Interactive Safety Graphics:
Starting with Hepatotoxicity

PhUse US Connect, Baltimore
Feb 25, 2019

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

https://safetygraphics.github.io/

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?
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.

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The statistician’s challenge, and opportunity

Modern Statistician Should be a Data Scientist

4 essential skill sets
- Business
- Statistics
- Programming
- Communication

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

Most Frequent On-Therapy Adverse Events Sorted by Risk Difference

![Graph showing adverse events and risk difference](https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome)

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

![Graph showing cumulative incidence and study week](https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome)

From Jim Buchanan, JSM, 2018
Rho 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

Data Preview for Example data

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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

The advent of interactivity creates both opportunity & challenge

Requires:
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• 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?