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

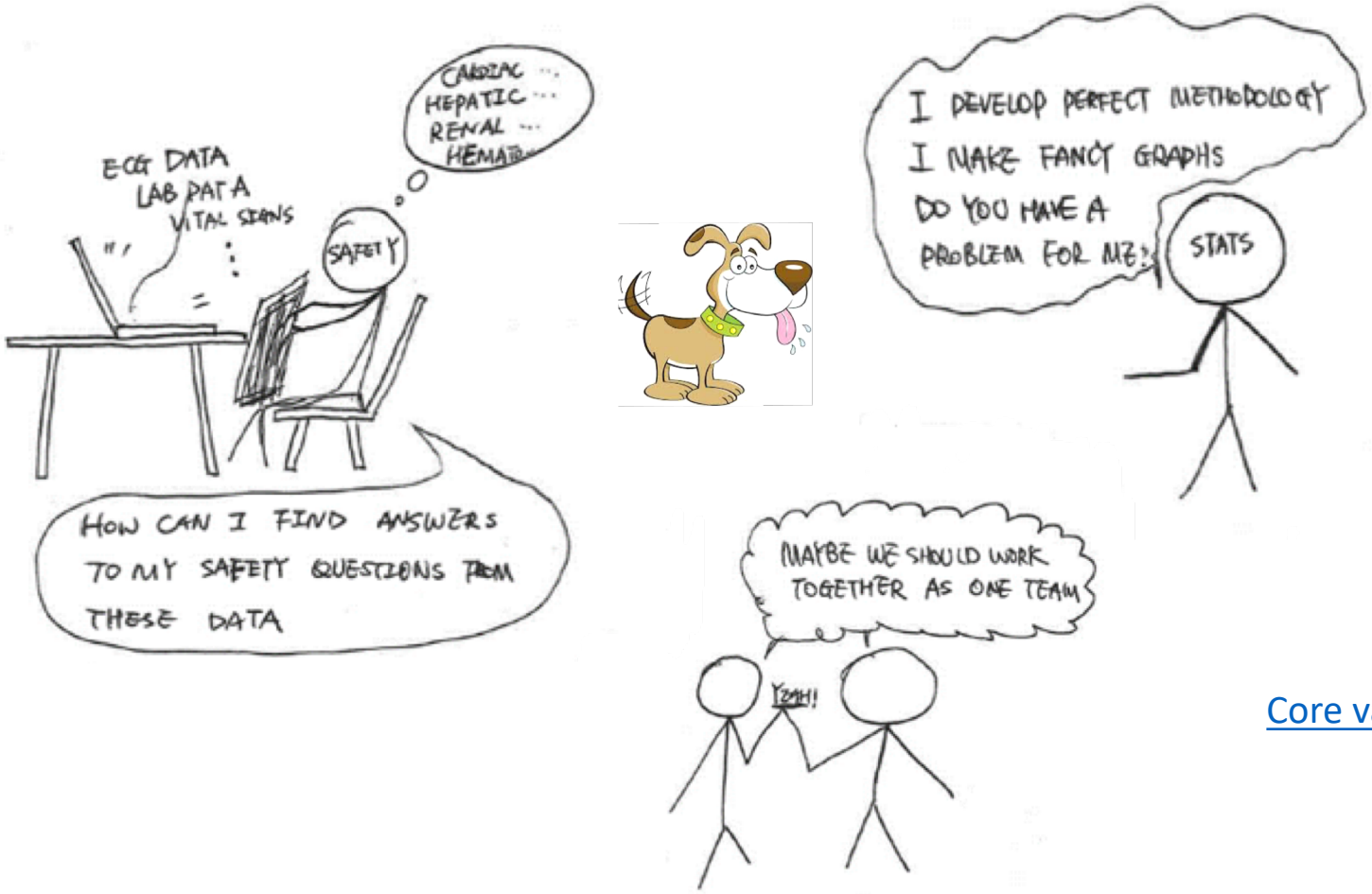
Statisticians create outputs and tools

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

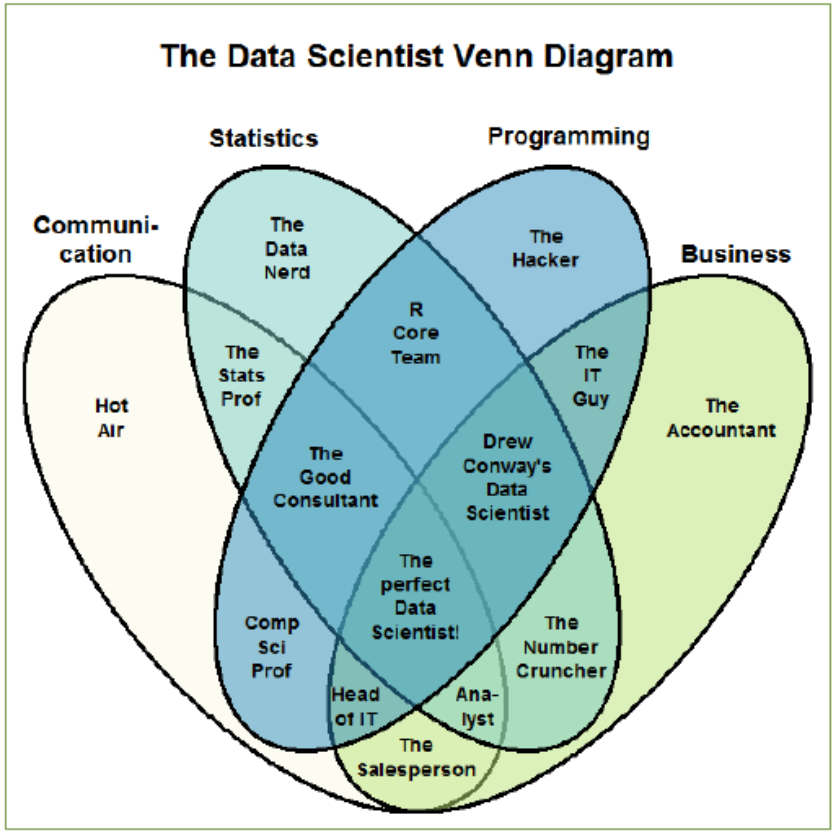
- The safetyGraphics and safety-eDish projects are maintained by the **ASA Biopharm-DIA Safety Working Group's Interactive Safety Graphics Taskforce**, which includes stakeholders from across the pharmaceutical industry, including the FDA. All work is free and open source with an MIT License.
- We are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

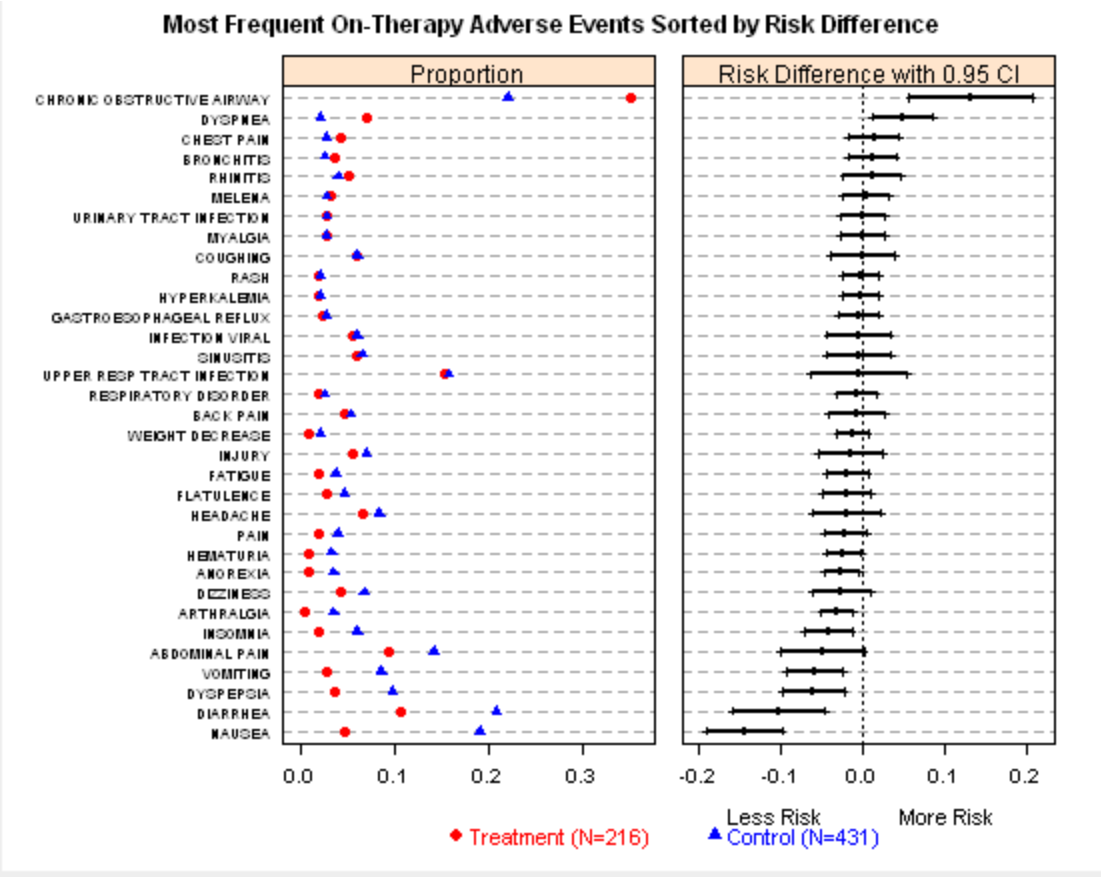
From Xiao Ni, Novartis, DIA Annual Meeting, 2018

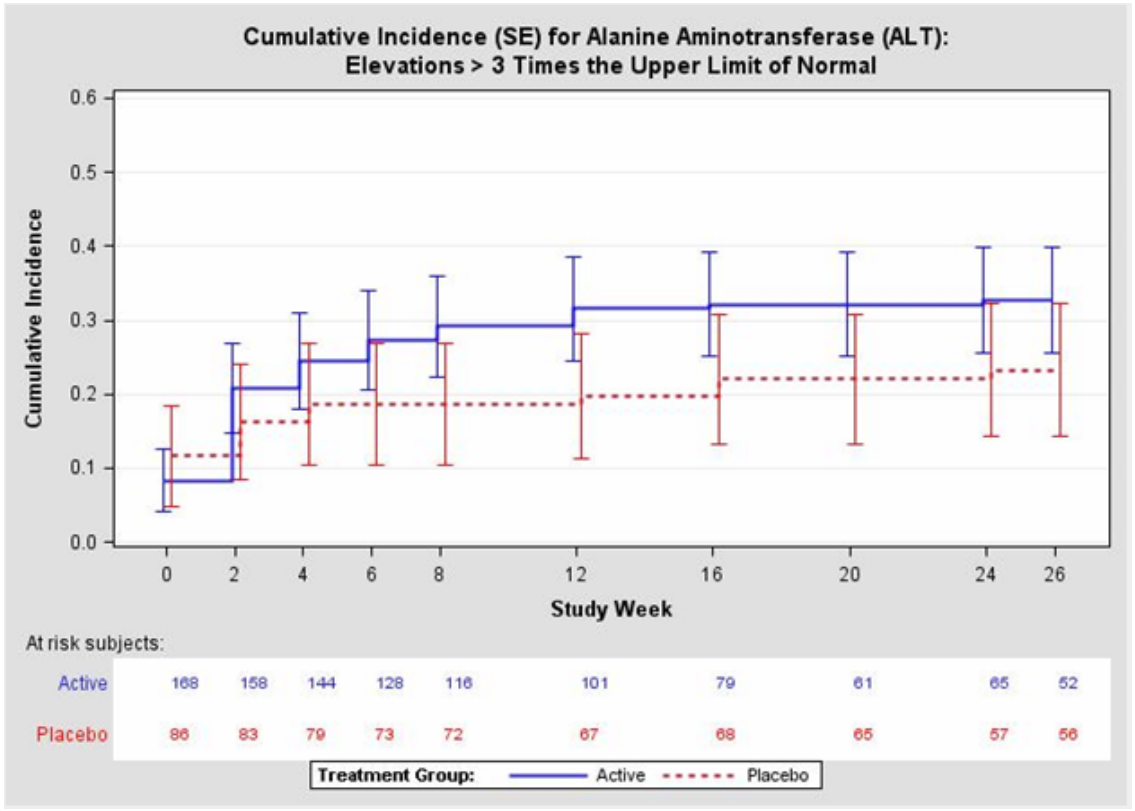
The Problem
Safety Clinicians Desire a Safety Evaluation Toolkit

- 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

From Jim Buchanan, JSM, 2018

CTSPedia

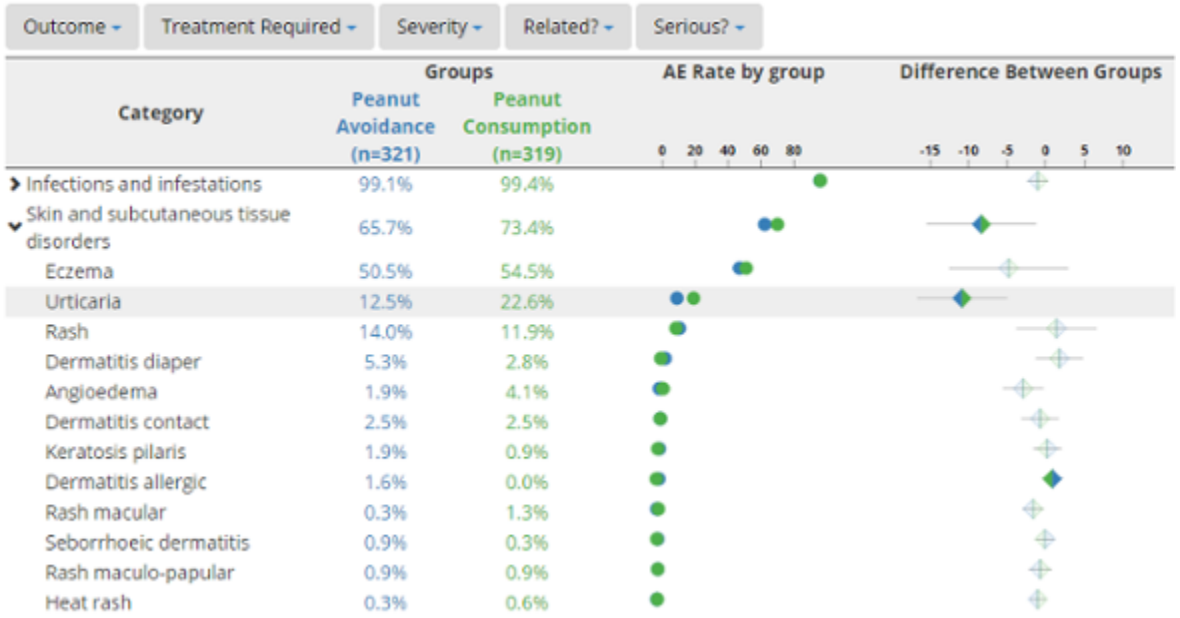


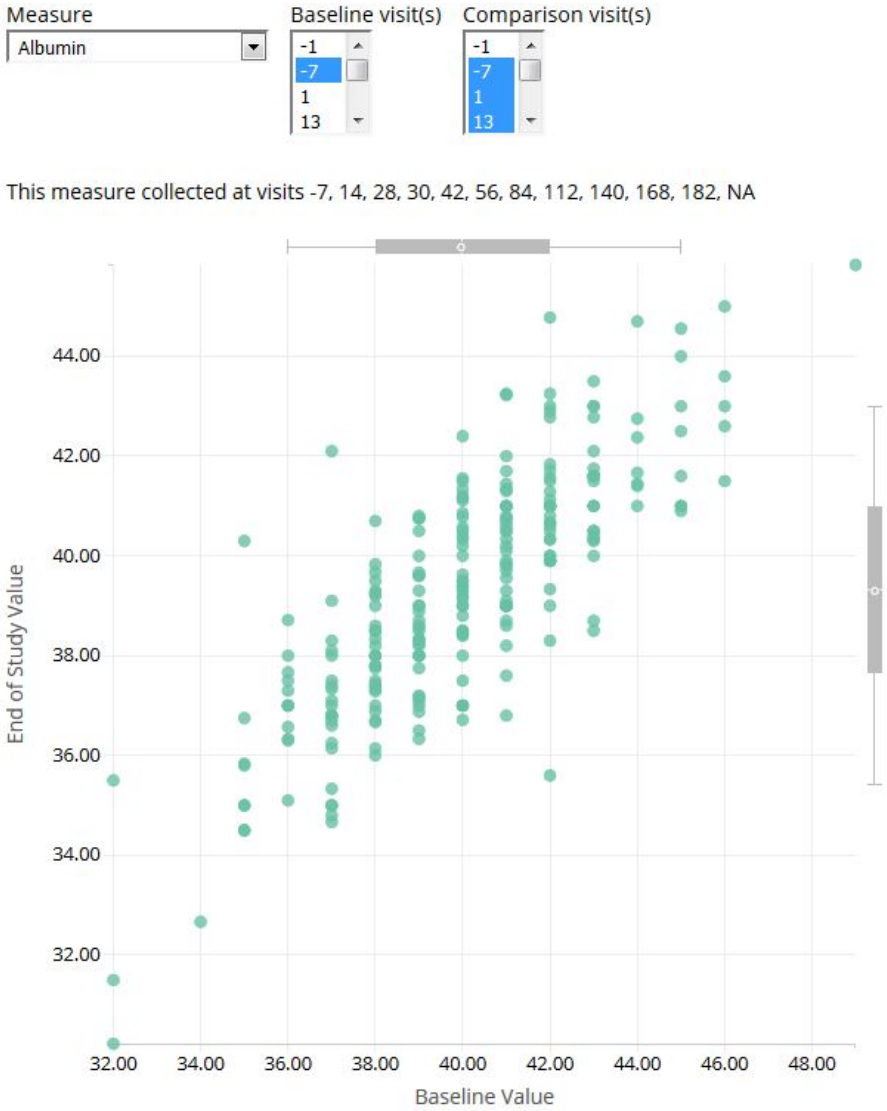


https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome

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

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

From Jeremy Wildfire, RStudio Conference, 2019

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:

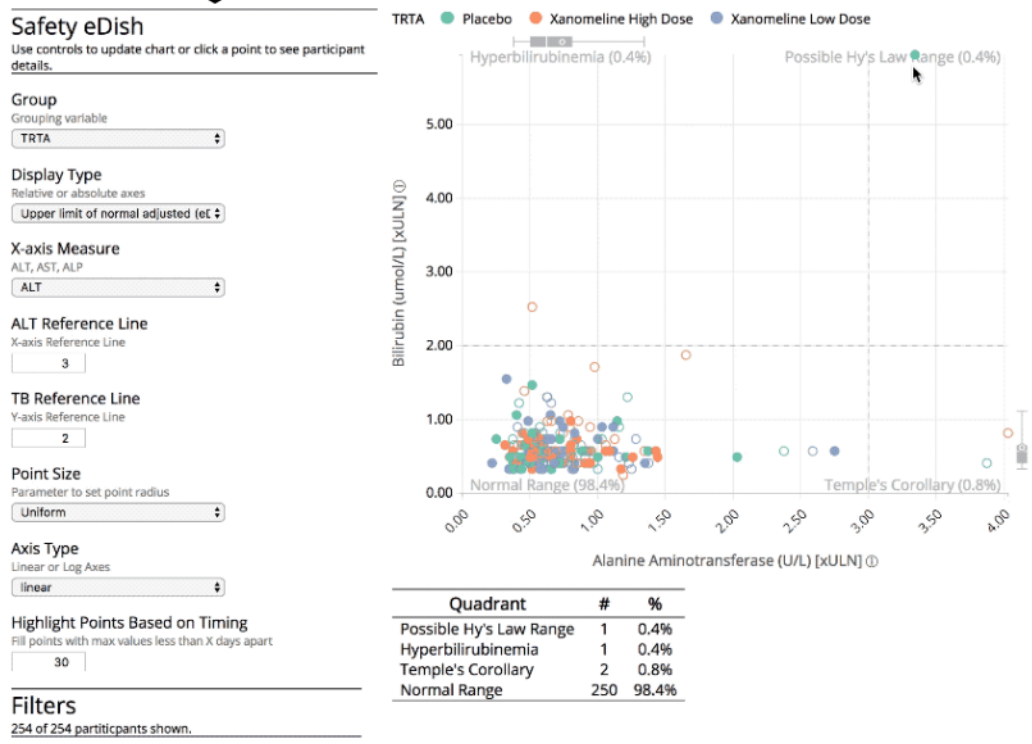
- Hepatotoxicity and other labs
- QT prolongation
- Adverse event evaluation

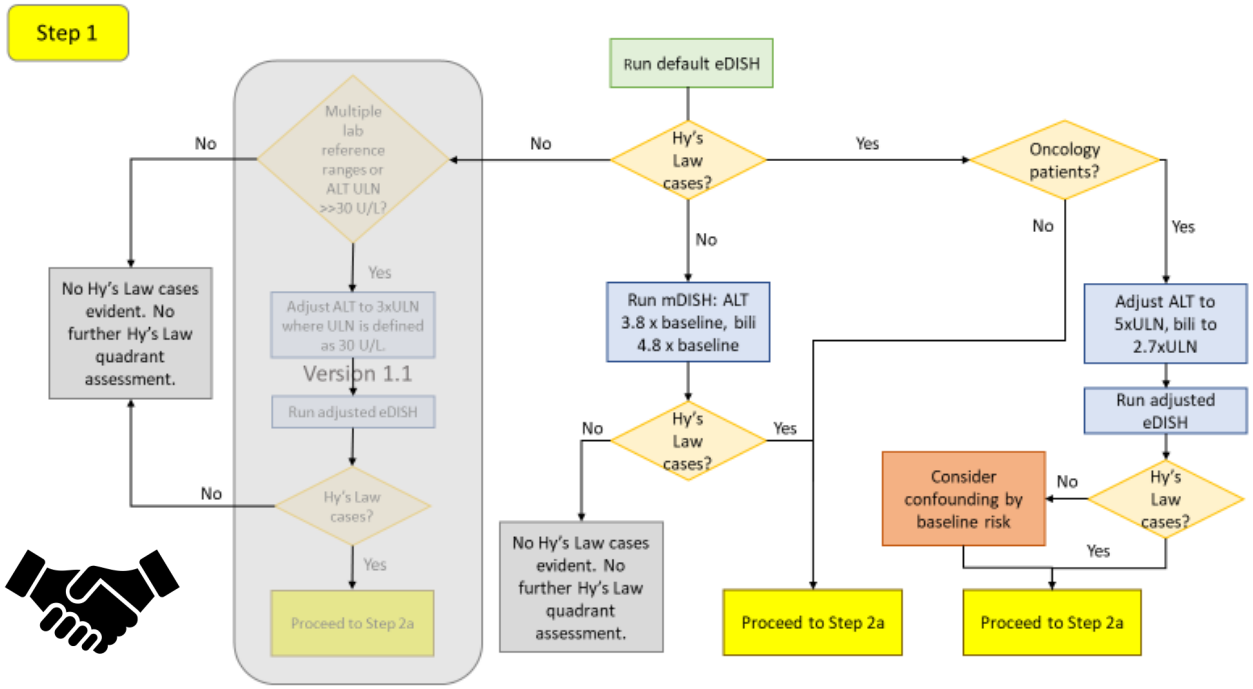
Interactive eDISH plot & Clinical Workflow

safetygraphics R Package

Links: CRAN | GitHub | Interactive Chart

Related Tools: SafetyExploreR | safety-eDish

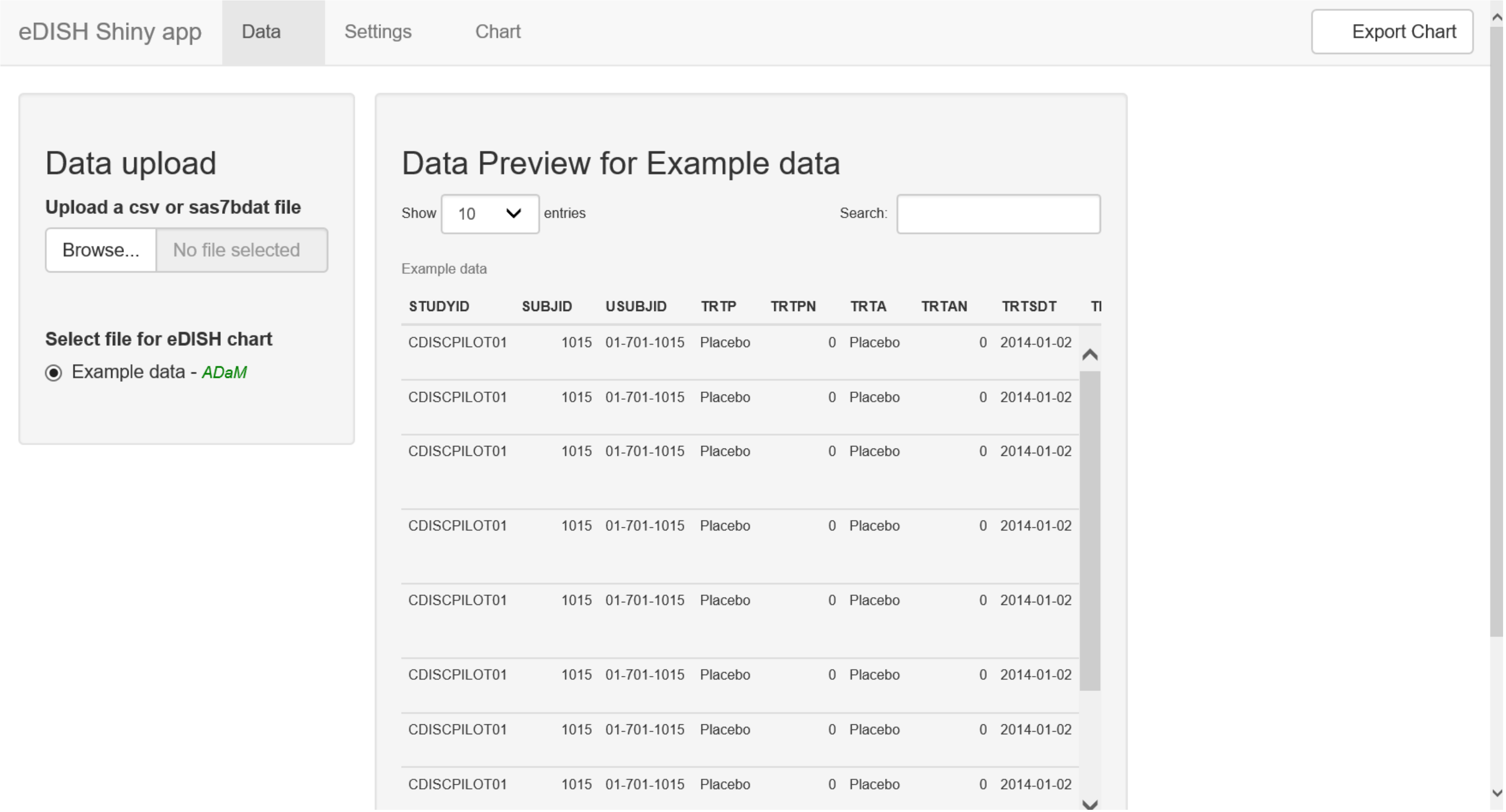




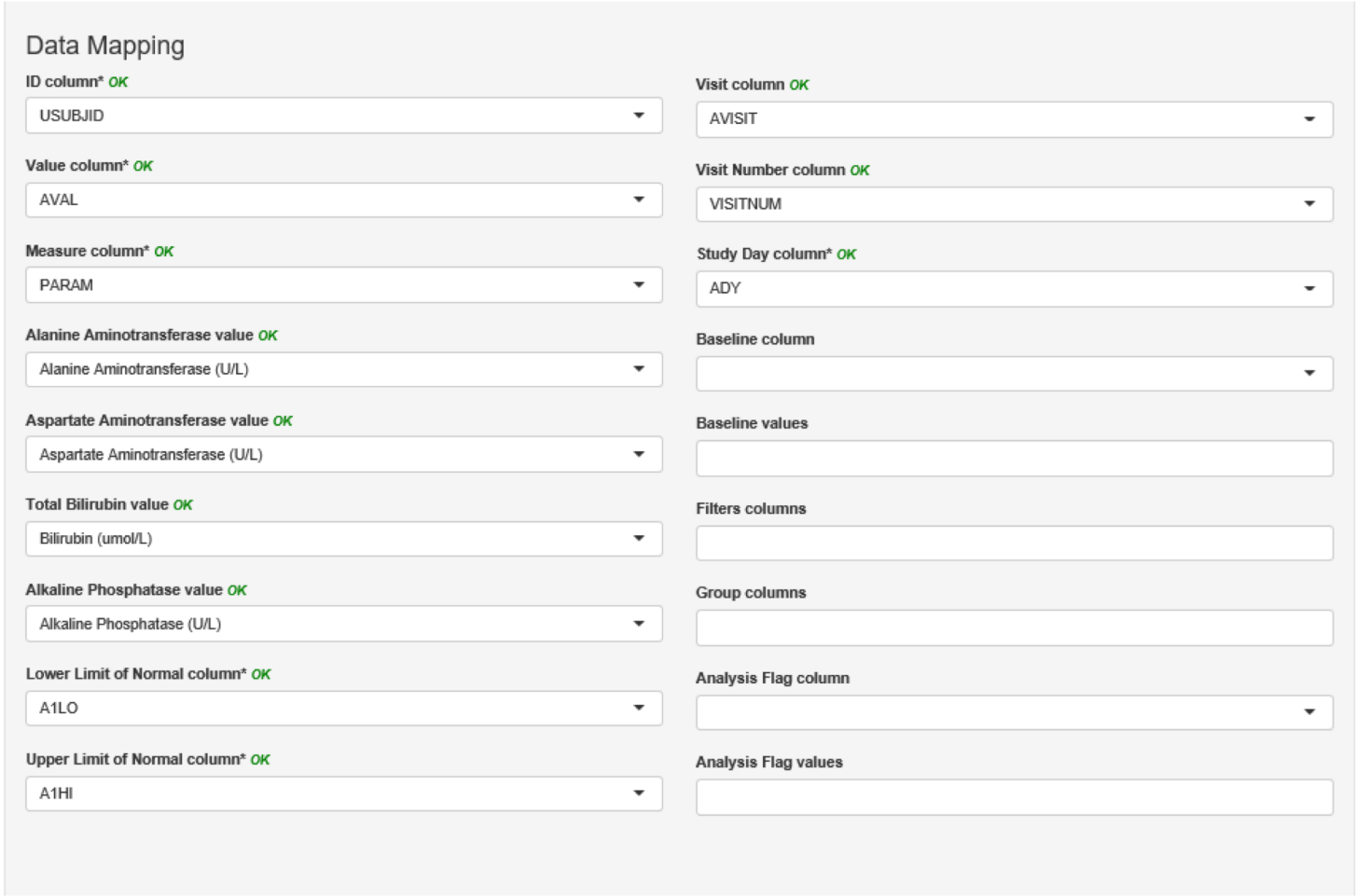

```
#Code to initialize shiny application
install.packages("safetyGraphics")
library("safetyGraphics")
safetyGraphicsApp()
```

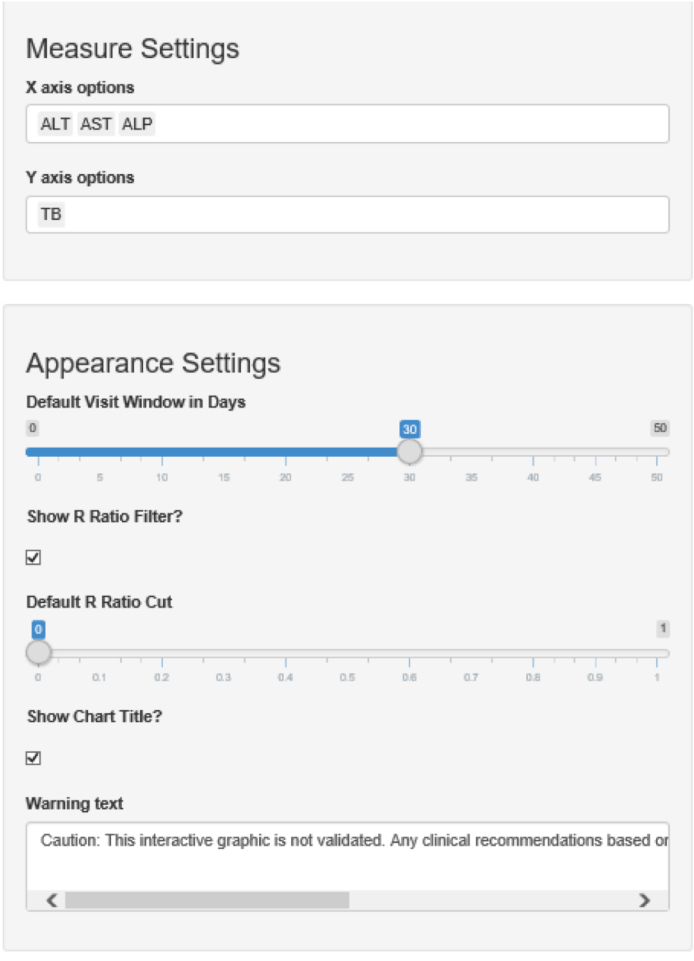
https://safetygraphics.github.io/

eDish RShiny app – Data upload

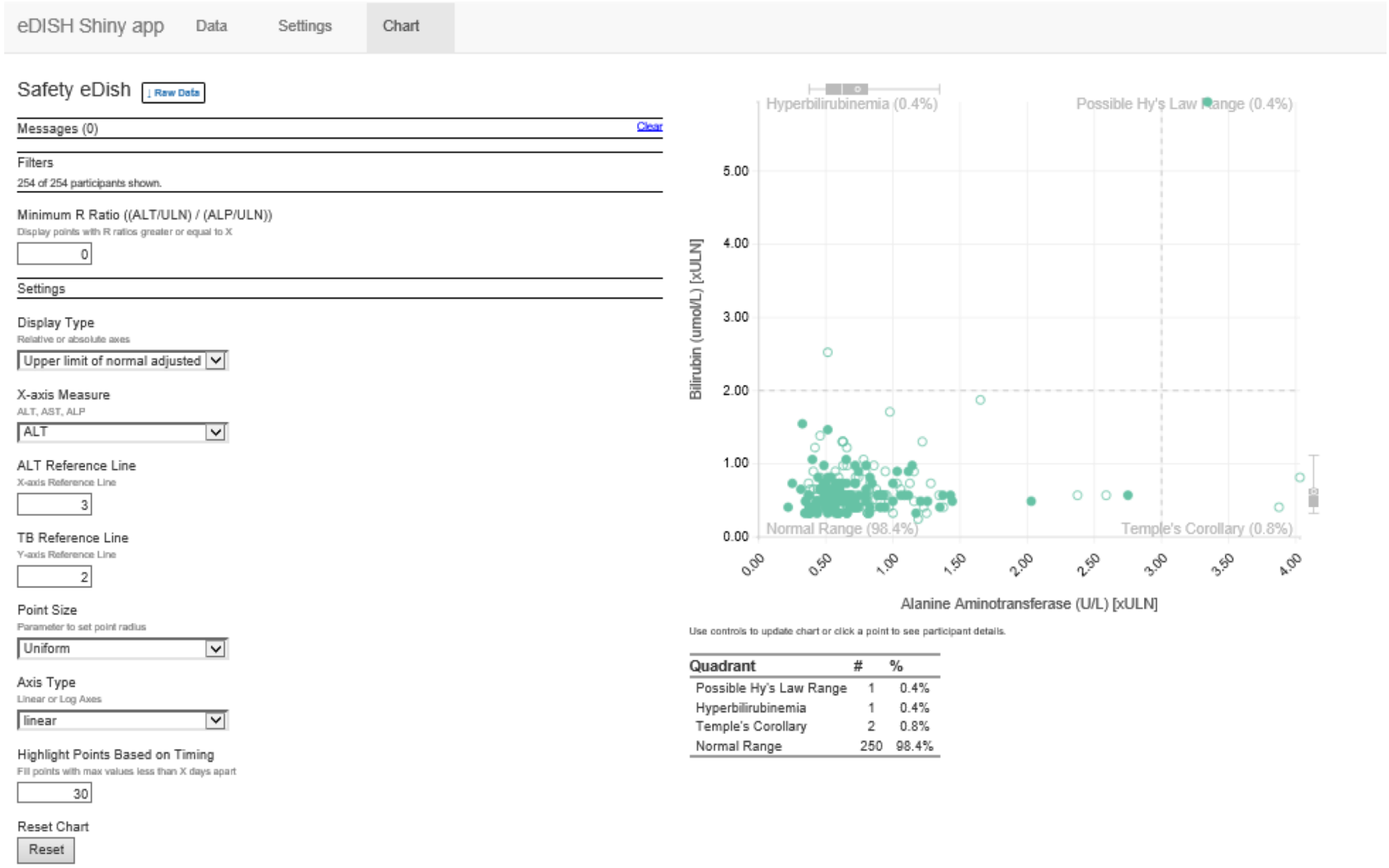


eDish RShiny app – Data mapping

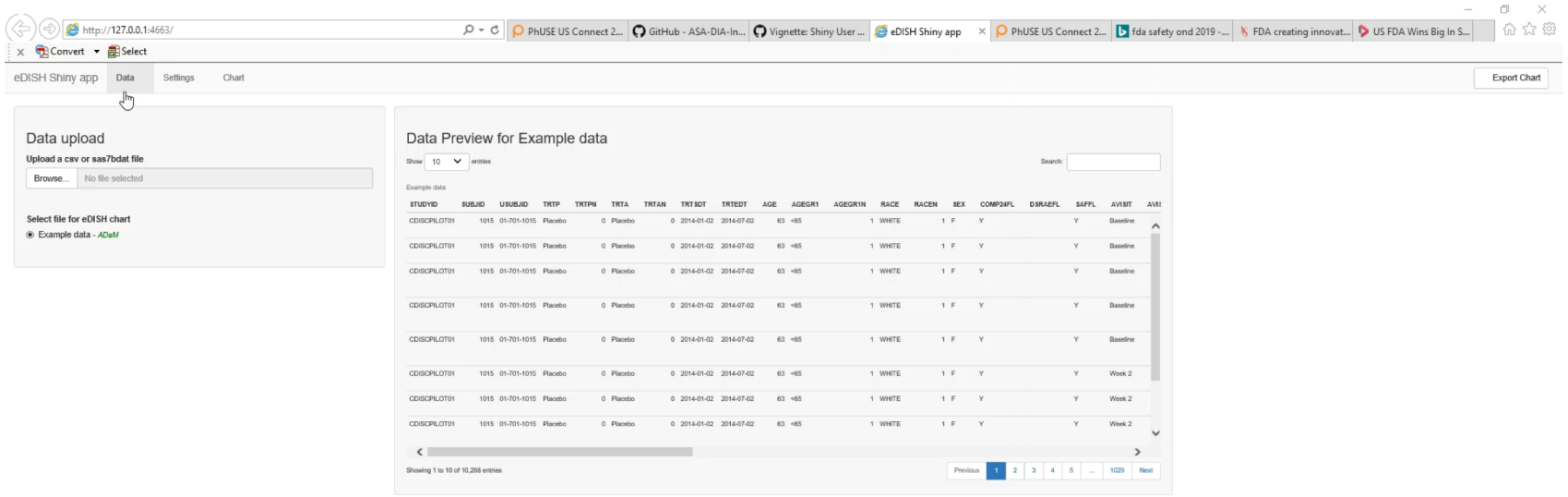




eDish RShiny app – Chart – Initial View



Investigating a Patient's Experience



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:

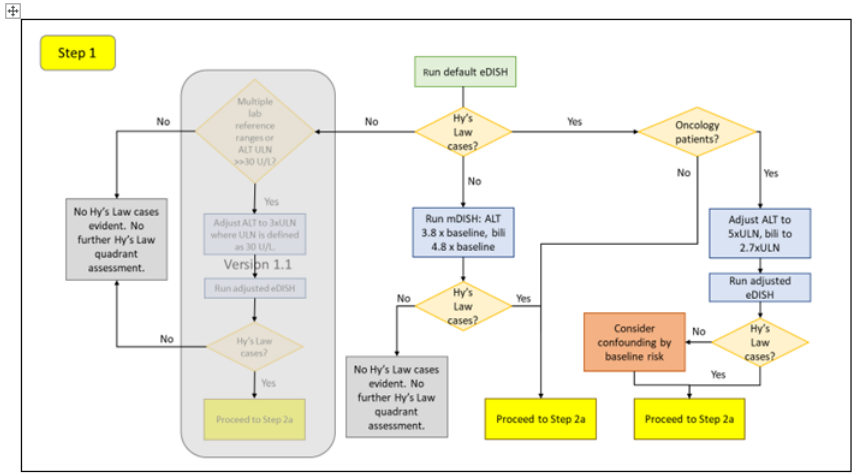
- Scientific rigor
- Replicability

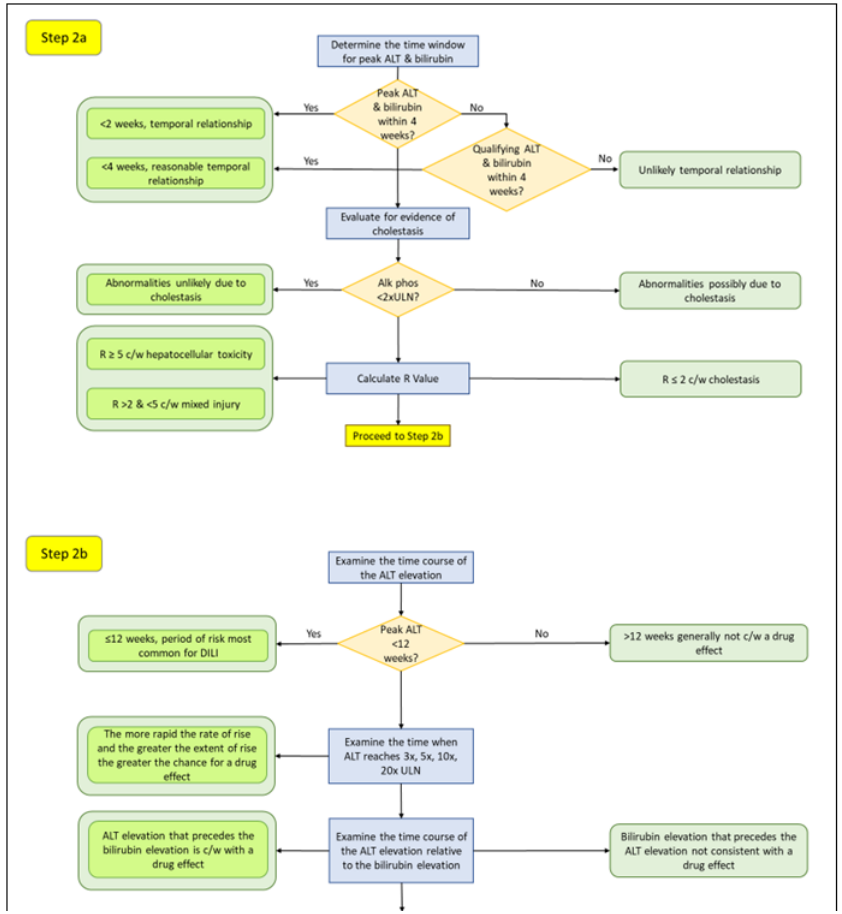
Clinically agreed workflow for tool's use

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

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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?

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