysis yields no Temple's Corollary cases, then further analyses are not necessary. (Note this will change when the fold change from a fixed ULN function is implemented in a later version) If the mDISH analysis yields one or more Temple's Corollary cases, proceed to Step 5a.

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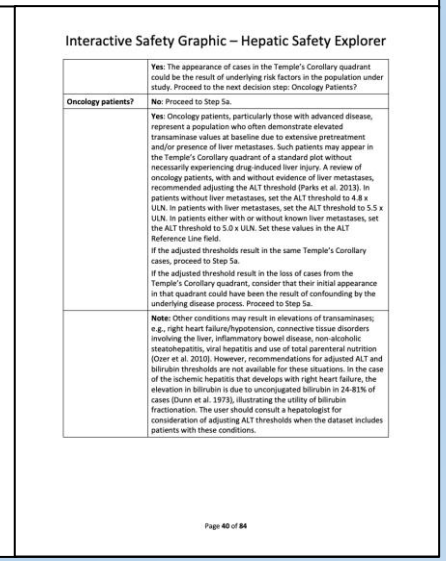

Interactive Safety Graphic – Hepatic Safety Explorer

	Yes: The appearance of cases in the Temple's Corollary quadrant could be the result of underlying risk factors in the population under study. Proceed to the next decision step: Oncology Patients?
Oncology patients?	**No:** Proceed to Step 5a.
	Yes: Oncology patients, particularly those with advanced disease, represent a population who often demonstrate elevated transaminase values at baseline due to extensive pretreatment and/or presence of liver metastases. Such patients may appear in the Temple's Corollary quadrant of a standard plot without necessarily experiencing drug-induced liver injury. A review of oncology patients, with and without evidence of liver metastases, recommended adjusting the ALT threshold (Parks et al. 2013). In patients without liver metastases, set the ALT threshold to 4.8 x ULN. In patients with liver metastases, set the ALT threshold to 5.5 x ULN. In patients either with or without known liver metastases, set the ALT threshold to 5.0 x ULN. Set these values in the ALT Reference Line field. If the adjusted thresholds result in the same Temple's Corollary cases, proceed to Step 5a. If the adjusted threshold result in the loss of cases from the Temple's Corollary quadrant, consider that their initial appearance in that quadrant could have been the result of confounding by the underlying disease process. Proceed to Step 5a.
	Note: Other conditions may result in elevations of transaminases; e.g., right heart failure/hypotension, connective tissue disorders involving the liver, inflammatory bowel disease, non-alcoholic steatohepatitis, viral hepatitis and use of total parenteral nutrition (Ozer et al. 2010). However, recommendations for adjusted ALT and bilirubin thresholds are not available for these situations. In the case of the ischemic hepatitis that develops with right heart failure, the elevation in bilirubin is due to unconjugated bilirubin in 24-81% of cases (Dunn et al. 1973), illustrating the utility of bilirubin fractionation. The user should consult a hepatologist for consideration of adjusting ALT thresholds when the dataset includes patients with these conditions.

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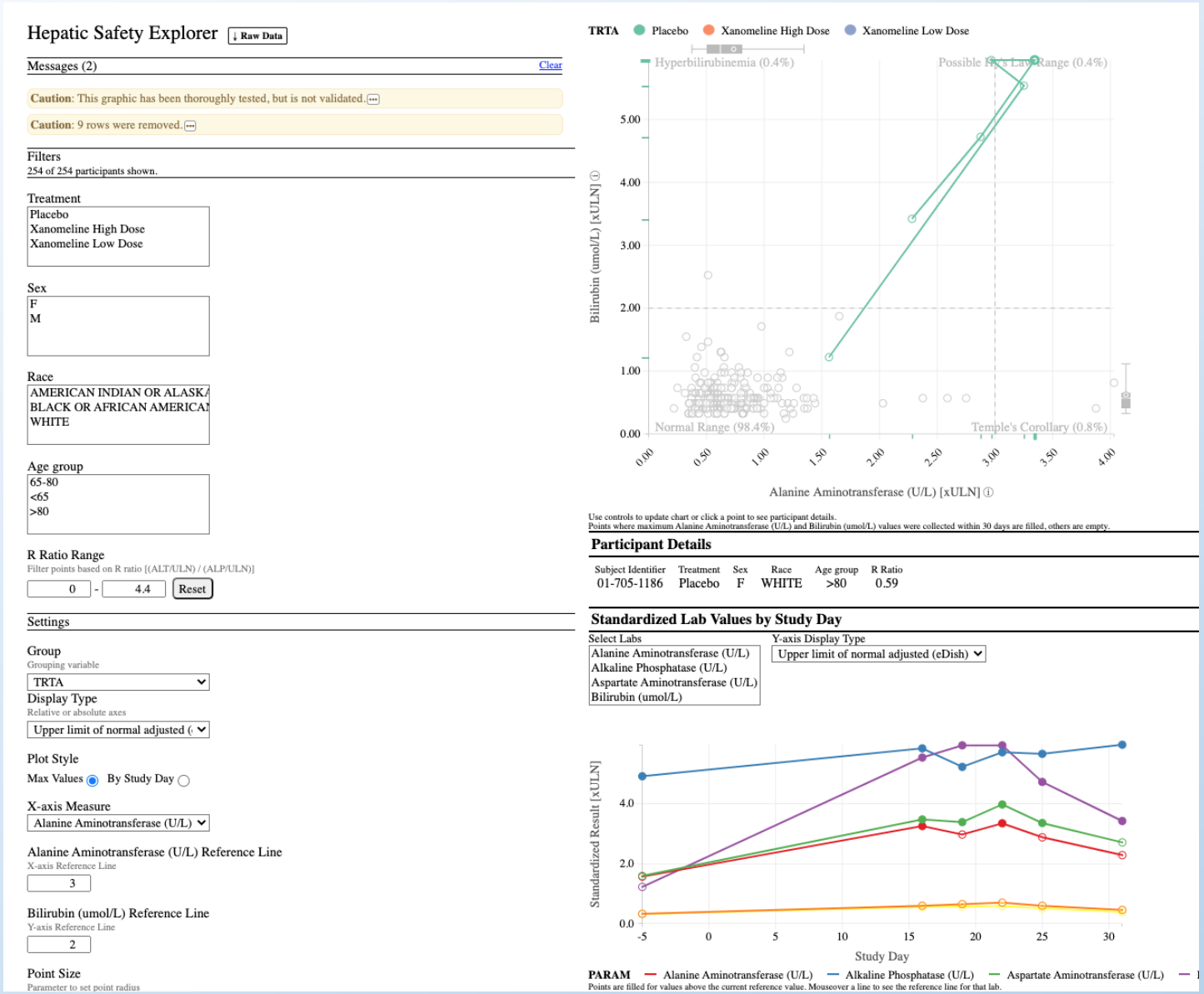
Hepatic Safety Explorer

Demo – Repo – Clinical Workflow – Paper



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DIA

ORIGINAL RESEARCH

A New Paradigm for Safety Data Signal Detection and Evaluation Using Open-Source Software Created by an Interdisciplinary Working Group

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Abstract
Techniques to evaluate large amounts of safety data continue to evolve based on a greater understanding of how the brain processes visual information and the advancement of programing tools. The Interactive Safety Graphics Task Force of the American Statistical Association Biopharmaceutical Safety Working Group has assembled a multidisciplinary team of experts in a variety of domains to develop the next generation of open-source visual analytical tools for safety data based on these advances. The multidisciplinary approach resulted in the rapid development of the first tool, a novel interactive version of the familiar Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) graphic along with a unique clinical workflow to guide the reviewer through the data analysis. This now serves as the model for the team to expand the open-source platform into a suite of other interactive safety analysis tools.

Keywords Drug safety · Pharmacovigilance · Interactive graphics

Background

Safety monitoring during clinical trials is an essential component in drug development. Thorough reviews of medical safety data at regular intervals are critical to characterize the drug safety profile as early as possible to protect patient safety and, eventually, public health. Traditionally, safety data were only comprehensively reviewed at the end of trials. Safety data from ongoing studies, when available, are typically presented in long tedious listings, which are time-consuming to review and less intuitive to inform critical insights. Hence, a thorough review is difficult to conduct on an ongoing basis. As analytical tools became available, comprehensive safety data could be reviewed in using static graphics, usually at certain planned time points. While an improvement on the less informative listings, static graphics are still of limited utility since they do not allow patient-level data exploration, nor population-level ad hoc analyses related to questions arising during the review process. With these inefficient methods, safety data reviews during clinical trials are less frequent and less comprehensive than they ideally should be performed. The result is that safety signals are not identified promptly, and the evaluation of these signals is delayed leading to unnecessary risk in the study patient population. Obviously, this is not in the best interest of any of the various stakeholders during clinical development.

An interactive graphical tool would facilitate ongoing, timely, and flexible safety data exploration to identify safety signals as well as offer capabilities to evaluate events of interest at a population level and the cases of interest at a patient level. Yet, interactive safety displays also have limitations; many such tools do not guide the user as to how to best utilize their features to resolve the important clinical questions when evaluating a safety signal. Graphical display tools are most powerful when paired with an appropriate medical approach to interrogate the data for evidence for or against a causal association between the safety finding and the study drug. Thus, the development of a medically valid clinical workflow with suggested evaluations and guidance as to their interpretation greatly improves the utility of the interactive tool, while also encouraging

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Springer

Hepatic Safety Explorer
Demo – Repo – Clinical Workflow – Paper

Use Case: Novartis DMC

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Data monitoring committees for clinical trials evaluating treatments of COVID-19

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ARTICLE INFO

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ABSTRACT

The first cases of coronavirus disease 2019 (COVID-19) were reported in December 2019 and the outbreak of SARS-CoV-2 was declared a pandemic in March 2020 by the World Health Organization. This sparked a plethora of investigations into diagnostics and vaccination for SARS-CoV-2, as well as treatments for COVID-19. Since COVID-19 is a severe disease associated with a high mortality, clinical trials in this disease should be monitored by a data monitoring committee (DMC), also known as data safety monitoring board (DSMB). DMCs in this indication face a number of challenges including fast recruitment requiring an unusually high frequency of safety reviews, more frequent use of complex designs and virtually no prior experience with the disease. In this paper, we provide a perspective on the work of DMCs for clinical trials of treatments for COVID-19. More specifically, we discuss organizational aspects of setting up and running DMCs for COVID-19 trials, in particular for trials with more complex designs such as platform trials or adaptive designs. Furthermore, statistical aspects of monitoring clinical trials of treatments for COVID-19 are considered. Some recommendations are made regarding the presentation of the data, stopping rules for safety monitoring and the use of external data. The proposed stopping boundaries are assessed in a simulation study motivated by clinical trials in COVID-19.

1. Introduction

The first clusters of Coronavirus disease 2019 (COVID-19) cases were reported in December 2019 and January 2020 [1–4]. On 11 March 2020, the World Health Organization declared the outbreak of SARS-CoV-2 a pandemic [5]. As of 18 July 2020, over 14 million cases and over 600,000 deaths of COVID-19 were confirmed according to the Center for Systems Science and Engineering at Johns Hopkins University [6,7].

A search in clinicaltrials.gov for studies targeting the conditions "COVID-19", "COVID", or "SARS-CoV-2" shows that the first studies surrounding COVID-19 were registered in late January 2020 and until July 2020 over 2500 studies were registered. Clinical trials studying interventions for COVID-19 primarily focus on short-term endpoints assessing mortality, morbidity, the requirement for mechanical ventilation or ICU care. For instance, the primary endpoint in the RECOVERY trial (ClinicalTrials.gov Identifier: NCT04381936) is all-cause mortality at 28 days [8], the primary endpoint in the Adaptive COVID-19 Treatment Trial (ACTT; ClinicalTrials.gov Identifier: NCT04280705) was time to recovery within 28 days after enrollment [9], and the primary endpoint in the GS-US-540-5773 trial (ClinicalTrials.gov Identifier: NCT04292899) was the clinical status on day 14, assessed on a 7-point ordinal scale [10].

Well-conducted double-blind randomized controlled trials are considered the gold standard for clinical trials and there have been calls for their rigorous application in COVID-19 [11]. However, conducting a clinical trial for a pandemic disease to established standards in the midst of an evolving pandemic poses a number of challenges [12]. For instance, the location of areas with high numbers of infections changes over time. Therefore, clinical trial sites might need to pause or even stop recruitment which in turn means that new sites have to be opened in different locations. Sites in locations severely affected by the pandemic might be able to screen, randomize and treat a large number of subjects within a short period of time, however, this brings challenges for on-site trial personnel to properly document the cases and enter the data in a timely manner into the study database. Moreover, due to the seriousness of COVID-19, standard of care or best available therapy instead of placebo are included as comparator in many trials, at least as of Summer 2020, but what constitutes standard of care or best available therapy is changing rapidly due to efficacious treatments being

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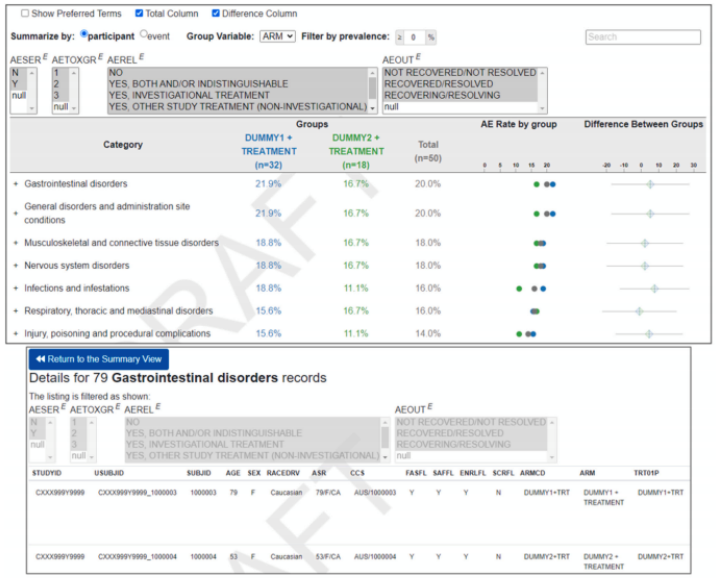


Fig. 1. Screenshots of an interactive display of adverse event data. Top: interactive display of the comparison of adverse event rates between groups by system organ class is shown. Bottom: Details of the subjects for whom a gastrointestinal disorder was reported. The details are obtained by clicking on 'Gastrointestinal disorder' in the interactive display shown on top.

and 0.25, i.e. $P(\text{Event within 4 weeks} \mid \text{TRT}) = 0.15, 0.175, 0.2, 0.25$. To monitor for harm, a test of $H_0 : HR = 1$ with a one-sided significance level for $\alpha = 0.025$, 0.05 based on the Cox regression is performed at each data look. The monitoring is conducted on a weekly basis starting one week after the randomization of the first subject. Based on the probabilities that an event occurs within four weeks after randomization in the treatment group and the control group, the hazard ratios in the Cox model may be calculated.

Fig. 3 shows the probability for rejecting the null hypothesis H_0 in favor of the one-sided alternative hypothesis H_1 prior to or at monitoring time point t. The results are presented for two planned total sample sizes, four different probabilities of experiencing an event within the four weeks follow-up under treatment, that is $P(\text{Event within 4 weeks} \mid \text{TRT})$, and two one-sided significance levels α. The red line shows that due to the repeated testing of the null hypothesis H_0 at the one-sided significance level α, the cumulative probability to wrongfully reject the null hypothesis during at least one monitoring time point increases to about 0.1 for $\alpha = 0.025$ and to 0.2 for $\alpha = 0.05$. Fig. 3 also shows that probability to detect differences in the event rate between the treatment group and the control group increases with the sample size and that larger differences are naturally easier to detect. Moreover, the probability to detect differences between the groups increases with increasing significance level α, but the probability to wrongfully detect differences also increases.

Although we are not recommending to use formal statistical methods for safety monitoring, it is worth highlighting that the proposed procedure, i.e. monitoring harm by testing the null hypothesis at each time point with a fixed significance level, corresponds to a group sequential design with a Pocock boundary for which not the global type I error rate but the significance level at each time point is chosen [50]. Therefore, a large sample approximation of the simulation results presented in Figs. 1 and S1 can be obtained through standard group sequential software such as the R package *gsDesign* [51]. In detail, the cumulative probability for rejecting H_0 at or prior to the time point t, that is

$$P(\text{Reject } H_0 \text{ at time} \le t) = P(T_k \ge q_{1-\alpha} \text{ for any } k \in \{t_1, t_2, \ldots\})$$

with $t_1, t_2, \ldots$ the monitoring time points, $q_{1-\alpha}$ the $(1-\alpha)$-quantile of a standard normal distribution, and T_k the Wald statistic for testing H_0. The joint distribution of test statistics T_k can be approximated by a multivariate normal distribution where each component has mean $\beta\sqrt{m_k r_T r_C}$ and variance one [52,53]. Here, m_k is the expected number

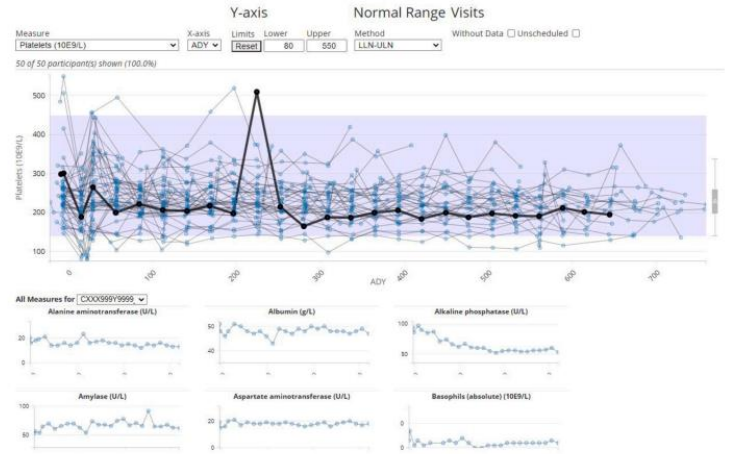


Fig. 2. Interactive display of laboratory values (here: Platelet counts).

Table 1
Specifications for the simulation study to assess the monitoring procedure's operating characteristics.

Parameter	Value
Uniform recruitment period	8 weeks
Sample size	$n = 500, 1000$
Treatment allocation	1:1
$P(\text{Event within 4 weeks} \mid \text{CTL})$	0.15
$P(\text{Event within 4 weeks} \mid \text{TRT})$	0.15, 0.175, 0.2, 0.25
Hazard ratio (as a result of assumptions above)	1, 1.18, 1.37, 1.77
One-sided significance level α	0.025, 0.05
Monitoring frequency	Weekly

of events at time point k, and r_T and r_C is the proportion of subjects in the treatment and control group, respectively. The correlation of test statistics from time points $t_1 < t_2$ is approximated by $\sqrt{m_{t_1}/m_{t_2}}$. This normal approximation can then be used to calculate the cumulative probability for rejecting H_0 at or prior to the time point t [48]. Fig. 4 shows that the approximation is satisfactory, in particular for the setting with total sample size of $n = 1000$.

3.3. Incorporating external data

A DMC does not consider data from the trial monitored in isolation, rather data in the context of other available or emerging data. We refer to any data outside the monitored trial as external data. These may be from randomized controlled trials or other types of studies including clinical registries. In particular, in situations of rapidly changing external landscapes such [illegible] new safety or efficacy [illegible] with similar mechani[illegible]

of trials ongoing assessing the efficacy and safety of hydroxychloroquine. The perception of hydroxychloroquine changed quite dramatically over the course of only a few weeks. At first it was considered a promising treatment option, then suspected to be unsafe and finally dismissed for lack of efficacy [15].

If there is agreement that external data should be included, the question remains how this could be achieved. In principle, the evidence could be included informally, e.g. by considering data side by side but not combining them statistically, or formally, e.g. by using meta-analytic approaches [54]. One critical point in combining data is the similarity of the monitored trial and the studies providing the external evidence in terms of study design, patient population, standard of care etc. When integrating the data formally, e.g. through a random-effects meta-analysis, this will be capture in the between-trial heterogeneity. In the following we make some recommendations on the formal integration of external evidence with regard to adverse events [45].

Unfortunately, it is still common to pool adverse event data naively across studies by "simply combin[ing] the numerator events and the denominators for the selected studies" [55], although this might lead to bias due to Simpson's paradox [56–58]. Therefore, the use of meta-analysis techniques is encouraged. These may account for heterogeneity in the control group outcomes across studies and, if random-effects meta-analysis is used, also in treatment differences. A number of problems are faced with safety analyses (see, e.g. [59]). These include varying follow-up times between studies, rare events and small numbers of studies included in the meta-analysis. The latter makes estimates of the between-study heterogeneity in the treatment differences uncertain with negative consequences for the inference regarding the overall treatment effect [60]. Bayesian approaches using weakly in[illegible]

Data Monitoring committees for clinical trials evaluating treatments of COVID-19. Tobias Mütze and Tim Friede. 2020 - Paper

{volcanoPlot}

Adverse Event Incidence Analysis

- Background
- Visualization Approach
- Demo
- Improvements

Background

- AE incidence analyses help describe an intervention’s safety profile

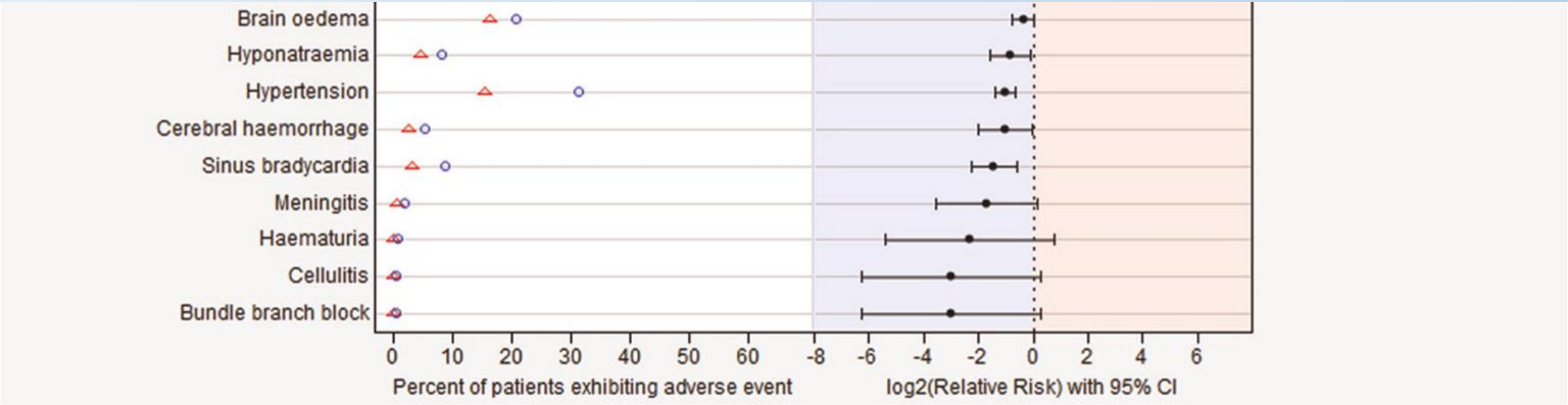
Background

- AE incidence analyses help describe an intervention's safety profile
- Traditionally captured in lengthy summary tables

	Nicardipine (*n* = 447)	**Placebo (*n* = 455)**
Blood and lymphatic system disorders	195 (44)	203 (45)
Anaemia	137 (31)	160 (35)
Platelet destruction increased	29 (6)	16 (4)
(5 more)		
Cardiac disorders	156 (35)	175 (38)
Ventricular extrasystoles	39 (9)	41 (9)
Sinus bradycardia	15 (3)	41 (9)
(24 more)		
Gastrointestinal disorders	95 (21)	90 (20)

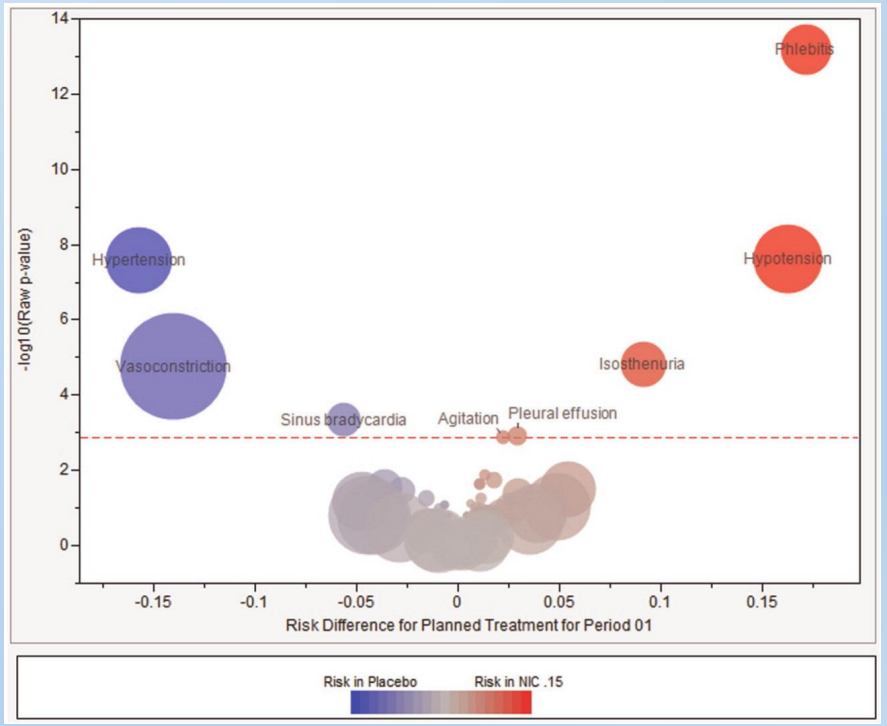
Background

- AE incidence analyses help describe an intervention's safety profile
- Traditionally captured in lengthy summary tables
- Combination dot plot + relative risk plot present a condensed view



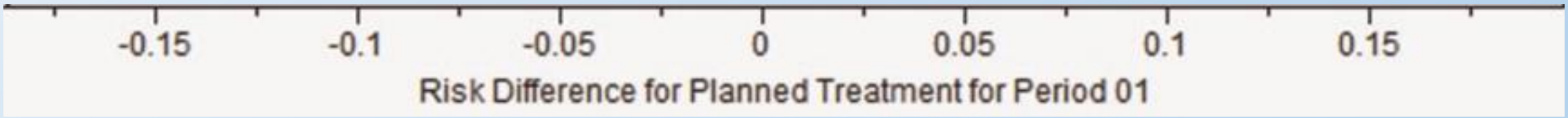
Background

- AE incidence analyses help describe an intervention's safety profile
- Traditionally captured in lengthy summary tables
- Combination dot plot + relative risk plot present a condensed view
- Volcano plot:
  - Saves space
  - Emphasizes safety findings
  - Minimizes noise
  - Incorporates multiplicity adjustments



Visualization Approach

- Plot statistic of interest on x-axis
  - Difference in proportion
  - Relative risk
  - Odds ratio

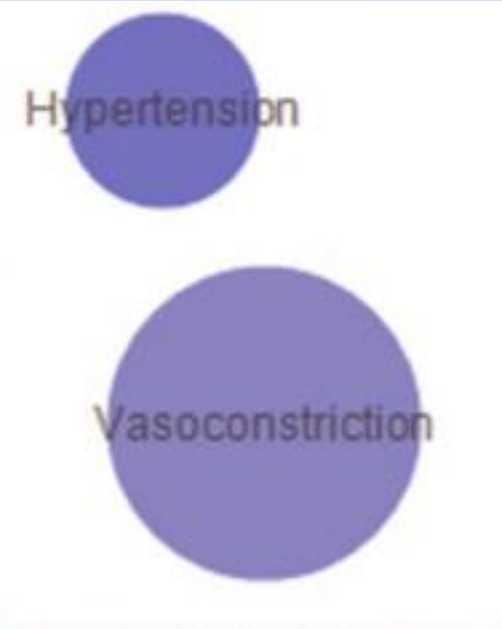


Visualization Approach

- Plot statistic of interest on x-axis
  - Difference in proportion
  - Relative risk
  - Odds ratio
- Plot significance on y-axis

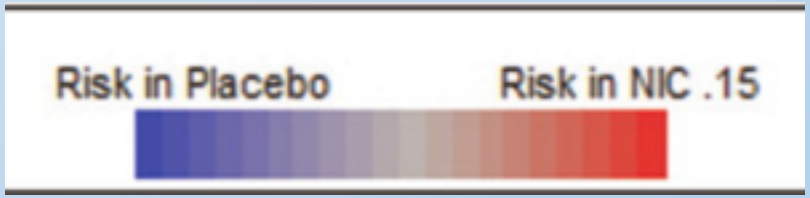
Visualization Approach

- Plot statistic of interest on x-axis
  - Difference in proportion
  - Relative risk
  - Odds ratio
- Plot significance on y-axis
- Size points by event frequency

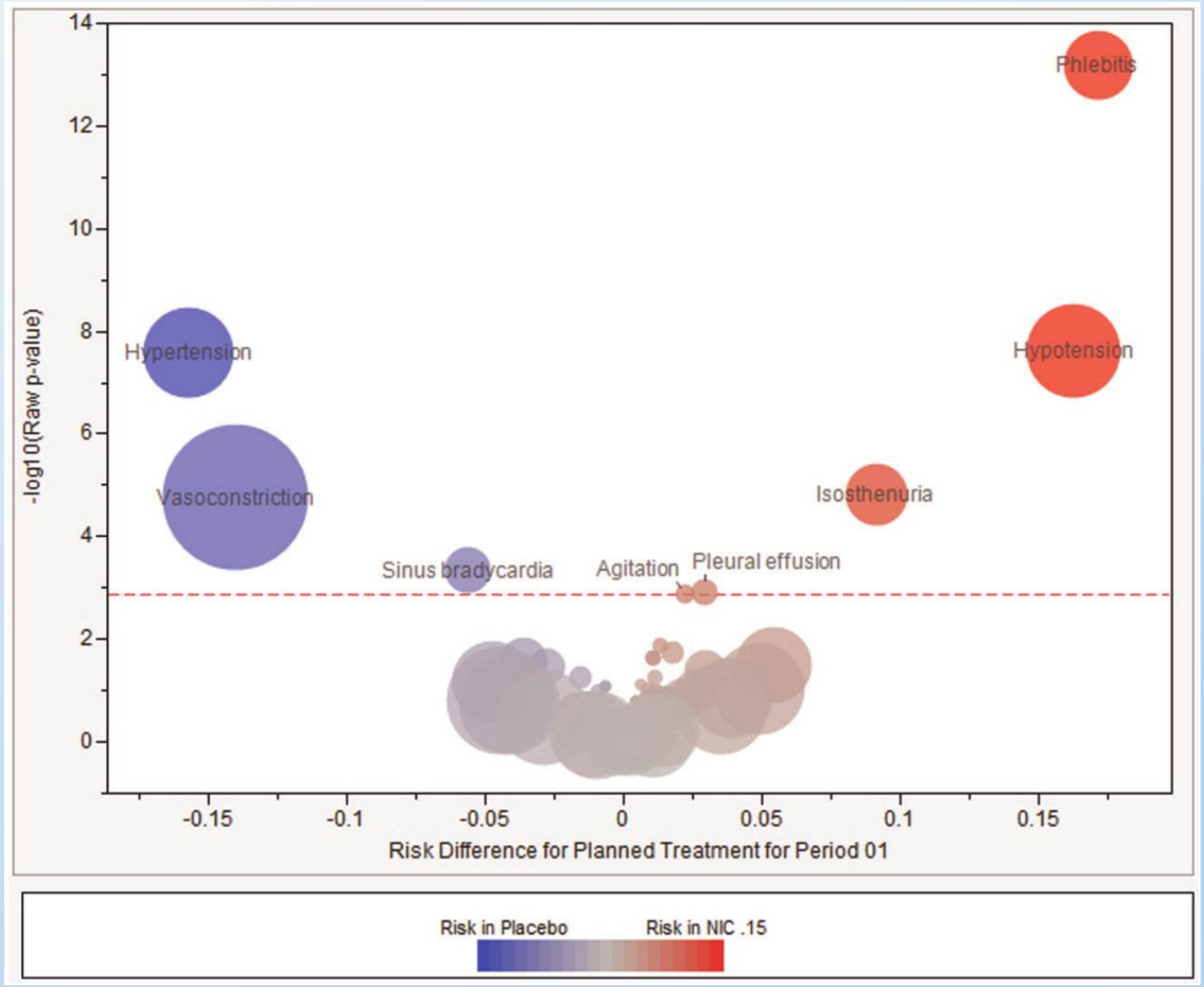


Visualization Approach

- Plot statistic of interest on x-axis
  - Difference in proportion
  - Relative risk
  - Odds ratio
- Plot significance on y-axis
- Size points by event frequency
- Color points to distinguish direction of treatment risk
- Saturate points to emphasize significance



Visualization Approach



Demo

Improvements

- Incorporate multiplicity adjustment
  - False discovery rate
  - Bonferroni
- Incorporate time intervals
- Include in {safetyGraphics} by default
- Improve aesthetics

{nepExplorer}

Renal Explorer

Renal Explorer

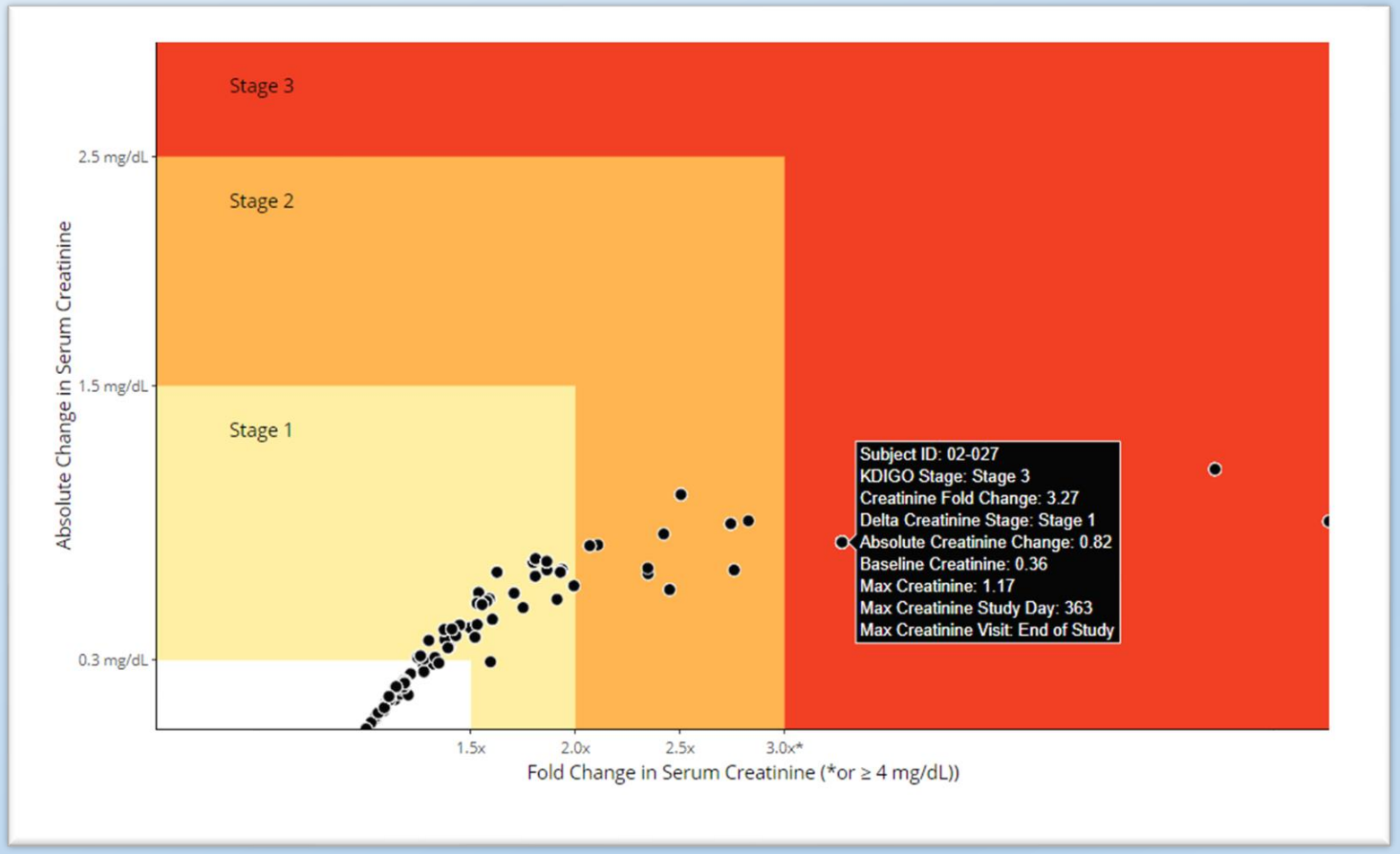
{nepExplorer}

- R Package for acute kidney injury evaluation on a clinical trial population
- Leverages KDIGO & Delta Creatinine criteria for classifying changes in Serum Creatinine
- R shiny provides interactive elements such as hover and drill-down to facilitate exploration of kidney function across a population and within a patient over time
- Associated clinical workflow provides guidance to end-users concerning use and assumptions of the tool

KDIGO Creatinine Scatterplot

FIND PATIENTS WITH LARGEST CREATININE CHANGES

- One point per Patient
- Maximum Fold Change by Maximum Absolute Change in Creatinine plotted
- Color Ranges indicate KDIGO & Delta Creatinine Criteria
- Hover, Zoom, and Click Functionality



Renal Explorer
{nepExplorer}

Aggregate KDIGO TABLE

IS THERE A STUDY-LEVEL RENAL SAFETY SIGNAL?

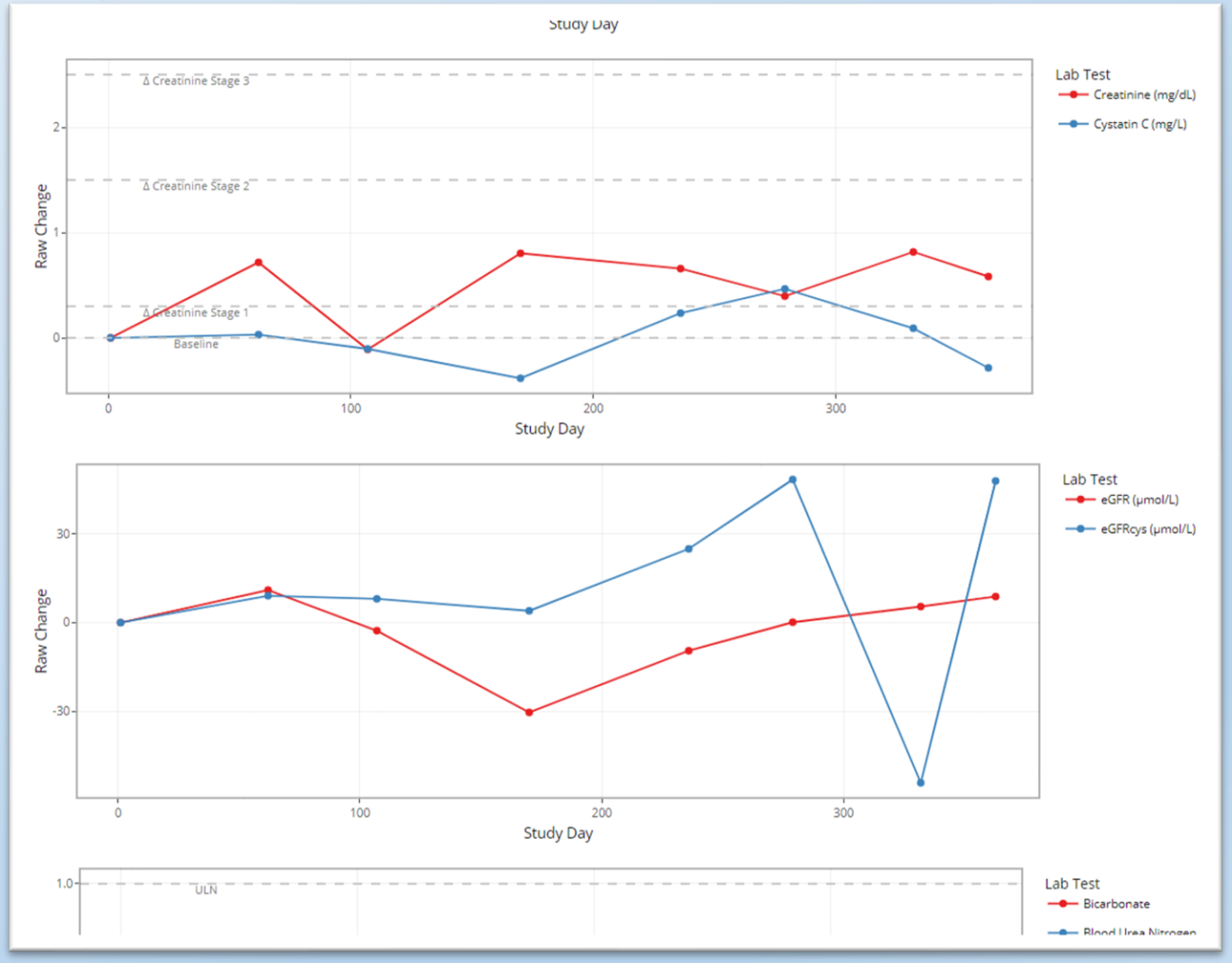
- Maximum Fold Change and Maximum Absolute Change
- Summarized by KDIGO & Delta Creatinine Criteria
- Counts and Percentage of patients with an event meeting within relevant stage

KDIGO	Fold Change in Serum Creatinine		Absolute Change in Serum Creatinine	
	N	%	N	%
Stage 3	3	3%	0	0%
Stage 2	10	9%	0	0%
Stage 1	23	20%	50	43%
Stage 0	79	69%	65	57%

Longitudinal Renal Profile

LABORATORY VALUES FOR PATIENT OVER TIME

- Interactively displays data for selected patients
- Line charts of key renal markers and electrolytes
- Information on hover



Renal Explorer
{nepExplorer}

Plans for 2024

PREPARING FOR PRODUCTION USE

- Integrate with safetyGraphics framework
- Integrate with safetyProfile
- Real-world pilots
- Develop technical documentation
- Finalize clinical workflow
- Get feedback from academic, industry and FDA nephrologists

Demo

https://github.com/SafetyGraphics/nep-explorer/

Acknowledgements

Development

- Preston Burns
- Lovemore Gakava
- Jared Woolfork
- Eli Miller

Clinical

- Dr. James Buchanan
- Dr. Barbara Hendrickson
- Siu-Chi Sun
- Dr. Sara Jandeska

Interactive {safetyProfile} Shiny Application for Monitoring Clinical Trial Safety

Natalia Andriychuk

Data Scientist, Pfizer

Safety Working Group Quarterly Scientific Webinar - Q1 2024

Developers

Agustin Calatroni – Senior Director, Biostatistics at Rho

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Natalia Andriychuk – Statistical Data Scientist at Pfizer

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Stephanie Lussier - Sr Manager Biostatistics at Moderna

What is safetyProfile?

- Shiny application that contain flexible shiny modules
- Subject-level profile reports
- Domains include
  - participant demographics data
  - laboratory results
  - concomitant medications
  - adverse events

Installation

1. Install package from GitHub:

```
devtools::install_github('safetyGraphics/safetyProfile', ref="main")
```

2. Run stand-alone app:

```
library(safetyProfile)
profileApp()
```

Demo

ID 01-701-1130 treatment_col Placebo sex_col M race_col WHITE age_col 84

Overview | Event Timeline | Measures Over Time

Participant Data Listings

Select Data Domain

aes

- dm
- aes
- labs
- cm

Search:

	STUDYID	DOMAIN	USUBJID	TRTA	TRTAN	AGE	AGEGR1	AGEGR1N	RACE	RACEN	SEX	SAFFL	TRTSDT	TRTEDT	ASTDT	ASTDTF	ASTDY	AENDT	AENDY	ADURN	ADURU	AETERM	AEL
1	CDISCPILOT01	701	01-701-1130	Placebo	0	84	>80	3	WHITE	1	M	Y	2014-02-15	2014-08-16	2014-03-09		23	2014-03-16	30	8	DAY	URINARY TRACT INFECTION	URI TRA INFI
2	CDISCPILOT01	701	01-701-1130	Placebo	0	84	>80	3	WHITE	1	M	Y	2014-02-15	2014-08-16	2014-03-09		23	2014-03-09	23	1	DAY	PYREXIA	FEV
3	CDISCPILOT01	701	01-701-1130	Placebo	0	84	>80	3	WHITE	1	M	Y	2014-02-15	2014-08-16	2014-03-09		23	2014-03-16	30	8	DAY	URINARY TRACT INFECTION	URI TRA INFI
4	CDISCPILOT01	701	01-701-1130	Placebo	0	84	>80	3	WHITE	1	M	Y	2014-02-15	2014-08-16	2014-05-09		84	2014-05-09	84	1	DAY	EYE SWELLING	EYE SW
5	CDISCPILOT01	701	01-701-1130	Placebo	0	84	>80	3	WHITE	1	M	Y	2014-02-15	2014-08-16	2014-05-09		84	2014-05-09	84	1	DAY	EYE ALLERGY	EYE ALL
6	CDISCPILOT01	701	01-701-1130	Placebo	0	84	>80	3	WHITE	1	M	Y	2014-02-15	2014-08-16	2014-05-22		97					EYE PRURITUS	EYE
7	CDISCPILOT01	701	01-701-1130	Placebo	0	84	>80	3	WHITE	1	M	Y	2014-02-15	2014-08-16	2014-05-22		97					PRURITUS	ITCI BOT
8	CDISCPILOT01	701	01-701-1130	Placebo	0	84	>80	3	WHITE	1	M	Y	2014-02-15	2014-08-16	2014-05-22		97					NASAL CONGESTION	NAS CON

Showing 1 to 8 of 8 entries

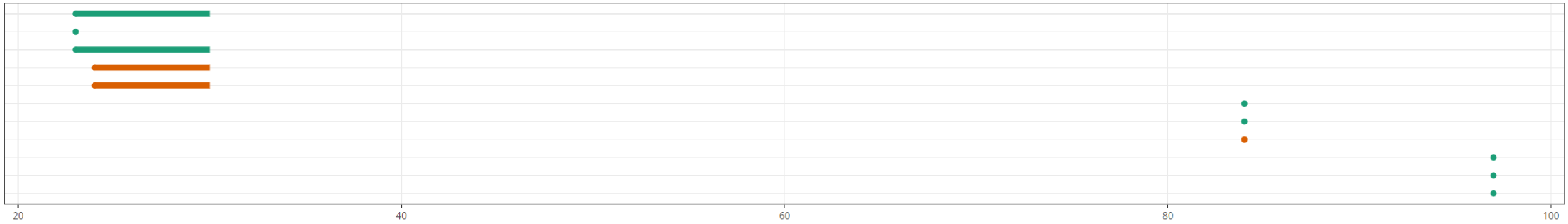
Previous 1 Next

ID 01-701-1130 treatment_col Placebo sex_col M race_col WHITE age_col 84

Overview | Event Timeline | Measures Over Time

Study Event Timeline

8 Adverse Events, 3 Concomitant Medications



Dropped 52 rows with missing start and end dates.

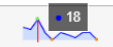
Search:

Subject ID	Start Day	End Day	Event Details	Domain
01-701-1130	23	30	SITEID: 701 AEBODSYS: INFECTIONS AND INFESTATIONS AEDECOD: URINARY TRACT INFECTION AESEV: MILD	aes
01-701-1130	23	23	SITEID: 701 AEBODSYS: GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS AEDECOD: PYREXIA AESEV: MILD	aes
01-701-1130	23	30	SITEID: 701 AEBODSYS: INFECTIONS AND INFESTATIONS AEDECOD: URINARY TRACT INFECTION AESEV: MILD	aes
01-701-1130	84	84	SITEID: 701 AEBODSYS: EYE DISORDERS AEDECOD: EYE SWELLING AESEV: MILD	aes
01-701-1130	84	84	SITEID: 701 AEBODSYS: EYE DISORDERS AEDECOD: EYE ALLERGY AESEV: MILD	aes

ID 01-701-1130 treatment_col Placebo sex_col M race_col WHITE age_col 84

Overview | Event Timeline | Measures Over Time

Search:

		Measure	LLN	ULN	Trend
1	⊖	Alanine Aminotransferase (U/L)	6	35	

Visit	Study Day	Result
Baseline	-6	15
Week 2	15	14
Week 4	29	18
Week 6	43	13
Week 8	57	10
Week 12	91	13
Week 16	113	12
Week 20	138	11
Week 24	169	13
End of Treatment	169	13
Week 26	183	10

2	⊕	Alanine Aminotransferase (U/L) change from previous visit, relative to normal range	NA	NA	
3	⊕	Albumin (g/L)	35	46	
4	⊕	Albumin (g/L) change from previous visit, relative to normal range	NA	NA	
5	⊕	Alkaline Phosphatase (U/L)	35	115	
6	⊕	Alkaline Phosphatase (U/L) change from previous visit, relative to normal range	NA	NA	
7	⊕	Aspartate Aminotransferase (U/L)	11	36	
8	⊕	Aspartate Aminotransferase (U/L) change from previous visit, relative to normal range	NA	NA	
9	⊕	Bilirubin (umol/L)	3	21	
10	⊕	Bilirubin (umol/L) change from previous visit, relative to normal range	NA	NA	
11	⊕	Blood Urea Nitrogen (mmol/L)	1	9	
12	⊕	Blood Urea Nitrogen (mmol/L) change from previous visit, relative to normal range	NA	NA	
13	⊕	Calcium (mmol/L)	2	3	
14	⊕	Calcium (mmol/L) change from previous visit, relative to normal range	NA	NA	

Safety Working Group Quarterly Scientific Webinar

safetyGraphics wiki
https://github.com/SafetyGraphics/safetyGraphics/wiki

Vignette:
https://github.com/SafetyGraphics/safetyGraphics/wiki/Intro

nepExplorer:
GitHub - SafetyGraphics/nep-explorer: Interactive Graphic for Exploring Kidney Function Data in Clinical Trials

ASA Biopharmaceutical Section

Safety Working Group Quarterly Scientific Webinar