

Single Day Events



CVARS - Transforming Drug Safety Analytics for Enhanced and Comprehensive E2E Review, Analysis, Signal Detection, Reporting, and Regulatory Submissions with the Aid of AI

Neetu Sangari, PhD, Pragma Tech Leaders

Co-Authors: Melvin S. Munsaka, PhD, AbbVie, Jiang (Jessica) Hu, PhD, FDA

Disclaimer

- The discussions and conclusions in this presentation have not been formally disseminated by the US Food and Drug Administration and should not be construed to represent any Agency determination or policy.

Outline

- Introduction & Overview
- Key Considerations & Examples
- Question-Based Approach to Safety Review
- CVARS Approach & Current Capabilities
- CVARS Ongoing/Planned Enhancements
- E2E Safety Review & Signal Detection
- Acknowledgments & Q&A

Introduction and Overview

- Drug safety analysis is complex → data curation, interpretation, reporting challenges
- Collaboration is essential → regulators, sponsors, investigators, safety boards
- Limitations of traditional outputs → static tables = slow review, harder to interpret
- Visual analytics (Forest, Volcano, OCMQs) → faster insights, clearer communication
- Expanding capabilities → AI, GenAI, Bayesian methods, Agent AI

Key Considerations

- Shift focus → from static tables to interactive graphical outputs
- Reduce volume → avoid generating hundreds of PDF tables; prioritize key visuals
- Best practices → adopt structured safety review & signal detection frameworks
- Stakeholder alignment → design outputs for regulators, clinicians, and data monitors
- Regulatory compliance → align with evolving standards (OCMQs, benefit–risk guidance)
- Balanced approach → visuals should enhance, not replace, medical discernment

Example: Shift Focus

- *Data display is critical to data analysis. Graphs allow us to explore data to see overall patterns and to see detailed behavior; no other approach can compete in revealing the structure of data so thoroughly - Cleveland*

Tabular Outputs only versus Tabular Plus Graphical Outputs

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



Sponsor Company Study ABC

Table 5.B
Adverse Events by Maximum Severity

ARM A
(N=35)

System Organ Class Preferred Term	MM	Moderate	Severe
All Adverse Events	27 (75.6)	16 (27.8)	6 (8.6)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)
Neuropathy	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)
Palpitations	0 (0.0)	0 (0.0)	0 (0.0)
Stroke Ischaemic	0 (0.0)	0 (0.0)	0 (0.0)
Congenital, hereditary and genetic disorders	0 (0.0)	0 (0.0)	0 (0.0)
Dilated Cardiomyopathy	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)
Stomatitis	0 (0.0)	0 (0.0)	0 (0.0)
Food Poisoning	0 (0.0)	0 (0.0)	0 (0.0)
Toothache	0 (0.0)	1 (2.7)	0 (0.0)
Swelling	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)
Cold	0 (0.0)	0 (0.0)	0 (0.0)

Program AE_Table B
Note: Adverse events were coded using MedDRA Version 9.1
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Sponsor Company Study ABC

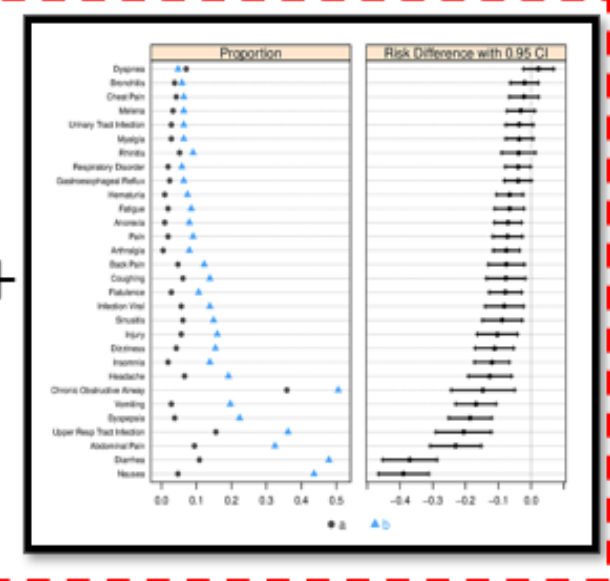
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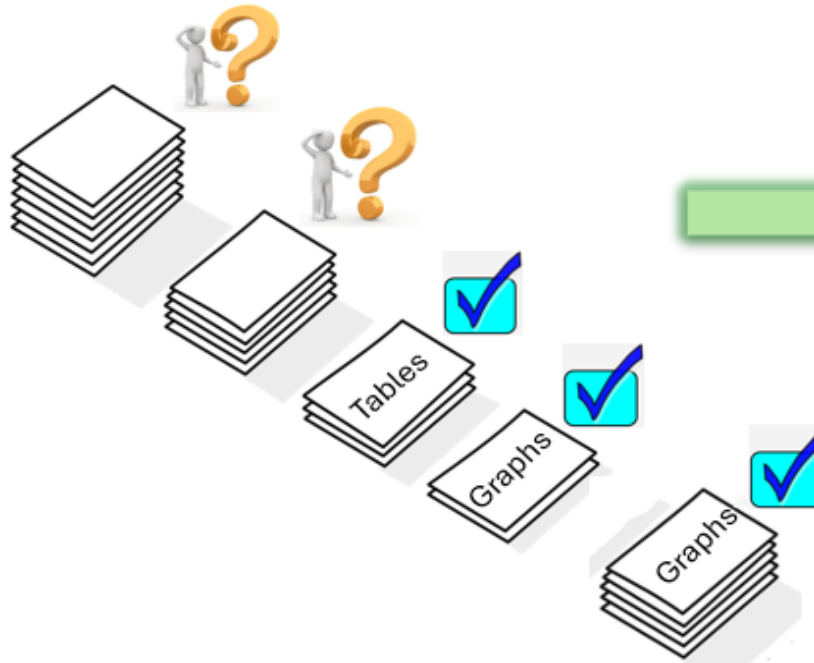
Example: Reduce Volume

- Do we really need hundreds of tables in PDFs?

Typical practice



Maybe we only need a few outputs with graphs

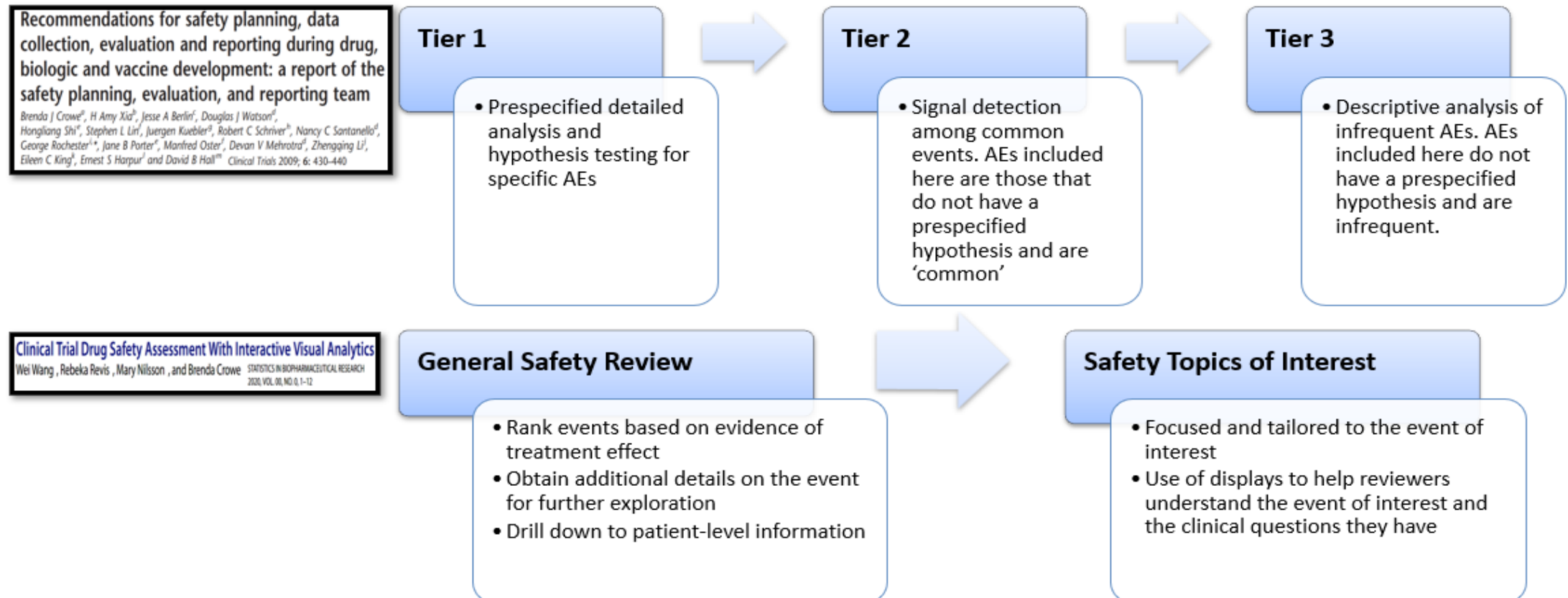


Drug Safety Profiling and Benefit-Risk/Label



Example: Best Practices in Safety Review

- Ensuring best practices by applying structured safety review and signal detection approaches.



Example: Stakeholder Alignment

- Regulatory practices and emerging regulatory practice

Safety Review: Approach & Tools
Alan M Shapiro, MD, PhD, FAAP
2019 CDISC Japan Interchange
July 12, 2019

FDA U.S. FOOD & DRUG ADMINISTRATION
OFFICE OF COMPUTATIONAL SCIENCE

Summary –Overall Safety Review Approach

➤ Safety review should include:

- ✓ Assessment of Submitted Data
- ✓ Adequacy of Applicant's Safety Assessment
- ✓ Assessment of Data Integrity
- ✓ Assessment of Overall Submission Quality



➤ Reviewer Tasks:

- ✓ Evaluate adequacy of data to support safety analyses
- ✓ Identify and examine serious adverse events related to drug exposure
- ✓ Identify and estimate frequency of common adverse events
- ✓ Identify unresolved safety concerns
- ✓ Identify factors associated with adverse reactions to drug and evaluate approaches to mitigate or manage these reactions
- ✓ Provide comprehensive evaluation of risks associated with product use to include into labeling



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Reviewer Guidance

Conducting a Clinical Safety Review of
a New Product Application and
Preparing a Report on the Review

Use of New Tools for Safety Analysis

Chuck Cooper, M.D.
Clinical Reviewer
Division of Biometrics VI
Office of Biostatistics
CDER, FDA

New Standards for Safety Review

- Deaths
 - Overall mortality
 - Cause specific
 - Expected vs unexpected
 - Dose response
 - Time to death analysis
 - Subgroup analysis
 - Interaction analysis
- SAEs
 - Overall rates
 - Rates by event
 - Dose response
 - By duration of exposure
 - By person-time exposure as denominator
 - Assessment according to alternative explanation
 - Assessment of interaction by subgroup
- Dropouts and other SAEs
 - Overall rates
 - Profile of dropouts (by reason)
 - AEs associated with Dropouts
 - Exposure response
 - Time dependency
- Other significant AEs as defined by ICH
 - Marked lab abnormalities
 - Any AE leading to dropout or intervention
 - Potentially important abnormalities not meeting above definition
- Construct of algorithms of combo's of clinical findings
 - Identify possible combinations of clinical findings that may be a marker for a particular toxicity
- Identify possible consequences of a safety signal from any source
- Common AEs
 - Incidence for subsets -controlled studies
 - LLT's should be compared to mapped PT's
 - Assess for causality
 - Comparison of severity between treatment arms
- Dose dependency for AEs
 - Titration studies
- Time to onset for AEs
 - Particularly for events that occur commonly
- AE incidence by interaction
 - demographic
 - race, gender, age
 - Drug-drug interaction
 - Underlying medical problems such as DM or renal disease
 - Dose response
 - body weight-adjusted dose
 - cumulative dose
 - Body surface area-adjusted dose
 - dosing schedule
 - Exposure adjusted event rates "person-time approach"
 - When hazard rate is constant over time
 - Break observation period into intervals
- AE incidence by interaction (cont.)
 - Relative risks and attributable risks for subgroup differences
 - Life table/ time-to-event analyses/ cumulative incidence analyses
 - Hazard rates – risk over time estimation

Example: Regulatory Compliance & Balance

- Regulatory alignment: Evolving practices encourage the use of visuals alongside traditional tables.
- Graphical outputs: Can complement or replace tabular outputs when validated and reproducible.
- Quantitative methods: Bayesian and frequentist approaches to strengthen safety assessments.
- Balanced approach: Ensure outputs remain fit-for-purpose and support structured benefit–risk review.

**FDA U.S. FOOD & DRUG
ADMINISTRATION**

**STANDARD SAFETY
TABLES AND FIGURES:**

INTEGRATED GUIDE


FDA Medical Queries (FMQs)
Vaishali Popat MD, MPH
Associate Director
Biomedical Informatics and Regulatory Review Science
CDER/Office of New Drugs



Statistical Considerations for Premarketing Risk Assessment

[illegible]

```

graph LR
    A[Initial Algorithm Developed] --> B[Programs Created to Apply Algorithm to Clinical Data]
    B --> C[Algorithms Applied to NDA/BLA Clinical Trial Database]
    C --> D[Results Analyzed by Clinical Experts]
    D --> E[Desired Results Achieved Based on Sensitivity and Specificity]
    E --> F[Algorithms Adjusted Based on Findings]
    F --> C

```

Based on:

- Clinical expert opinion
- Medical literature

Methods:

- SAS, R, Python

Based on:

- Clinical expert feedback

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

Figure 5. Patients With Adverse Events' ≥X% in Any Treatment Arm by FDA Medical Query (Narrow), Safety Population, Trial 1

Adverse Event	Red (%)	Blue (%)
Constipation	5.0%	18.3%
Abdominal pain	4.0%	10.3%
Rash	3.0%	8.0%
Symptomatic hypotension	2.3%	8.0%
Cough	2.3%	8.0%
Dyspnea	2.0%	9.0%
Arthritis	2.0%	3.3%
Nausea	2.0%	3.3%
Headache	1.7%	3.3%
Pharyngitis	2.0%	3.3%
Nitazoxanide	3.3%	12.3%
Decreased appetite	2.0%	3.3%
Respiratory infection	1.7%	8.0%
Diarrhea	2.0%	3.3%
Hepatic injury	2.0%	4.0%
Anxiety	3.3%	11.3%
Respiratory disorder	2.0%	3.3%
Acid reflux	1.7%	8.0%
Headache	1.7%	8.0%
Hemorrhage	0.6%	7.0%
Fatigue	0.6%	15.0%
Stomach pain	0.6%	15.0%
Dizziness	0.6%	7.0%
Muscle pain	0.6%	7.0%
Diarrhea	0.6%	12.3%

Legend: ■ redarm (N = 33), ■ bluearm (N = 33)

Source: [Include Applicant source, datasets and/or software tools used]

Abbreviations: FMC, FDA Medical Query; N, number of patients in treatment arm

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).

Single PT: Anxiety

Group	Percentage of Patients
Drug A	~1.8%
Placebo	~0.8%

FMQ Grouping: Anxiety

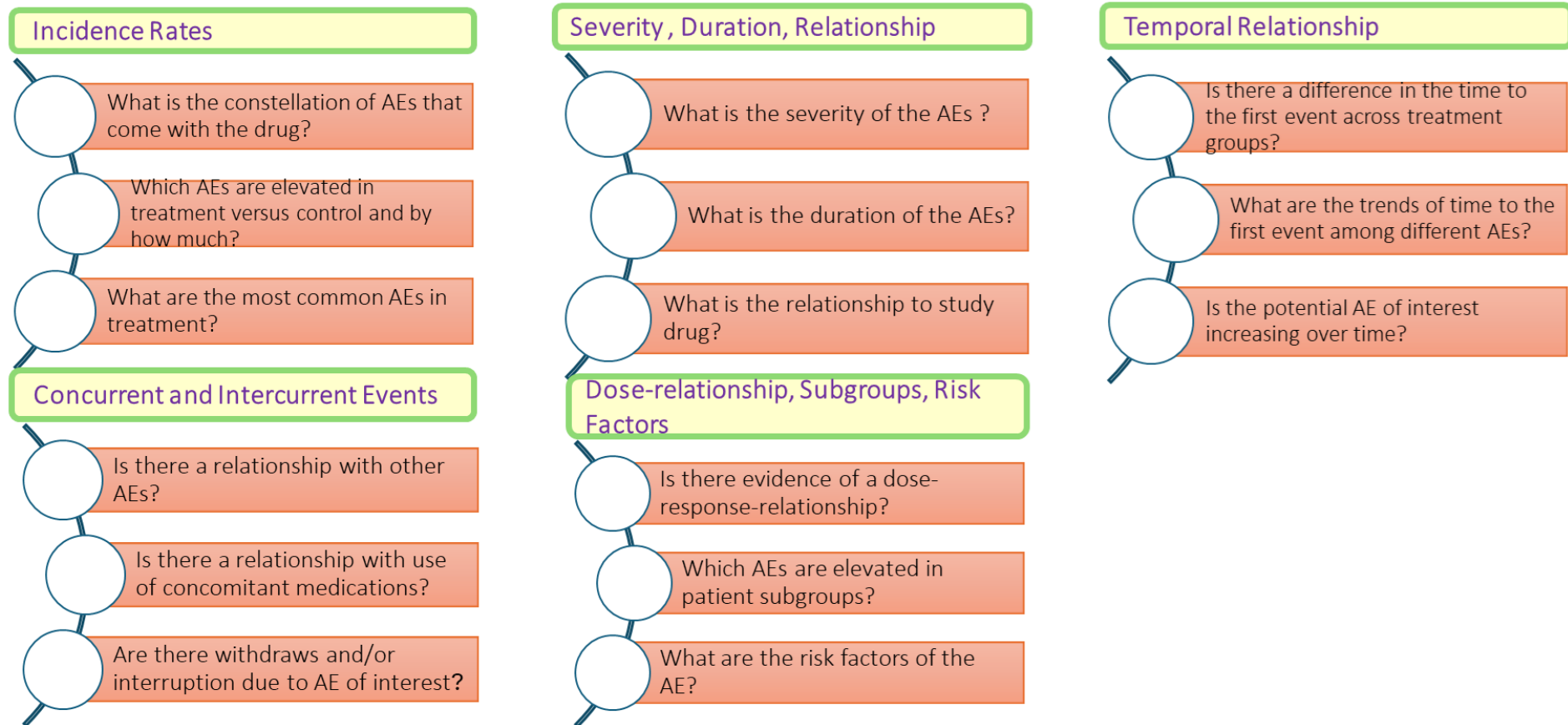
Group	Percentage of Patients
Drug A	~2.2%
Placebo	~1.2%

Appropriate Integrated Analyses

- For a comparison of interest (e.g., drug vs. placebo), typically should include only trials with both treatments
 - May need different trial groupings for different comparisons
- Generally, include only controlled trials/trial periods
 - **CAUTION!** Analyses that include uncontrolled trial periods (e.g., open-label extensions) subject to confounding and bias
- Stratify analyses by trial
 - **CAUTION!** Unstratified analyses of multiple trials may be subject to confounding (see next slide) – Simpson's Paradox
 - **Stratified analyses are always appropriate**

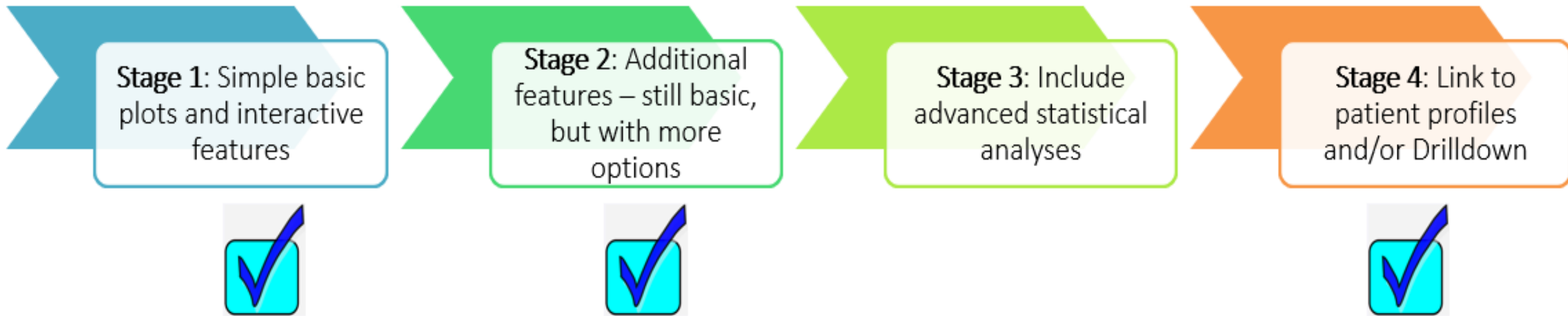
Question-Based Approach to Safety Review

- For example, adverse events



CVARS Staged Development Approach

- Planned, stepwise development to ensure regulatory readiness
- Consider functionality, output modality, reproducibility, and stakeholder needs at each stage



Stage 1: Core plots and basic interactive features

Stage 2: Expanded functionality and visualization options

Stage 3: Integration of advanced statistical analyses (e.g., Bayesian, clustering, subgroup)

Stage 4: Link to patient profiles and drill-down exploration

CVARS Current

- Current version provides an intuitive interface for data input and configuration
- Supports upload, report generation, and customizable filters
- Output available in tabular/graphical formats, exportable to HTML, PDF, DOCX, PPTX

CVARS

Report Inputs

Data Check

Table Output

Graph Output

Read/Upload Data

Data Source

Default (CDISC Pilot Data)

This option is only available for training and understanding app using CDISC data

CDISC ADaM Data

ADSL ADAE CM

Run Report

Download Report

pdf

Save Report

Report Selection

Report base domain

Report Name

adsl

Therapeutic Area

Report Number

Report Type

Report Description

Treatment & Population Selection

Treatment Variable

Treatment Sort Variable

Population Filter

Subsetting Conditions

Analysis Subset Condition

Denominator Subset Condition

USUBJID!="

STUDYID!="

AE Summary Table Inputs

Treatment Big N

Total treatment

Add Missing Grouping Variable

Calculate Risk

☐ Y ☒ N

☐ Y ☒ N

☐ Y ☒ N

☐ Y ☒ N

Generic Inputs

Adverse Event Filter(s)

Period

Residual period (in days)

Any

Overall Duration

30

Higher Level Event Term

Lower Level Event Term

Summary By

Body System or Organ Class (AEBODSYS)

AE Dictionary-Derived Term (AEDECOD)

Participants

Measure of Association

Alpha Value(CI)

p Value Cutoff

Risk Ratio

0.05

0.05

Risk Reference Lines

Risk Axis Scale

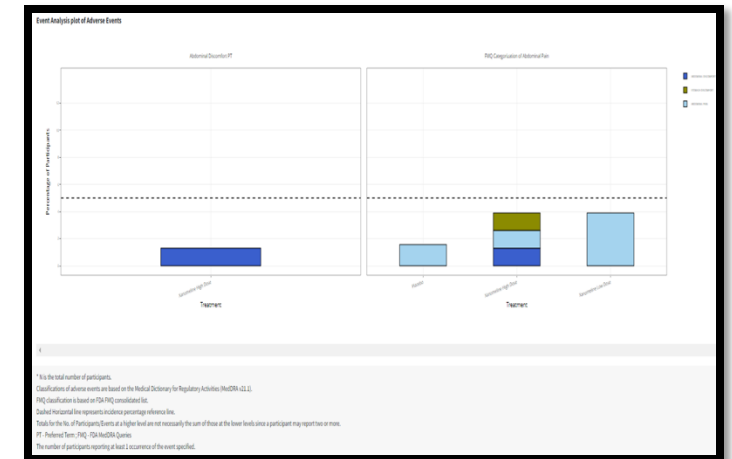
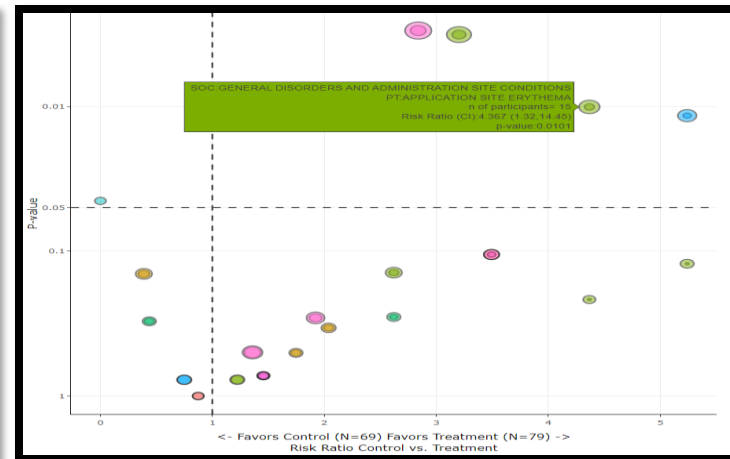
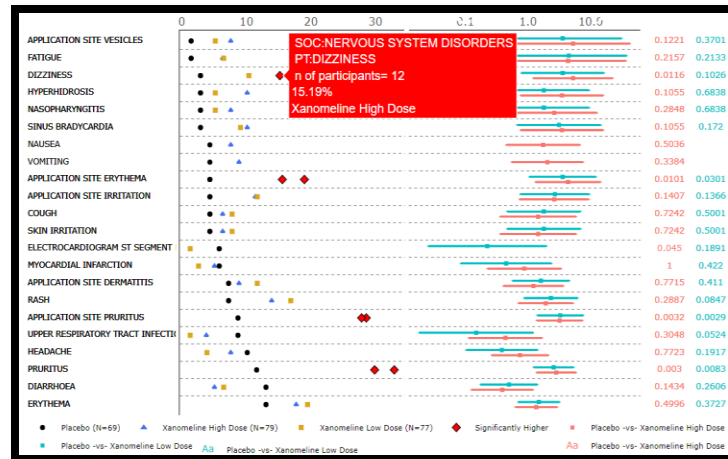
0

Log10

Reference Line (%)

CVARS Current

- Current version – forest plots, volcano plots, FMQs(*OCMQs), tabular output, patient profiles, listings



CVARS Ongoing/Planned Enhancements

- Advanced analytics: Bayesian methods for signal detection, Clustering & subgroup exploration, Dose–response and time-to-event modeling

On quantitative methods for clinical safety monitoring in drug development *Statistics in Biopharmaceutical Research*
William Wang, Ed Whalen, Melvin Munsaka, Judy Li, Michael Fries, Carolyn Kirsch, Matilde Sanchez-Kam, Krishan Singh & Jefe Zhou
Received 18 Oct 2016, Accepted 19 Nov 2017, Accepted author version posted online 19 Dec 2017

The role of quantitative safety evaluation in regulatory decision making of drugs *Journal of Biopharmaceutical Statistics*
Aloka G. Chakravarty, Rima Item, Stephanie Keeton, Clara Y. Kim, Mark S. Levenson & Mat Soukup
Pages 17-29 | Received 03 Aug 2015, Accepted 03 Aug 2015, Accepted author version posted online 15 Sep 2015, Published online 15 Sep 2015

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

AE Line Plot

Choose CSV File
Browse... No file selected

Multiplicity Adjustment Method
Fisher's Exact Test

Number of Subjects in Control Group
216

Number of Subjects in Treatment Group
431

Threshold for p-Value
0.05

Threshold for Posterior Probability
0.8

Download Example Data

Multiplicity Adjustment Method

Fisher's Exact Test

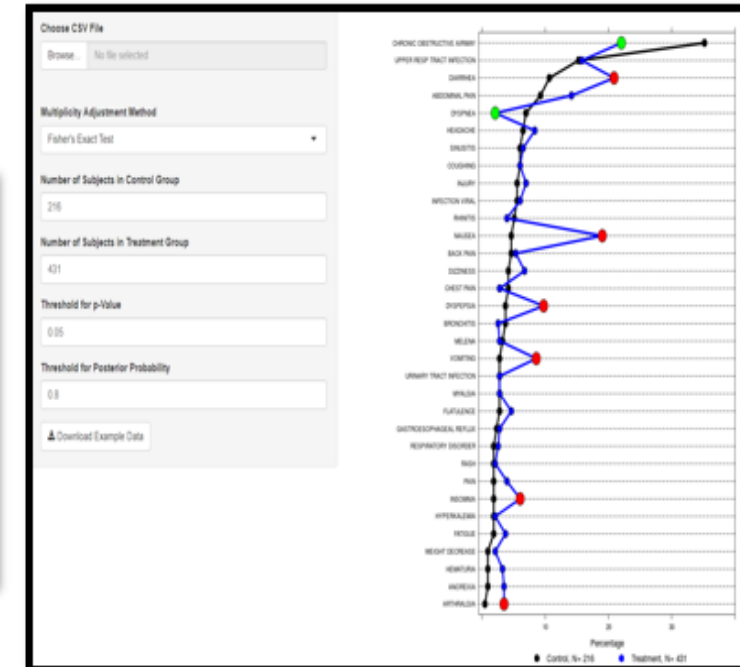
Fisher's Exact Test

Bonferroni Correction

Benjamini-Hochberg Procedure

Double False Discovery Rate

Berry and Berry Three-Level Hierarchical Model



CVARS Ongoing/Planned Enhancements

- AI Assistant → query interface for rapid review (“Which AEs are elevated in old patients?”)
- Data Explorer → drill-down by population, treatment arm, or severity
- GenAI Narratives → automated patient profiles and benefit–risk summaries

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 Search:

	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

Previous 1 Next

Adverse Event Analysis

Analysis Dashboard

AI Assistant

Data Explorer

Select Analysis

AE Summary Table

Filter by Severity

☒ Mild

☒ Moderate

☒ Severe

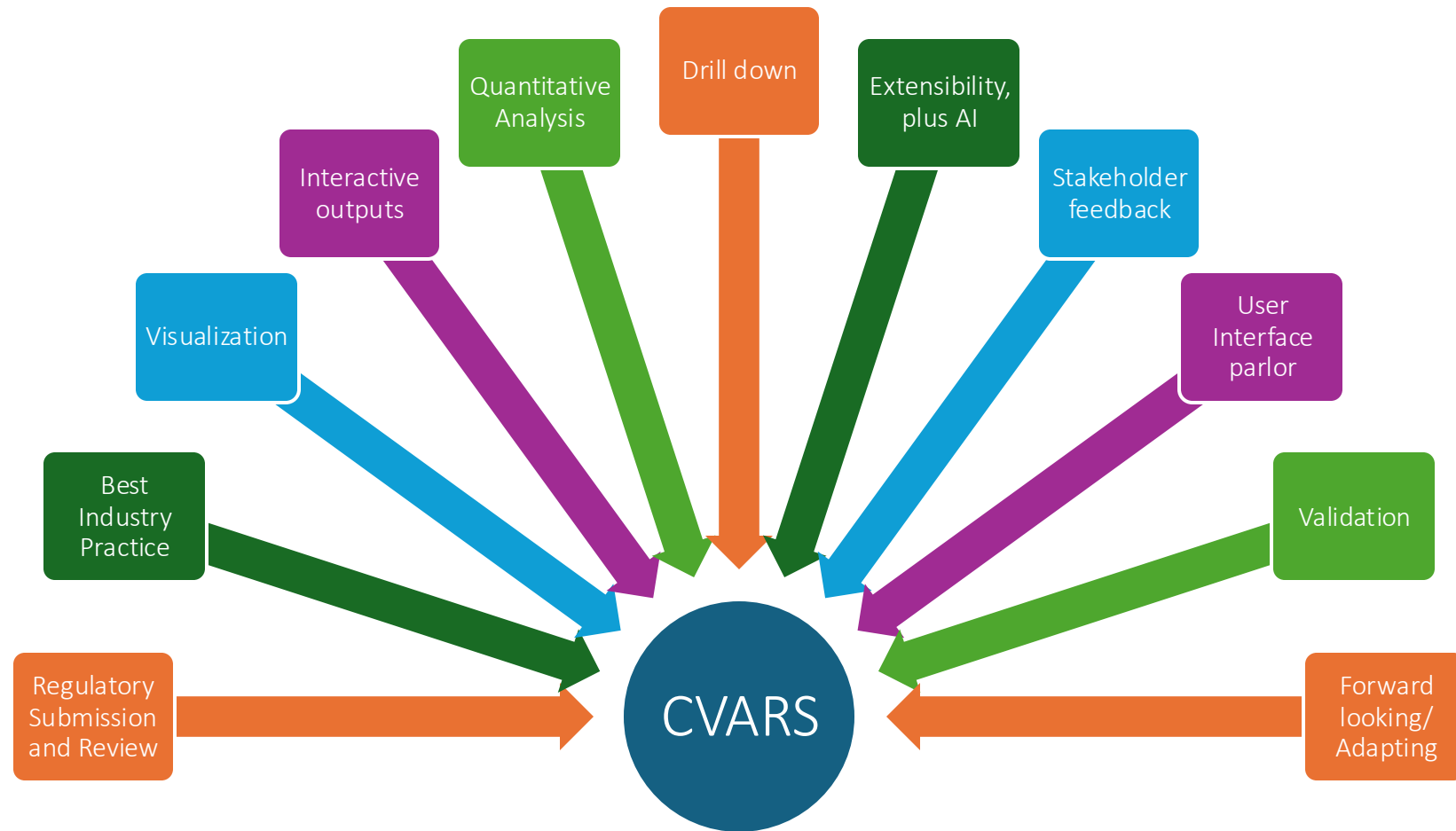
☐ Show Only Serious AEs

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CVARS Ongoing/Planned Enhancements



E2E Safety Review and Signal Detection

- Data Ingestion & Preparation
 - LLMs for data pipelines, Automated lineage, consistency checks, and audit trails
- Core Safety Analytics
 - Expanded visual analytics, Interactive Outputs, reproducible, submission-ready
- Signal Detection & Advanced Methods
 - Bayesian signal detection, Clustering & subgroup exploration, Dose–response and time-to-event modeling
- AI/GenAI-Enabled Interpretation
 - GenAI support → narrative interpretation, AI assistant → reviewer Q&A
- Regulatory Alignment & Continuous Improvement
 - Adaptation to OCMQs & benefit–risk frameworks
 - Continuous stakeholder input from regulators & clinicians

Executive Summary

- CVARS modernizes drug-safety analytics by coupling standardized tables, interactive, question-led visualizations.
- Expanded capabilities include additional core safety plots, OCMQs, and patient-profile views, supported by robust multi-format export.
- The roadmap adds Bayesian signal detection, advanced subgrouping, dose–response and time-to-event modeling, and AI/GenAI features for reviewer Q&A and narrative generation.
- Across all releases, CVARS prioritizes regulatory alignment, reproducibility, and stakeholder usability to accelerate insight while preserving clinical judgment.

Result: Faster reviews, Clearer signals, and Stronger, Submission-ready outputs.

Acknowledgments & Q&A

Thanks to PHUSE Working Group, ASA, FDA collaborators
& Programming volunteers

