



Enhancing the DMC Data Package Using Opensource Software, Artificial Intelligence, and LLMs

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On Behalf of the ASA BIOP Safety Working Group

32nd Annual Biopharmaceutical Applied Statistics Symposium, 2025

Disclaimer

- The views and opinions expressed in the following PowerPoint slides are those of the presenter and should not be attributed to his employer.

Acknowledgements/Disclosures

- This work is part of ongoing work of the ASA BIOP Scientific Safety Working Group - WS2 Task Forces focusing on visual analytics of drug safety data and opensource tools and machine learning and AI
- This is part of a presentation that was give at the: *2025 Global Pharmacovigilance and Risk Management Strategies Conference*, a Short course on *Hands-on Short Course on Enhancing the DMC Package Using Opensource Software, AI, and LLMs* and the *2025 Q3 ASA Safety Working Group Quarterly Scientific Webinar on Reimagining Drug Safety with AI: A Quantitative Leap Forward*

- Introduction
- A Call to Leverage Visualization in Drug Safety Analytics
- Framework/Structure for Drug Safety Analytics
- Leveraging a Question-Based Approach
- Leveraging Quantitative Methods
- Focusing on Visual Analytics in DMCs
- Tools and Resources
- The AI and LLMs Angle
- Closing Remarks

Take Home Messages

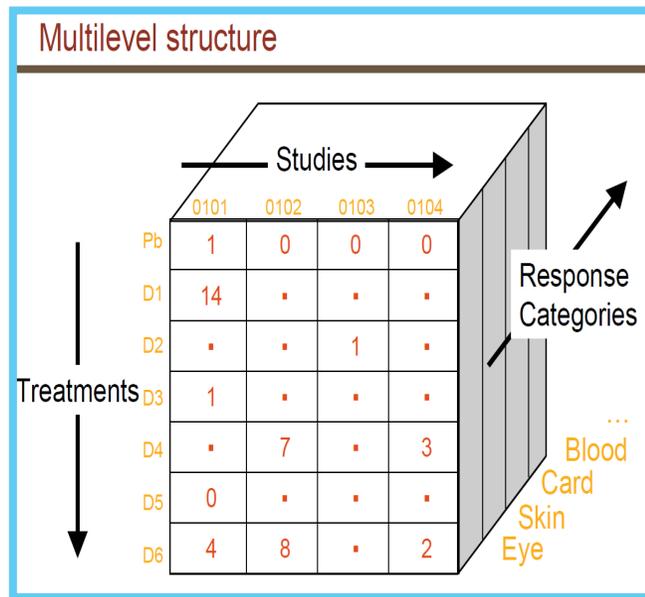
- There are challenges in the analysis and presentations of drug safety data using tabular outputs
- There is immense value in leveraging visual analytics in drug safety and hence in DMC deliverables
- This can be further enhanced by leveraging quantitative methods for drug safety analytics and benefit-risk in decision making in DMCs
- There are readily available opensource tools to implement enhancement of DMC deliverables for both visual analytics and quantitative analysis
- Use of AI and LLMs can greatly help enhance creation and review of outputs in the DMC data package

Introduction

- Nature of drug safety data and analysis
- Challenges – many!

Drug safety assessment in clinical trials:
methodological challenges and opportunities

Sonal Singh and Yoon K. Loke *Trials* 2012, **13**:138



Variety

Labs

Vital
Signs

ECG

Etc

- Safety data present many challenges with regards to analysis and interpretation
 - Clinical trials are not powered to detect safety signals
 - Safety data are multidimensional and interrelated in nature
 - Pathological features of diseases lead to heterogeneous subpopulations and data with non-normal distributions

- Analysis and interpretation
 - Entirely tabular outputs
 - Tabular outputs and graphs
 - Tabular outputs and graphs and visual analytics

A Call to Leverage Visualization in Drug Safety Analytics

- Surely we can do better - an old story!

Tabular Outputs only versus Tabular Plus Graphical Outputs

Guideline for Industry
Structure and Content of Clinical
Study Reports ICH E3



Table 5.8
Adverse Events by Maximum Severity

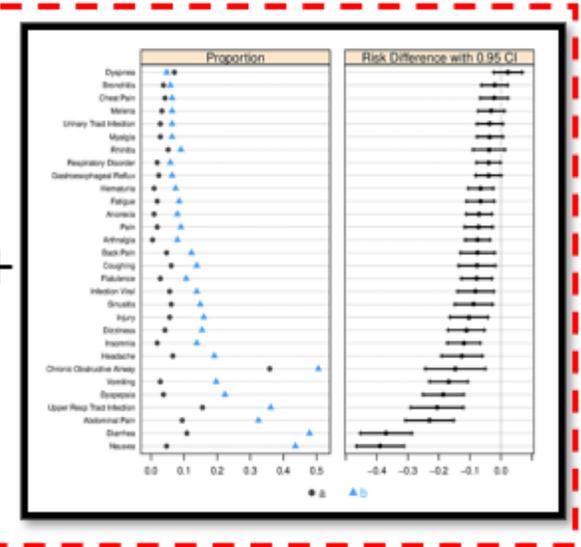
System Organ Class Preferred Term	ARM A (N=25)		
	MI	Moderate	Severe
All Adverse Events	27 (75.8)	18 (27.6)	8 (8.0)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)
Neutropenia	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)
Fatigability	0 (0.0)	0 (0.0)	0 (0.0)
Sinus Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)
Conjunctival, keratitis and general disorders	0 (0.0)	0 (0.0)	0 (0.0)
Dermatoid Cyst	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	0 (0.0)
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine disorders	0 (0.0)	0 (0.0)	0 (0.0)
Parathyroid Disorder	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	1 (2.7)	0 (0.0)
Dysphagia	0 (0.0)	0 (0.0)	0 (0.0)
Food Poisoning	0 (0.0)	0 (0.0)	0 (0.0)
Taurocholic	0 (0.0)	1 (2.7)	0 (0.0)
Yeasting	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	2 (5.4)	0 (0.0)	0 (0.0)
Application Site Hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)
Application Site Irritation	0 (0.0)	0 (0.0)	0 (0.0)
Chest Pain	0 (0.0)	0 (0.0)	0 (0.0)
Cyst	0 (0.0)	0 (0.0)	0 (0.0)

Program AE_Table 8
Note: Adverse events were coded using MedDRA Version 9.1
2024-02-08 19:47:37 023487 Confidential Page 1 of 16

Table 5.9
Adverse Events by Maximum Severity

System Organ Class Preferred Term	ARM A (N=25)		
	MI	Moderate	Severe
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Program AE_Table 9
Note: Adverse events were coded using MedDRA Version 9.1
2024-02-08 19:47:37 023487 Confidential Page 1 of 16



Regulatory perspectives on data monitoring
Robert T. O'Neill *Statist. Med.* 2002; 21:2831-2842

2002

Paper PO10
Clinical Adverse Events Data Analysis and Visualization
Shi-Tao Yeh, GlaxoSmithKline, King of Prussia, PA.

2007

Graphical Approaches to the Analysis of
Safety Data from Clinical Trials
Ohad Amit, Richard M. Heiberger and Peter W. Lane
Pharmaceut. Statist. 2008; 7: 20-35

2008

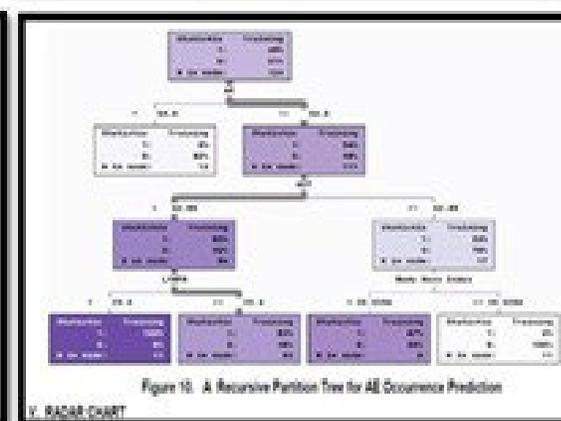
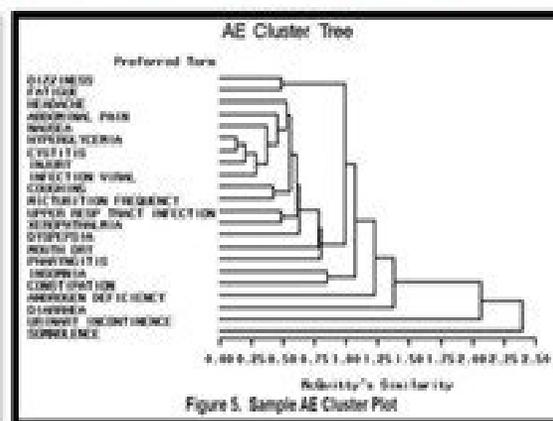
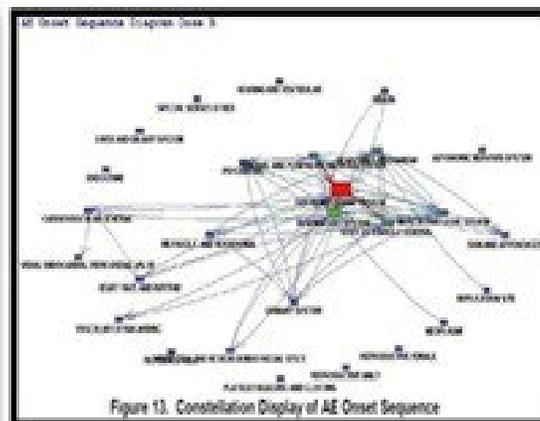
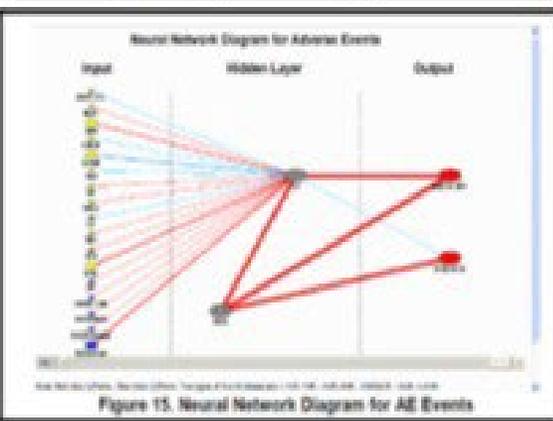
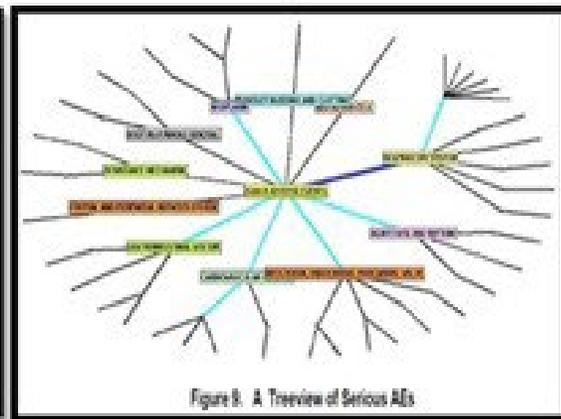
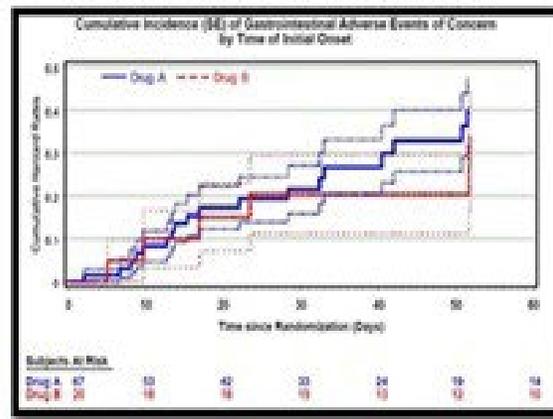
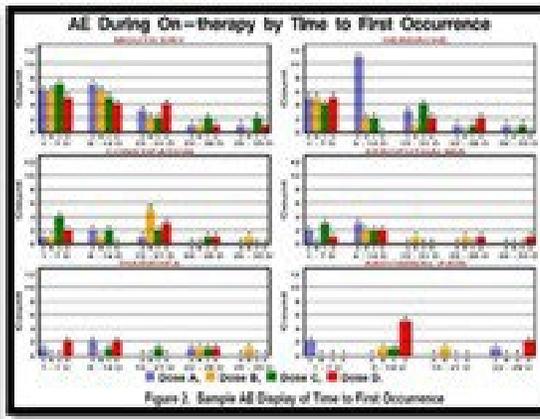
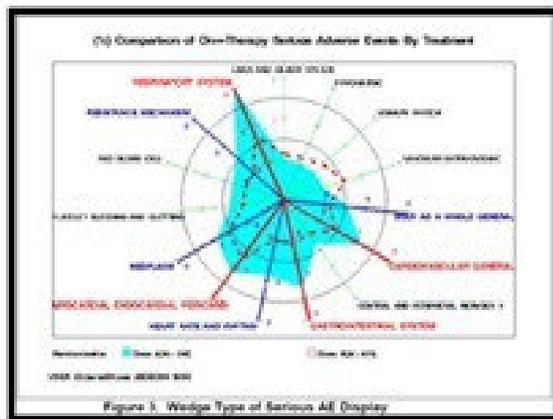
Advantages of visualisations to evaluate
and communicate adverse event
information in randomised controlled trials
Victoria Cornelius, Suzie Cro and Rachel Phillips

2020

A Call to Leverage Visualization in Drug Safety Analytics

2007

Paper PO10
Clinical Adverse Events Data Analysis and Visualization
 Shi-Tao Yeh, GlaxoSmithKline, King of Prussia, PA.

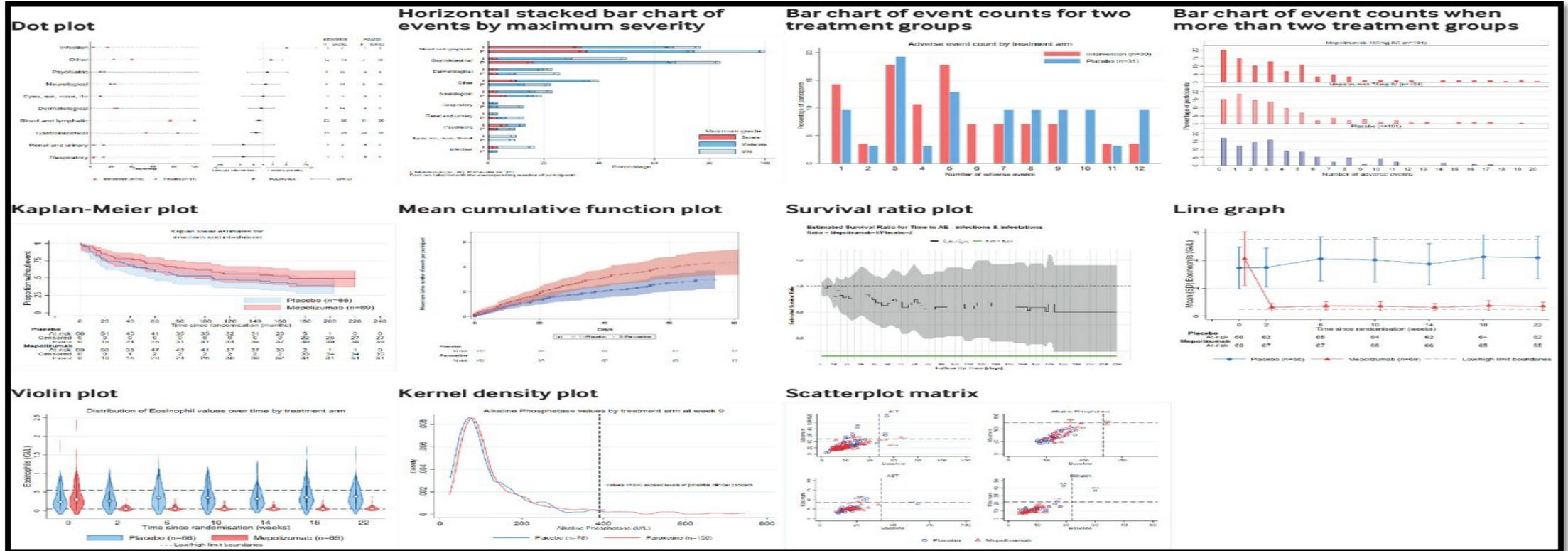


A Call to Leverage Visualization in Drug Safety Analytics

- A continuing story! And some traction!

2022

Visualising harms in publications of randomised controlled trials: consensus and recommendations
 Rachel Phillips, et al *BMJ* 2022;377:e068983



A Call to Leverage Visualization in Drug Safety Analytics

- Regulators are talking about it!

FDA U.S. Food and Drug Administration Protecting and Promoting Public Health www.fda.gov

Quantitative Safety Evaluation at CDER

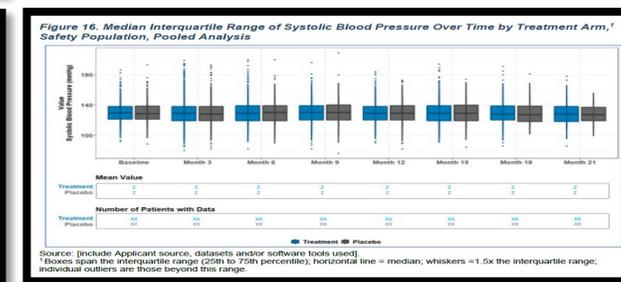
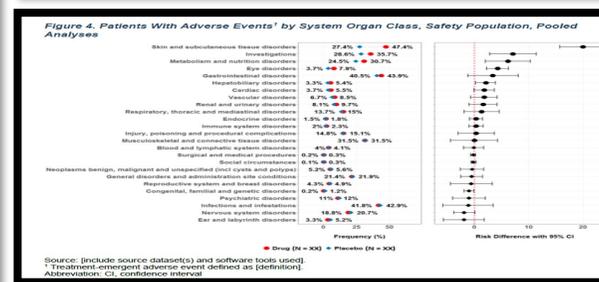
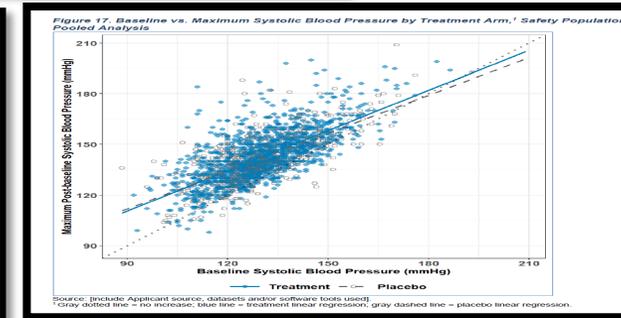
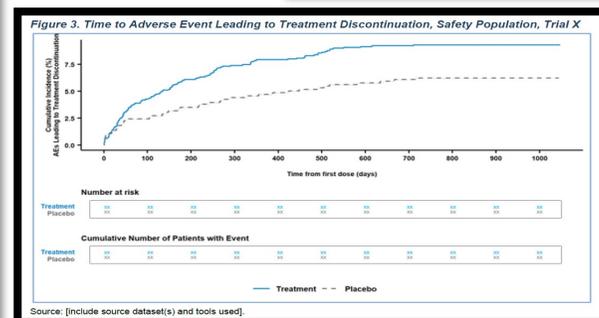
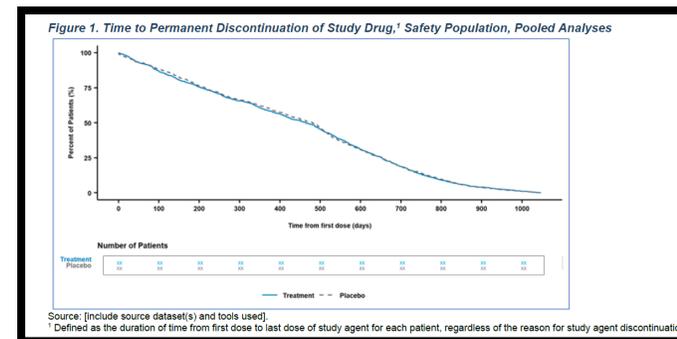
Aloka Chakravarty,
Director, Division of Biometrics VII
Office of Biostatistics, OTS, CDER, FDA

FDA U.S. Food and Drug Administration Protecting and Promoting Public Health www.fda.gov

Why Graphics for Safety?

- Safety information is often times presented in the form of tables and line listings
- But tables and line listings *may not* be the most effective means for conveying information
 - When understanding variable relationships
 - When there is information overload
 - When data summaries do not capture the full extent of the data
 - When integrating information over time
 - When presenting multivariate information for a single subject

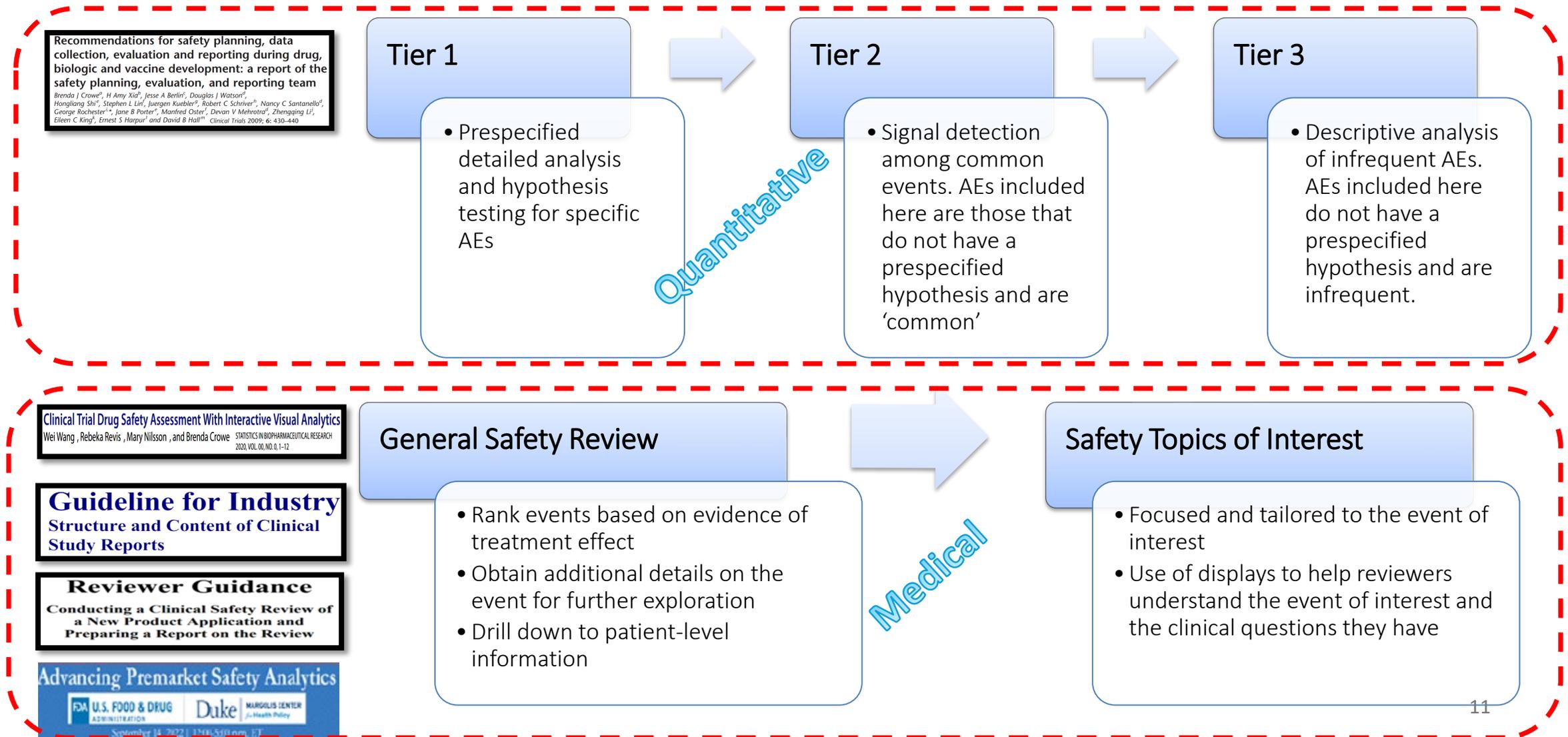
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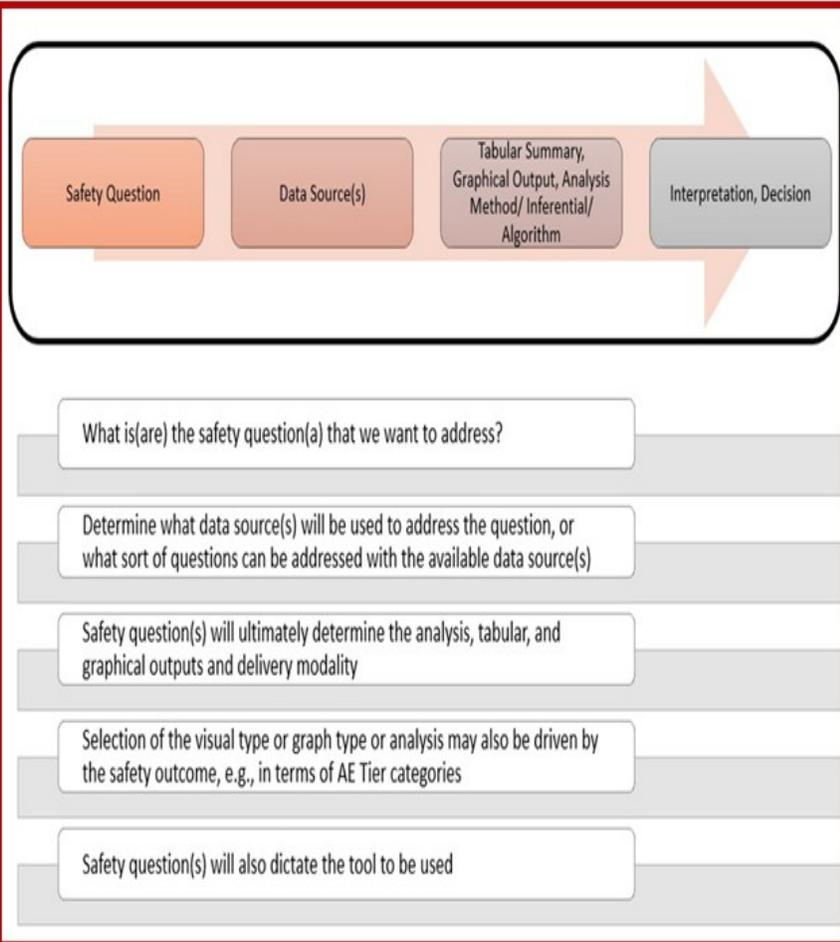
- [Duke-Margolis/FDA Workshop on Advancing Premarket Safety Analytics, 2022 September](#)

Frameworks/Structure for Drug Safety Analytics

- Recommend to work via a framework or structure
- FDA – *screen and deep dive (TAGS – Targeted Analysis Guides)*



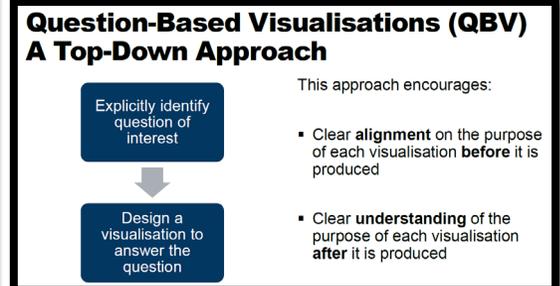
Leveraging a Question-Based Approach



Category	Question
Incidence Rates	<ul style="list-style-type: none"> • What is the constellation of AEs that come with the drug? • Which AEs are elevated in treatment versus control and by how much? • What are the most common AEs in treatment?
Severity , Duration, Relationship	<ul style="list-style-type: none"> • What is the severity of the AEs ? • What is the duration of the AEs? • What is the relationship to study drug?
Temporal Relationship	<ul style="list-style-type: none"> • Is there a difference in the time to the first event across treatment groups? • What are the trends of time to the first event among different AEs? • Is the potential AE of interest increasing over time?
Dose-relationship, Subgroups, Risk Factors	<ul style="list-style-type: none"> • Is there evidence of a dose-response-relationship? • Which AEs are elevated in patient subgroups? • What are the risk factors of the AE?
Concurrent and Intercurrent Events	<ul style="list-style-type: none"> • Is there a relationship with other AEs? • Is there a relationship with use of concomitant medications? • Are there withdraws and/or interruption due to AE of interest?

Chapter 11
A Question-Based Approach to the Analysis of Safety Data
 Melvin S. Munsaka
 © Springer Nature Singapore Pte Ltd. 2018
 K. E. Peace et al. (eds.), *Biopharmaceutical Applied Statistics Symposium*, ICOSA Book Series in Statistics, https://doi.org/10.1007/978-981-10-7826-2_11

Show me the question: Putting the questions front and centre
 Andrew Wright
 RSS Conference, September 2019



- Three Applications of QBVs**
- Replacement for tables, listings and figures in static reports (e.g. CSRs)
 - Structure for interactive Shiny apps
 - Framework for exploratory data analyses

Our Most Important Discovery: The Question
 Scott R. Evans^{a,b} STATISTICS IN BIOPHARMACEUTICAL RESEARCH
 2022, VOL. 14, NO. 4, 398–407

Leveraging Quantitative Methods

2008

Challenges and Opportunities to Improve Premarketing Safety Planning, Evaluation and Reporting
Robert T. O'Neill Ph.D. 2008

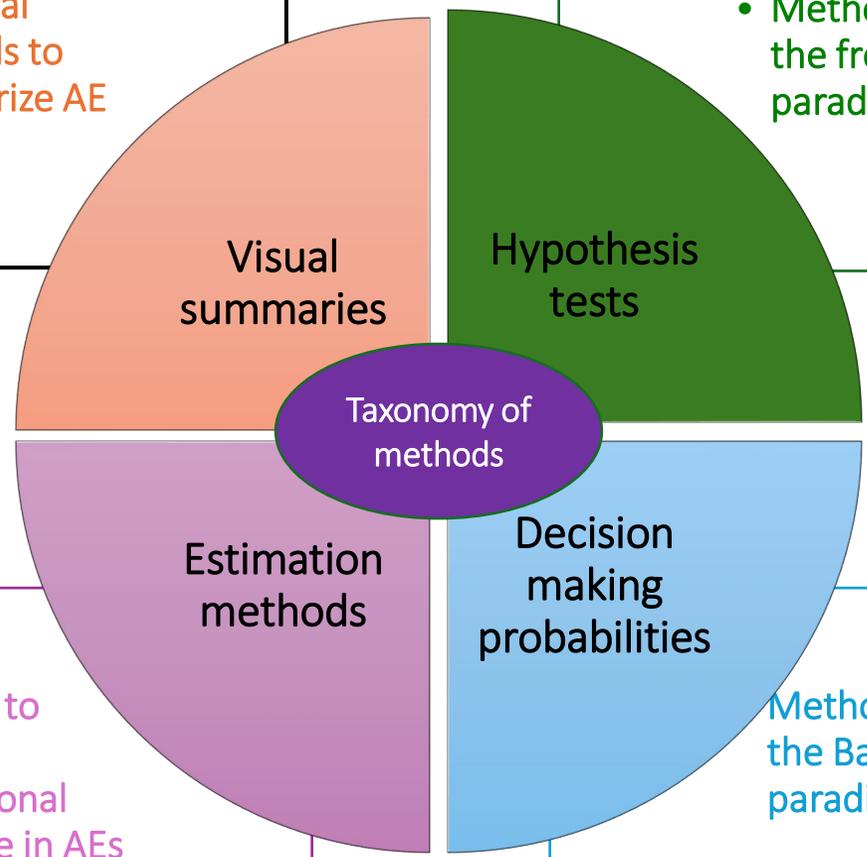
Statistical methods for the analysis of adverse event data in randomised controlled trials: a scoping review and taxonomy *BMC Medical Research Methodology* 20, Article number:288 (2020)
Rachel Phillips, Odile Sauzet & Victoria Cornelius

• Graphical methods to summarize AE data

• Methods under the frequentist paradigm

Culture change is needed for prospective planning for safety evaluation that improves our quantification of risk and uncertainty. Safety evaluation is hard...the pre-market process, the post-approval process and the life-cycle perspective all need to be considered

• Methods to quantify distributional difference in AEs



2013
2016
2018
2024

The Practice of Pre-Marketing Safety Assessment in Drug Development *Journal of Biopharmaceutical Statistics*
Christy Chuang-Stein, H. Amy Xia

The role of quantitative safety evaluation in regulatory decision making of drugs *Journal of Biopharmaceutical Statistics*
Moka G. Chakravarty, Rima Azem, Stephanie Keeton, Clara Y. Kim, Mark S. Levenson & Mat Soukup

On quantitative methods for clinical safety monitoring in drug development *Statistics in Biopharmaceutical Research*
William Wang, Ed Whalen, Melvin Munsaka, Judy Li, Michael Fries, Karolyn Kracht, Matilde Sanchez-Kam, Krishan Singh & KeFei Zhou

Statistical Considerations for Premarketing Risk Assessment
Greg Levin, PhD, May 16, 2024, Mat Soukup, PhD
Associate Director for Statistical Science and Policy, Deputy Director, Division of Biometrics VII, Office of Biostatistics/OTS/CDER/FDA

Appropriate Analysis Approaches

- Focus on comparisons to estimate risk and uncertainty, not on hypothesis testing
- Metrics for estimating risk
 - Summary measures of risk
 - Appropriate statistical methods for the summary measure of interest and given the design
 - On-treatment vs. on-study analyses
- Integrated analyses

...and now Machine Learning, AI, LLMs

The Use of Machine Learning in Regulatory Drug Safety Evaluation
Di Zhang, Jaejoon Song, Sai Dharmarajan, Tae Hyun Jung, Hana Lee, Yong Ma, ...show all
Pages 519-523 | Received 20 Dec 2021, Accepted 21 Jul 2022, Published online: 23 Sep 2022

"Artificial Intelligence" for Pharmacovigilance: Ready for Prime Time?
Robert Ball, Gerald Dal Pan
Drug Safety (2022) 45:429-438

Leveraging Quantitative Methods

- The sophistication is out there!

When to Stop a Clinical Trial Early for Benefit: Lessons Learned and Future Approaches

Faiez Zannad, MD, PhD; Wendy Gattis Stough, PharmD; John J.V. McMurray, MD; Willem J. Remme, MD; Bertram Pitt, MD; Jeffrey S. Borer, MD; Nancy L. Geller, PhD; Stuart J. Pocock, PhD
Circ Heart Fail. 2012;5:294-302.

When is it safe to stop for safety?

S. SCHULMAN, A. CARLSSON and S. LAPORTE
2012 International Society on Thrombosis and Haemostasis

Statistical Evaluation of Drug Safety Data

H. Amy Xia, PhD¹, and Qi Jiang, PhD¹
Therapeutic Innovation & Regulatory Science 2014, Vol 48(1) 109-120

Sequential monitoring of time-to-event safety endpoints in clinical trials

Michael J Martens¹, Qinghua Lian¹, Nancy L Geller², Eric S Leifer² and Brent R Logan¹
Clinical Trials 1-12 2024

Statistical rules for safety monitoring in clinical trials

Michael J Martens and Brent R Logan
Clinical Trials 2024, Vol. 21(2) 152-161

Issues in designing sequential stopping rules for monitoring side effects in clinical trials

Anne I. Goldman
Controlled Clinical Trials
Volume 8, Issue 4, December 1987, Pages 327-337

Early Stopping Rules in Clinical Trials Based on Sequential Monitoring of Serious Adverse Events

A. Kramar, PhD, C. Bascoul-Mollevi, PhD
MEDICAL DECISION MAKING/MAY-JUNE 2009

SAE: An R package for early stopping rules in clinical trials

C. Bascoul-Mollevi^a, A. Laplanche^b, M.C. Le Deley^b, A. Kramar^c
Computer Methods and Programs in Biomedicine
Volume 104, Issue 2, November 2011, Pages 243-248

Statistical Considerations on the Evaluation of Imbalances of Adverse Events in Randomized Clinical Trials

Haijun Ma, PhD¹, Chunlei Ke, PhD¹, Qi Jiang, PhD¹, and Steven Snapinn, PhD¹
Therapeutic Innovation & Regulatory Science 2015, Vol. 49(6) 957-965

A Benefit-risk Model to Facilitate DMC-sponsor Communication and Decision Making

Andreas Sashegyi, PhD

Bayesian methods for the DMC

Mauro Gasparini,
VIII BIAS Annual Congress, Verona 30/06/2016

Interactive medical and safety monitoring in clinical trials with clinDataReview: a validated and open-source reporting tool

Laure Cougnaud^{1*}, Margaux Faes^{2*}, Dirk Van Krunckelsven², Arne De Roeck², Michela Pasetto³, Ann Fieuw², Claus A. Andersen² and Paul Meyvisch²

Pre-Market Safety Must Balance Statistics With Clinical Discernment – FDA

"The Pink Sheet" Nov. 10, 2008, Vol. 70, No. 045

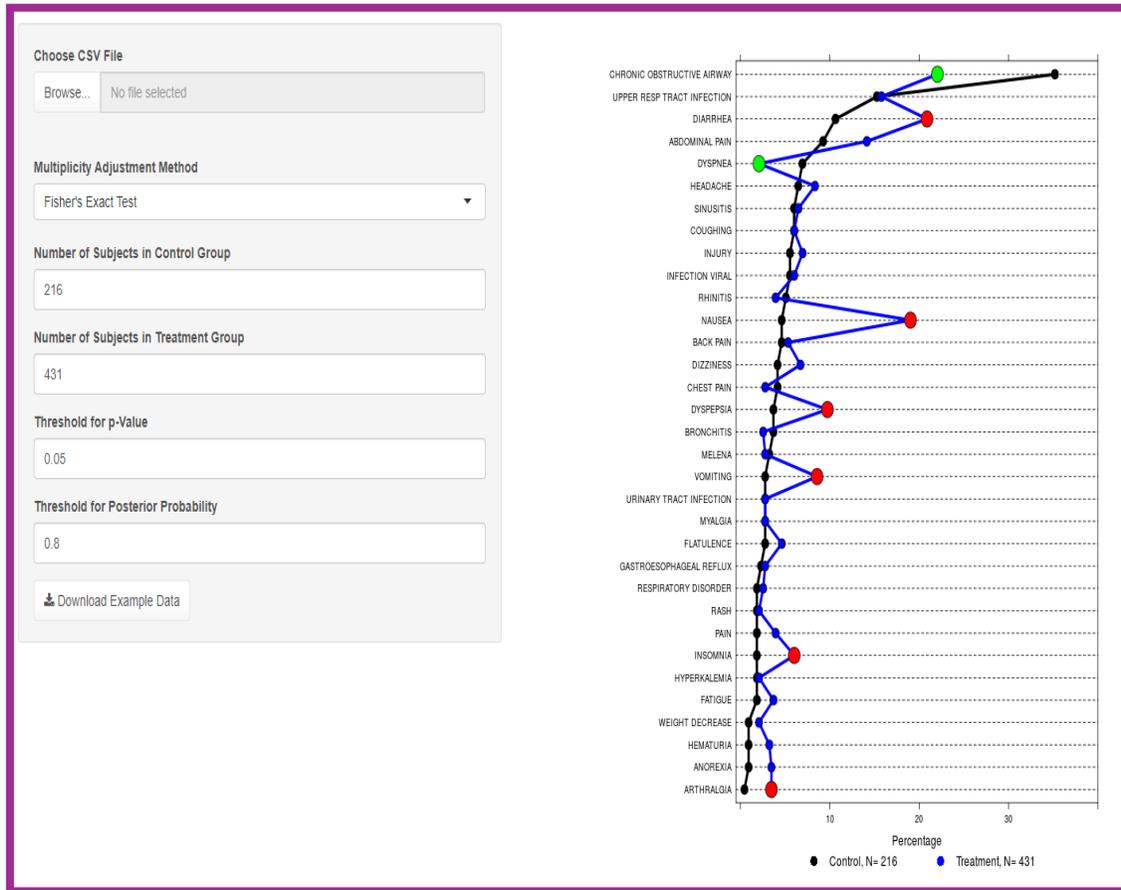
Safety evaluation is probably much harder than efficacy evaluation because in many ways it's reading the tea leaves. It's a lot of multiplicity, a lot of false discovery, a lot of it-is-real or is-it-not-real...But nonetheless, you can't even approach that discussion if you can't quantify it in a reasonable way...*statisticians for the most part have not been involved in safety evaluations...The sophistication is out there, it just has not been brought to bear on routine safety assessment for chronically used drugs.*

2008

Leveraging Quantitative Methods

- The sophistication is out there!

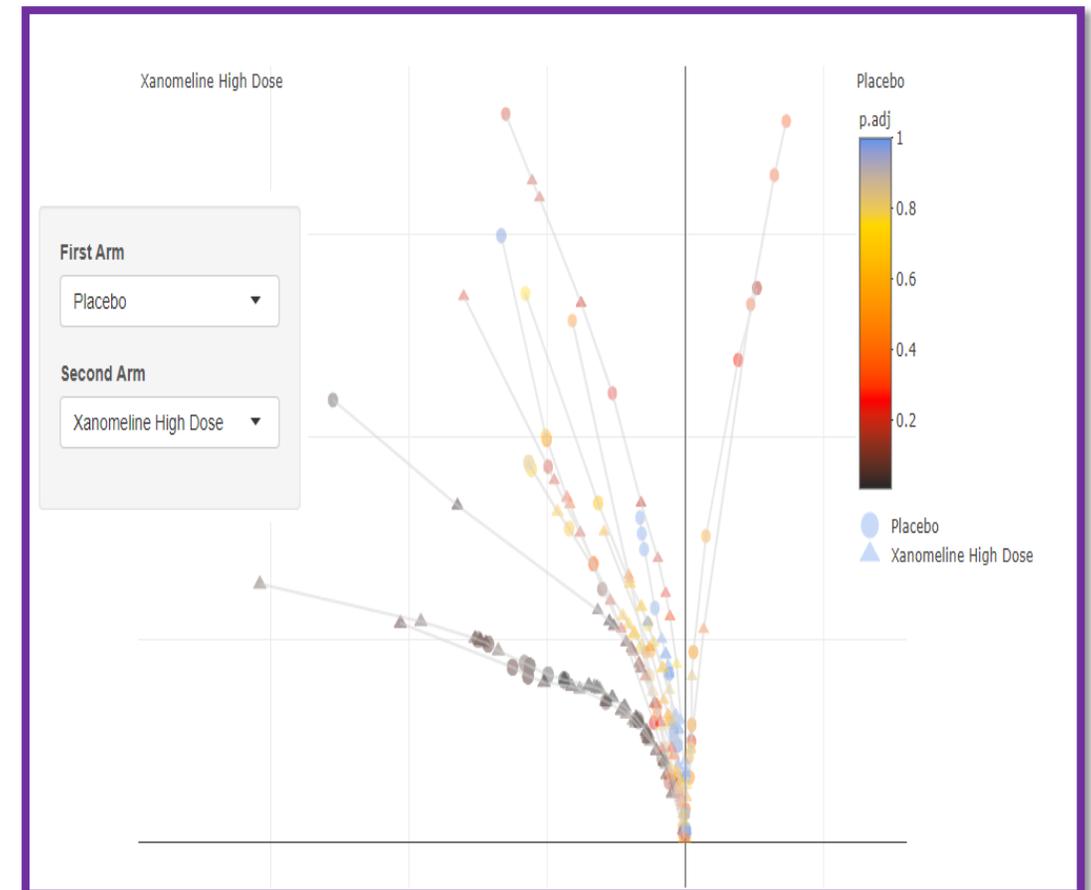
Enhanced dot plot



Which AEs are elevated in treatment versus control and by how much?

- Source: <https://chenchenstat.shinyapps.io/ae-line-plot-c212/>

Tendril plot

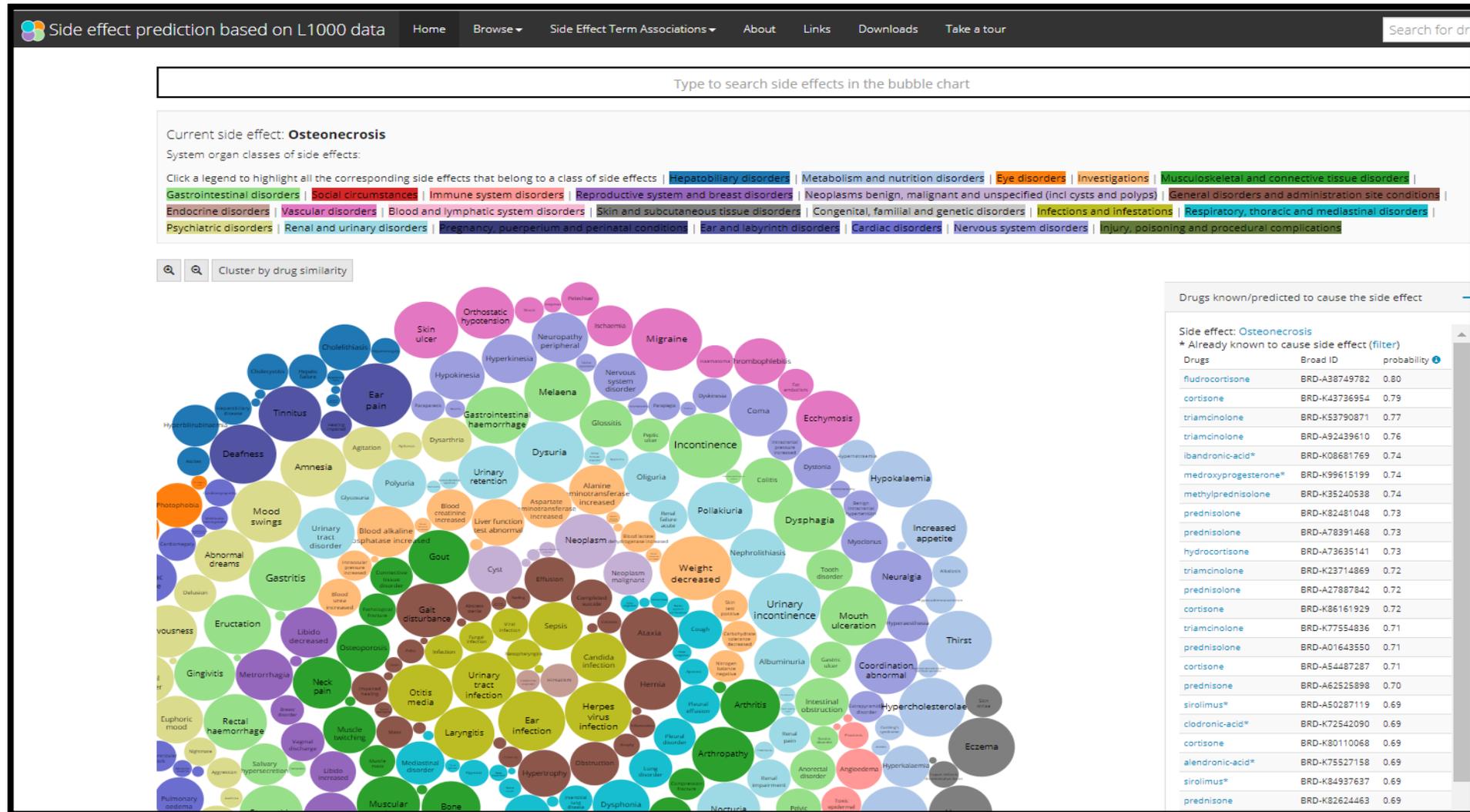


Which AEs are more in treatment versus control and when do they occur?

- Source: <https://xiao-ni.shinyapps.io/patprofile/>

Leveraging Quantitative Methods

- The sophistication is out there!



Source: <http://maayanlab.net/SEP-L1000/>

Leveraging Quantitative Methods

- The sophistication is out there!
 - Assessment of Drug Induced Liver Injury (DILI, hepatotoxicity)
 - Statistical methods – laboratory data
 - ML, AI, DL, NLP - **Multisource**

**Guidance for Industry
Drug-Induced Liver Injury:
Premarketing Clinical
Evaluation**

Methodology to Assess Clinical Liver Safety Data

Michael Merz · Kwan R. Lee · Gerd A. Kullak-Ublick ·
Andreas Brueckner · Paul B. Watkins *Drug Saf* (2014) 37 (Suppl 1):S33–S45

**Liver Safety of Fasiglifam (TAK-875) in Patients with Type 2
Diabetes: Review of the Global Clinical Trial Experience**

John F. Marcinak¹ · Melvin S. Munsaka¹ · Paul B. Watkins² · Takashi Ohira³ ·
Neila Smith¹ *Drug Saf* (2018) 41:625–640

**Multivariate extreme value modelling of
laboratory safety data from clinical studies**

Harry Southworth* and Janet E. Heffernan *Pharmaceut. Statist.* 2012, 11 367–372

**DeepDILI: Deep Learning-Powered Drug-Induced Liver Injury
Prediction Using Model-Level Representation**

Ting Li, Weida Tong, Ruth Roberts, Zhichao Liu*, and Shraddha Thakkar*
Chem. Res. Toxicol. 2021, 34, 2, 550–565

**Comparing Machine Learning Algorithms for Predicting Drug-Induced
Liver Injury (DILI)** Cite this: *Mol. Pharmaceutics* 2020, 17, 7, 2628–2637

Eni Minerali, Daniel H. Foil, Kimberley M. Zorn, Thomas R. Lane, and Sean Ekins*

**Prediction of clinically relevant drug-induced liver injury from
structure using machine learning** *J Appl Toxicol.* 2019;39:412–419.

Felix Hammann | Verena Schöning | Jürgen Drewe

The Promise of AI for DILI Prediction

Andreu Vall^{1,2*}, Yogesh Sabnis³, Jiye Shi³, Reiner Class³, Sepp Hochreiter^{1,2,4} and
Günter Klambauer^{1,2*}

Frontiers in Artificial Intelligence | www.frontiersin.org April 2021 | Volume 4 | Article 638410

Leveraging Quantitative Methods

- Spontaneous Reporting Systems Data, e.g., FAERS, CAERS, VigiBase, etc
 - Machine Learning
 - Deep Learning
 - Artificial Intelligence

PREDICTING SAFETY INFORMATION OF DRUGS USING DATA MINING TECHNIQUE
By V. Umashanti, C. Rathika
International Journal of Computer Engineering & Technology (IJ CET)
Volume 10, Issue 2, March–April, 2019, pp. 83-90.

Predicting adverse drug reaction outcomes with machine learning
Andy W. Chen *Int J Community Med Public Health*. 2018 Mar;5(3):901-904

Prediction of Adverse Drug Reaction (ADR) Outcomes with use of Machine Learning. Feed-Forward Artificial Neural Network with Backpropagation Kamil Szymanski

Predicting potential adverse events using safety data from marketed drugs
Chathuri Daluwatte, Peter Schotland, David G. Strauss, Keith K. Burkhardt and Rebecca Racz
BMC Bioinformatics (2020) 21:163

Predicting adverse drug reactions based on patient demographic information and other factors
Anthony Olvera and Annie Lydens

How to Use Machine Learning to Forecast Adverse Drug Reactions
Improving patient outcomes with Machine Learning

Detecting early safety signals of infliximab using machine learning algorithms in the Korea adverse event reporting system
Jaegun Lee^{1,2}, Ju Hwan Kim^{1,2}, Ji Hwan Bae², Inmyung Song² & Ju-Young Shin^{1,2,3,4,5}
Scientific Reports | (2022) 12:14869

Machine Learning for Detection of Safety Signals From Spontaneous Reporting System Data: Example of Nivolumab and Docetaxel
Ji-Hwan Bae¹, Yeon-Hoe Baek¹, Jaegun Lee¹, Inmyung Song², Jee-Hyong Lee² and Ju-Young Shin^{1,4*}
Frontiers in Pharmacology | January 2021 | Volume 11 | Article 602368

A Comparison Study of Algorithms to Detect Drug-Adverse Event Associations: Frequentist, Bayesian, and Machine-Learning Approaches *Drug Safety* (2019) 42:743–750
Minh Pham · Feng Cheng · Kandethody Ramachandran

Systematic Analysis of Adverse Event Reports for Sex Differences in Adverse Drug Events
YueYu^{1,2}, Jun Chen², Dingcheng Li², Liwei Wang¹, Wei Wang¹ & Hongfang Liu²
SCIENTIFIC REPORTS | 6:24955 | DOI: 10.1038/srep24955



Using Machine Learning to Identify Adverse Drug Effects Posing Increased Risk to Women
Payal Chandak, Nicholas P. Tatonetti *Patterns* 1, 100108, October 9, 2020

Focusing on Visual Analytics in DMCs

- An old story!

2002

Regulatory perspectives on data monitoring

Robert T. O'Neill *Statist. Med.* 2002; 21:2831–2842

A DMC may be faced with evaluating a potential safety concern for which the patient level data on multiple laboratory values and events that pertain to safety suggests the increased toxicity is confounded with the disease being studied. Where there is a background of multiple concomitant diseases, or drugs, it is often difficult to ascertain for a specific patient the full profile of what is occurring in multiple organ or multiple adverse outcomes. DMC members can be faced with this situation in the evaluation of individual patient outcomes and in the evaluation of accumulated comparative safety events of groups of patients that are compared with each other for evidence of differential safety outcomes. It is my personal opinion that a tool that may be useful to DMC members, especially for safety assessment, is the concept of graphical patient profiles, which places on one page virtually every exposure, measurement and outcome associated with an individual's experience in a clinical trial from entry to completion. This would include entry and withdrawal status and indicators for time on and off study. Consider a plot of all the relevant time dependent multiple outcomes and repeated measures that reflect the status of a patient in a trial from entrance to completion of the trial.

2002

Automated Statistical Reporting for Data Monitoring Committees in Clinical Trials

Frank E Harrell Jr

- Enhance safety and risk/benefit review by DMC
- Provide efficient and state-of-the-art statistical reporting
- High-quality graphics (a la Bill Cleveland) and tables
- Hard copy and on-screen review

Focusing on Visual Analytics in DMCs

- An old story continues!

2020

Presenting Risks and Benefits: Helping the Data Monitoring Committee Do Its Job *Annals of Internal Medicine*
Scott R. Evans, PhD; Robert Bigelow, PhD; Christy Chuang-Stein, PhD; Susan S. Ellenberg, PhD; Paul Gallo, PhD; Weili He, PhD; Qi Jiang, PhD; and Frank Rockhold, PhD

These evaluations may be improved by broader access to data and more effective analyses and presentation. Data monitoring committees should have access to all data, including efficacy data, at each interim review. The DMC reports should include graphical presentations that summarize benefits and harms in efficient ways. Benefit-risk assessments should include summaries that are consistent with the intention-to-treat principle and have a pragmatic focus. This article provides examples of graphical summaries that integrate benefits and harms, and proposes that such summaries become standard in DMC reports.

Data Visualization for Data Monitoring Committees for Clinical Trial
Adam Hamm, *PhUSE US Connect 2018 Paper DV17*

2018

Enhancing clarity of clinical trial safety reports for data monitoring committees
Sonia M. Thomas^a, Kwanhye Jung^b, Hengrui Sun^c, Matthew A. Psioda^b, Pedro Miguel Quibrera^a, and Stephen M. Strakowski^d
JOURNAL OF BIOPHARMACEUTICAL STATISTICS
2020, VOL. 30, NO. 6, 1147-1161

2020

2020

Data monitoring committees for clinical trials evaluating treatments of COVID-19 Tobias Mütze , Tim Friede *Contemporary Clinical Trials* 98 (2020) 106154

DMC reports should be have a clear structure and ideally be a single document that includes a table of content. The graphical and interactive visualization of data may ease the exploration of the data and enhance the readers' understanding of the data. DMC reports are no exception to this. Examples for DMC reports that fulfill the previously described principles are for instance provided by the University of Wisconsin-Madison. In addition, Evans et al. recently recommended to show forest plots of risk differences/ratios for key safety and efficacy endpoints. plots of rates of ranked desirable outcomes so-called "desirability of outcome ranking" (DOOR) plots, or so-called la-sagna plots that summarize the benefit-risk over time by treatment. In addition to a report, the DMC may review data during their meeting using interactive displays. Interactive displays can for example be created with Shiny, an R package for building interactive web apps from R.

What Types of Safety Outputs Does the DMC Receive?
David Kerr and Nand Kishore Rawat

2023

Focusing on Visual Analytics in DMCs

- And the story continues! What are the questions of interest?

2018

Reports to Independent Data Monitoring Committees: An Appeal for Clarity, Completeness, and Comprehensibility
 Kevin A. Buhr, PhD¹, Matthew Downs, MPH², Janelle Rhorer, MS², Robin Bechhofer, BA¹, and Janet Wittes, PhD²
Therapeutic Innovation & Regulatory Science 2018, Vol. 52(4) 459-468

Tables replete with missing data or multiple rows of zeros are distracting; graphs that hide what is missing can be deceptive.

2022

Estimands: bringing clarity and focus to research questions in clinical trials
 Timothy Peter Clark^{1,2}, Brennan C Kahan,¹ Alan Phillips,² Ian White,¹ James R Carpenter^{1,3}
BMJ Open

Table 1. Sample Content and Organization of Open and Closed IDMC Reports.

Section	Open	Closed	Sample of questions answered in section:
Recruitment	×	×	<ul style="list-style-type: none"> ● Is enrollment meeting projections? ● Are a few clinical centers dominating enrollment?
	×	×	<ul style="list-style-type: none"> ● Is treatment roughly balanced within region and country? Are stratification factors balanced?
Availability of data	×	×	<ul style="list-style-type: none"> ● How much follow-up data are available?
	×	×	<ul style="list-style-type: none"> ● Are sites entering data in a timely fashion?
	×	×	<ul style="list-style-type: none"> ● Are there endpoint events that occurred before the last report's data cut-off but are only first reported in the current report?
	×	×	<ul style="list-style-type: none"> ● Do any sites have anomalously low (or high) AE reporting rates?
Baseline characteristics	×	×	<ul style="list-style-type: none"> ● Is treatment roughly balanced by baseline prognostic factors? Could baseline differences account for safety or efficacy findings?
	×	×	<ul style="list-style-type: none"> ● Do the distributions of baseline characteristics match those expected in the study population?
Disposition	×	×	<ul style="list-style-type: none"> ● Is there evidence of errors when specifying stratification factors at randomization?
	×	×	<ul style="list-style-type: none"> ● In what phase of the study (eg, screening, treatment, follow-up) are participants? (For particularly complex study designs, a diagram of disposition may be useful.)
	×	×	<ul style="list-style-type: none"> ● Are discontinuation rates and reasons comparable between the study arms? Does the timing of discontinuations differ between study arms?
Treatment exposure	×	×	<ul style="list-style-type: none"> ● Are both treatment discontinuation and study discontinuations clear?
	×	×	<ul style="list-style-type: none"> ● What proportion of participants fail to receive study treatment?
Protocol adherence	×	×	<ul style="list-style-type: none"> ● Is the intensity of received treatment similar by study arm?
	×	×	<ul style="list-style-type: none"> ● Is the study being conducted in a manner that will allow it to answer the research questions?
Adverse events	×	×	<ul style="list-style-type: none"> ● Do any sites have particularly high rates of deviations?
	×	×	<ul style="list-style-type: none"> ● Do the groups differ with respect to AE findings?
	×	×	<ul style="list-style-type: none"> ● Do the observed safety data match the expected safety profile of the intervention under study?
Laboratory, ECG, and/or vital sign parameters	×	×	<ul style="list-style-type: none"> ● Are the observed safety data consistent with the expected background event rates in the study population?
	×	×	<ul style="list-style-type: none"> ● Do the groups differ with respect to safety findings?
Efficacy	×	×	<ul style="list-style-type: none"> ● Are the laboratory findings consistent with findings from the AE data?
	×	×	<ul style="list-style-type: none"> ● Are particular events, like cases of Hy's Law, easily identifiable in the data (eg, via listings, patient-profile plots, tables/plots of specific labs)
	×	×	<ul style="list-style-type: none"> ● Are the preliminary efficacy data consistent with the possibility of a favorable risk: benefit profile of the agent under study? (Recommend evaluating this question at each safety review, not just interim efficacy reviews)
		×	<ul style="list-style-type: none"> ● Have predefined efficacy or futility criteria been met?

- And the story continues! What are the questions of interest?

2024

Data Monitoring Committee Reports: Telling the Data's Story

Lijuan Zeng¹ · Toshimitsu Hamasaki^{1,2} · Scott R. Evans^{1,2} Therapeutic Innovation & Regulatory Science

Table 3 Closed report sections and review questions to consider

Section	Questions to consider
Adverse events (AE) <ul style="list-style-type: none"> • High-level summary table of different types of AEs (leading to death, serious, severity, AE of special interest) • DOOR forest plot • Volcano plot • AE tables by MedDRA system organ class/high level class/preferred term • Risk differences line plot • Tendrils plot 	What are the total number and types of AE reported? Which AEs show the most significant differences between treatment groups? Are the AEs reported expected? If not, what are the implications, and are there any follow-up questions and actions needed regarding these events? Are there any notable differences in AEs within specific subgroups? Considering the overall risk and benefit (efficacy outcomes), are the risks justified for continuing treatments in those experiencing AEs?
Laboratory assessment, vital signs, and physical assessment <ul style="list-style-type: none"> • Boxplots/mean plots (continuous parameters), supplemented with tables if needed • Shift plots for categorical changes for select parameters 	Are there any abnormal values that are clinically significant? Are the changes from baseline expected? Are there any significant differences in values between treatment groups that need further investigation? Are there any correlations between abnormal results and reported AEs?

Focusing on Visual Analytics in DMCs

- Make the DMC package interactive!
- Or create an interactive DMC data packages

2019

A New Model for Statistical Reports for RCT Data Monitoring Committees

Frank Harrell Trial Innovation Network Series 2019-11-04

The image displays two side-by-side screenshots of interactive DMC reports. The left screenshot shows the 'Example Closed Meeting Data Monitoring Committee Report' with a sidebar menu listing various sections like Philosophy, Notation, Introduction, Accrual, Baseline Variables, Longitudinal Adverse Events, Incidence of Adverse Events at Any Follow-up, Longitudinal EKG Data, Longitudinal Clinical Chemistry Data, Time to Hospitalization and Surgery, Computing Environment, Programming, and References. The main content area shows the 'Philosophy' section, which discusses reporting tools and lists five points about graphical representation of data. The right screenshot shows the 'DSMB Report for EXAMPLE Trial' with a sidebar menu listing sections like Introduction, Accrual, Exclusions, Baseline Variables, Ordinal Outcome Summary, Medication Usage Over Time, Time to Hospitalization and Surgery, and Adverse Events. The main content area shows the 'Introduction' section, which discusses semi-interactive graphs and figure captions. Both reports include a 'Code' button and a user profile for FE Harrell.

<https://hbiostat.org/r/hreport/report>

<https://hbiostat.org/r/hreport/test>

Focusing on Visual Analytics in DMCs

- Include quantitative benefit-risk assessment and visualization

2012

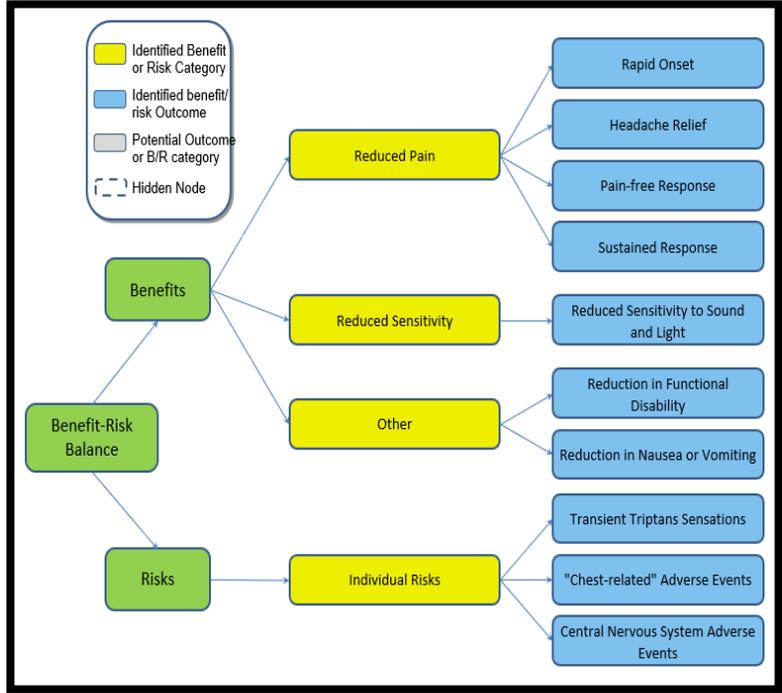
When to Stop a Clinical Trial Early for Benefit: Lessons Learned and Future Approaches
 Faiez Zannad, MD, PhD; Wendy Gattis Stough, PharmD; John J.V. McMurray, MD;
 Willem J. Remme, MD; Bertram Pitt, MD; Jeffrey S. Borer, MD; Nancy L. Geller, PhD; Stuart J. Pocock, PhD
Circ Heart Fail. 2012;5:294-302.

DMCs must not only consider statistical stopping guidelines when making decisions regarding the early termination of a trial for benefit, but they also must consider the uptake and acceptance of the result by the clinical community. If the data are relatively insubstantial, clinicians are skeptical of the results, and the trial may be viewed as an unnecessary loss of time, resources and, potentially, lives.

Planning Benefit-Risk Assessments Using Visualizations
 Michael W. Colopy¹ · Lovemore Gakava² · Chen Chen³
Therapeutic Innovation & Regulatory Science (2023) 57:1123–1135

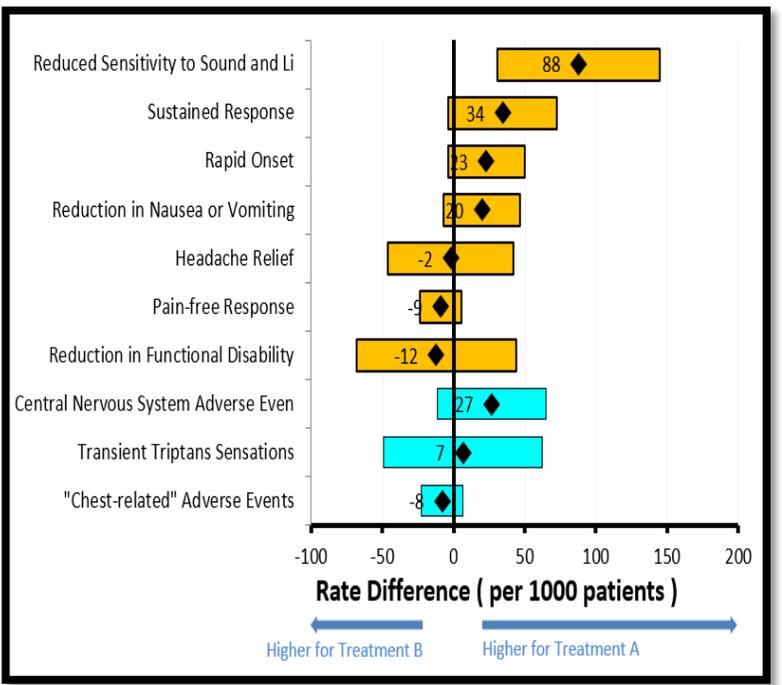
2023

Value tree



What are the benefits and what are the risks?

Benefit risk forest plot



How do the benefits and risks balance out?

Focusing on Visual Analytics in DMCs

- Include quantitative benefit-risk assessment and visualization

Multi-Criteria Decision Analysis for Benefit-Risk Analysis by National Regulatory Authorities

Orin Chisholm^{1,2,3*}, Patrick Sharry^{2,4} and Lawrence Phillips⁵

Structured benefit-risk evaluation for medicinal products: review of quantitative benefit-risk assessment findings in the literature

Marie-Laure Kürzinger¹, Ludvine Douarin, Ievgenia Uzun, Chantal El-Haddad, William Hurst, Juhaeri Juhaeri² and Stéphanie Tcherny-Lessenot

Advancing structured decision-making in drug regulation at the FDA and EMA

Aris Angelis¹ | Lawrence D. Phillips

Benefit-risk Assessment of Cladribine Using Multi-criteria Decision Analysis (MCDA) for Patients With Relapsing-remitting Multiple Sclerosis

Patrick Vermersch, MD, PhD¹; Vittorio Martinelli, MD²; Claudia Pflieger, MD, PhD³; Peter Rieckmann, MD^{3,4}; Lucia Alonso-Magdalena, MD⁵; Andrew Galazka, MD⁶; Fernando Dangond, MD⁷; and Lawrence Phillips, PhD⁸

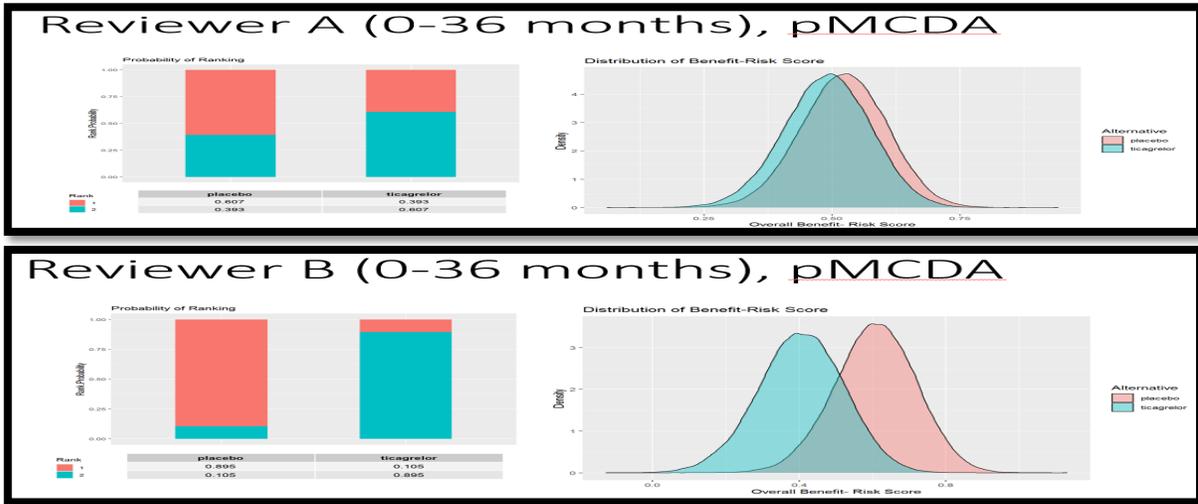
Incorporating Prior Data in Quantitative Benefit-Risk Assessments: Case Study of a Bayesian Method

Therapeutic Innovation & Regulatory Science
https://doi.org/10.1007/s43441-023-00611-4

Sai Dharmarajan, PhD¹✉ · Zhong Yuan, MD, PhD² · Yeh-Fong Chen, PhD³ · Leila Lackey, MHS, DEnv³ · Saurabh Mukhopadhyay, PhD⁴ · Pritibha Singh, MSc, MBA⁵ · Ram Tiwari, PhD⁶

Case Study of Multiple Criteria Decision Analysis for Quantitative Benefit Risk Assessment

ASA Biopharmaceutical Meeting 2020
Sai Dharmarajan
FDA/CDER/OTS/OB



Decision analysis for benefit-risk

Introduction, Data and Preferences

Data Source

Select source of data

Example dataset

Upload dataset

This is a fabricated dataset

Use dataset

Range and Utility functions

Weights

MCDA

Probabilistic MCDA

SMAA

Generate Report

Select column containing alternatives

X1

Benefit criteria

Nothing selected

Risk criteria

Nothing selected

Select column containing number of subjects

Nothing selected

Select columns containing variance(s)

Nothing selected

Prior Study Indicator

X1

Select criteria which are event counts

Nothing selected

Select criteria with continuous scores

Nothing selected

Select criteria where lower scores are better

- In above example, can replace Reviewer A by Region X Reviewer and Reviewer B by Region Y Reviewer
 - Requires lots planning in the MRCT setting!
- Source: https://www.ema.europa.eu/en/documents/variation-report/gardasil-h-c-703-ws-523-epar-assessment-report-variation_en.pdf
- Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/022433Orig1s028.pdf
- Source: https://github.com/saidee27/BayesianMCDA_SMAA
- Source: https://sai-dharmarajan.shinyapps.io/BayesianMCDA_SMAA/

Focusing on Visual Analytics in DMCs

- Include quantitative benefit-risk assessment and visualization
 - At the patient level → Desirability of Outcome Ranking (DOOR)

The screenshot displays the DOOR software interface. At the top, there are navigation links for 'DOOR Standard Edition', 'DOOR Professional Edition', 'DOOR Sample Size', 'DOOR PIPS', and 'ITD Standard Edition'. Below this is a dark navigation bar with 'DOOR Analyses: Standard Edition' and several analysis options: 'Data Input Table', 'Descriptive Analysis', 'DOOR Probability-Based Analysis', 'Partial Credit Analysis', and 'Support'. The main content area is split into two sections. On the left, the 'Configurations' panel includes sections for 'Analysis Dataset' (with radio buttons for 'Your own data' and 'Demo data'), 'Pre-specified Settings' (with a 'Default' dropdown), 'Comparison Group' (with input fields for 'Test Intervention Label' containing 'Treatment' and 'Control Intervention Label' containing 'Control'), and 'DOOR and DOOR Components' (with a 'Data Format' field). On the right, the 'Data Input Table' section is titled 'DOOR Distribution by Intervention'. It contains a table with two columns: 'DOOR (Most desirable to least desirable) Rank' and 'Treatment'. The table lists ranks from 1 to 5, and a 'Total (N)' row, with corresponding treatment labels in the adjacent column.

DOOR (Most desirable to least desirable) Rank	Treatment
Rank 1	
Rank 2	
Rank 3	
Rank 4	
Rank 5	
Total (N)	

- <https://methods.bsc.gwu.edu/>
- <https://cran.r-project.org/web/packages/door/index.html>

Using Outcomes to Analyze Patients Rather than Patients to Analyze Outcomes: A Step toward Pragmatism in Benefit:risk Evaluation Scott R. Evans^{1,2} and Dean Follmann³
Stat Biopharm Res. 2016 ; 8(4): 386–393

Tools and Resources

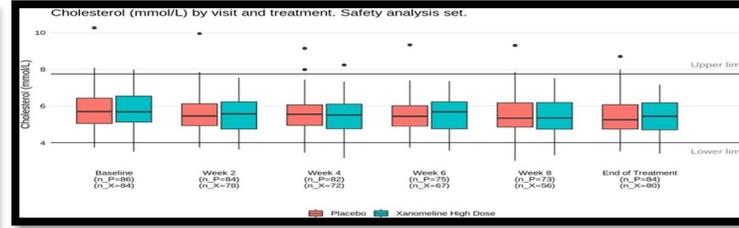
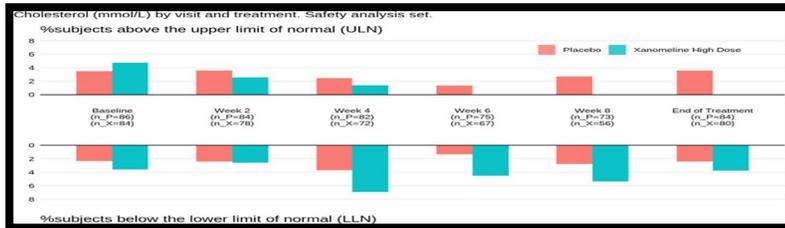
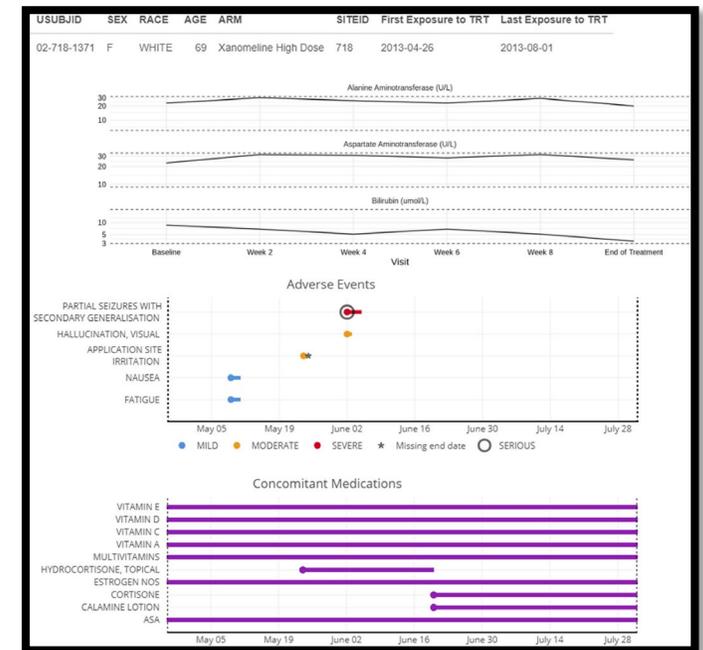
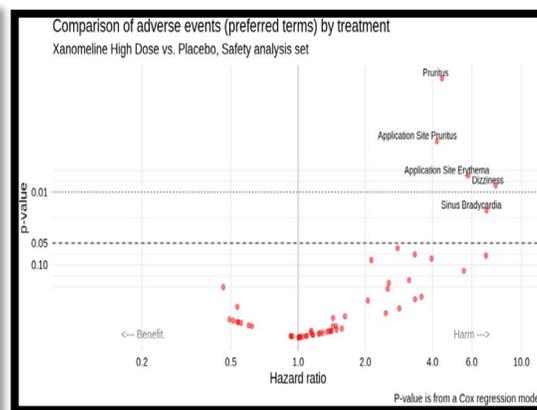
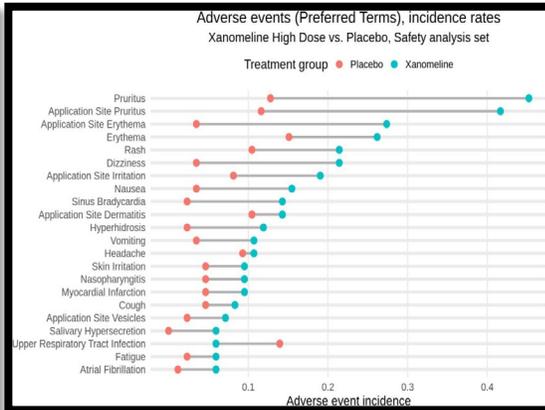
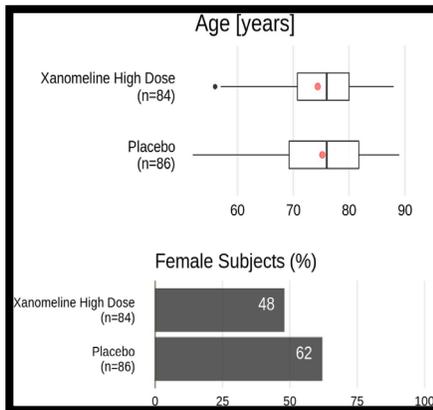
- Plenty of emerging tools - opensource!
- Opensource tools are your friend!

2023

DMC reports in the 21st century: towards better tools for decision-making

Marc Vandemeulebroecke¹, Mark Baillie¹, Ardalan Mirshani² and Emmanuel Lesaffre^{3*}
Trials (2023) 24:289

Data Monitoring Committees (DMCs) have the important task to protect the safety of current and future patients during the conduct of a clinical study. Unfortunately, their work is often made difficult by voluminous DMC reports that are poorly structured and difficult to digest. In this article, we suggest improved solutions. Starting from a principled approach and building upon previous proposals, we offer concrete and easily understood displays, including related computer code. While leveraging modern tools, the most important is that these displays support the DMC's workflow in answering the relevant questions of interest. We hope that the adoption of these proposals can ease the task of DMCs, and importantly, lead to better decision-making for the benefit of patients.



<https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-023-07290-4>

<https://github.com/DMC21cent/DMC21cent>



Implementation of {teal} Shiny Apps in DMC Activity

R/Pharma Virtual Session

Peng Zhang, PhD
Assistant Director, Innovative Data Sciences
CIMS Global, Somerset, NJ

Oct, 2024



Implementation of {teal} Shiny Apps in DMC Activity

On-Demand Talk

IMPROVING MONITORING OF PATIENTS' SAFETY DURING CLINICAL TRIALS

Using Quarto Interactive Reports and a Shiny application within a small to mid-size CRO

Leonard Daniël Samson
Medical Monitor & Clinical Data Scientist
GCP-Service International Ltd. & Co. KG

VIRTUAL EVENT
WED, OCT 25, 2023



Tools and Resources – the AI and LLMs Angle

- How can we use AI and LLMs in the DMC package
 - Can leverage AI and LLM tools to help with efficient and timely creation, *packaging*, and interpretations of the DMC data package prior to, during, and post DMC meetings – harness visual analytics
- Low hanging fruit and practical applications
 - Use AI and LLMs to help generation of the DMC package: coding and code interpretation, data wrangling, debug errors, code comments, code reformat code, table and plots creation
- Advanced use, but still practical applications – use AI and LLMs to:
 - Create analysis apps for safety data exploration and analysis
 - Create *beefed-up* (interactive and with drill down) packaged DMC data packages, leveraging visual analytics and custom reports
 - Implement chatbot type interactivity and analysis interpretations, including functionality to allow stakeholders to interact with certain delivery modalities as appropriate
- No hype! Real use cases!

Tools and Resources – the AI and LLMs Angle

- Some typical AI and LLMs usage
 - Directly from https API
 - Implement within programming environment – R Studio, Positron
 - Data upload (use test data) tools
 - Multi-agent tools, etc
- Variety of Tools
 - Direct from https API: [Claude](#), [ChatGPT](#), [Gemini](#), [Copilot](#), [Perplexity](#), [Qwen](#), [Deepseek](#), [Grok](#) , MaxAI, etc
 - R/R Studio ecosystem, Positron: [ellmer](#), [ellmer assistant](#), [chatlas](#), [chattr](#), [shinyapps assistant](#), [shinychat](#), [mall](#), [gptstudio](#), [chatAI4R](#), [tidyllm](#), [gander](#), [LLMAgentR](#), [rgentai](#), [querychat](#), etc
 - [Large Language Model tools for R](#) (Luis D. Verde Arregoitia)

Shiny & LLMs: Landscape and Applications in Pharma
Phil Bowsher PharmaSUG 2025 – Paper OS-395



Tools and Resources – the AI and LLMs Angle

- Data Upload, examples:
 - [Julius](#),
 - [R Tutor](#),
 - [Datably](#)
 - [Vizly](#)
 - Etc
- Others – Multiple Agents, examples :
 - [Poe](#)
 - [NinjaChat](#)
 - Etc
- Things to be aware/think about:
 - Free versus paid – can create a free account with all of them
 - API (and credit card) needed in use within programming environment
 - Prompting – need to be clear and precise
 - Hallucinations
 - Accuracy – variety, but tools are getting better and evolving

- Examples of prompts tried out – can be advanced:
 - *What are the various tables and graphs that data monitoring committees need? Create r code and quarto markdown reports for the tables and figures.*
 -
 - *Create R code to generate all outputs needed for data monitoring committee including tables and graphs. Create the slides using quarto. The graphs should be interactive.*
 -
 - *Can you create an r shiny app for the method described in this paper: SAE: An R package for early stopping rules in clinical trials. C. Bascoul-Mollevi, A. Laplanche, M. Deley, and A. Kramar. Computer Methods and Programs in Biomedicine, 104 (2): 243-248 (2011)*
 -
 - *Create R code to perform the analysis described in this paper by: Chris Barker, Exploratory method for summarizing concomitant medication data--the mean cumulative function. Pharm Stat, 2010 Oct-Dec;9(4):331-6. doi: 10.1002/pst.395, <https://onlinelibrary.wiley.com/doi/10.1002/pst.395>. the input datasets are the ADAM datasets ADSL and ADCM. Also include sample ADSL and ADCM datasets to run the R code. Also include comments explaining the code.*

- Examples of prompts tried out – can be advanced:
 - *Are you familiar with the Berry and Berry model for a three-level hierarchical mixture model for analysis of adverse event counts. The model exploits hierarchies in adverse event coding structure namely the nesting of preferred terms (PT) within system organ classes (SOC). It is described in this paper: Berry, SM and Berry, DA (2004). “Accounting for multiplicities in assessing drug safety: a three-level hierarchical mixture model” Biometrics 60(2) 418-426.*
 - *Yes*
 - *Provide some R code that implements this model. The code should be well commented in terms of the various details and workflow.*
 - *What is the best R package for implementing the Berry and Berry model*
 - *The best R package for implementing the Berry and Berry model is c212. It's specifically designed for detecting safety signals in clinical trials and includes functions for fitting this model.*
 - *Provide example code with some explanation using the c212*

 - *Create r code to generate the graphs described in this paper: Clinical Adverse Events Data Analysis and Visualization, by Shi-Tao Yeh, <https://www.lexjansen.com/pharmasug/2007/po/PO10.pdf>. The code should include sample data comments on the code. Also create a colorful R shiny version of the code and a colorful quarto dashboard.*

Tools and Resources – the AI and LLMs Angle

- Plenty of resources/example for use of these tool – stick to newer resources
- ASA SWG WS2 compiling some resources and examples
- Great YouTube videos from POSIT team and others, examples:

Workshop
Demystifying LLMs with Ellmer
Joe Cheng
CTO, Posit

R Medicine 2025

**Harnessing LLMs
for Data Analysis**

Wednesday, May 28th
11:00 am ET

posit

Led by **Joe Cheng**
CTO at Posit PBC

ShinyConf 2025
Powered by Asaaban

Winston Chang

KEYNOTE

AI and Shiny

KEYNOTE
**SUMMER IS COMING: AI FOR R, SHINY,
AND PHARMA**

Joe Cheng
Posit

TUE, OCT 29, 2024
10:10AM EDT

**Build Shiny
applications
with the
help of AI**

Shiny

Write me a Shiny app!

WINSTON CHANG

Tools and Resources – the AI and LLMs Angle

Welcome to the data dashboard! I'm here to help you explore and analyze the data. Here are some examples of what you can ask me to do:

- "Filter the dashboard to show only subjects older than 65."
- "What is the average baseline BMI?"
- "Find subjects who discontinued due to an adverse event."

Feel free to ask any specific questions or request assistance with filtering and sorting the data.

The analyses performed when utilizing subgroups or other subsets of the source data sets are considered **exploratory**.

Enter a message...

ARM	Shown	Total
Placebo	86	86
Xanomeline High Dose	84	84
Xanomeline Low Dose	84	84

Subjects: 254/254

TRT01A — Placebo — Xanomeline Low Dose — Xanomeline High Dose

The shaded areas are 95% CI of the survival probability for each group
2024-10-29 09:57:55.95963

utilizing subgroups or other subsets of the source data sets are considered **exploratory**.

What demographic variables do you have access to?

The demographic variables I have access to include:

1. **Age:** Represented by the columns AGE, AGEGR1 (Pooled Age Group 1), AGEGRIN (Pooled Age Group 1 (N)), and AGEU (Age Units).
2. **Race:** Represented by the columns RACE and RACEN (Race (N)).
3. **Sex:** Represented by the column SEX.
4. **Ethnicity:** Represented by the column ETHNIC.
5. **Baseline BMI, Height, and Weight:** Represented by the columns BMIBL (Baseline BMI), BMIBLGR1 (Pooled Baseline BMI Group 1), HEIGHTBL (Baseline Height), and WEIGHTBL (Baseline Weight).

Enter a message...

ARM	Shown	Total
Placebo	86	86
Xanomeline High Dose	84	84
Xanomeline Low Dose	84	84

Subjects: 254/254

TRT01A — Placebo — Xanomeline Low Dose — Xanomeline High Dose

The shaded areas are 95% CI of the survival probability for each group
2024-10-29 09:57:55.95963

AGE, AGEGR1 (Pooled Age Group 1), AGEGRIN (Pooled Age Group 1 (N)), and AGEU (Age Units).

2. **Race:** Represented by the columns RACE and RACEN (Race (N)).

3. **Sex:** Represented by the column SEX.

4. **Ethnicity:** Represented by the column ETHNIC.

5. **Baseline BMI, Height, and Weight:** Represented by the columns BMIBL (Baseline BMI), BMIBLGR1 (Pooled Baseline BMI Group 1), HEIGHTBL (Baseline Height), and WEIGHTBL (Baseline Weight).

6. **Years of Education:** Represented by the column EDUCYR.

These variables help describe various demographic characteristics of the subjects in the study.

Show only subjects of age 70 or greater

SELECT * FROM an1 WHERE AGE >= 70

Subjects: 194/254

ARM	Shown	Total
Placebo	64	86
Xanomeline High Dose	64	84
Xanomeline Low Dose	66	84

TRT01A — Placebo — Xanomeline Low Dose — Xanomeline High Dose

The shaded areas are 95% CI of the survival probability for each group
2024-10-29 10:22:23.012869

the mean Time to Event (TTE) varies by years of education due to technical difficulties. If you have specific details or questions about the data that I can assist with, please let me know!

How does the mean TTE vary by treatment arm?

SELECT ARM, AVG(AVAL) AS mean_tte FROM an1 WHERE PARAM = 'Time to First D' GROUP BY ARM ORDER BY ARM

ARM	mean_tte
Placebo	3.77
Xanomeline High Dose	1.19
Xanomeline Low Dose	1.54

The mean Time to Event (TTE) for each treatment arm is as follows:

- Placebo: 3.77
- Xanomeline High Dose: 1.19
- Xanomeline Low Dose: 1.54

These values represent the average time to the first dermatologic event for each treatment arm.

Enter a message...

ARM	Shown	Total
Placebo	64	86
Xanomeline High Dose	64	84
Xanomeline Low Dose	66	84

Subjects: 194/254

TRT01A — Placebo — Xanomeline Low Dose — Xanomeline High Dose

The shaded areas are 95% CI of the survival probability for each group
2024-10-29 10:22:23.012869

Tools and Resources – the AI and LLMs Angle

- Example:
 - <https://posit.co/blog/ai-powered-shiny-app-prototyping/>
 - <https://ivelasq-pharma-adae-shiny-app.share.connect.posit.cloud/>

Adverse Event Analysis

Select Analysis: AE Summary Table

Filter by Severity:
 MILD
 MODERATE
 SEVERE
 Show Only Serious AEs

Analysis Results: Show 10 entries

	AEDECOD	Drug
1	dcd A.1.1.1.1	
2	dcd A.1.1.1.2	
3	dcd B.1.1.1.1	

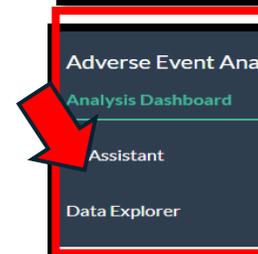


Adverse Event Analysis

Select Analysis: AE Summary Table

Analysis Results: Show 10 entries

	AEDECOD	n_A: Drug X	n_B: Placebo	n_Combination
1	dcd A.1.1.1.1	62	44	
2	dcd A.1.1.1.2	61	62	
3	dcd B.1.1.1.1	58	55	



Adverse Event Analysis | Analysis Dashboard | Data Summary

Select Analysis: AE Summary Table

Filter by Severity:
 Mild
 Moderate
 Severe
 Show Only Serious AEs

Analysis Results: Show 10 entries

	AEDECOD	n_Drug A	n_Placebo	n_serious_Drug A	n_serious_Placebo
1	Dizziness	21	18	2	0
2	Fatigue	21	19	1	3
3	Headache	17	22	3	0
4	Nausea	25	20	2	2
5	Rash	16	23	0	3

Showing 1 to 5 of 5 entries

Adverse Event Analysis | Analysis Dashboard | Assistant | Data Explorer

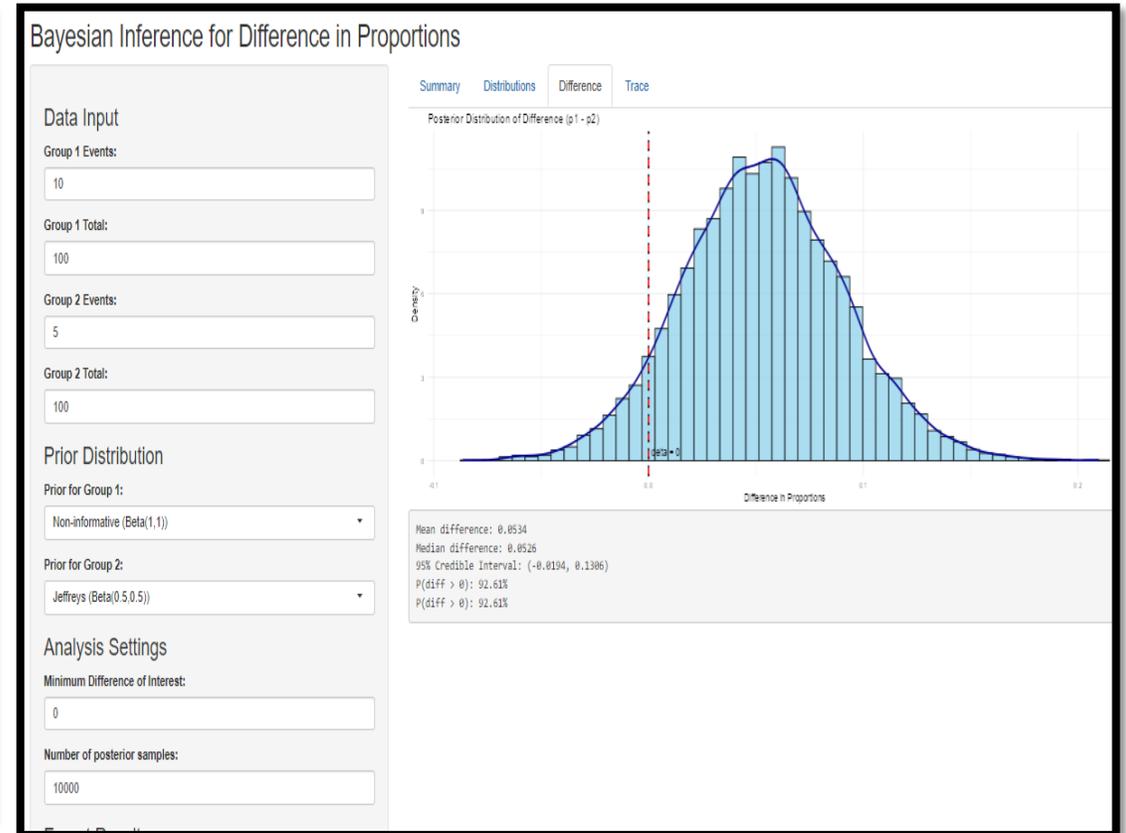
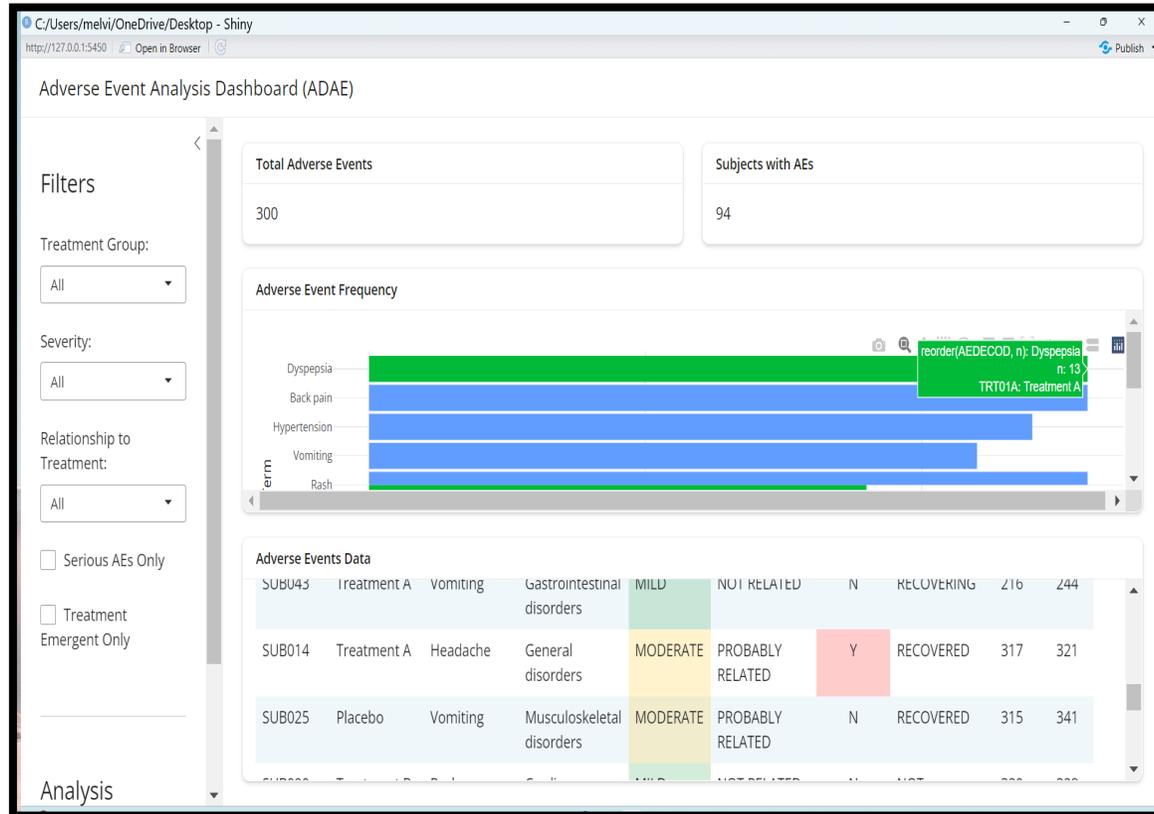
Select Analysis: AE Summary Table

Filter by Severity:
 Mild
 Moderate
 Severe
 Show Only Serious AEs

Analysis Results: Show 10 entries

	AEDECOD	n_Drug A	n_Placebo	n_serious_Drug A	n_serious_Placebo
1	Dizziness	21	18	2	
2	Fatigue	21	19	1	36
3	Headache	17	22	3	

Tools and Resources – the AI and LLMs Angle



- Are you familiar with the ADAE dataset?
 - ADAE datasets are crucial for safety analysis in clinical trials and drug development....
 - Would you like me to help you create a Shiny app that works with ADAE data for a specific analysis or visualization?
- Yes
- Change the code so that the input dataset is ADAE
- Can you add some compelling visualizations along with interactivity?

- Create an R shiny app for Bayesian inference that the difference between two binomial proportions is greater than some specified value delta. The app should allow for different priors for the two proportions including non informative prior, skeptical prior, Jeffrey's prior, and informative prior. The app should also allow for plotting of the prior, likelihood, and posterior distribution. The app should also allow for outputs for html and power point.

Closing Remarks

- We can surely and pretty much do better in delivering DMC data packages!
- We know what to do! We have talked about it a lot!
- The time is now! Enough talk!
- AI and LLMs to the rescue!

2020

**Safety Analyses:
The Cinderella of Biostatistics?**
\\ Regulatory perspective \\
EFSPI Statistics Leaders Meeting
23.07.2020
PD Dr. **Benjamin Hofner**
Head of Section Biostatistics

Outlook

- Graphical display instead of extensive tables
 - Use graphics such as forest plots to show safety profiles
- Appropriate statistical methods / summary measures are urgently needed
 - Training of clinicians and statisticians dealing with safety needed
- Estimand framework need to be further developed and discussed in the light of safety analyses
 - Clinical and statistical input needed
- Do we need a paradigm shift in safety reporting?

Summary

- Safety assessment often based on
 - plethora of „unconnected“ (and potentially statistically inadequate) frequency tables
- Statistical considerations not well developed
 - partly due to imprecise / inappropriate questions („equivalence of safety“)
 - complexity of situation
 - partly due to rare events
- Multiple analyses (from different angles) required to provide a good overview and understanding of all safety aspects

Questions

- What about...
 - ... timing of AEs?
 - ... duration of AEs?
 - ... severity of AEs?
 - ... reversibility of AEs?
 - ... recurrence of AEs?
 - ... the impact of dose (reduction)?
 - ... timing and frequency of treatment?
 - ... intercurrent events such as rescue treatment?
 - ... (unequal / short) duration of follow up?
 - ... competing risks (e.g. death)?

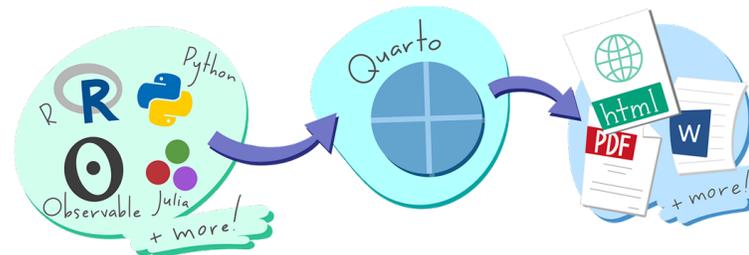
Variable / endpoint
Population
Intercurrent events
Summary measure

Closing Remarks

- Safety data are complex and draw on several data domains and sources
- There are inadequacies and incompleteness in current DMC data packages
- Visual analytics offers opportunities to complement traditional tabular presentations
- Can combine both tabular visualization and analytics to allow for more insights into the data
- Can also leverage appropriate quantitative methods for enhanced decision-making
- Use of structured approaches to safety analysis can help for a more focused safety analysis
- Question-based approach can improve and enhance analysis of safety data by facilitating for a guided, focused, structured, and comprehensive analysis leveraging both tabular and visual analytics along with clinical discernment – translates into the right prompting
- There are readily available opensource to generate visualizations, including interactive visualizations and tools with many possible delivery modalities
- Can leverage AI and LLMs for timely and efficient creation, analysis, and interpretation

**Data Safety and Monitoring Boards
Should Be Required for Both Early-
and Late-Phase Clinical Trials**
Gail A. Van Norman, MD JACC: Basic to Translational Science • Volume 6, Number 11

2021



+ AI and LLMs

How many patients could we save with LLM priors?
Shota Arai¹, David Selby², Andrew Vargo¹, Sebastian Vollmer^{1,2}
<https://api.semanticscholar.org/CorpusID:281103802>

2025

