

# Interactive Safety Graphics: Starting with Hepatotoxicity

DV08

PhUse US Connect, Baltimore

Feb 25, 2019

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

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*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



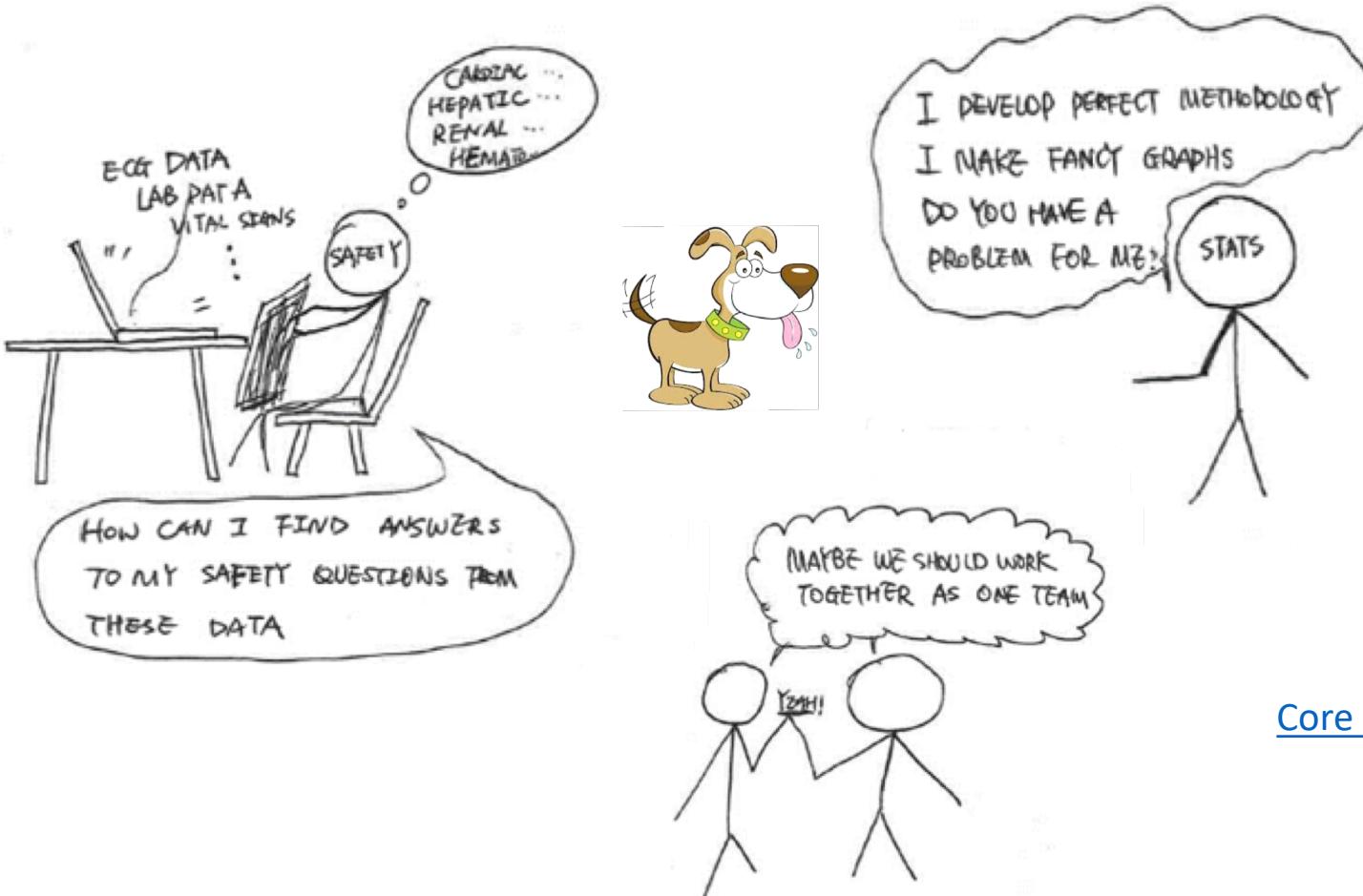
Does the tail wag the dog?

# 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

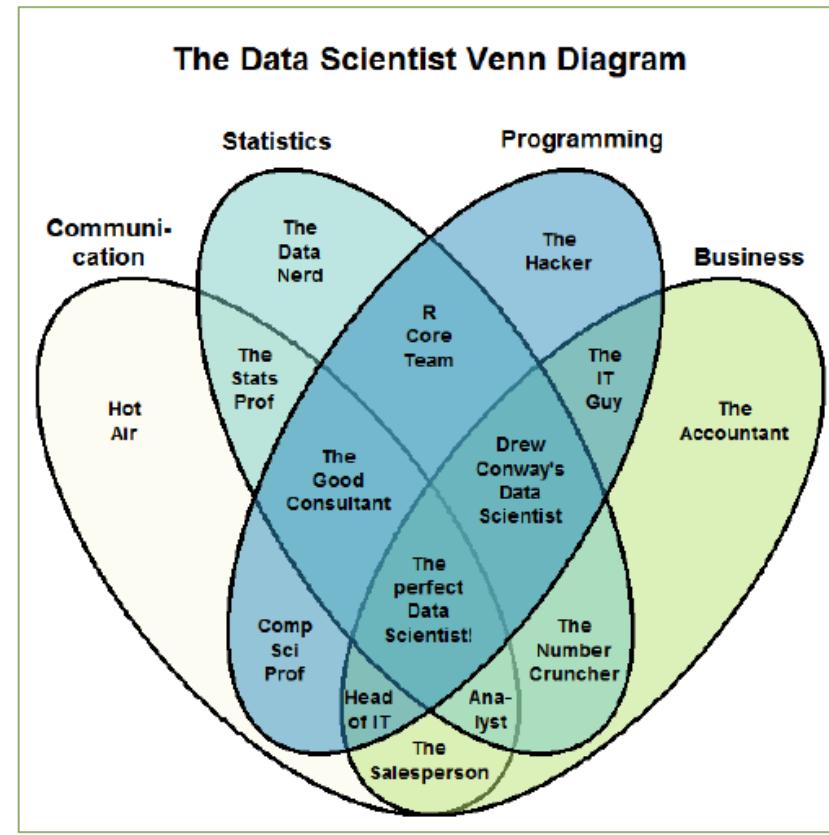
- The safetyGraphics and safety-eDish projects are maintained by the **ASA Biopharm-DIA Safety Working Group's Interactive Safety Graphics Taskforce**, which includes stakeholders from across the pharmaceutical industry, including the FDA. All work is free and open source with an MIT License.
- We are 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 Skrivanek (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



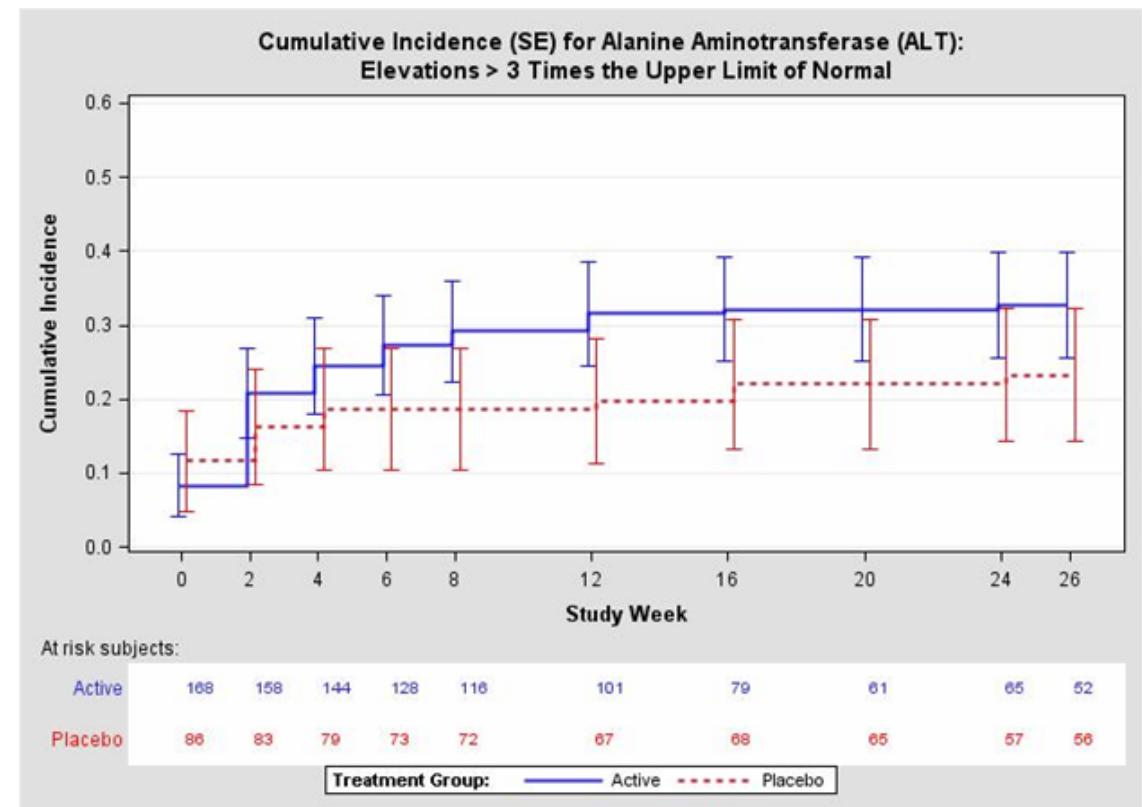
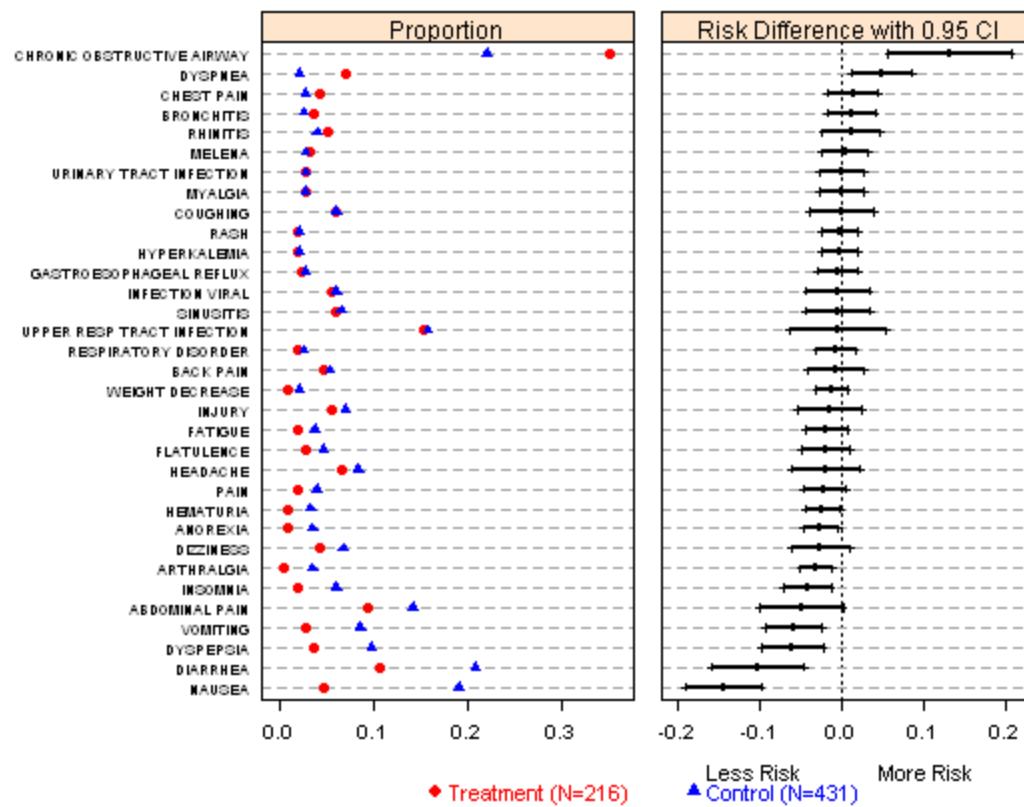
Courtesy of Stephan Kolassa

# 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

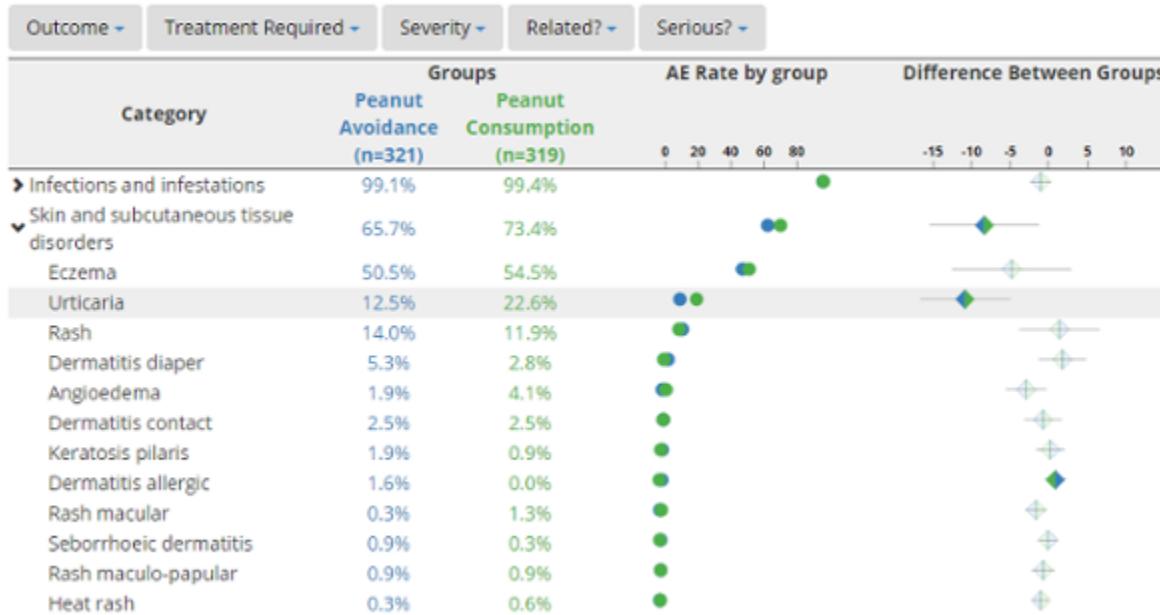
Most Frequent On-Therapy Adverse Events Sorted by Risk Difference



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

From Jim Buchanan, JSM, 2018

# Rho Safety Monitoring

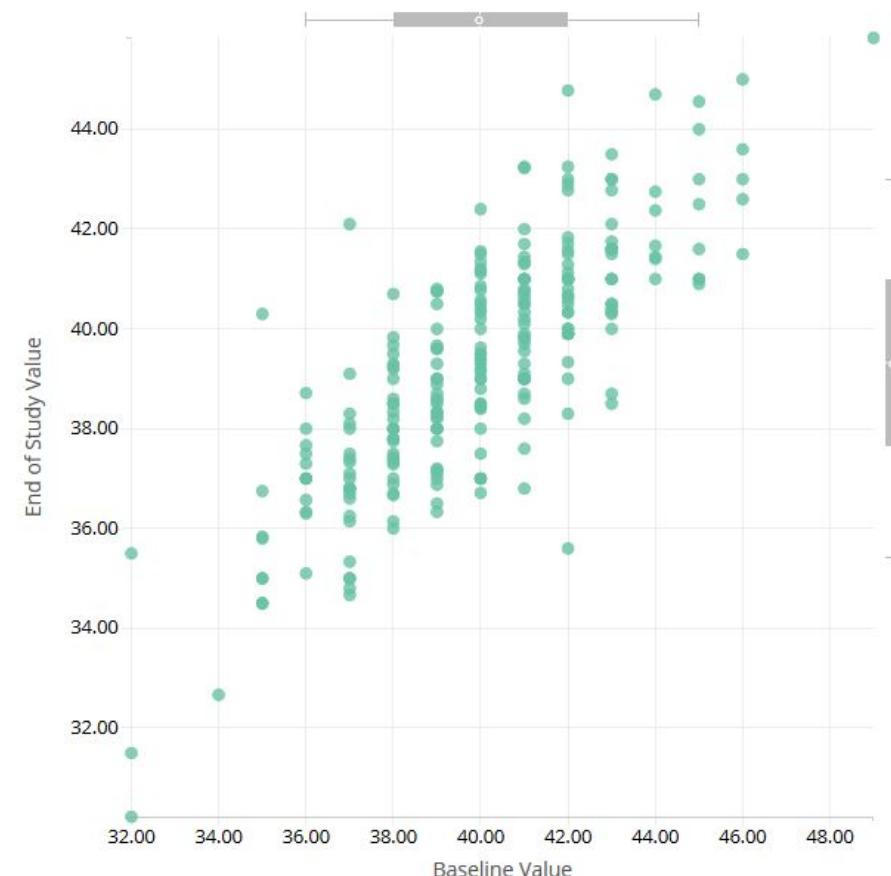


Measure

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



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

# 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

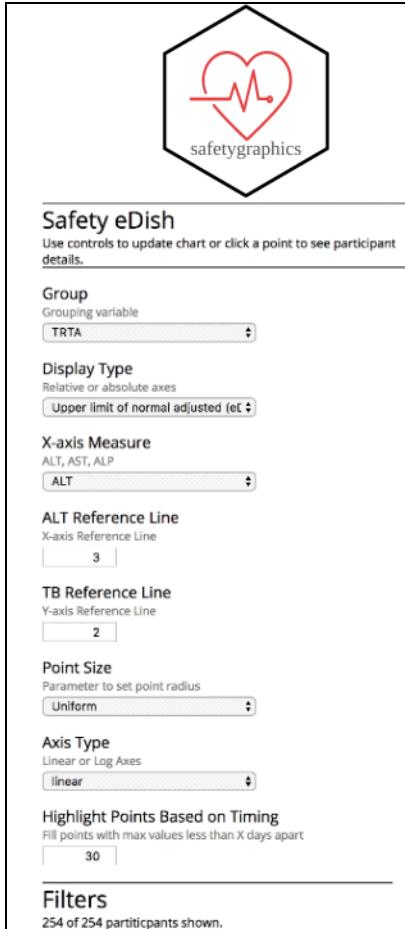
# ASA-DIA Biopharm Safety Working Group

## Safety Topics to Target:

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

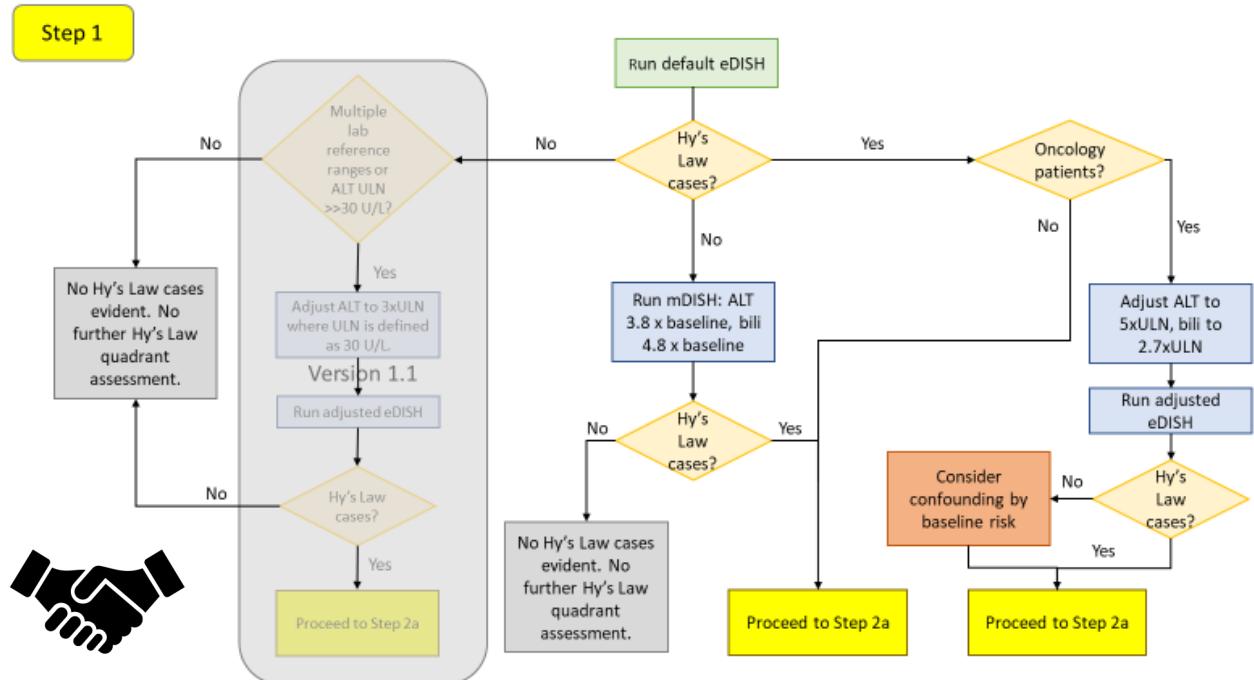


# Interactive eDISH plot & Clinical Workflow



## safetygraphics R Package

Links: [CRAN](#) | [GitHub](#) | [Interactive Chart](#)  
Related Tools: [SafetyExploreR](#) | [safety-eDish](#)



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

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

# eDish RShiny app – Data upload

eDISH Shiny app Data Settings Chart Export Chart

## Data upload

Upload a csv or sas7bdat file

No file selected

### Select file for eDISH chart

Example data - [ADaM](#)

## Data Preview for Example data

Show  entries Search:

Example data

STUDYID	SUBJID	USUBJID	TRTP	TRTPN	TRTA	TRTAN	TRTSDT	TI
CDISCPILOT01	1015	01-701-1015	Placebo	0	Placebo	0	2014-01-02	
CDISCPILOT01	1015	01-701-1015	Placebo	0	Placebo	0	2014-01-02	
CDISCPILOT01	1015	01-701-1015	Placebo	0	Placebo	0	2014-01-02	
CDISCPILOT01	1015	01-701-1015	Placebo	0	Placebo	0	2014-01-02	
CDISCPILOT01	1015	01-701-1015	Placebo	0	Placebo	0	2014-01-02	
CDISCPILOT01	1015	01-701-1015	Placebo	0	Placebo	0	2014-01-02	
CDISCPILOT01	1015	01-701-1015	Placebo	0	Placebo	0	2014-01-02	
CDISCPILOT01	1015	01-701-1015	Placebo	0	Placebo	0	2014-01-02	
CDISCPILOT01	1015	01-701-1015	Placebo	0	Placebo	0	2014-01-02	
CDISCPILOT01	1015	01-701-1015	Placebo	0	Placebo	0	2014-01-02	

# 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  

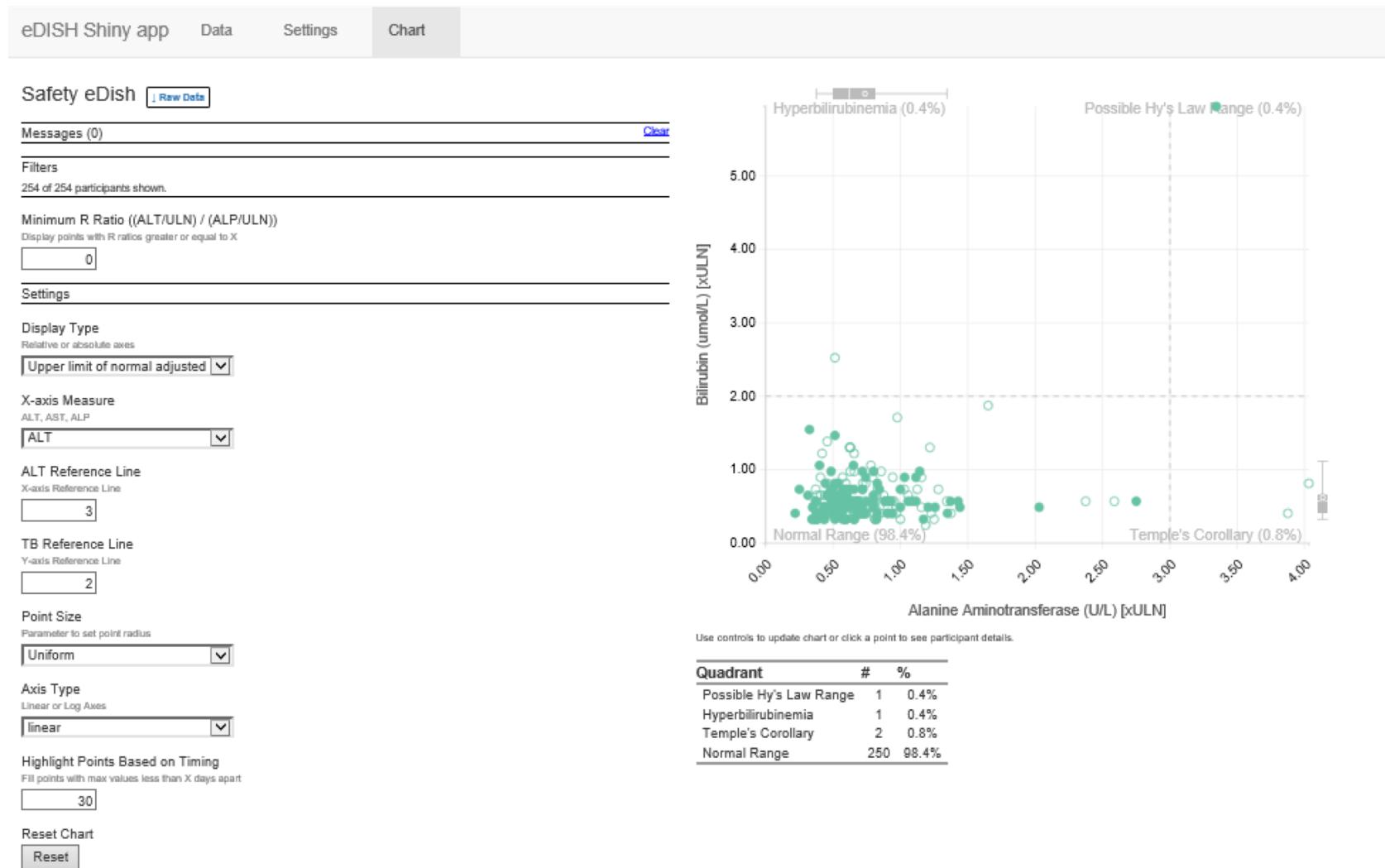

Show R Ratio Filter?

Default R Ratio Cut  


Show Chart Title?

Warning text  
Caution: This interactive graphic is not validated. Any clinical recommendations based on this data are the responsibility of the user.

# eDish RShiny app – Chart – Initial View



# Investigating a Patient's Experience

The screenshot shows a web browser window with the URL <http://127.0.0.1:4663/>. The browser tab bar includes links for PhUSE US Connect 2..., GitHub - ASA-DIA-In..., Vignette: Shiny User ..., eDISH Shiny app (which is the active tab), PhUSE US Connect 2..., fda safety and 2019 ..., FDA creating innovat..., and US FDA Wins Big In S... . The main content area of the browser displays the eDISH Shiny app interface.

The app has a header with tabs: Data, Settings, and Chart. The Data tab is selected. On the left, there is a sidebar titled "Data upload" with a "Browse..." button and a message "No file selected". Below it is a section titled "Select file for eDISH chart" with a radio button labeled "Example data - [ADM](#)".

The main area is titled "Data Preview for Example data". It shows a table with 10 rows of data. The columns are: STUDYID, SUBJID, USUBJID, TRTP, TRTPN, TRTA, TRTAN, TRTSOT, TRTEDT, AGE, AGEGR1, AGEGRIN, RACE, RACEN, SEX, COMP2FL, DSRAEFL, SAFFL, AVSIT, and AVT. The data is as follows:

STUDYID	SUBJID	USUBJID	TRTP	TRTPN	TRA	TRTAN	TRTSOT	TRTEDT	AGE	AGEGR1	AGEGRIN	RACE	RACEN	SEX	COMP2FL	DSRAEFL	SAFFL	AVSIT	AVT
CDISCIPLOT01	1015_01-701-1015	Placebo	0	Placebo	0	2014-01-02	2014-07-02	63 <65	1	WHITE	1	F	Y	Y	Baseline				
CDISCIPLOT01	1015_01-701-1015	Placebo	0	Placebo	0	2014-01-02	2014-07-02	63 <65	1	WHITE	1	F	Y		Y			Baseline	
CDISCIPLOT01	1015_01-701-1015	Placebo	0	Placebo	0	2014-01-02	2014-07-02	63 <65	1	WHITE	1	F	Y		Y			Baseline	
CDISCIPLOT01	1015_01-701-1015	Placebo	0	Placebo	0	2014-01-02	2014-07-02	63 <65	1	WHITE	1	F	Y		Y			Baseline	
CDISCIPLOT01	1015_01-701-1015	Placebo	0	Placebo	0	2014-01-02	2014-07-02	63 <65	1	WHITE	1	F	Y		Y			Baseline	
CDISCIPLOT01	1015_01-701-1015	Placebo	0	Placebo	0	2014-01-02	2014-07-02	63 <65	1	WHITE	1	F	Y		Y			Week 2	
CDISCIPLOT01	1015_01-701-1015	Placebo	0	Placebo	0	2014-01-02	2014-07-02	63 <65	1	WHITE	1	F	Y		Y			Week 2	
CDISCIPLOT01	1015_01-701-1015	Placebo	0	Placebo	0	2014-01-02	2014-07-02	63 <65	1	WHITE	1	F	Y		Y			Week 2	
CDISCIPLOT01	1015_01-701-1015	Placebo	0	Placebo	0	2014-01-02	2014-07-02	63 <65	1	WHITE	1	F	Y		Y			Week 2	
Showing 1 to 10 of 10,288 entities																			
Previous																			
1 2 3 4 5 ... 1029 Next																			

At the bottom of the browser window, the address bar shows <http://127.0.0.1:4663/#tab-3700-1>.

# 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

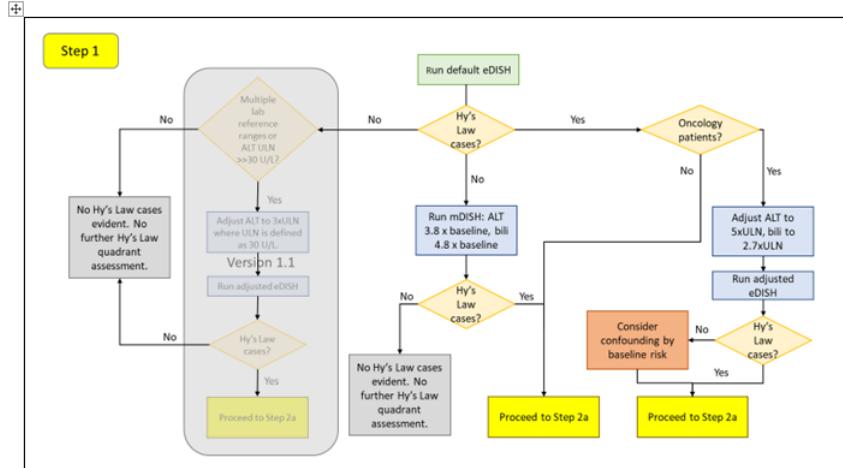
# Clinically agreed workflow for tool's use

## 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.

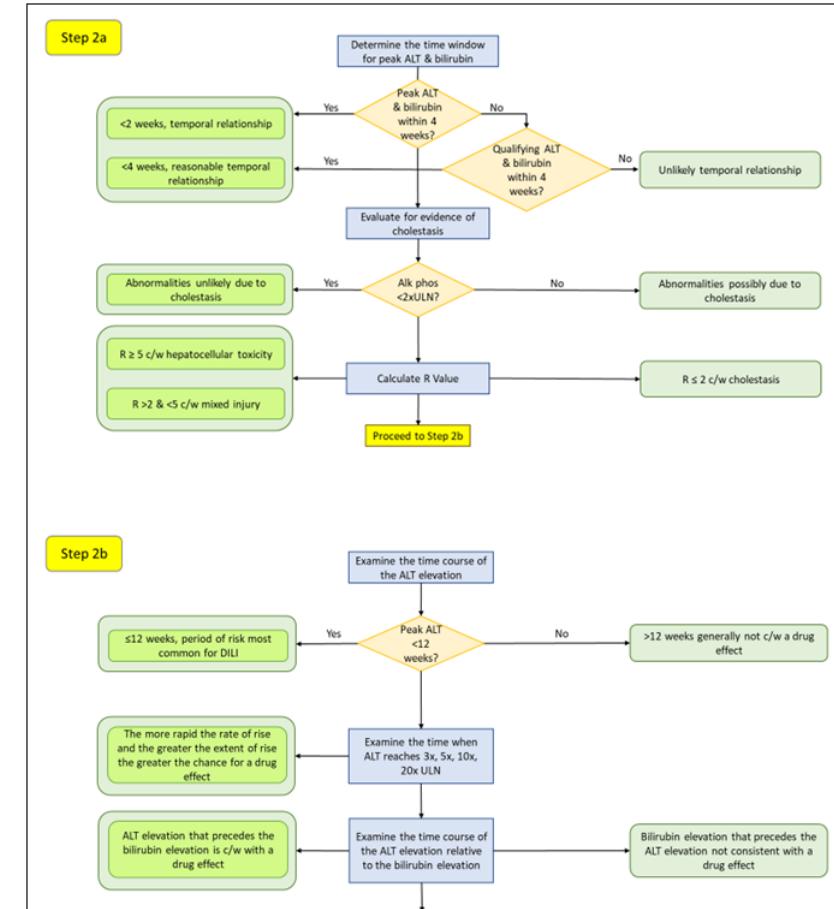
Development of this open source hepatotoxicity tool and recommended clinical workflow for liver signals is our taskforce's first objective. Adverse events and EKG are the topics we will turn our attention to next.



The advent of interactivity creates both opportunity & challenge

Requires:

- Scientific rigor
- Replicability



# 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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