

# Interactive Safety Graphics: Starting with Hepatotoxicity

*DV08*

PhUse US Connect, Baltimore  
Feb 25, 2019

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

Susan Duke, FDA  
Jeremy Wildfire, Rho Inc  
Jim Buchanan, Covilance LLC

*A taskforce of the ASA Biopharm /  
DIA Safety WG*



*American Statistical Assn, Biopharm Section &  
Drug Information Association*

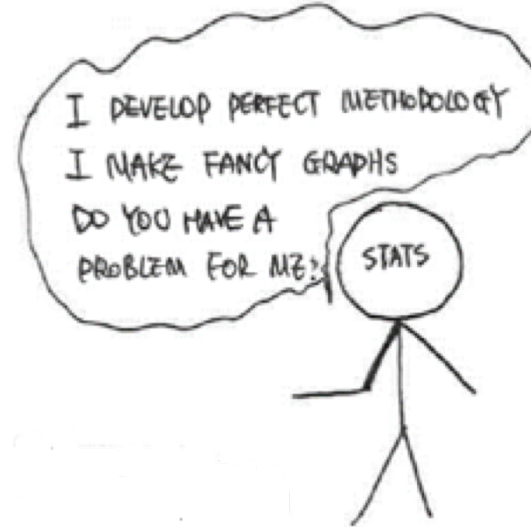
# Safety Clinician's Dilemma



# Statistician Perspective



# Each has their own Perspective





# Aha! Where might this lead?



Cartoon by Mengchun Li, MD  
TB Alliance  
Co-chair, ASA Biopharm/DIA Safety Assessment Scientific Working Group  
Nov 2017|

# Statisticians create outputs and tools



Does the tail wag the dog?

# Safety Clinicians need outputs and tools



Does the dog ask the tail?

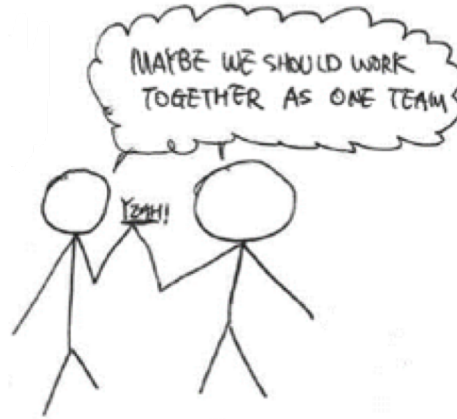
Does the tail wish to engage with the dog?

# Mutual Learning Perspective



[Core values of Mutual Learning teams](#)

# Mutual Learning Perspective



## Core values of Mutual Learning teams

- ❖ Transparency
- ❖ Curiosity
- ❖ Informed choice
- ❖ Accountability
- ❖ Compassion

# Acknowledgments

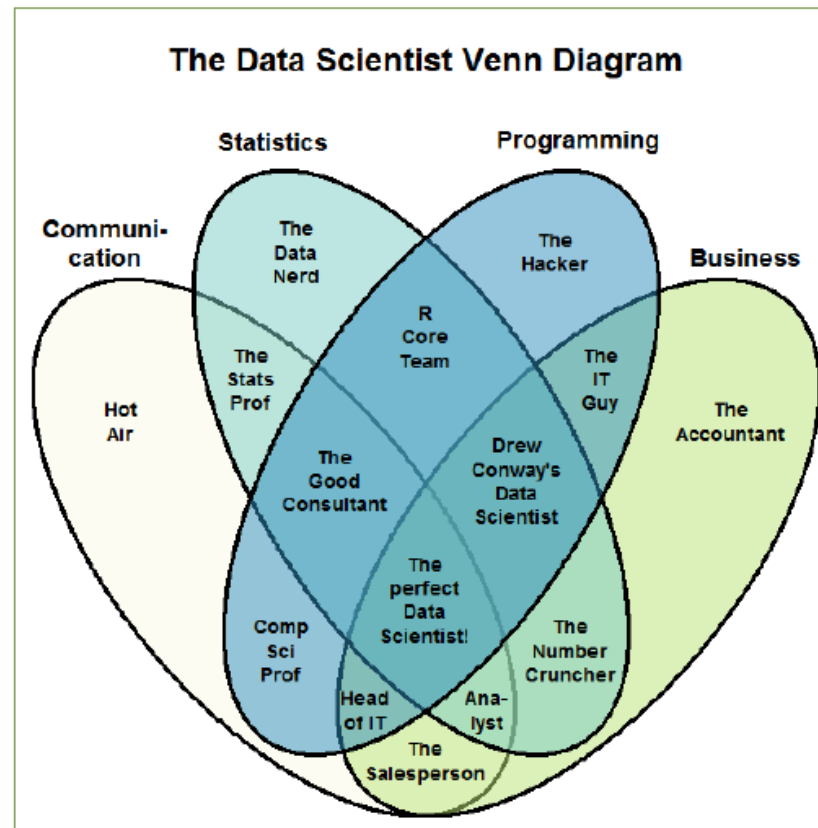
- The safetyGraphics and safety-eDish projects are maintained by the **ASA Biopharm-DIA Safety Working Group's Interactive Safety Graphics Taskforce**, which includes stakeholders from across the pharmaceutical industry, including the FDA. All work is free and open source with an MIT License.
- We are indebted to the **ASA Biopharm-DIA Safety WG** for agreeing to sponsor this Interactive Safety Graphics (ISG) Taskforce. **Jeremy Wildfire (Rho)** developed the initial Javascript code, and worked with **Rebecca Krouse (Rho)** and **Preston Burns (Rho)** to develop the associated safetyGraphics R package, with an assist from **Xiao Ni (Novartis)**; **James Buchanan (Covilance)** authored the User's Guide; **Zackary Skrivaneck (Lilly)** and **Melvin Munsaka (AbbVie)** authored the beta test plan; **Rinki Jajoo (Merck)** and **Nathan Li (Merck)** serve as our project managers (previously Susan Duke); Xiao Ni (previously Susan Duke) represents ISG on the **WG's Communications Team**. **Frank Harrell (Vanderbilt University and FDA)** provided invaluable advice at many steps along the way.
- Clinicians who provided invaluable feedback on tool features and the clinical workflow include James Buchanan, **Eileen Navarro (FDA)**, **Dennis O'Brien (Boehringer-Ingelheim)**, **Barbara Hendrickson (AbbVie)**, **Jonathan Seltzer (ACI Clinical)**, **Mengchun Li (TB Alliance)** and **Mary Furnari (Celgene)**. Their willingness to enter their comments into GitHub not only improved the tool but also demonstrated their interest and need for it.
- In addition to the data scientists and statisticians noted above, our other members include **Karl Brand & Stella Guo (Bayer)**, **Brian Cohen (ACI Clinical)**, **Rachel Dlugash (FDA)**, **Robert Gordon (J&J)**, **Hong Wang (Boehringer-Ingelheim)** and **Richard Zink (Target Pharma Solutions)**.
- The ASA Biopharm/DIA Safety Working Group is ably lead by **Judy Li (Celgene)** and **William Wang (Merck)**.
- Eileen Navarro, **Mat Soukup**, **Gregory Levin**, **Lei Nie**, **Paul Schuette**, Rachel Dlugash, Susan Duke and Frank Harrell at Center for Drug Evaluation, FDA provided helpful feedback for consideration on tool features and usage, and technical help within the CDER environment.

# The statistician's challenge, and opportunity

## Modern Statistician Should be a Data Scientist

4 essential skill sets

- Business
- Statistics
- Programming
- Communication



Courtesy of Stephan Kolassa

# The Problem

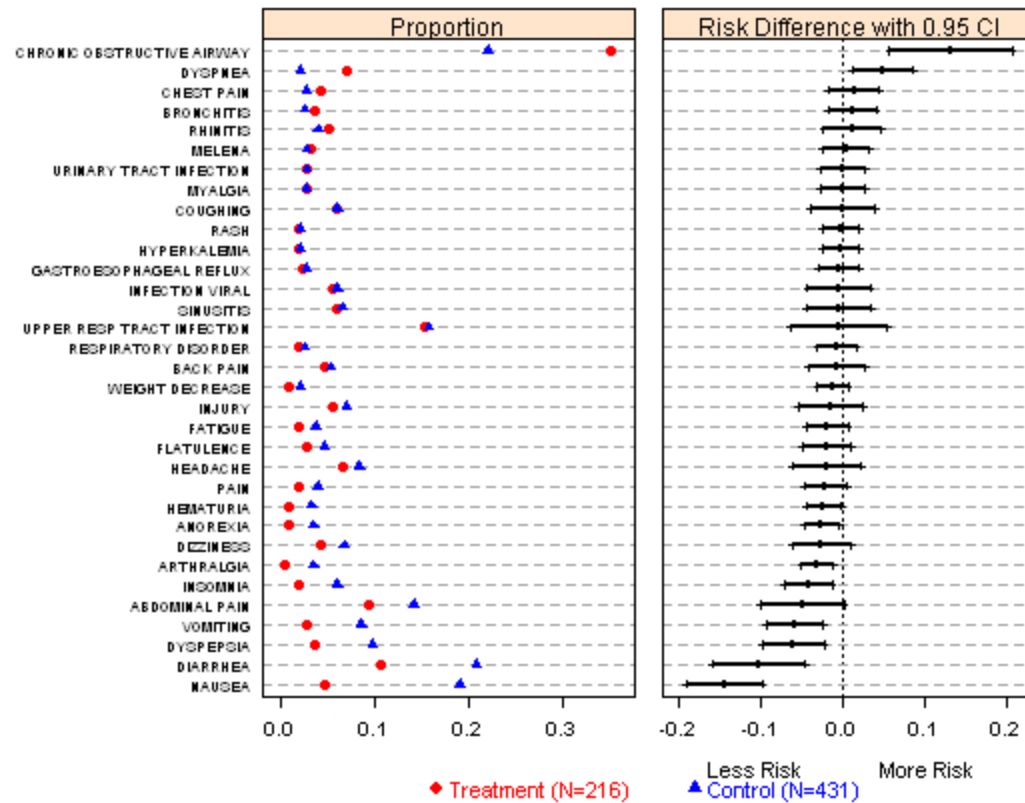
## Safety Clinicians Desire a Safety Evaluation Toolkit

- Methodology Guidance
  - FDA Pre-Marketing Risk Assessment
  - FDA Good Pharmacovigilance Practices and Pharmacoepidemiology
  - FDA Reviewer Guidance
- Proprietary Tools
  - Spotfire, JMP, Qlik, Tableau, J Review, etc.
- Open Source Tools
  - CTSPedia, Rho Safety Monitoring

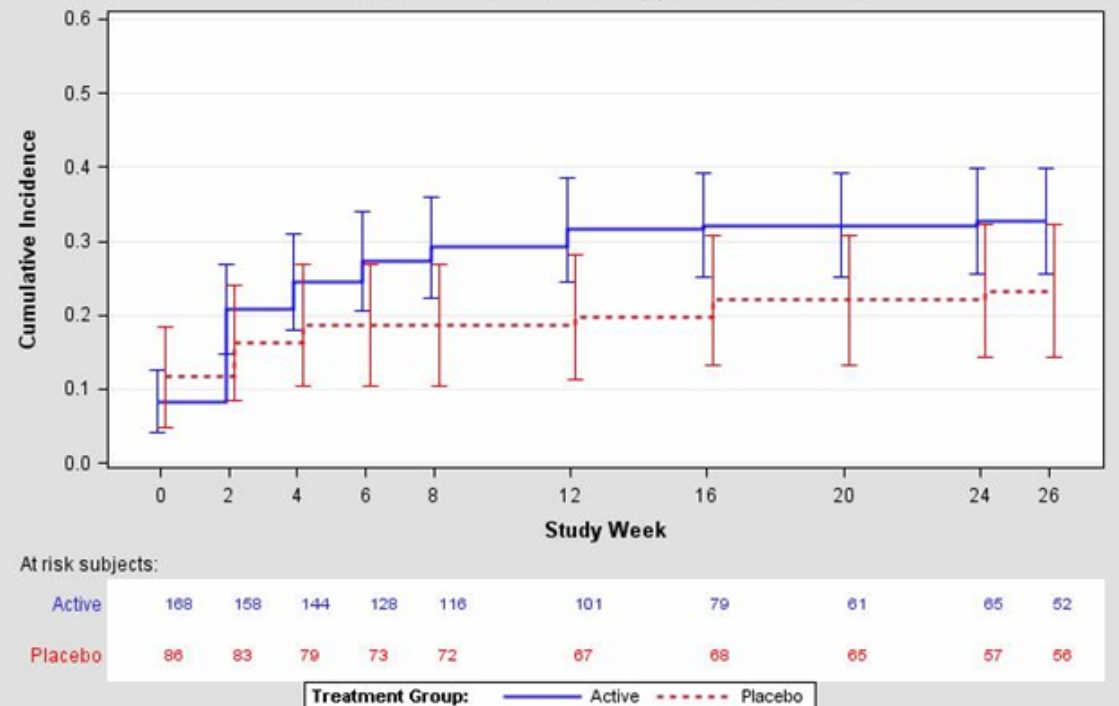


# CTSPedia

Most Frequent On-Therapy Adverse Events Sorted by Risk Difference



Cumulative Incidence (SE) for Alanine Aminotransferase (ALT): Elevations > 3 Times the Upper Limit of Normal



At risk subjects:

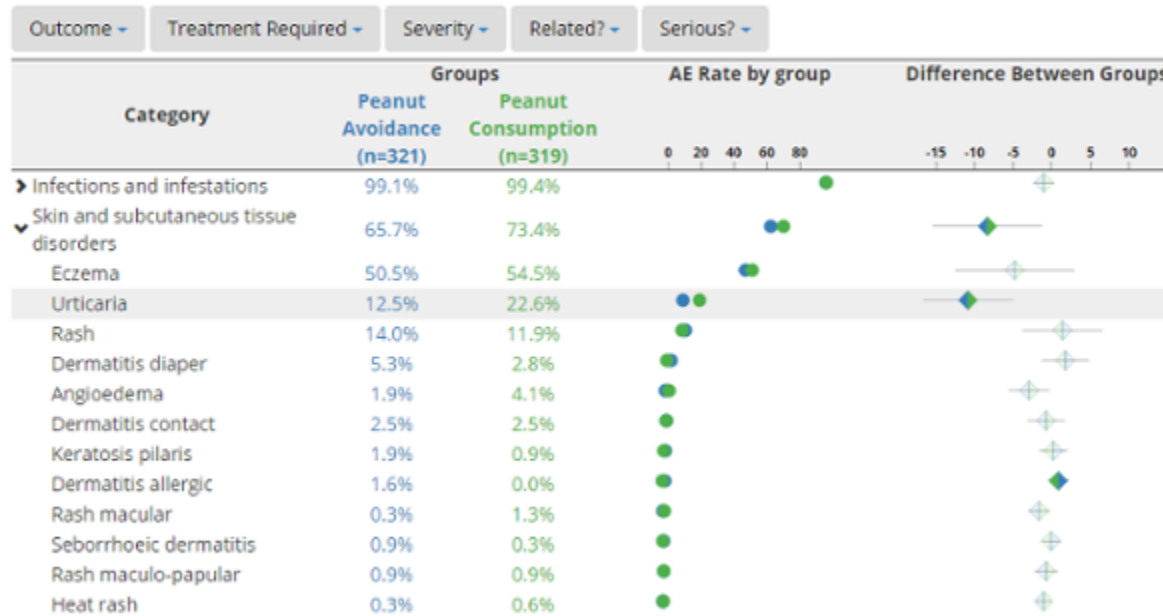
Active	168	158	144	128	116	101	79	61	65	52
Placebo	86	83	79	73	72	67	68	65	57	56

Treatment Group: — Active - - - Placebo

<https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome>

From Jim Buchanan, JSM, 2018

# Rho Safety Monitoring



<http://resources.rhoworld.com/blog/an-interactive-suite-of-data-visualizations-for-safety-monitoring>

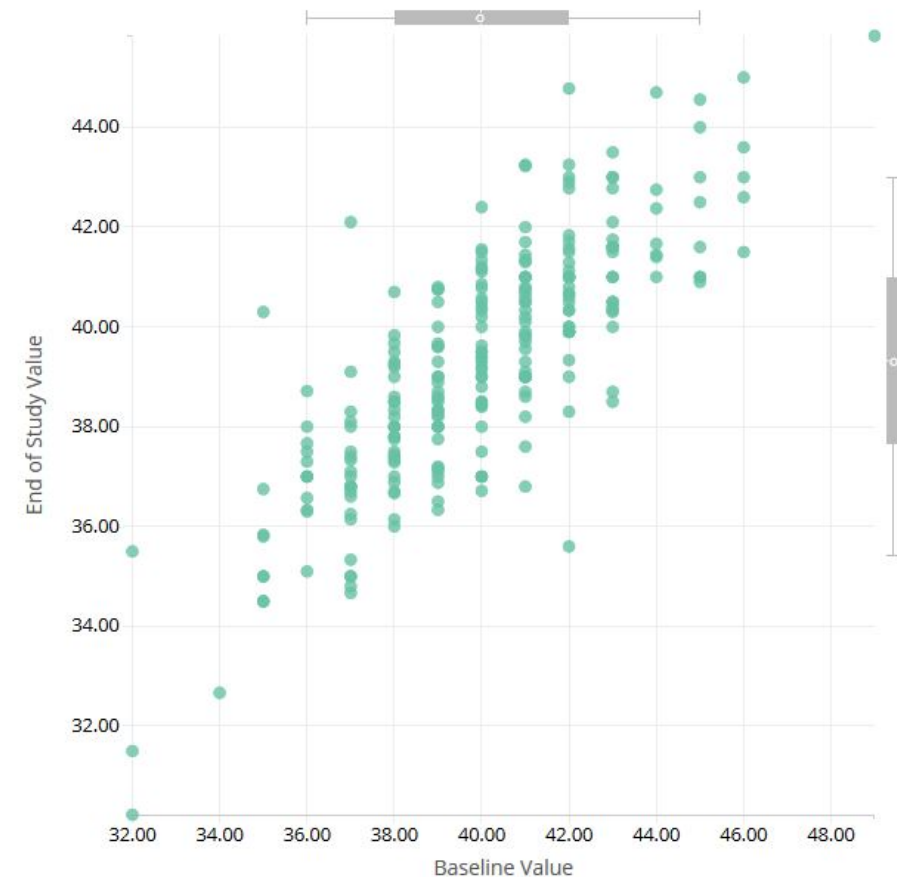
From Jim Buchanan, JSM, 2018

Measure: Albumin ▾

Baseline visit(s): -1, -7, 1, 13 ▾

Comparison visit(s): -1, -7, 1, 13 ▾

This measure collected at visits -7, 14, 28, 30, 42, 56, 84, 112, 140, 168, 182, NA



# Our team's approach

- **Problems**

- Drug development research is highly regulated and notoriously slow moving.
- Manual review of huge data listings is still common.
- Existing analysis tools are expensive, difficult to customize and tend to use proprietary formats, limiting reproducibility.

- **Solutions** Create interactive tools that are:

- Open Source - Transparent. Customizable. Free!
- Interactive - Users can explore their data.
- Easy to Use - Just open up a webpage.
- Easy to Configure - Streamlined configuration with R.
- Compliant with Data Standards - Support ADaM and SDTM by default.
- Highly Collaborative – Clinicians, Statisticians, and Programmers working together.
- Agile - Frequent releases with GitHub.
- Engaging - Regular Feedback from users. Pilot testing. Open issue tracking.
- Industry-wide, multidisciplinary collaborative – *developers & users working together, earn each others' trust*

- **Purpose** *Common Answers* for the Common Drug Development Safety Questions


# ASA-DIA Biopharm Safety Working Group

## Workstream 1b: Safety Evaluation and Identification of Risk

- Identify common safety questions
- Develop interactive signal detection and evaluation tools
- Make available to drug safety/pharmacovigilance departments, safety assessment committees, data monitoring committees, regulatory authorities
- Provide training to support the adoption and efficient use of the tools

# ASA-DIA Biopharm Safety Working Group

## Safety Topics to Target:

-  Hepatotoxicity and other labs
- QT prolongation
- Adverse event evaluation



# Interactive eDISH plot & Clinical Workflow



## safetygraphics R Package

Links: [CRAN](#) | [GitHub](#) | [Interactive Chart](#)

Related Tools: [SafetyExploreR](#) | [safety-eDish](#)

### Safety eDish

Use controls to update chart or click a point to see participant details.

#### Group

Grouping variable

TRTA

#### Display Type

Relative or absolute axes

Upper limit of normal adjusted (et)

#### X-axis Measure

ALT, AST, ALP

ALT

#### ALT Reference Line

X-axis Reference Line

3

#### TB Reference Line

Y-axis Reference Line

2

#### Point Size

Parameter to set point radius

Uniform

#### Axis Type

Linear or Log Axes

linear

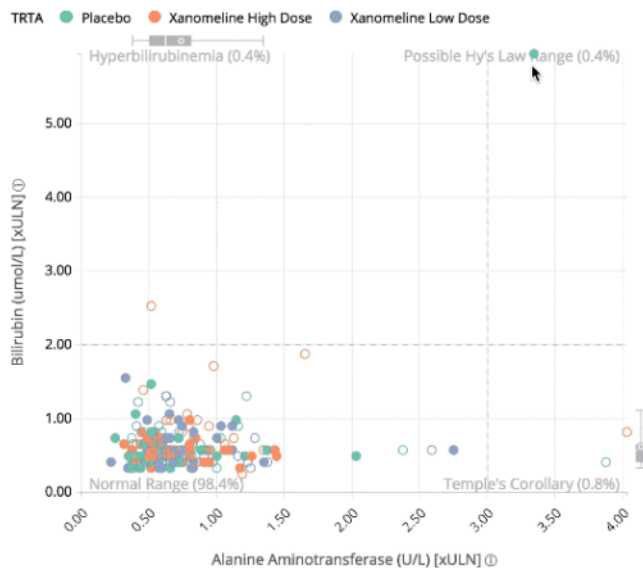
#### Highlight Points Based on Timing

Fill points with max values less than X days apart

30

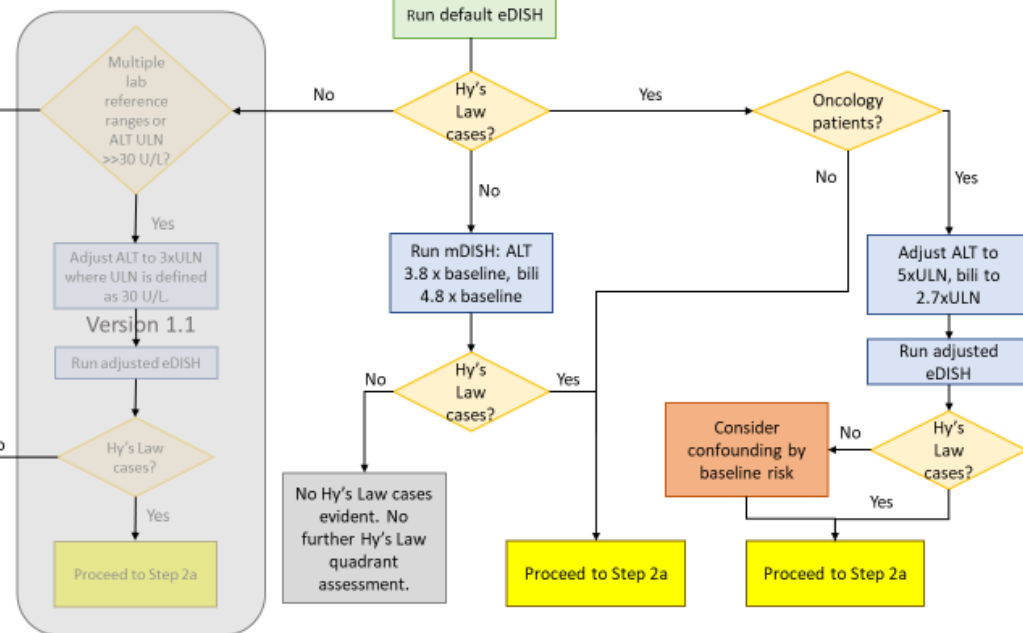
#### Filters

254 of 254 participants shown.



Quadrant	#	%
Possible Hy's Law Range	1	0.4%
Hyperbilirubinemia	1	0.4%
Temple's Corollary	2	0.8%
Normal Range	250	98.4%

### Step 1



```
#Code to initialize shiny application
install.packages("safetyGraphics")
library("safetyGraphics")
safetyGraphicsApp()
```

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

# eDish RShiny app – Data upload

[illegible]

# eDish RShiny app – Data mapping

### Data Mapping

ID column\* OK

USUBJID

Value column\* OK

AVAL

Measure column\* OK

PARAM

Alanine Aminotransferase value OK

Alanine Aminotransferase (U/L)

Aspartate Aminotransferase value OK

Aspartate Aminotransferase (U/L)

Total Bilirubin value OK

Bilirubin (umol/L)

Alkaline Phosphatase value OK

Alkaline Phosphatase (U/L)

Lower Limit of Normal column\* OK

A1LO

Upper Limit of Normal column\* OK

A1HI

Visit column OK

AVISIT

Visit Number column OK

VISITNUM

Study Day column\* OK

ADY

Baseline column

Baseline values

Filters columns

Group columns

Analysis Flag column

Analysis Flag values

### Measure Settings

X axis options

ALT AST ALP

Y axis options

TB

### Appearance Settings

Default Visit Window in Days

0 30 50

Show R Ratio Filter?

☒

Default R Ratio Cut

0 1

Show Chart Title?

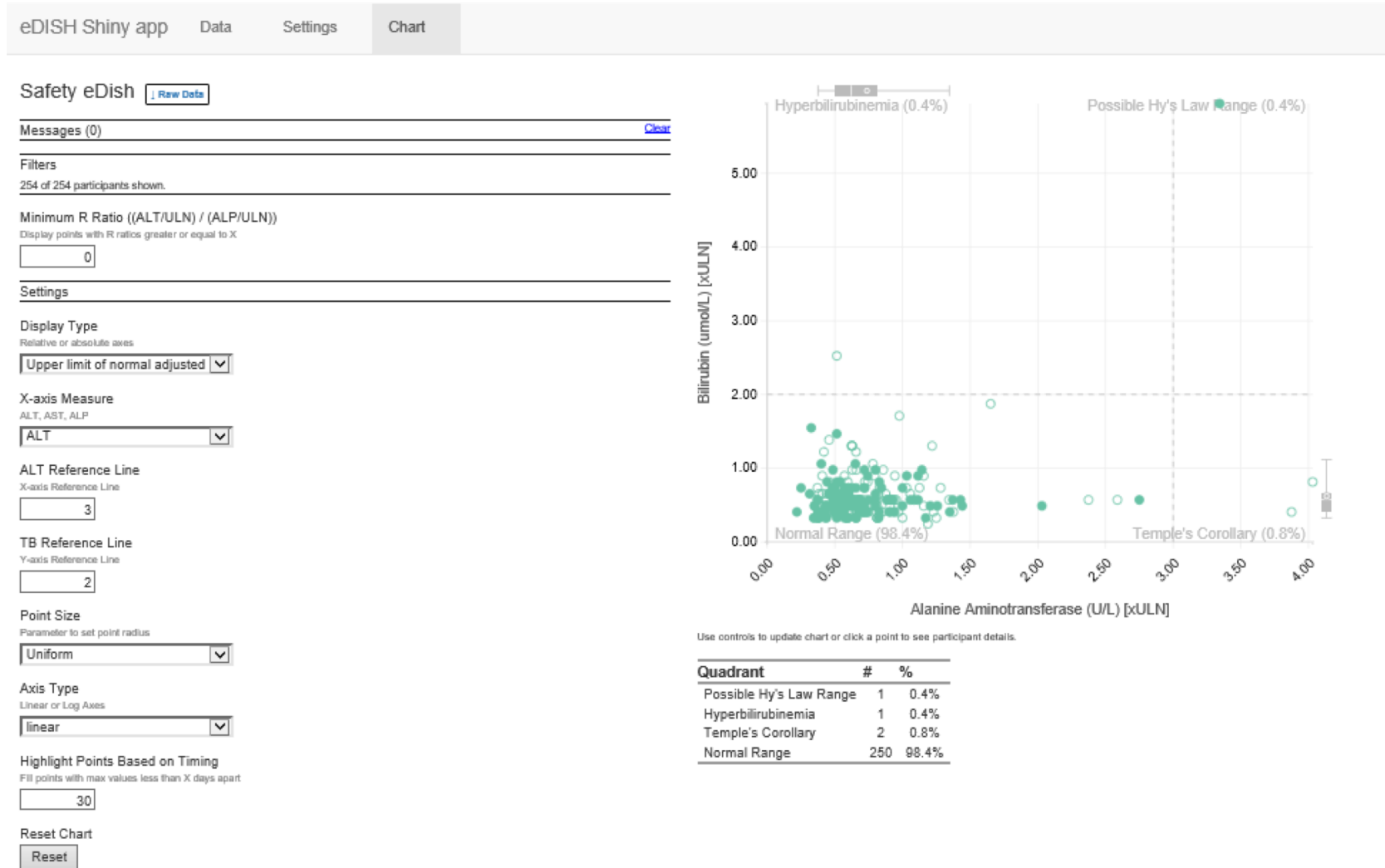
☒

Warning text

Caution: This interactive graphic is not validated. Any clinical recommendations based on



# eDish RShiny app – Chart – Initial View



# Investigating a Patient's Experience

The screenshot displays the eDISH Shiny app interface. The top navigation bar includes tabs for 'Data', 'Settings', and 'Chart'. The 'Data' tab is active, showing a 'Data upload' section on the left and a 'Data Preview for Example data' section on the right.

**Data upload section:**

- Upload a csv or sas7bdat file
- Browse... (No file selected)
- Select file for eDISH chart
- Example data - [ACaI](#)

**Data Preview for Example data section:**

Showing 1 to 10 of 10,288 entries

STUDYID	SUBJID	USUBJID	TRTPT	TRTPN	TRTA	TRTAN	TRTSDT	TRTEDT	AGE	AGEGR1	AGEGR1N	RACE	RACEN	SEX	COMP2AFL	DSRAEFL	SAFFL	AVISIT	AVI1
CDISCPL0T01	1015	01-701-1015	Placebo	0	Placebo	0	2014-01-02	2014-07-02	63	<65		1	WHITE	1	F	Y		Baseline	
CDISCPL0T01	1015	01-701-1015	Placebo	0	Placebo	0	2014-01-02	2014-07-02	63	<65		1	WHITE	1	F	Y		Baseline	
CDISCPL0T01	1015	01-701-1015	Placebo	0	Placebo	0	2014-01-02	2014-07-02	63	<65		1	WHITE	1	F	Y		Baseline	
CDISCPL0T01	1015	01-701-1015	Placebo	0	Placebo	0	2014-01-02	2014-07-02	63	<65		1	WHITE	1	F	Y		Baseline	
CDISCPL0T01	1015	01-701-1015	Placebo	0	Placebo	0	2014-01-02	2014-07-02	63	<65		1	WHITE	1	F	Y		Baseline	
CDISCPL0T01	1015	01-701-1015	Placebo	0	Placebo	0	2014-01-02	2014-07-02	63	<65		1	WHITE	1	F	Y		Week 2	
CDISCPL0T01	1015	01-701-1015	Placebo	0	Placebo	0	2014-01-02	2014-07-02	63	<65		1	WHITE	1	F	Y		Week 2	
CDISCPL0T01	1015	01-701-1015	Placebo	0	Placebo	0	2014-01-02	2014-07-02	63	<65		1	WHITE	1	F	Y		Week 2	

Showing 1 to 10 of 10,288 entries

Previous 1 2 3 4 5 ... 1028 Next

# Clinically agreed workflow for tool's use

Based on the literature and safety clinician's advice

The advent of interactivity creates both opportunity & challenge

Requires:

- Scientific rigor
- Replicability

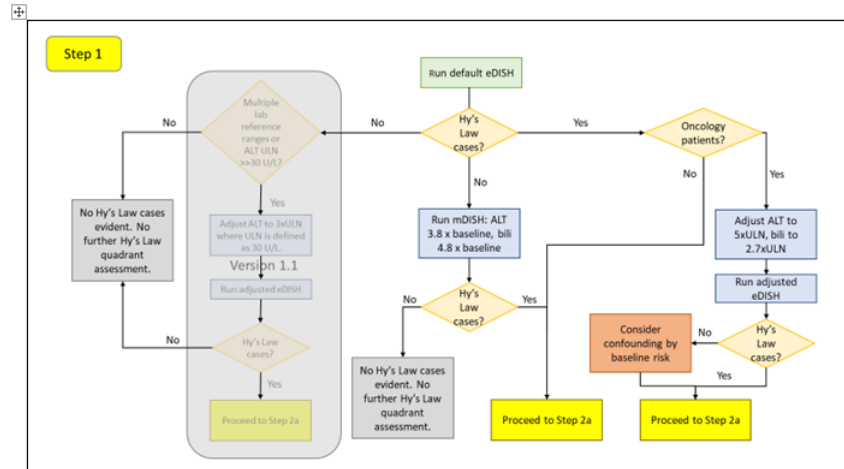
# Clinically agreed workflow for tool's use

## Based on the literature and safety clinician's advice



quickly created value and excitement in the tool and process we're endeavoring to create with our interdisciplinary team members (for membership, see acknowledgements below). For a WG to be successful, its members need to find it rewarding and enjoyable, and we're glad for that too.

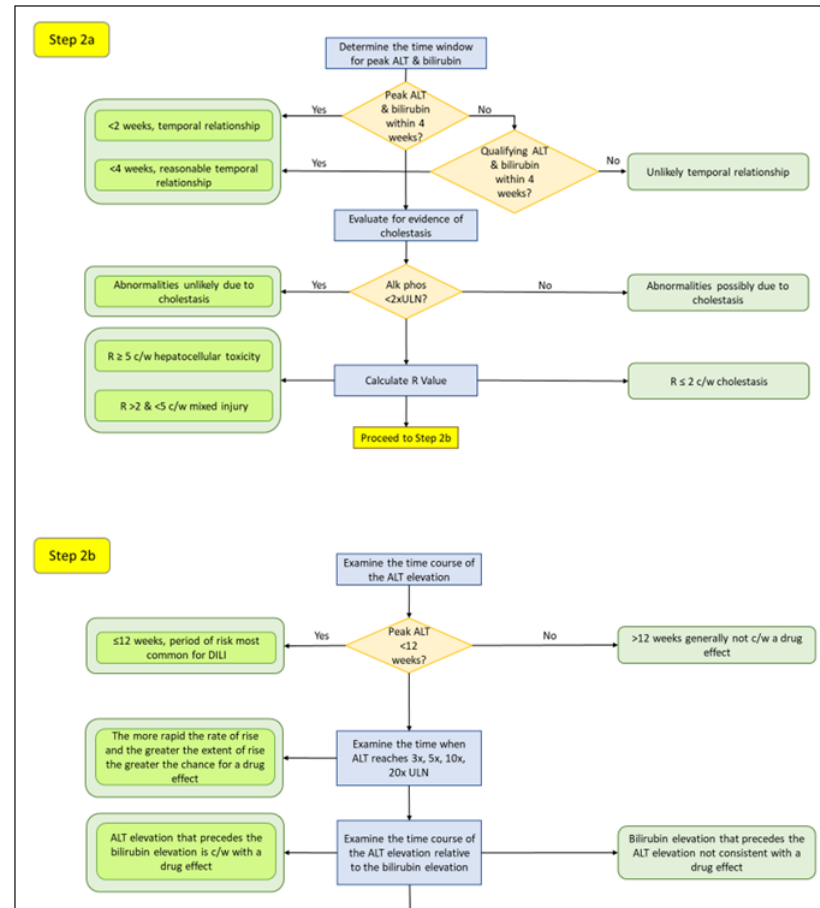
Development of this open source hepatotoxicity tool and recommended clinical workflow for liver signals is our taskforce's first objective. Adverse events and EKG are the topics we will turn our attention to next.



The advent of interactivity creates both opportunity & challenge

Requires:

- Scientific rigor
- Replicability





ASA Biopharm & DIA

# Discussion

- “A new way to develop software”?
  - User/developer collaboration within a WG to create the tool itself
  - Open source platform
- Goal: **lingua franca** for monitoring/characterizing common drug safety questions
  - Is there a downside to patients/science in attempting this?
- *It's an audacious goal!*
  - Are there any big issues we haven't considered?

# THANK YOU



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