



# Open Source Collaboration in Pharma safetyGraphics v2.0

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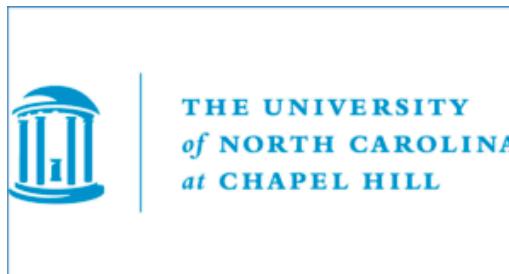
Presented on Behalf of the Interactive Safety Graphics Working Group



# Interactive Safety Graphics (ISG) Working Group

<https://safetygraphics.github.io/>

Sub-team of DIA &  
ASA-Biopharm Safety  
Working Group



abbvie



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Ingelheim

Covalence

FDA U.S. FOOD & DRUG  
ADMINISTRATION



Lilly



NOVARTIS

Rho®

TARGET  
PharmaSolutions

Alkermes®



## Building Open Source Tools for Safety Monitoring: Advancing Research Through Community Collaboration

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Interactive Safety Graphics Taskforce

R in Pharma 2019



# safetyGraphics v1.0

An open source framework for evaluation of clinical trial safety

*Links:* [CRAN](#) | [GitHub](#) | [Demo](#)

Initialize App:

```
install.packages('safetyGraphics')
library(safetyGraphics)
safetyGraphicsApp()
```

# safetyGraphics Workflow

safetyGraphics Shiny app    Home    Data    Settings    Charts ▾    Reports

About    [Shiny App User Guide](#)    [Hep Explorer workflow](#)

## Welcome to the Safety Graphics Shiny App

The Safety Graphics Shiny app is an interactive tool for evaluating clinical trial safety using a flexible data pipeline. This application and corresponding [safetyGraphics](#) R package have been developed as part of the [Interactive Safety Graphics \(ISG\) workstream](#) of the ASA Biopharm-DIA Safety Working Group.

### Using the app

Detailed instructions about using the app can be found in our [vignette](#). In short, the user will begin by loading a data file, adjust settings as needed and view the interactive charts. Finally, the user may export a self-contained, fully reproducible snapshot of the charts that can be easily shared with others.

### Clinical Workflow

This shiny app has been developed in parallel with a well-documented [clinical workflow](#) for monitoring hepatotoxicity. The workflow, written by expert physicians, provides a detailed description of how the interactive graphics can be used as part of a safety clinician's monitoring practice.

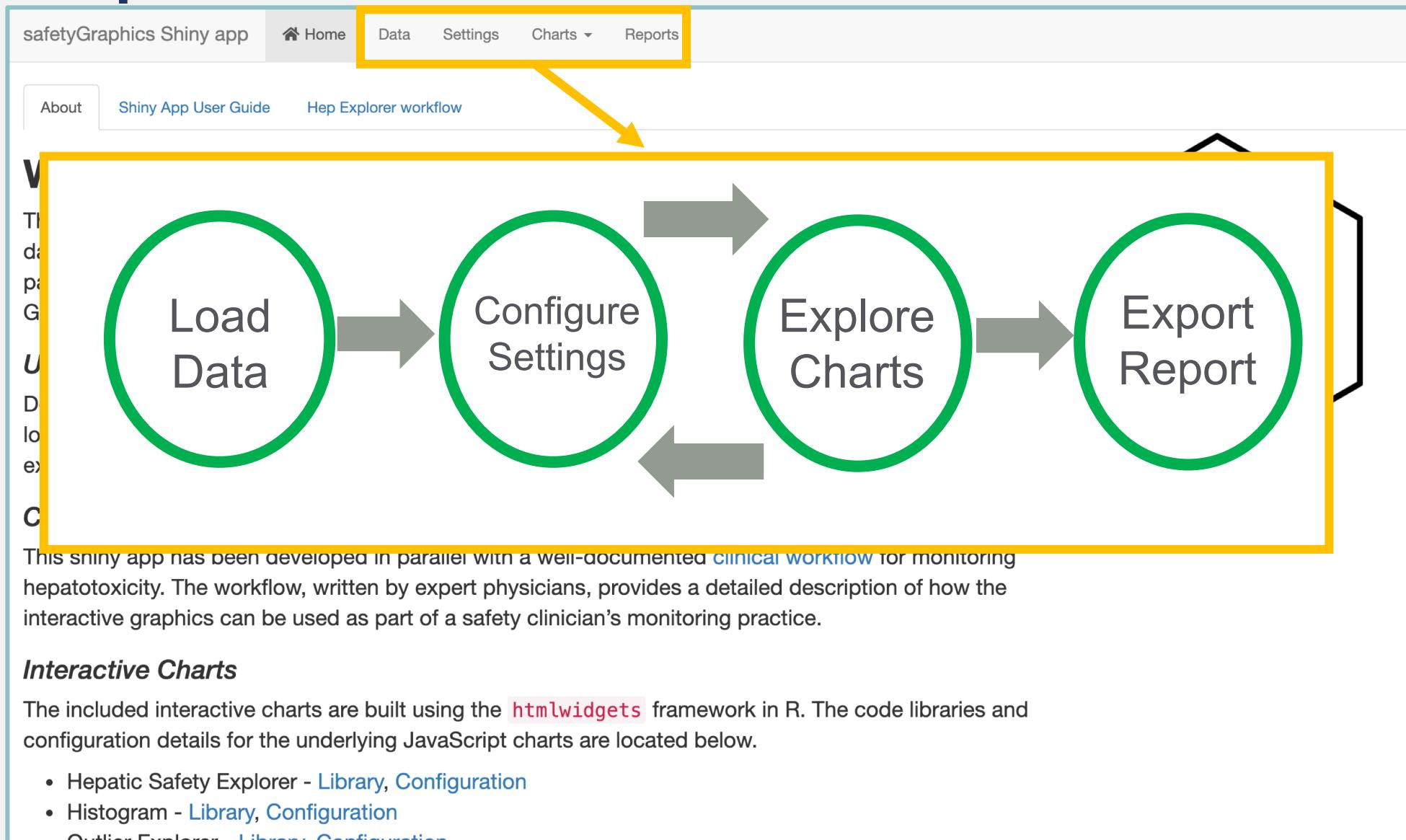
### Interactive Charts

The included interactive charts are built using the [htmlwidgets](#) framework in R. The code libraries and configuration details for the underlying JavaScript charts are located below.

- Hepatic Safety Explorer - [Library](#), [Configuration](#)
- Histogram - [Library](#), [Configuration](#)
- Outlier Explorer - [Library](#), [Configuration](#)



# safetyGraphics Workflow



# safetyGraphics Workflow

## Step 1: Load Data

safetyGraphics Shiny app    Home    Data    Settings    Charts ▾    Reports

### Data upload

Upload a csv or sas7bdat file

Browse...    4 files

Upload complete

Select file for safetyGraphics charts

Example data - *AdAM*

SampleData\_PartialSDTM.csv - *Partial SDTM (6/12 data settings)*

SampleData\_NoStandard.csv - *No Standard Detected*

SampleData\_PartialADaM.csv - *Partial AdAM (9/12 data settings)*

SampleData\_SDTM.csv - *SDTM*

### Data Preview for Example data

Show 10 entries    Search:

Example data

STUDYID	SUBJID	USUBJID	TRTP	TRTPN	TRTA	TRTAN	TRTSDT	TRTEDT	AGE	AGEGR1
CDISCPILOT01	1015	01-701-1015	Placebo	0	Placebo	0	1/2/14	7/2/14	63	<65
CDISCPILOT01	1015	01-701-1015	Placebo	0	Placebo	0	1/2/14	7/2/14	63	<65
CDISCPILOT01	1015	01-701-1015	Placebo	0	Placebo	0	1/2/14	7/2/14	63	<65
CDISCPILOT01	1015	01-701-1015	Placebo	0	Placebo	0	1/2/14	7/2/14	63	<65
CDISCPILOT01	1015	01-701-1015	Placebo	0	Placebo	0	1/2/14	7/2/14	63	<65
CDISCPILOT01	1015	01-701-1015	Placebo	0	Placebo	0	1/2/14	7/2/14	63	<65
CDISCPILOT01	1015	01-701-1015	Placebo	0	Placebo	0	1/2/14	7/2/14	63	<65
CDISCPILOT01	1015	01-701-1015	Placebo	0	Placebo	0	1/2/14	7/2/14	63	<65
CDISCPILOT01	1015	01-701-1015	Placebo	0	Placebo	0	1/2/14	7/2/14	63	<65

# safetyGraphics Workflow

## Step 2: Configure Settings

safetyGraphics Shiny app    Home    Data    **Settings**    Charts ▾    Reports

**Charts** 

Hepatic Safety Explorer    Histogram    Outlier Explorer    Shift Plot    Results Over Time    Paneled Outlier Explorer

**Data Mappings** 

ID column (6) USUBJID [Unique Subject Identifier]

Value column (6) AVAL [Analysis Value]

Measure column (6) PARAM [Parameter]

Alanine Aminotransferase value (1) Alanine Aminotransferase (U/L)

Aspartate Aminotransferase value (1) Aspartate Aminotransferase (U/L)

**Measure Settings** 

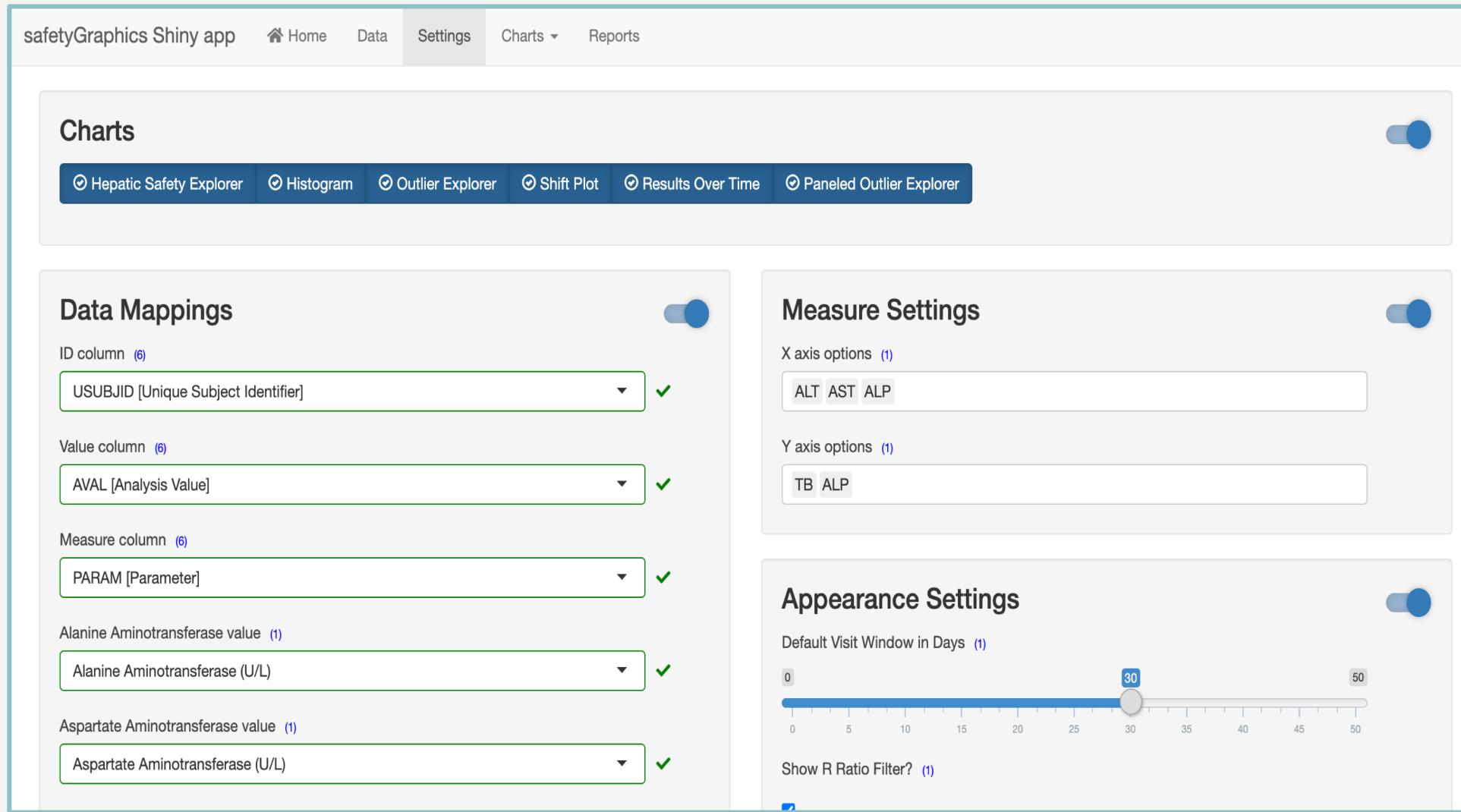
X axis options (1) ALT AST ALP

Y axis options (1) TB ALP

**Appearance Settings** 

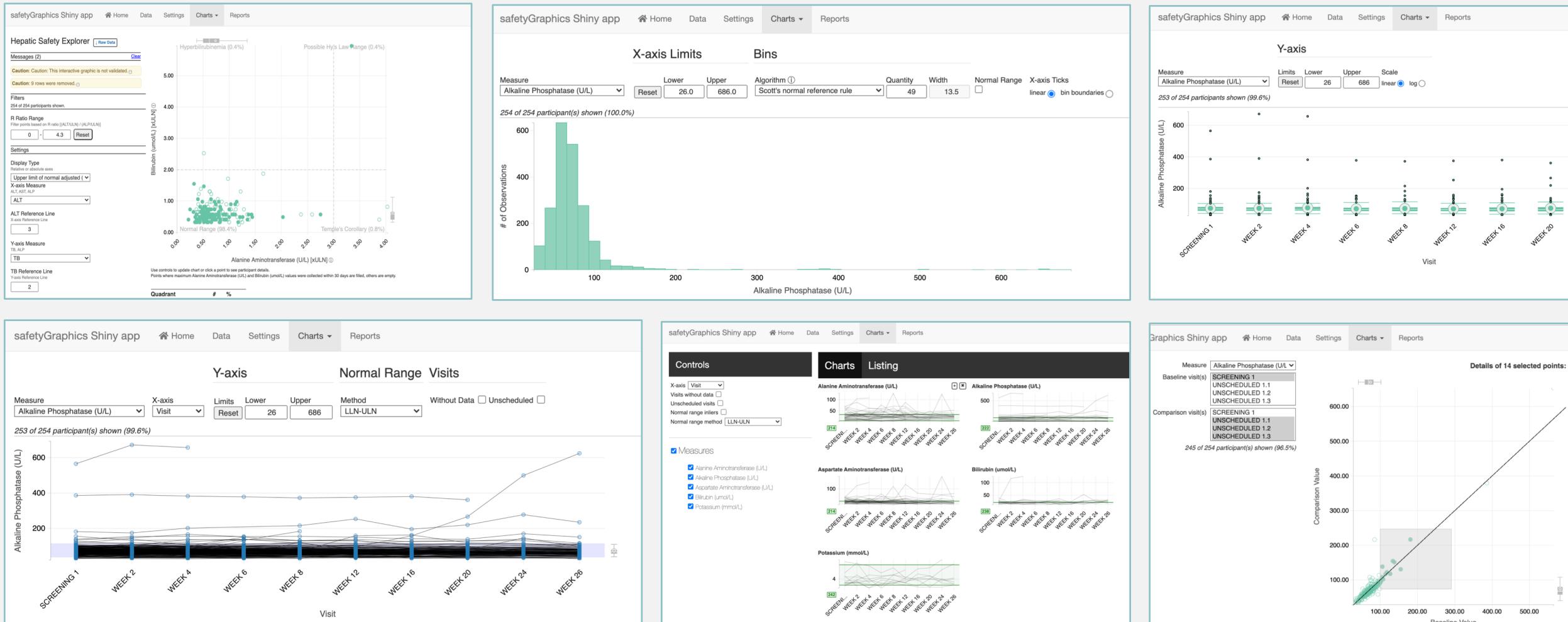
Default Visit Window in Days (1) 0 5 10 15 20 25 30 35 40 45 50

Show R Ratio Filter? (1) 



# safetyGraphics Workflow

## Step 3: Explore Charts



safetyGraphics Workflow  
**Steps 2/3: Customize Charts**

Group columns (2)

TRTA [Actual Treatment] |

STUDYID [Study Identifier]

SUBJID [Subject Identifier for the Study]

USUBJID [Unique Subject Identifier]

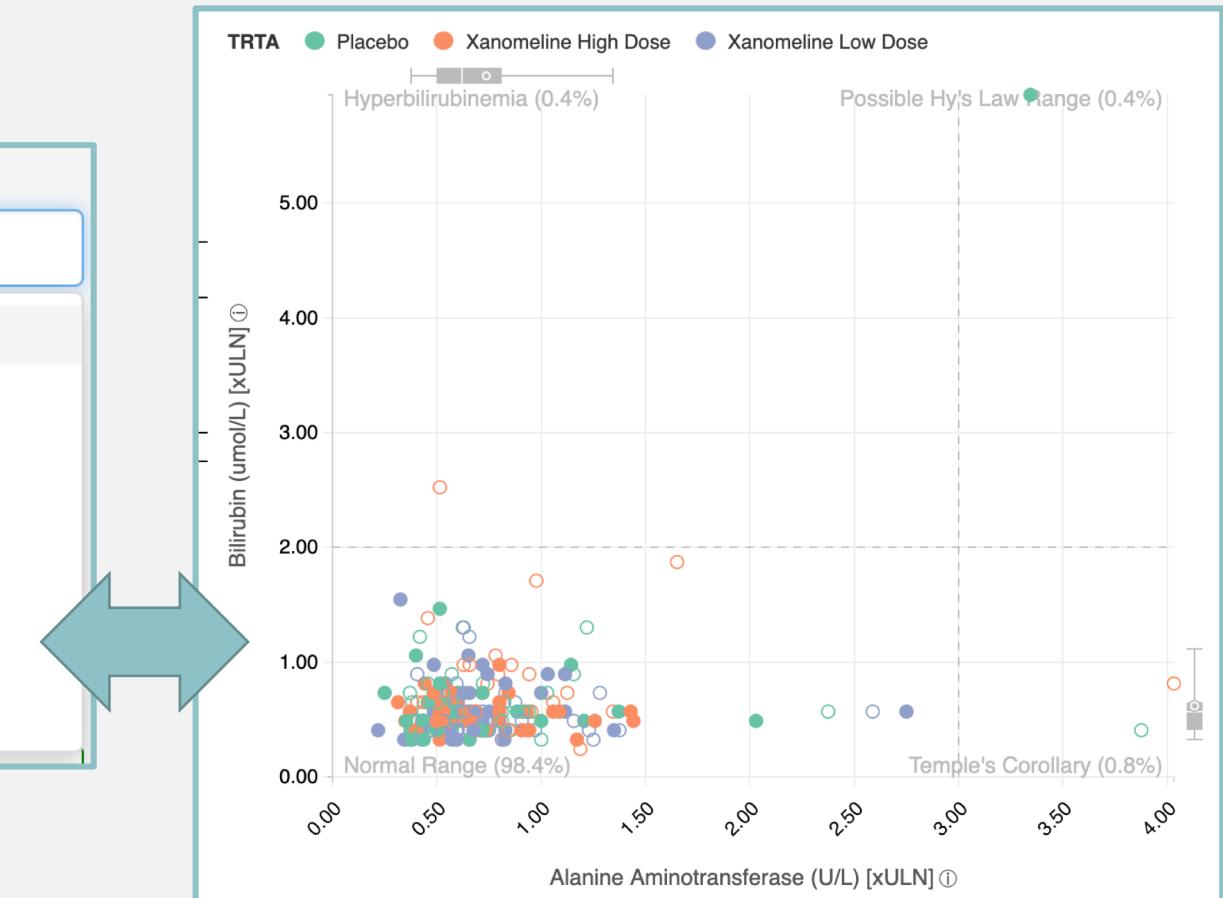
TRTP [Planned Treatment]

TRTPN [Planned Treatment (N)]

TRTAN [Actual Treatment (N)]

TRTSDT [Date of First Exposure to Treatment]

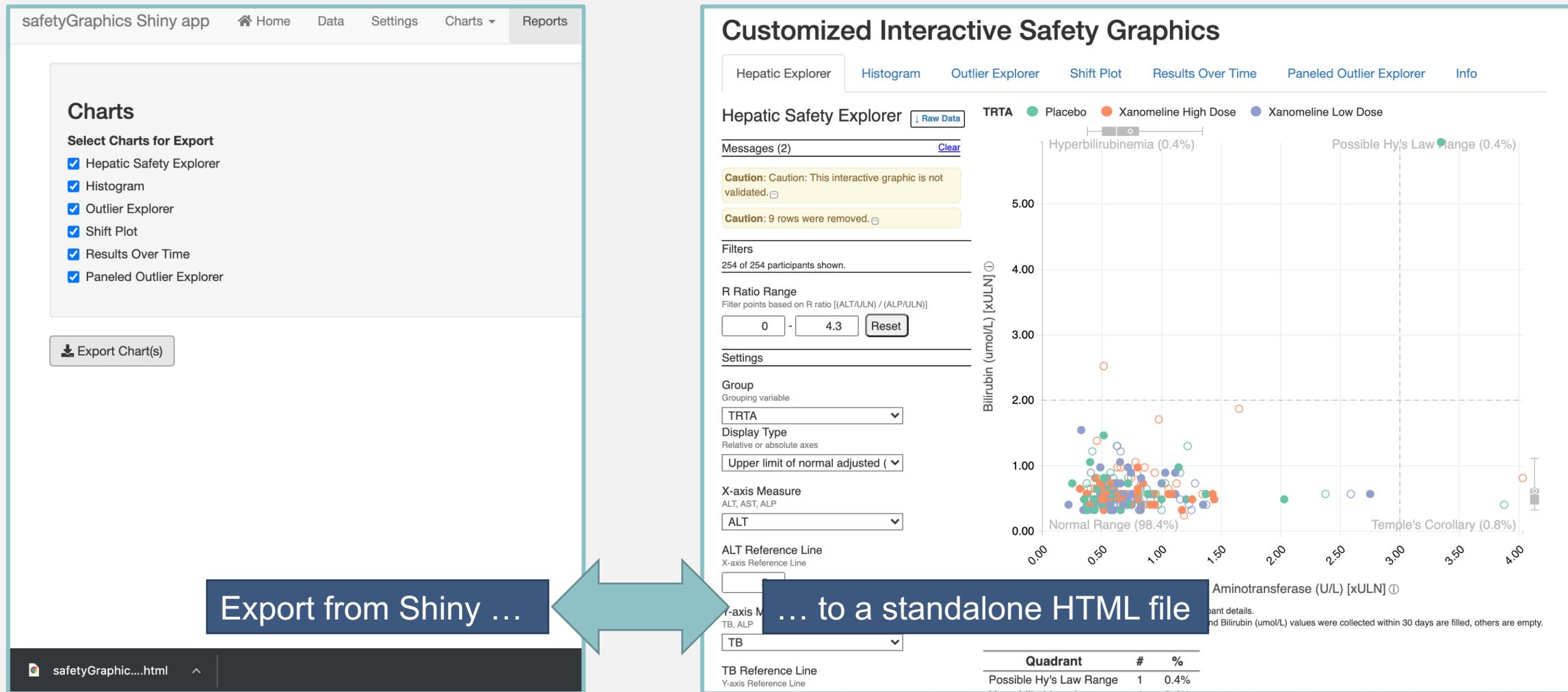
TRTEDT [Date of Last Exposure to Treatment]



Repeat Steps 2 & 3 to customize charts in real time

# safetyGraphics Workflow

## Step 4: Export Report





# safetyGraphics v2.0

Coming Soon!

An open source framework for evaluation of clinical trial safety

Links: [CRAN](#) | [GitHub](#) | [Demo](#)

Try the Prototype now:

```
Devtools::install_github("safetyGraphics/safetyGraphics", "dev")
library(safetyGraphics)
safetyGraphicsApp()
```

CRAN release by the end of 2020!

# {safetyGraphics} v1.0 - Lessons Learned

## What Worked

- Shared Data and Settings
- Flexible data standards
- Modular Shiny Framework
- Exported HTML Reports

## Updates Needed

- Lab Data only
- HTML Widgets only
- Adding New Charts
- Testing in Shiny
- Saving Customizations

# {safetyGraphics} v2.0 - Updates

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## Updates Needed in V1

- Lab Data only
- HTML Widgets only
- Adding New Charts
- Testing in Shiny
- Saving App Customizations

## Improvements in v2

- Multiple Data Domains
- Multiple Chart Types
- Import Charts
- Automated Testing for Modules
- Initialize app w. data/settings

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## Technical Summary – Refactor entire codebase

- 50% reduction in codebase (3402 -> 1725 lines)
- Added 10 Shiny Modules (with automated tests!)
- Shiny code moved from /inst to /R

# safetyGraphics 2.0

## Multiple Data Domains

safetyGraphics    Home    Data ▾    Charts ▾    Reports    Settings ▾    V2

**AES** Dimension Standard  
1191x35 SDTM

**ID column**  
USUBJID

**Sequence column**  
AESEQ

**AE Start day column**  
AESTDY

**AE End day column**  
AEENDY

**Preferred Term Column**  
AETERM

**AE Body System**

**LABS** Dimension Standard  
10288x46 ADaM

**ID column**  
USUBJID

**Value column**  
AVAL

**Measure column**  
PARAM

Alanine Aminotransferase value  
Alanine Aminotransferase (U/L)

Aspartate Aminotransferase value  
Aspartate Aminotransferase (U/L)

Total Bilirubin value

**DM** Dimension Standard  
306x25 Partial ADaM

**ID column**  
USUBJID

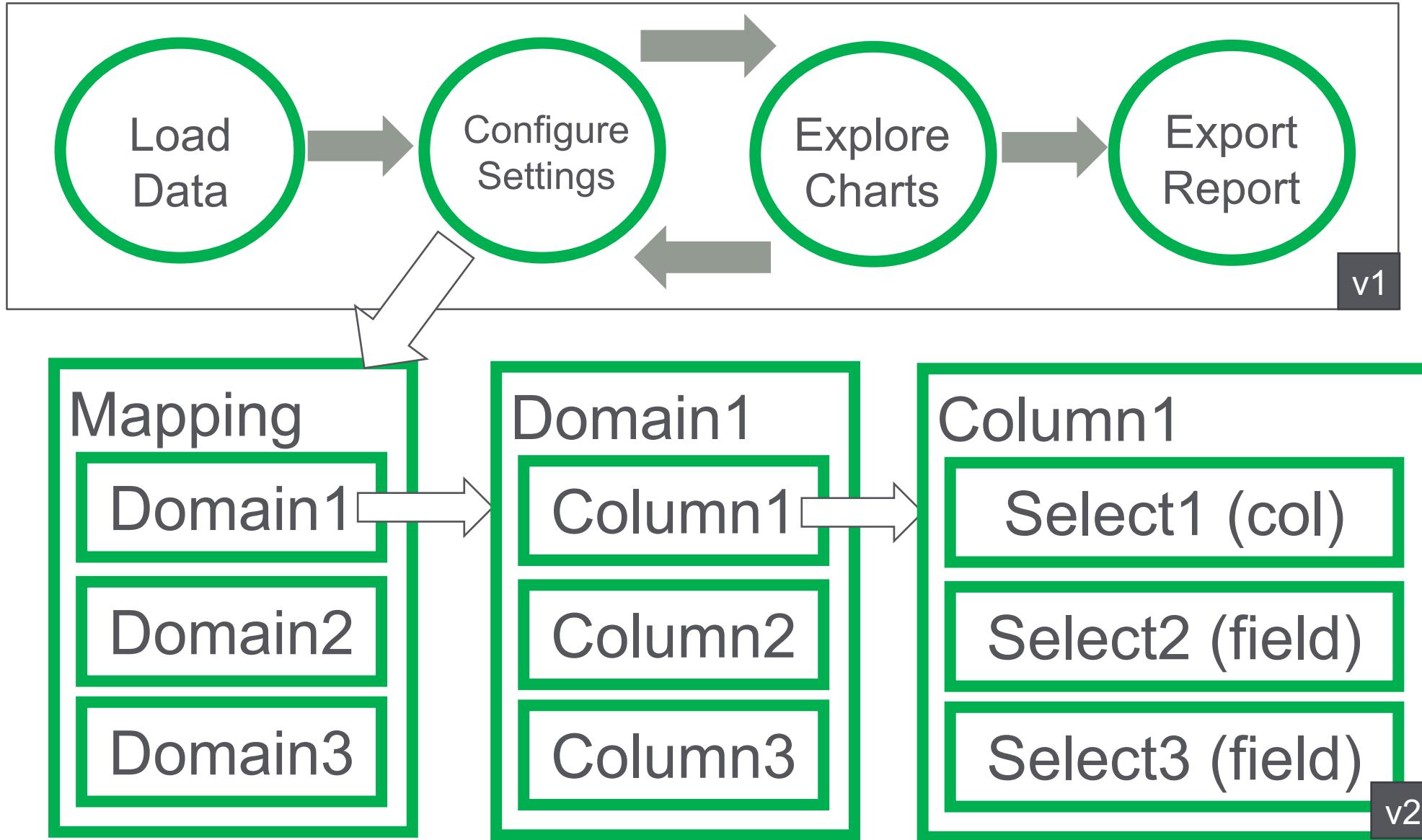
**Treatment Column**  
ARM

Treatment 1

Treatment 2

# safetyGraphics 2.0

## Multiple Data Domains



# safetyGraphics 2.0

## Multiple Data Domains

1 Mapping Tab Module

The screenshot displays the safetyGraphics 2.0 application interface with three data domains visible:

- AES (Dimension Standard 1191x35 SDTM):** Contains fields for ID column (USUBJID), Sequence column (AESEQ), AE Start day column (AESTDY), AE End day column (AEENDY), Preferred Term Column (AETERM), AE Body System (AEBODSYS), Details (red box), and Filters (red box).
- EDD (Dimension Standard 10288x46 ADaM):** Contains fields for ID column (USUBJID), Value column (AVAL), Measure column (PARAM), Alanine Aminotransferase value (Alanine Aminotransferase (U/L)), Aspartate Aminotransferase value (Aspartate Aminotransferase (U/L)), Total Bilirubin value (Bilirubin (umol/L)), Alkaline Phosphatase value (Alkaline Phosphatase (U/L)), and Lower Limit of Normal column (A1LO).
- DLT (Dimension Standard 306x25 Partial ADaM):** Contains fields for ID column (USUBJID), Treatment Column (ARM), Treatment 1 (red box), and Treatment 2 (red box).

# safetyGraphics 2.0

## Multiple Data Domains

3 Domain Modules

The screenshot displays the safetyGraphics 2.0 interface with three domain modules:

- AES**: Dimension Standard 1191x35 SDTM.
  - ID column: USUBJID
  - Sequence column: AESEQ
  - AE Start day column: AESTDY
  - AE End day column: AEENDY
  - Preferred Term Column: AETERM
  - AE Body System: AEBODSYS
  - Details: (red box)
  - Filters: (red box)
- LABS**: Dimension 10288x46 ADaM.
  - ID column: USUBJID
  - Value column: AVAL
  - Measure column: PARAM
    - Alanine Aminotransferase value: Alanine Aminotransferase (U/L)
    - Aspartate Aminotransferase value: Aspartate Aminotransferase (U/L)
    - Total Bilirubin value: Bilirubin (umol/L)
    - Alkaline Phosphatase value: Alkaline Phosphatase (U/L)
  - Lower Limit of Normal column: A1LO
- DIVI**: Dimension 306x25 Standard Partial ADaM.
  - ID column: USUBJID
  - Treatment Column:
    - Treatment 1: (red box)
    - Treatment 2: (red box)

# safetyGraphics 2.0

## Multiple Data Domains

14 Column Modules

The screenshot displays the safetyGraphics 2.0 interface with three data domains:

- AES**: Dimension Standard 1191x35 SDTM. Columns include: ID column (USUBJID), Sequence column (AESEQ), AE Start day column (AESTDY), AE End day column (AEENDY), Preferred Term Column (AETERM), AE Body System (AEBODSYS), Details, and Filters.
- LADS**: Dimension 10288x46 ADaM. Columns include: ID column (USUBJID), Value column (AVAL), Measure column (PARAM), Alanine Aminotransferase value (Alanine Aminotransferase (U/L)), Aspartate Aminotransferase value (Aspartate Aminotransferase (U/L)), Total Bilirubin value (Bilirubin (umol/L)), Alkaline Phosphatase value (Alkaline Phosphatase (U/L)), and Lower Limit of Normal column (A1LO).
- DIVI**: Dimension Standard 306x25 Partial ADaM. Columns include: ID column (USUBJID), Treatment Column (ARM), Treatment 1, and Treatment 2.

# safetyGraphics 2.0

## Multiple Data Domains

20 Select Modules

AES Dimension Standard 1191x35 SDTM	EDB Dimension Standard 10288x46 ADaM	DIV Dimension Standard 306x25 Partial ADaM
ID column USUBJID	ID column USUBJID	ID column USUBJID
Sequence column AESEQ	Value column AVAL	Treatment Column ARM
AE Start day column AESTDY	Measure column PARAM	treatment 1
AE End day column AEENDY	Alanine Aminotransferase value Alanine Aminotransferase (U/L)	treatment 2
Preferred Term Column AETERM	Aspartate Aminotransferase value Aspartate Aminotransferase (U/L)	
AE Body System AEBODSYS	Total Bilirubin value Bilirubin (umol/L)	
Details	Alkaline Phosphatase value Alkaline Phosphatase (U/L)	
Filters	Lower Limit of Normal column A1LO	

# Automated Testing for Modules

## Automated Testing with {testthat} and {shinytest}

1. Store Module code in /R folder
2. Create Test App showing several use cases for each Module
3. Create {testthat} script that:
  1. Initializes Test App with `app<-shinytest::shinyDriver$new()`
  2. Update app object and test expected for changes as shown below

### Sample Test

```
test_that("changing column input updates the field input values and input list",{
  app$setValue('ex4-measure_col-colSelect','PARAMCD')
  expect_equal(app$getValue("ex4-measure_col-colSelect"),"PARAMCD")
}
```

# safetyGraphics 2.0

## Shared Population Filters

This page dynamically filters the participants in the demographics (dm) data set. Only the selected participants are included in charts.

Number of rows: 117 / 306

117 / 306

**Participant Selection**

38%

Show entries Search:

STUDYID	DOMAIN	USUBJID	SUBJID	RFSTDTC	RFENDTC	RFXSTDTC	RFXENDTC	RFICDTC	RFPENDTC	DTHDTTC	DTHFL
CDISCPILOT01	DM	01-701-1023	1023	2012-08-05	2012-09-02	2012-08-05	2012-09-01		2013-02-18 00:00:00		
CDISCPILOT01	DM	01-701-1057	1057						2013-12-27 00:00:00		
CDISCPILOT01	DM	01-701-1111	1111	2012-09-07	2012-09-17	2012-09-07	2012-09-16		2013-02-22 00:00:00		
CDISCPILOT01	DM	01-701-1115	1115	2012-11-30	2013-01-23	2012-11-30	2013-01-23		2013-05-20 00:00:00		
CDISCPILOT01	DM	01-701-1133	1133	2012-10-28	2013-04-29	2012-10-28	2013-04-28		2013-04-29 10:13:00		

STUDYID DOMAIN USUBJID SUBJID RFSTDTC RFENDTC RFXSTDTC RFXENDTC RFICDTC RFPENDTC DTHDTTC DTHFL

Showing 1 to 5 of 117 entries

Previous 1 2 3 4 5 ... 24 Next

1,001 1,113 1,225 1,336 1,448

2012-07-09 2013-01-28 2014-09-02

2012-09-01 2015-03-05

2012-07-09 2014-09-02

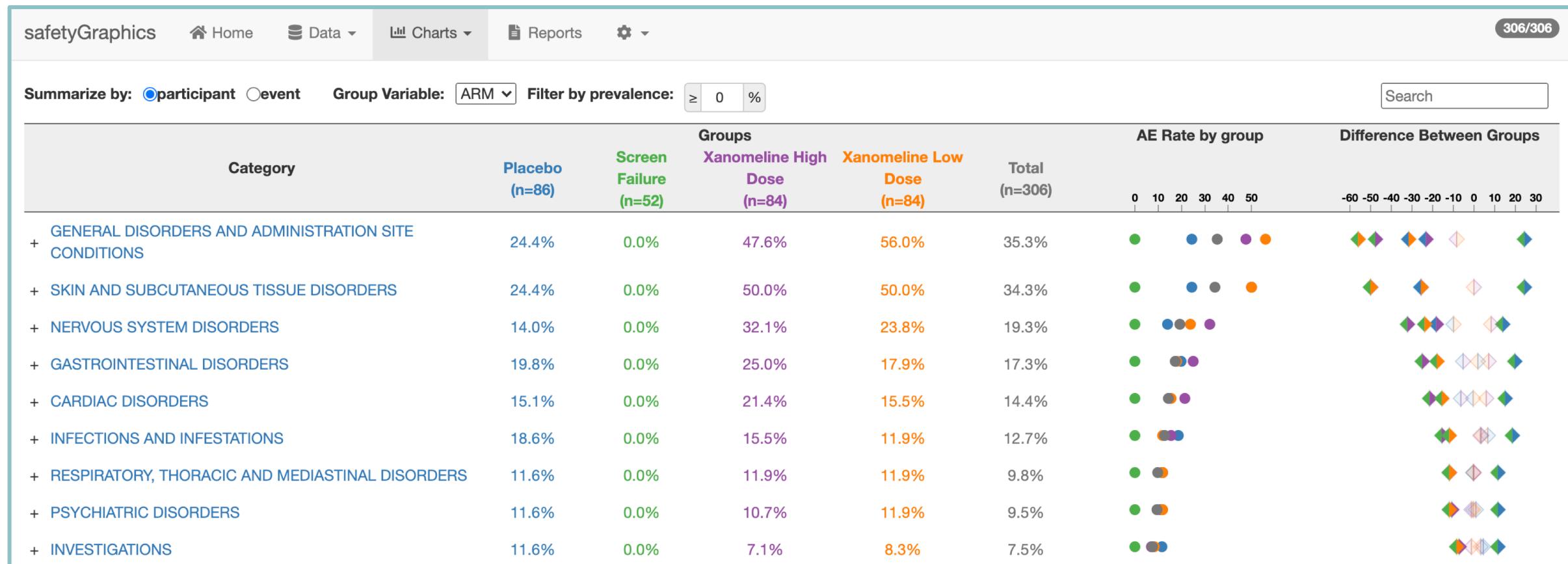
2012-08-28 2015-03-05

2012-08-12 20:00:00 2015-03-05 09:40:00

Shared Population filters with {esquisse} package

# safetyGraphics 2.0

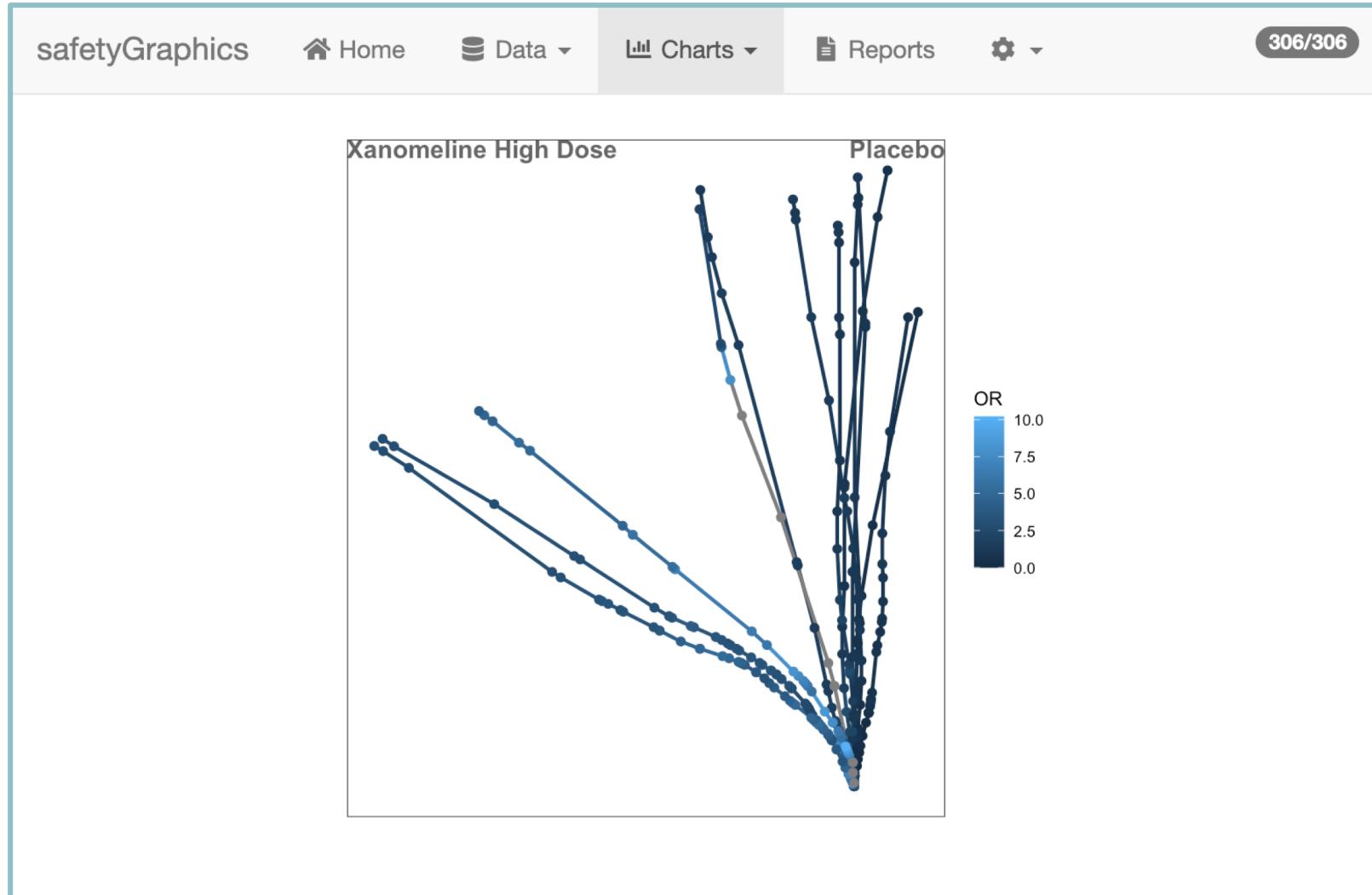
## Cross-Domain Charts



Use AE, Demographics and Treatment Data in a single chart

# safetyGraphics 2.0

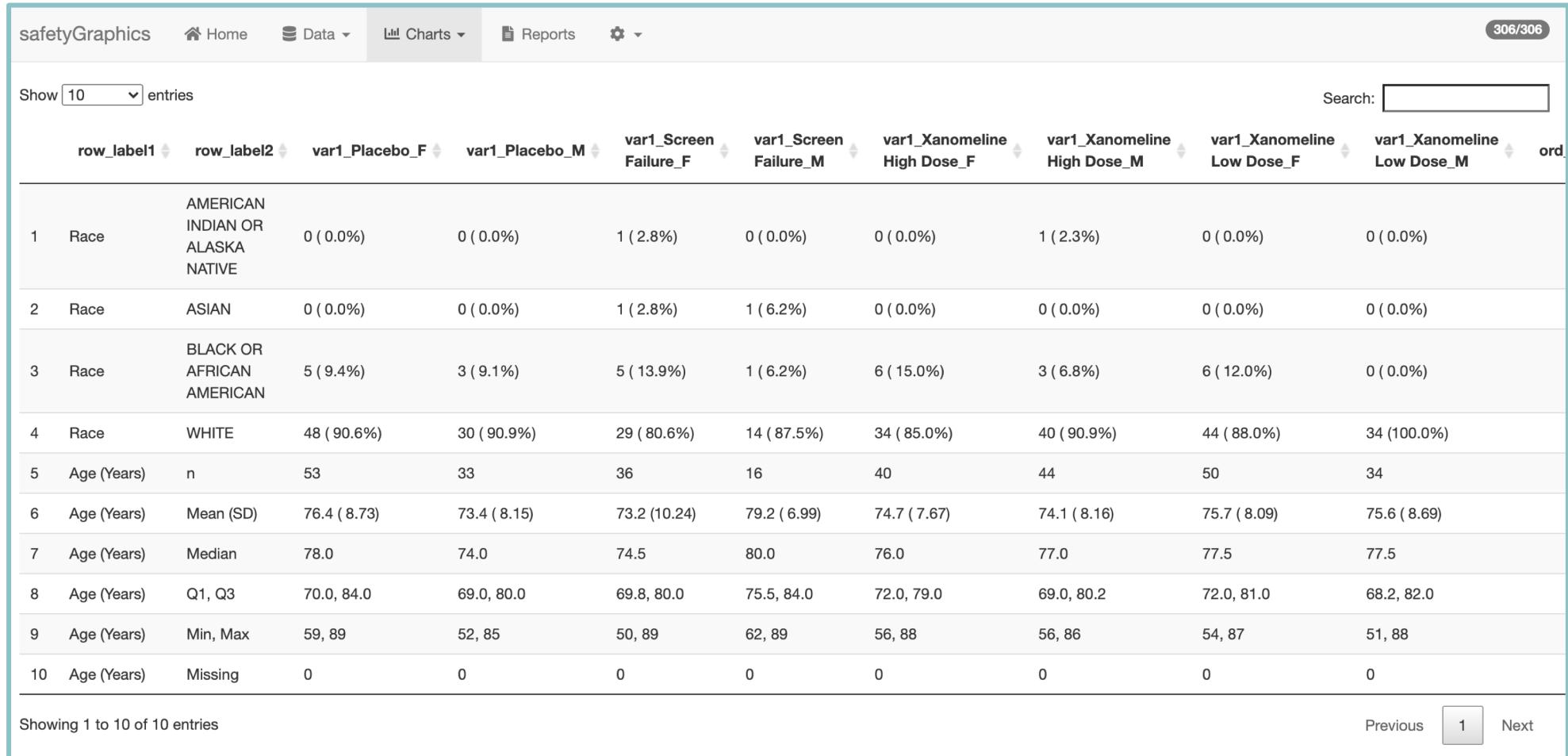
## Import Charts



Static plot created with {Tendril} package

# safetyGraphics 2.0

## Import Charts



The screenshot shows the safetyGraphics 2.0 application interface. At the top, there is a navigation bar with links for Home, Data, Charts, Reports, and settings. A status indicator on the right shows "306/306". Below the navigation bar is a search bar with the placeholder "Search: [ ]". The main content area displays a data table with the following columns:

		row_label1	row_label2	var1_Placebo_F	var1_Placebo_M	var1_Screen Failure_F	var1_Screen Failure_M	var1_Xanomeline High Dose_F	var1_Xanomeline High Dose_M	var1_Xanomeline Low Dose_F	var1_Xanomeline Low Dose_M	ord
1	Race	AMERICAN INDIAN OR ALASKA NATIVE		0 ( 0.0%)	0 ( 0.0%)	1 ( 2.8%)	0 ( 0.0%)	0 ( 0.0%)	1 ( 2.3%)	0 ( 0.0%)	0 ( 0.0%)	
2	Race	ASIAN		0 ( 0.0%)	0 ( 0.0%)	1 ( 2.8%)	1 ( 6.2%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)	
3	Race	BLACK OR AFRICAN AMERICAN		5 ( 9.4%)	3 ( 9.1%)	5 ( 13.9%)	1 ( 6.2%)	6 ( 15.0%)	3 ( 6.8%)	6 ( 12.0%)	0 ( 0.0%)	
4	Race	WHITE		48 ( 90.6%)	30 ( 90.9%)	29 ( 80.6%)	14 ( 87.5%)	34 ( 85.0%)	40 ( 90.9%)	44 ( 88.0%)	34 (100.0%)	
5	Age (Years)	n		53	33	36	16	40	44	50	34	
6	Age (Years)	Mean (SD)		76.4 ( 8.73)	73.4 ( 8.15)	73.2 (10.24)	79.2 ( 6.99)	74.7 ( 7.67)	74.1 ( 8.16)	75.7 ( 8.09)	75.6 ( 8.69)	
7	Age (Years)	Median		78.0	74.0	74.5	80.0	76.0	77.0	77.5	77.5	
8	Age (Years)	Q1, Q3		70.0, 84.0	69.0, 80.0	69.8, 80.0	75.5, 84.0	72.0, 79.0	69.0, 80.2	72.0, 81.0	68.2, 82.0	
9	Age (Years)	Min, Max		59, 89	52, 85	50, 89	62, 89	56, 88	56, 86	54, 87	51, 88	
10	Age (Years)	Missing		0	0	0	0	0	0	0	0	

At the bottom of the table, it says "Showing 1 to 10 of 10 entries". To the right, there are buttons for "Previous", a page number "1", and "Next".

Demographics Table created using {Tplyr} & rendered with {DT} package

# safetyGraphics 2.0

## Import Charts

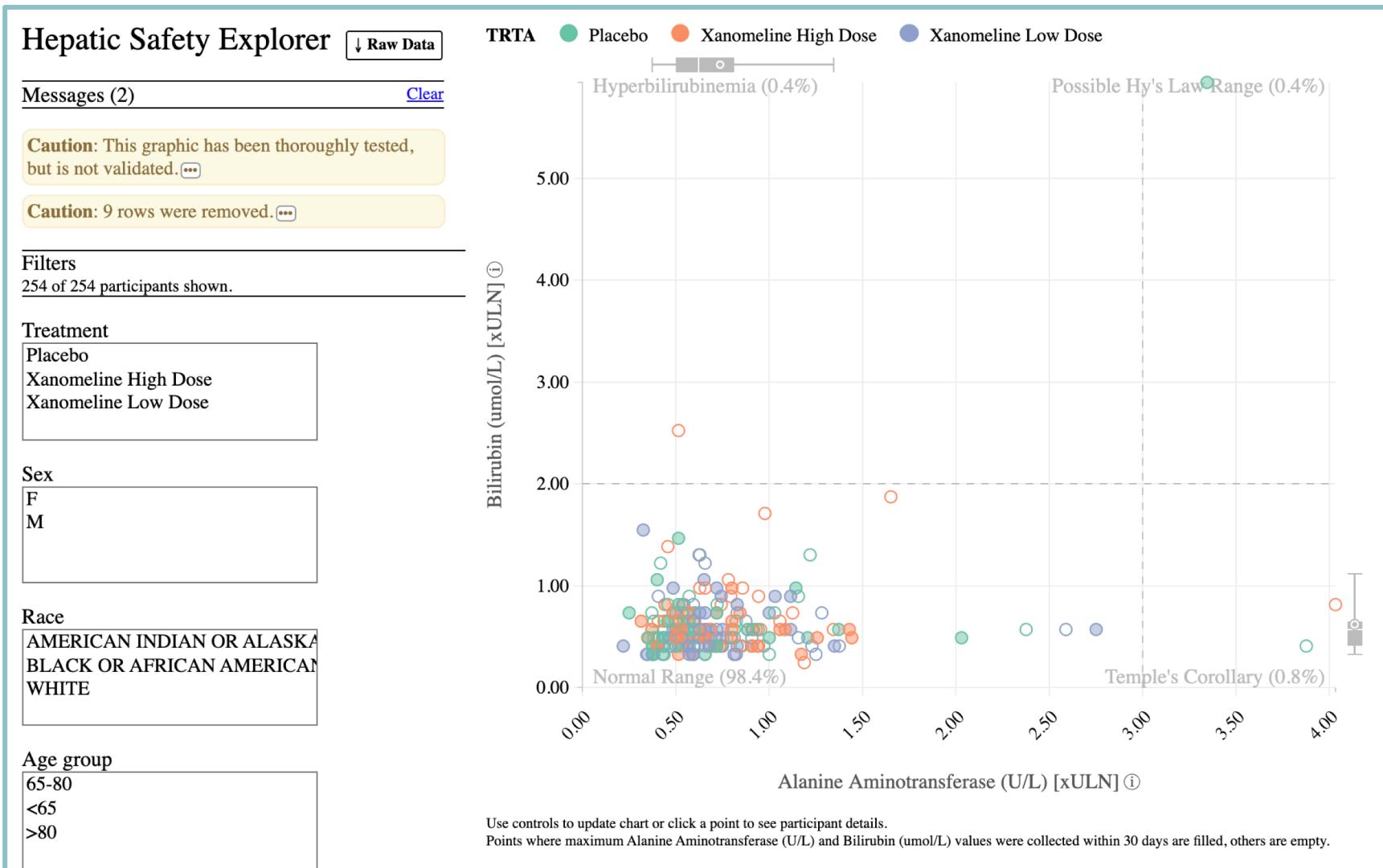
The screenshot shows the safetyGraphics 2.0 application interface. At the top, there is a navigation bar with tabs for Home, Data, Charts (selected), Reports, and Settings. A status indicator on the right shows "306/306". Below the navigation bar is a table with the following data:

row_label1	row_label2	row_label3	var1_Placebo_L	var1_Placebo_N	var1_Placebo_H	var1_Xanomeline High Dose_L	var1_Xanomeline High Dose_N	var1_Xanomeline High Dose_H	var1_Xanomeline Low Dose_L	var1_Xanomeline Low Dose_N	var1_Xano Low Dose
Alkaline Phosphatase (U/L)	SCREENING 1	L	0	0	0	0	0	0	0	0	0
Alkaline Phosphatase (U/L)	SCREENING 1	N	0	84	0	0	82	0	0	81	0
Alkaline Phosphatase (U/L)	SCREENING 1	H	0	0	2	0	0	1	0	0	0
Alkaline Phosphatase 1.1 (U/L)	UNSCHEDULED	L	0	0	0	0	0	0	0	0	0
Alkaline Phosphatase 1.1 (U/L)	UNSCHEDULED	N	0	7	0	0	5	0	0	7	0
Alkaline Phosphatase 1.1 (U/L)	UNSCHEDULED	H	0	0	1	0	0	1	0	0	0

Shift Table created using {Tplyr} & rendered with {kableExtra} package

# safetyGraphics 2.0

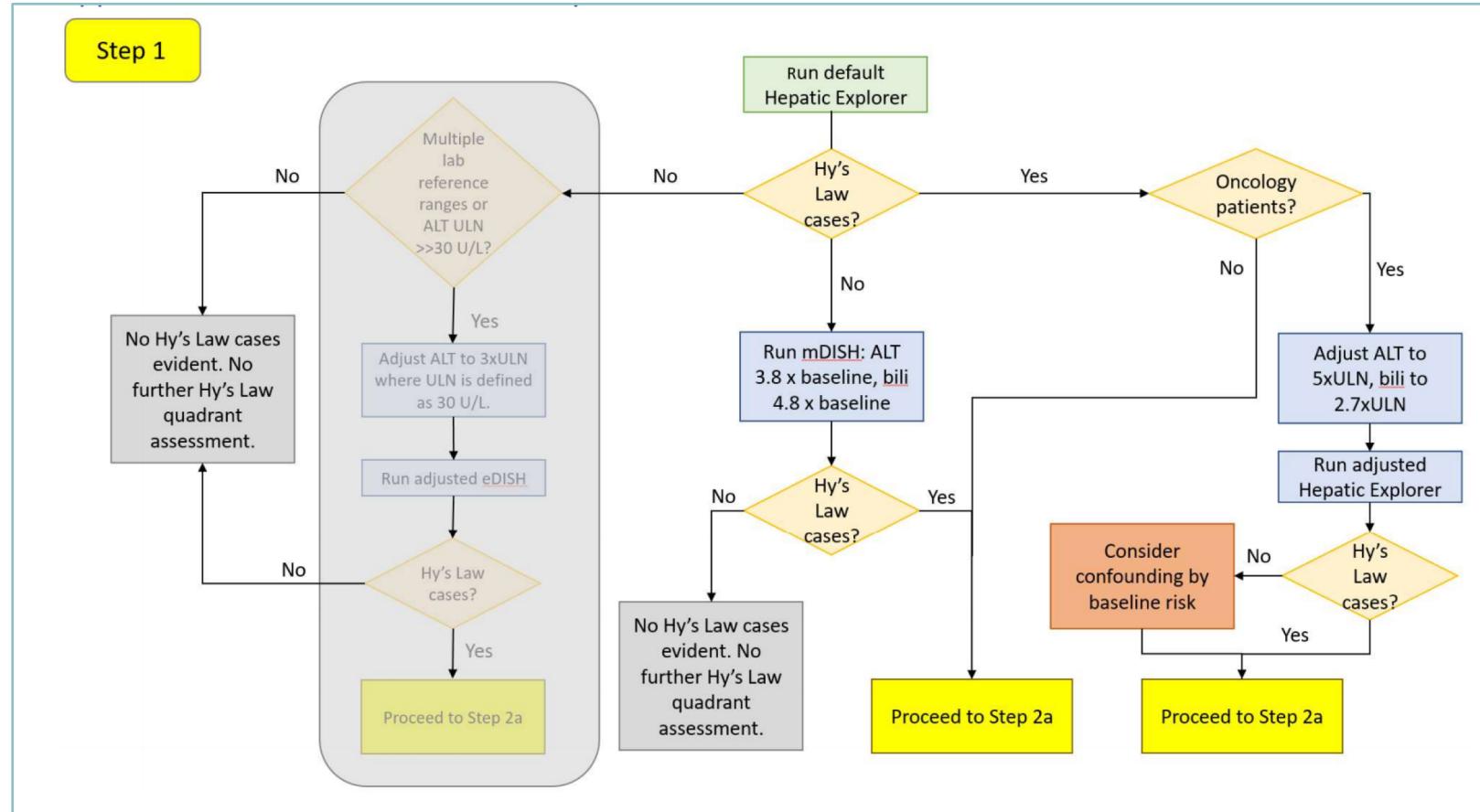
# Hepatic Explorer Updates



- Added innovative new biomarkers PALT and nR.
- Gap Minder style animation by visit.
- Any measure on any axis.
- PAlt added in collaboration with Paul Watkins and Rachel Church (UNC)
- nR added in collaboration with Maribel Isabel Lucena (Malaga Biomedical Research Institute, University of Malaga, Spain)
- Coding by Jeremy Wildfire & Spencer Childress (Rho)

## safetyGraphics 2.0

# Hepatic Explorer Updates - Clinical Workflow

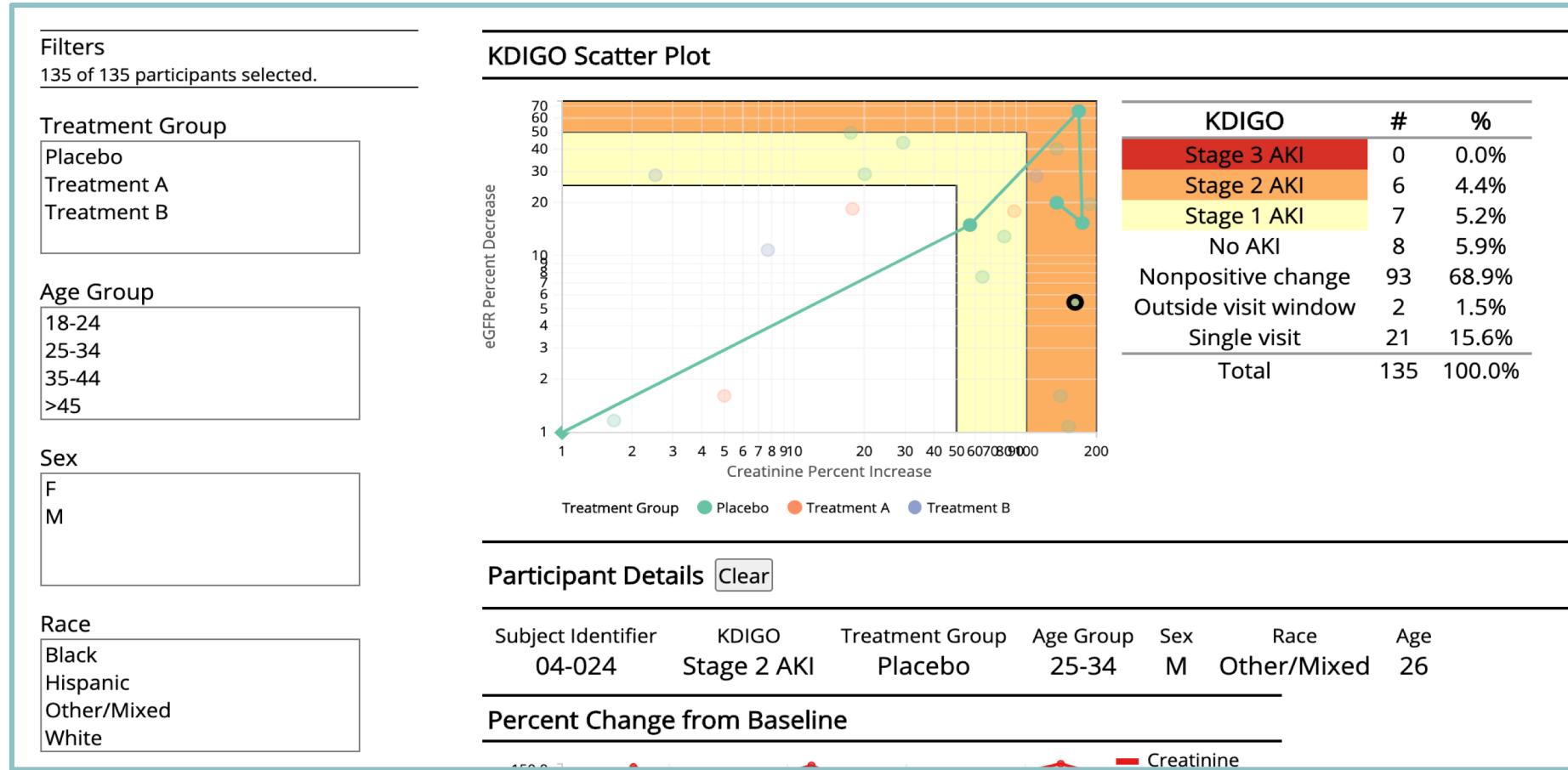


[Link to Clinical Workflow](#)

- Added innovative new biomarkers PALT and nR.
- Gap Minder style animation by visit.
- Any measure on any axis.
- PAIt added in collaboration with Paul Watkins and Rachel Church (UNC)
- nR added in collaboration with Maribel Isabel Lucena (Malaga Biomedical Research Institute, University of Malaga, Spain)
- Coding by Jeremy Wildfire & Spencer Childress (Rho)

# safetyGraphics 2.0

## New Chart - Nephrotoxicity Explorer

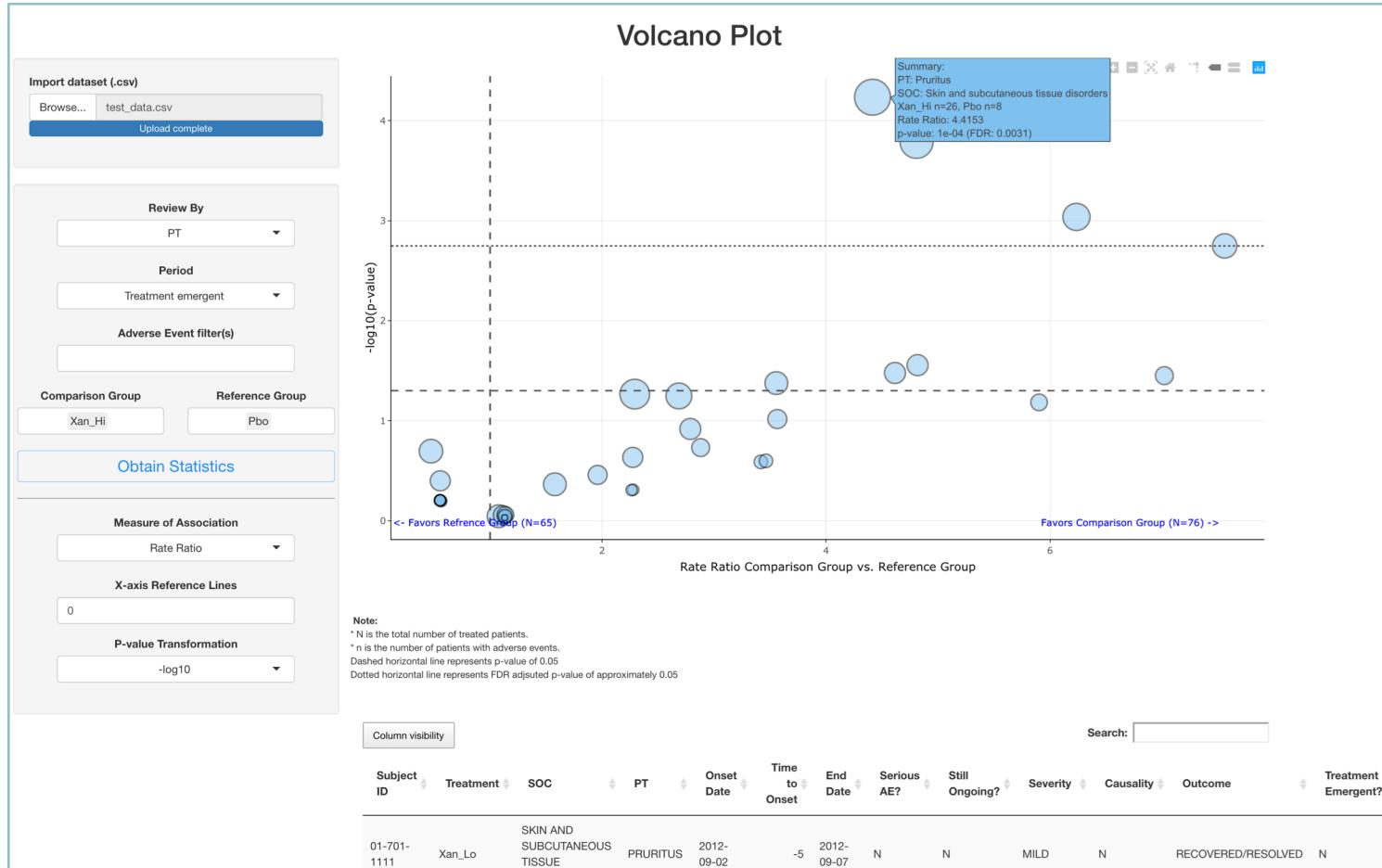


<https://github.com/SafetyGraphics/nep-explorer>

- Dynamic exploration of Kidney Function based on latest medical literature.
- Lit Review by Jim Buchanan (Covilance)
- Coding by Spencer Childress (MMS)

# safetyGraphics 2.0

## New Chart - Volcano Plot



- Dynamic Exploration of Adverse Event Data
- Prototype by Hong Wang, Ke Xiao and Dennis O'Brien (Boehringer Ingelheim)
- Additional Shiny coding by Isaac Zhao (Alkermes)

<https://github.com/SafetyGraphics/volcanoPlot>

# Collaboration in Pharma works!

Ways ISG collaborates:

- Across Companies
- Across Functional Areas
- Across Technologies
- Across Biotech Sectors
- With Regulators
- With Package Developers
- With YOU!

Join Us

[jwildfire@gilead.com](mailto:jwildfire@gilead.com)  
[@jwildfire](https://twitter.com/@jwildfire)

[www.github.com/safetyGraphics](https://www.github.com/safetyGraphics)

# THANK YOU

