

Update on the ASA/PHUSE/FDA Collaboration/Initiative on Interactive Safety Graphs for Regulatory Submissions

Melvin Munsaka, PhD, AbbVie

Neetu Sangari, PhD, Pfizer

Disclaimer

- Opinions expressed in this presentation are the authors' own and do not represent in any way opinions of their respective employers



Interactive Tools for Drug Safety Data Review - Update A Collaboration of



Recap: Overview

Some background

- Initiative put together to promote collaboration between ASA, FDA, and PHUSE
- ASA participation - Biopharmaceutical Section and SSPA – put aside some bureaucratic considerations
- PHUSE - participation is via Data Visualization and Open-Source Technology in Clinical Research
- Current team consists of participants from ASA, PHUSE, FDA, and Industry

Deliverables

- Spirited discussion of deliverable and where and how to deliver
- Focused on development of a tool for generating forest plots for adverse events
- Full R package - tool, guide, training, open source, submissions
- Reviewed PHUSE volcano pilot submission initiative as a point of reference
- Discussed different considerations and requirements for the tool



Recap: Project Scope

- Development of R-shiny application(s) to enable the generation of identified plots for direct inclusion in submission packages for regulatory agencies
- Initial scope is to develop tools to generate forest plots for inclusion in submission to FDA



Strategy/Some Considerations



- Start small - what are the minimal requirements/options:
 - Not expecting statistical expertise to user interface
 - Enough intuitive self-explanatory details/manual; Demos; Training materials; Self-contained instructions – explanations
- Consider end user perspectives/parlor and experience (who are the end users?)
 - Medical Reviewers in industry and regulatory agencies
 - May also include statistical reviewers/so part of submission package
- Challenges for developers?
- Where/how to share/deliver the tool?
- Need to keep track of recommendations

Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the safety planning, evaluation, and reporting team

Brenda J Crowe^a, H Amy Xia^b, Jesse A Berlin^c, Douglas J Watson^d, Hongliang Shi^e, Stephen L Lin^f, Juergen Kuebler^g, Robert C Schriver^h, Nancy C Santanelloⁱ, George Rochester^{j,k}, Jane B Porter^l, Manfred Oster^l, Devan V Mehrotra^l, Zhengqing Li^l, Eileen C King^g, Ernest S Harpur^l and David B Hall^m *Clinical Trials* 2009; 6: 430-440

Tier 1

- Prespecified detailed analysis and hypothesis testing for specific AEs

General Safety Review

Tier 2

- Signal detection among common events. AEs included here are those that do not have a prespecified hypothesis and are 'common'

Tier 3

- Descriptive analysis of infrequent AEs. AEs included here do not have a prespecified hypothesis and are infrequent.

Recap: Strategy/Some Considerations



- Staged development

- Opted for a staged development approach in terms of functionality focusing on AEs and forest plot



- Team agreed to incorporate volcano plot

Development Stages

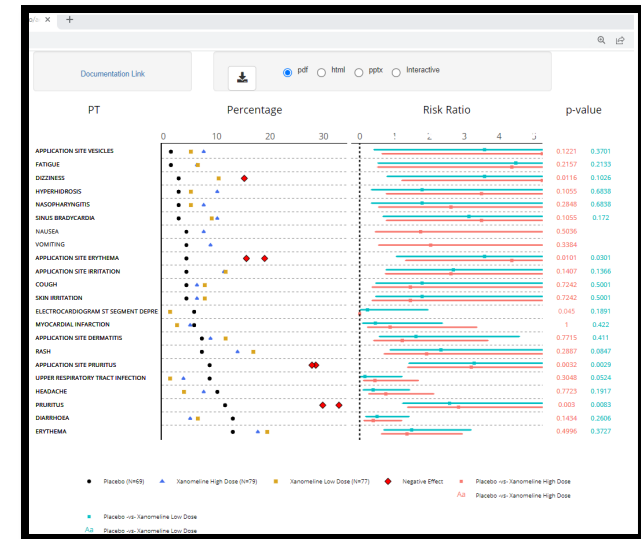
Stage 1

- Of note, this stage is:
 - Visual alternative to static pdf tables
 - Limited functionality with regards to a comprehensive/full safety review

PDF



HTML



Current Prototype – Forest Plot

Source:

- <https://github.com/phuse-org/aesummaries>
- <https://phuse-org.shinyapps.io/aesummaries/>

Advanced Visual Analytics for Drug Safety Review

pdf html pptx **Interactive**

Import data: Browse... adae.sas7bdat Upload complete

Treatment Variable: TRTA Population Filter: Overall Create

Overall Event Analysis

Report: Forest

Period: Overall Duration

Adverse Event filter(s):

Summary By: Participants Review By: SOC

Cutoff of Incidence (%): 5

Measure of Association: Risk Ratio

Risk Axis Scale: Log10

Graph Table

Sorting Option: Ascending

Sorting Variable: Count

Control Group: ☒ Placebo ☐ Xanomeline High Dose ☐ Xanomeline Low Dose

Treatment Group: ☒ Xanomeline High Dose ☐ Xanomeline Low Dose

X-axis Reference Lines: 0

P-value Transformation: None

Alpha Value(CI): 0.05

p Value Cutoff: 0.05

Table Inputs

AE Term Variable: AEDECOD

System Organ Class Variable: AEBODSYS

Total treatment: ☒ Y ☐ N

Treatment Big N: ☒ Y ☐ N

Percent Display by: Treatment

Treatment Pair: ☒ Placebo -vs- Xanomeline High Dose

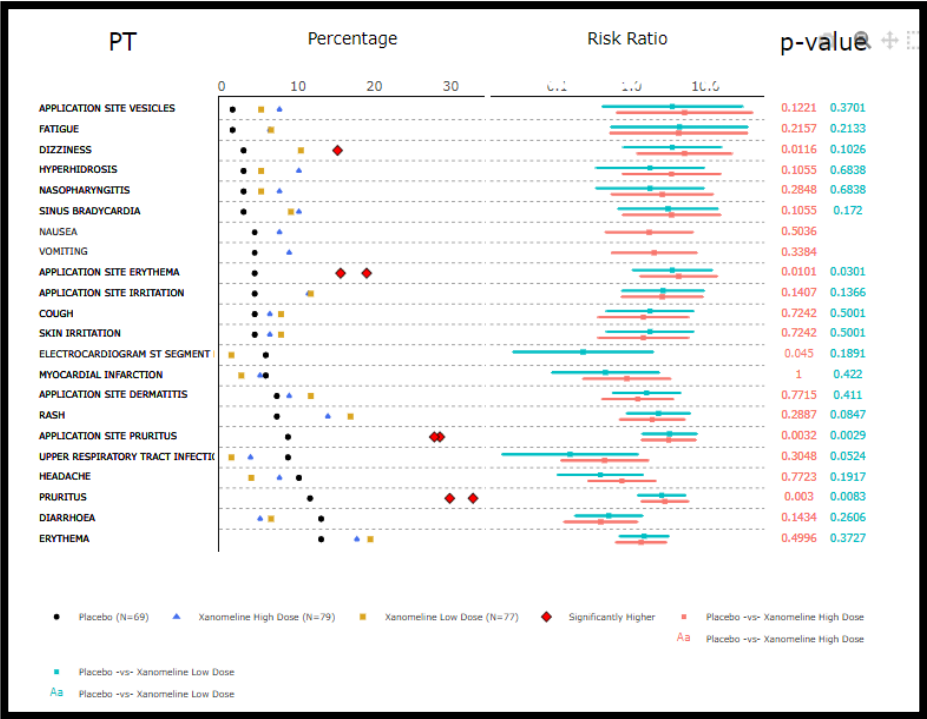


Working
Groups

phuse.global

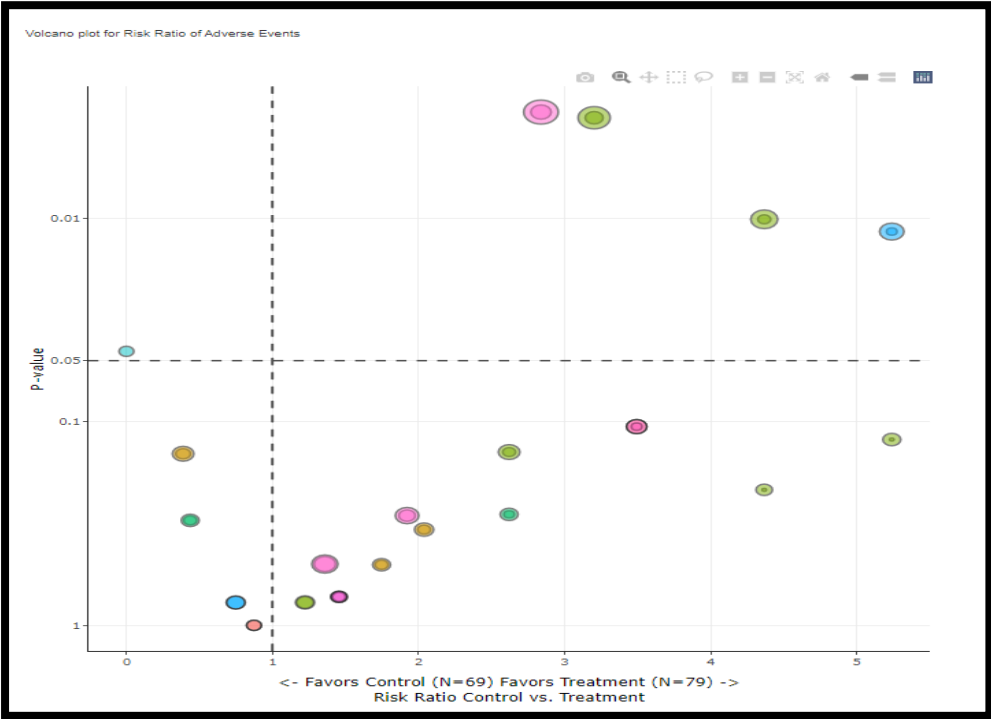
Current Prototype

Forest plot



Forest2023-03-26 (1).html

Volcano plot



Volcano2023-03-26 (1).html



phuse.global

Working
Groups

Current Prototype

- Other considerations
 - Duke-Margolis FDA Workshop input – FMQs
 - R Markdown template for submission

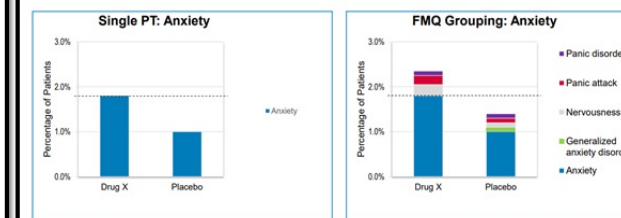


FDA Medical Queries (FMQs)

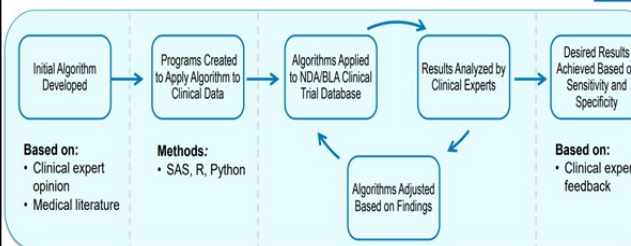
Vaishali Popat MD, MPH
Associate Director
Biomedical Informatics and Regulatory Review Science
CDER/Office of New Drugs

Single PT Analysis vs. FMQ Grouping

- Using a 2% cut-off for an AE analysis, "Anxiety" doesn't make the cut, but group these PTs, and a signal emerges at the 2% cut-off (no patient counted twice).



FMQ Algorithm Development and Testing Process



Standard Safety Tables & Figures Integrated Guide: Components

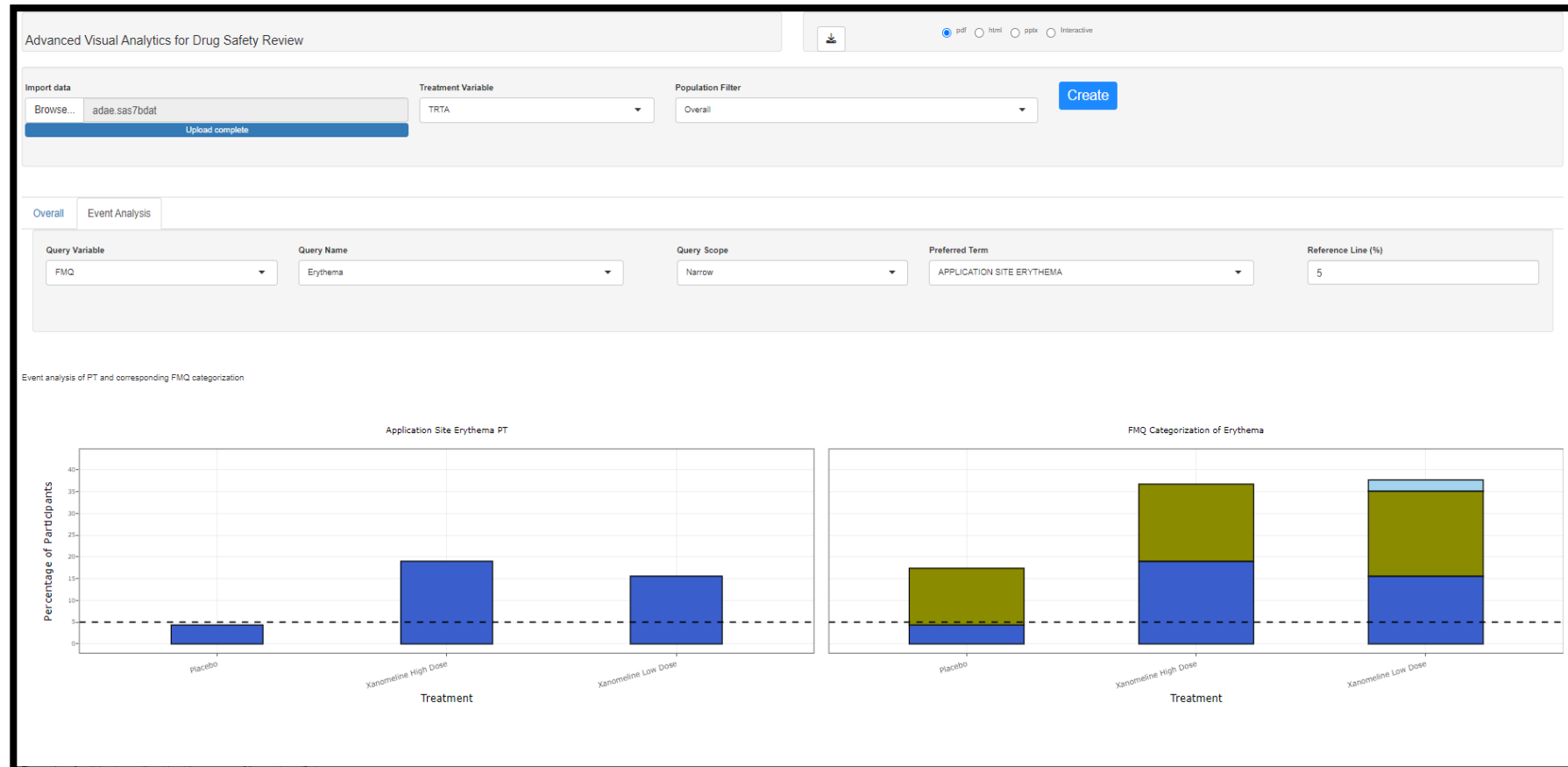
Integrated Guide						
General	Adverse Event Analyses	Subgroup Analyses	Laboratory Analyses	Vital Signs Analyses	Expanded Tables and Figures	Optional Tables and Figures
<ul style="list-style-type: none"> Clinical Trials Summary Demographic and Clinical Characteristics Patient Disposition Duration of Exposure 	<ul style="list-style-type: none"> Overview of Adverse Events Deaths Serious Adverse Events Adverse Events Leading to Discontinuation FDA Medical Queries (FMQs) 	<ul style="list-style-type: none"> Overview of certain AEs or SAEs across demographic characteristics 	<ul style="list-style-type: none"> Analyses of Central Tendency Analyses of Abnormalities and Outliers DLI Screening subsection: <ul style="list-style-type: none"> Missing Data Analysis Potential Hy's Law Screening Plot 	<ul style="list-style-type: none"> VS distribution by Treatment Group Baseline vs. Max/Min by Treatment Group Blood Pressure Post-Baseline Data 	<ul style="list-style-type: none"> Expanded AE Analyses SAEs TEAEs Expanded Laboratory Analyses Change Over Time Outlier Criteria Last Value on Treatment 	<ul style="list-style-type: none"> Optional AE Analyses Exposure-Adjusted Analyses Relatedness Analyses Additional FMQ Tables Optional Laboratory and Vital Signs Analyses Median and Interquartile Range Plots



Working
Groups

Current Prototype

Volcano plot



Working
Groups

Next Steps

- Complete ascertain of all Stage 1 requirements/additional input
- Take into consideration discussions from Duke-Margolis/FDA Workshop
- Complete Stage 1 tool validation
- Complete guidance documentation for Stage 1
- Continue with the remaining stages

Acknowledgments

- Vipin Arora, Eli Lilly
- Bryant Chen, FDA
- Maya Gans, Atorus
- Jiang Jessica Hu, FDA
- Harivardhan Jampala, Chiltern
- Mary Nilsson, Eli Lilly
- Paula Riley, PHUSE
- Mike Stackhouse, Atorus/PHUSE
- Hanming Tu, Frontage Lab/PHUSE
- Lauren White, PHUSE
- Jeremy Wildfire, Gilead



