Advancing Premarket Safety Analytics

September 14, 2022 | 12:00-5:00 p.m. ET

FDA U.S. FOOD & DRUG ADMINISTRATION | Duke MARGOLIS CENTER for Health Policy

Welcome & Introduction

Marianne Hamilton Lopez, PhD, MPA

Senior Research Director, Duke-Margolis Center for Health Policy

Agenda

- Opening Remarks from FDA
- FDA Presentation: Overview of the FDA Medical Queries
- Panel Discussion: Stakeholder Perspectives Exploring Premarket Adverse Event Grouping
- FDA Presentation: Overview of the Standard Safety Tables and Figures Integrated Guide
- Panel Discussion: Examining Strategies for Premarket Adverse Event Analysis

Statement of Independence

The Robert J. Margolis, MD, Center for Health Policy is part of Duke University, and as such it honors the tradition of academic independence on the part of its faculty and scholars. Neither Duke nor the Margolis Center take partisan positions, but the individual members are free to speak their minds and express their opinions regarding important issues.

For more details on relevant institutional policies, please refer to the Duke Faculty Handbook, including the Code of Conduct and other policies and procedures. In addition, regarding positions on legislation and advocacy, Duke University policies are available at http://publicaffairs.duke.edu/government.

Virtual Meeting Reminders

- Attendees are encouraged to contribute throughout the meeting with questions in the Zoom Q&A function.
- This meeting is being recorded, and the recording and slide deck will be posted on the Duke-Margolis event page in the weeks following the meeting.

Opening Remarks from FDA

Peter Stein and Vaishali Popat

U.S. Food and Drug Administration

U.S. FOOD & DRUG ADMINISTRATION

Advancing Pre-market Safety Analytics: An Introduction

Peter Stein, MD
Director, Office of New Drugs
Center for Drug Evaluation and Research

Duke-Margolis Meeting, September 2022

Regulatory framework: effectiveness and safety

Safety:

- The drug is *safe for use* under the conditions prescribed, recommended, or suggested in its proposed labeling

Effectiveness:

- Substantial evidence consisting of adequate and well-controlled investigations….that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling

FDA generally considers that a drug is "*safe for use….*" when the **benefits** of a drug outweigh the **risks**

- *Risks may be substantial – but if balanced by unmet needs, course of disease, and ability to monitor and manage risk, B/R may remain favorable*

21 CFR 314.125

The FDA benefit / risk framework

Benefit-Risk Integrated Assessment:		
Dimension	*Evidence and Uncertainties*	*Conclusions and Reasons*
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk Management		

Completed for each medical review – intended to summarize FDA's thinking, rationale for decision

Goals of FDA safety assessment

- Assess **adequacy** of data submitted to assess safety
  - Completeness, consistency of submitted information
  - Extent and type of exposure
- Characterize **overall safety profile**: identify ADRs, other safety findings (e.g., lab changes)
  - Determine approvability (benefit/risk balance), assess ability to manage (labeling or REMS)
- Determine **labeling information** to guide safe use
  - Identify patients *susceptible* to safety risk
  - Appropriate monitoring
  - Risk mitigation approaches
  - Appropriate management, including REMS
- Identify residual **uncertainties**
  - Further characterize identified ADRs, assess potential ADRs
  - Design of PMRs/PMCs

Some challenges for safety assessment

Program and Study Design Issues

- Phase 3 clinical studies typically designed for effectiveness, not powered for safety
- *Each individual* study in a Phase 3 program often has limited patient exposure – need for pooling
- Limitations of patient duration of exposure to fully characterize long lag-time safety events or events that slowly accrue
- Early withdrawal without follow-up, risks of informative censoring
- Challenges of identifying and characterizing rare events
- Susceptibility of studied patient population to safety concern
- Limited diversity of studied population – characterizing safety profile in groups with limited exposure (age, race/ethnicity, concomitant medications, or diseases)

Reporting or Analytic Issues

- Coding of adverse events: inconsistent or poor "translation" of verbatim to coded terms – and variable *reporting* of verbatim terms for same medical concept
- Inadequate "grouping" of likely or potentially related AEs
- Challenges when medical events present in different ways or are reported with different terms (e.g., hypersensitivity)
- Inadequate detail in collection of clinically important but non-serious AE reports
- Optimizing cross-safety data set analyses (using AE, labs, vital sign, etc.)
- Sorting true findings from random imbalances

Some challenges for safety assessment

Program and Study Design Issues

- Phase 3 clinical studies typically designed for effectiveness, not powered for safety
- *Each individual* study in a Phase 3 program often has limited patient exposure – need for pooling
- Limitations of patient duration of exposure to fully characterize long lag-time safety events or events that slowly accrue
- Early withdrawal without follow-up, risks of informative censoring
- Challenges of identifying and characterizing rare events
- Susceptibility of studied patient population to safety concern
- Limited diversity of studied population – characterizing safety profile in groups with limited exposure (age, race/ethnicity, concomitant medications, or diseases)

Reporting or Analytic Issues

- Coding of adverse events: inconsistent or poor "translation" of verbatim to coded terms – and variable *reporting* of verbatim terms for same medical concept
- **Inadequate "grouping" of likely or potentially related AEs**
- **Challenges when medical events present in different ways or are reported with different terms (e.g., hypersensitivity)**
- Inadequate detail in collection of clinically important but non-serious AE reports
- **Optimizing cross-safety data set analyses (using AE, labs, vital sign, etc.)**
- **Sorting true findings from random imbalances**

Today…

- Discuss several FDA projects focused on enhancing safety analytics
- Hear input on FDA efforts – and learn about novel approaches to safety analytics being developed

U.S. FOOD & DRUG ADMINISTRATION

Thank You

Opening Remarks:
DM-FDA Public Workshop on Advancing Pre-market Safety Analytics

Vaishali Popat

Associate Director, Biomedical Informatics and Regulatory Review Science

Office of New Drugs, CDER/FDA

OND Pre-Market Safety Review Working Group

Issues:

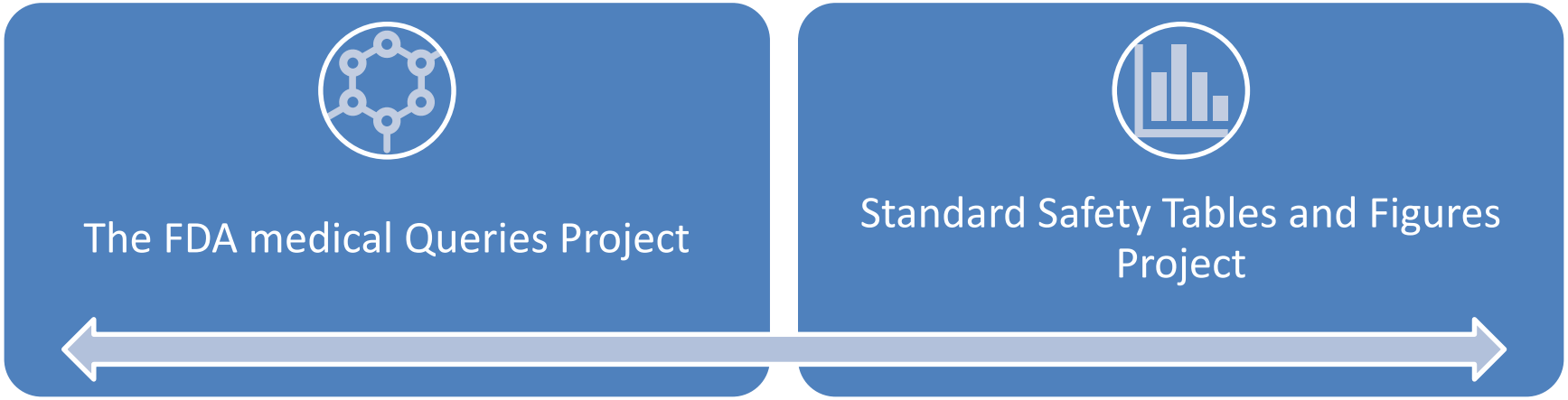
- No standardization of processes for NDA/BLA safety review

- Wide variations across Divisions

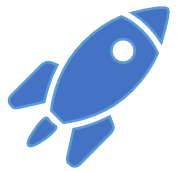
Objective: Perform detailed assessment of the NDA/BLA safety review process and develop an efficient, effective, standardized process – adaptable to different needs across teams/applications

OND: Office of New Drugs.

Two Important Safety Analytics Initiatives



- We are sharing approaches we typically take in safety analyses in the spirit of transparency. You may have seen some of the approaches in our published reviews. Today, we will provide more details on these approaches.
- Your input and feedback on these approaches is appreciated—and we encourage comments put into the docket that we've opened for that purpose. https://www.regulations.gov/docket/FDA-2022-N-1961/document
- Today's workshop is just the start of a conversation on premarket safety analytics.



Kick-off!

Overview of the FDA Medical Queries

Vaishali Popat, Scott Proestel, Eric Brodsky

U.S. Food and Drug Administration

FDA Medical Queries (FMQs)

Vaishali Popat MD, MPH

Associate Director

Biomedical Informatics and Regulatory Review Science
CDER/Office of New Drugs

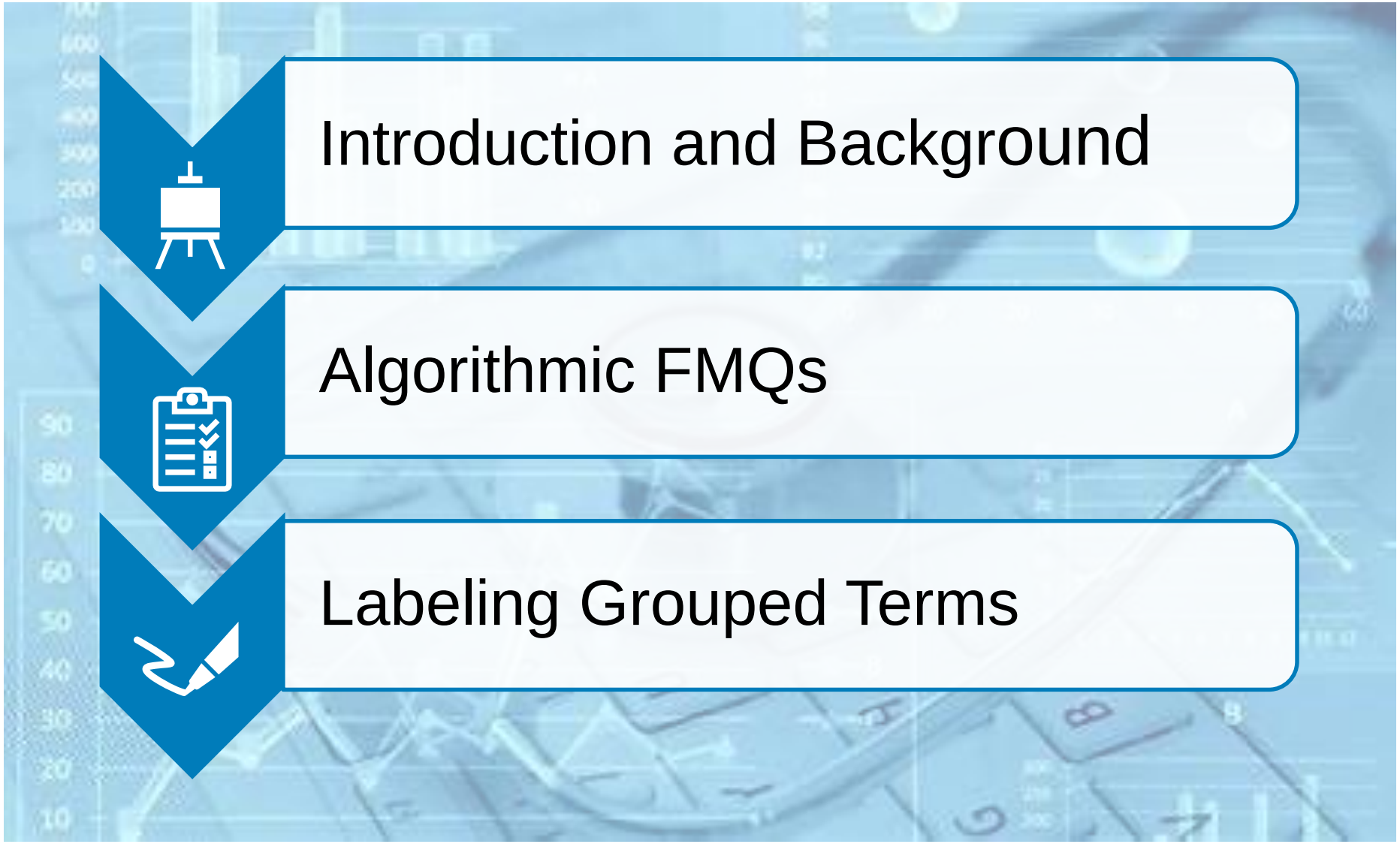
Today's Presenters

Vaishali Popat, MD, MPH
Associate Director,
Biomedical Informatics and Regulatory Review Science (BIRRS),
Office of New Drugs,
Center for Drug Evaluation and Research

Scott Proestel, MD
Senior Medical Officer,
Biomedical Informatics and Regulatory Review Science (BIRRS),
Office of New Drugs,
Center for Drug Evaluation and Research

Eric Brodsky, MD
Associate Director,
Labeling Policy Team,
Office of New Drugs,
Center for Drug Evaluation and Research

Agenda


Introduction and Background
Algorithmic FMQs
Labeling Grouped Terms

Why FDA Medical Queries?

Inconsistent Standards

- Investigators may report different verbatim terms for similar clinical events, resulting in varying coded MedDRA preferred terms for the same medical concept
  - A patient complaining of abdominal pain may be reported using verbatim terms coding to abdominal pain, abd. pain lower, abd. pain upper, gastrointestinal pain, visceral pain, abdominal discomfort, among others
- Adverse Events (AEs) may manifest in related, but different ways.
  - A patient with a rash related to drug hypersensitivity may present with an erythematous rash, a macular rash, a macular-papular rash, a papular rash, a morbilliform rash, etc., and each would be coded to a different PT
- When **related** PTs are not grouped, it's **possible to miss** important safety signals.

FDA Medical Queries

A Collective Way Forward

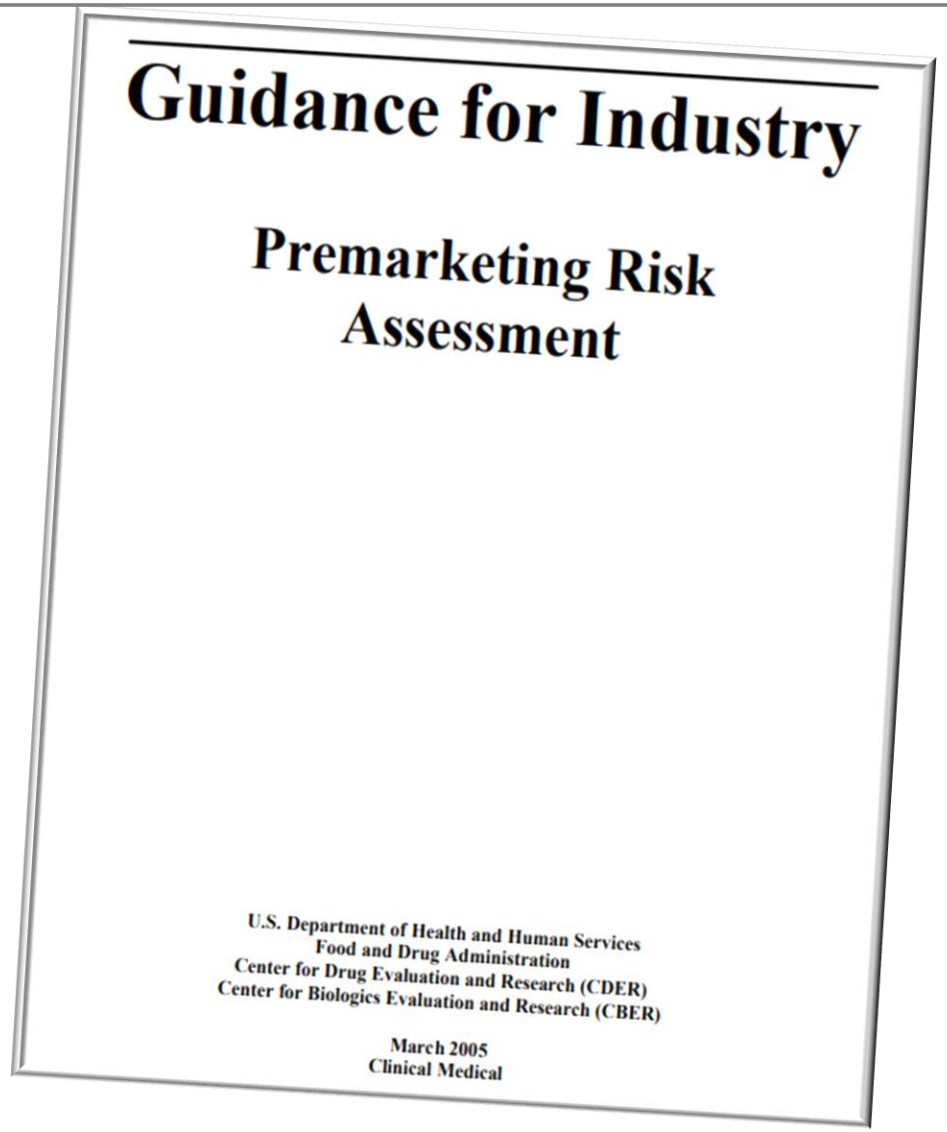
- Used natural language processing to determine most frequently encountered terms found in >38,000 labels of 1,254 active moieties
- Received requests from review divisions
- Evaluated existing queries
- Established the FMQ Working Group and collaborated with 80 reviewers across Divisions

An OND Standard

- Launched 104 FMQs
- Includes 4 Algorithmic FMQs
- Recommendations for FMQ labeling

OND= Office of New Drugs

Importance of Grouping Similar PTs Not a New Concept

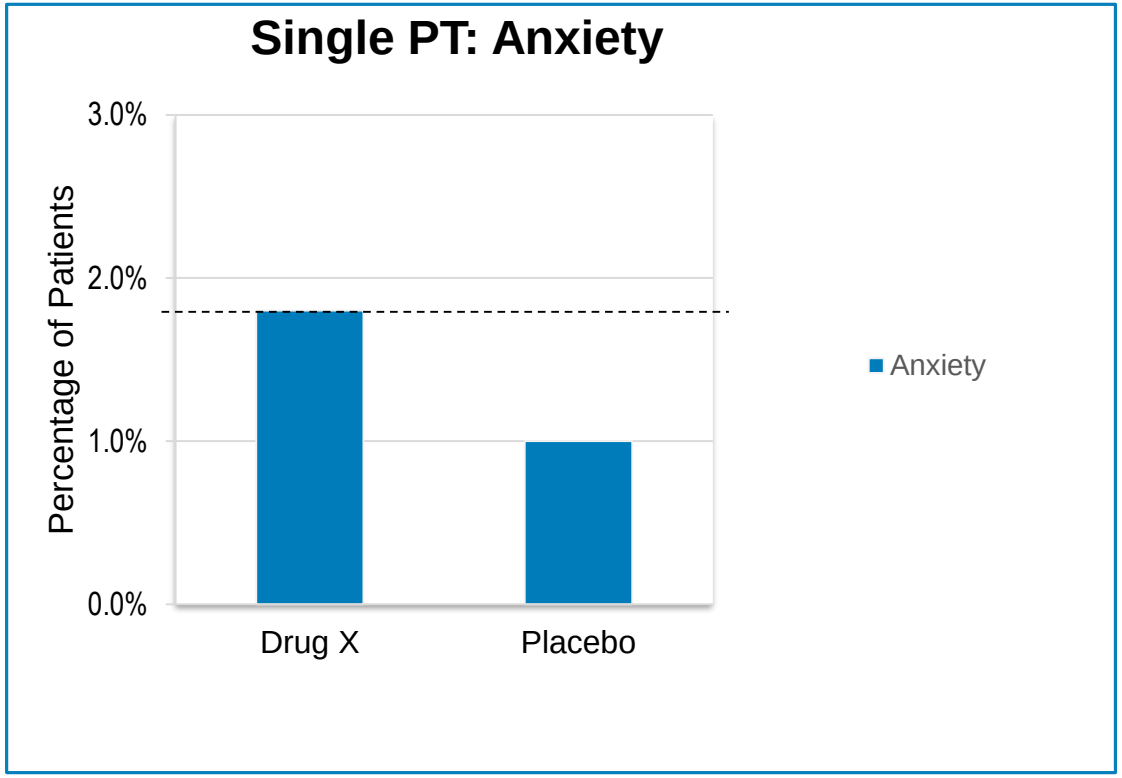


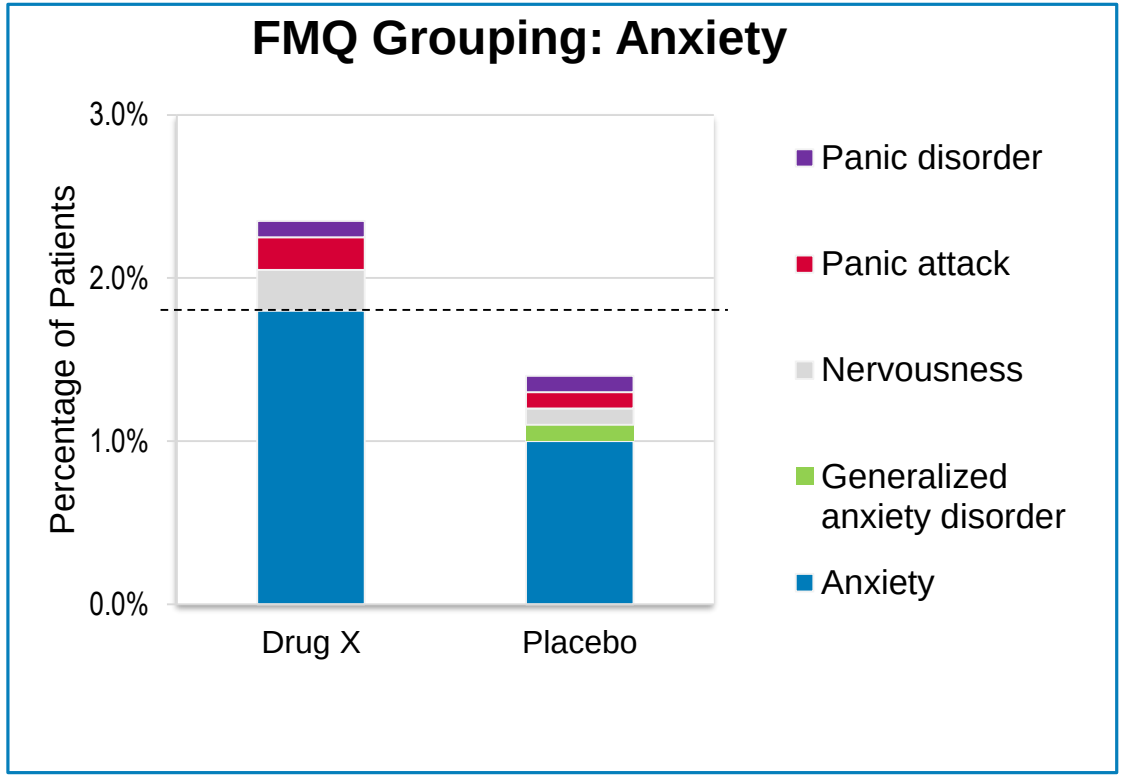
What are FMQs?

- Standardized groupings of related PTs developed by review staff primarily in FDA/CDER.
- MedDRA PTs are highly granular with >24000 PTs
- Each grouping represents a medical concept.
  - Example: “Initial insomnia,” “middle insomnia,” “early morning awakening,” combined to “insomnia.”
- Goal is to improve safety signal detection in clinical trial datasets.
- Standardized approach to increase efficiency and consistency.

Single PT Analysis vs. FMQ Grouping

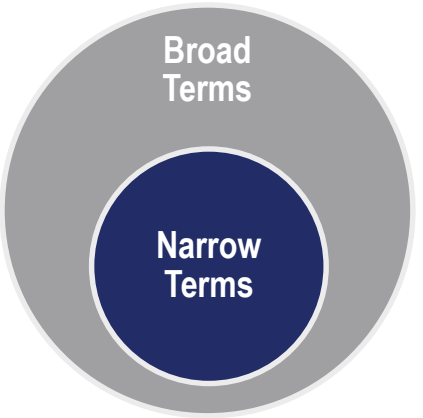
- Using a 2% cut-off for an AE analysis, “Anxiety” doesn’t make the cut, but group these PTs, and a signal emerges at the 2% cut-off (no patient counted twice).

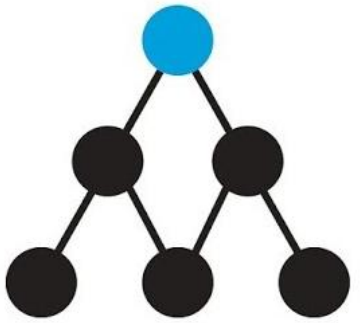




FMQ Concepts
Narrow vs. Broad vs. Algorithmic Queries

- Narrow FMQ terms:
  - Specific for the medical concept
  - Indicate that the FMQ occurred, More than ~90% probability
- Broad FMQ terms:
  - “Cast a wider net” than narrow query terms for signal detection
  - Less specific
  - Provide reasonable assurance (more than ~30% probability) that the medical concept occurred
- Algorithmic FMQs
  - Uses data from the laboratory, Concomitant medications, medical history datasets in addition to the AE datasets
  - Uses temporal associations





FMQ Ground Rules: Narrow Queries

Narrow Queries: Indicates FMQ concept occurred

- PTs that are near-synonyms of the FMQ concept
  - PT Abdominal Discomfort in FMQ Abdominal Pain
- PTs that are subgroups of the FMQ concept
  - PT Anaemia Neonatal in FMQ Anemia
- PTs that specify an etiology for the FMQ concept
  - PT Uremic Pruritus in FMQ Pruritus
- PTs that ensure the occurrence of the FMQ concept
  - PT Aortic Rupture in FMQ Hemorrhage

FMQ Ground Rules: Broad Queries

Broad Queries: Reasonably suggestive of FMQ concept occurrence

- PTs that may result in the FMQ concept
  - PT Osteopenia in FMQ Osteoporosis
- PTs that provide laboratory, radiologic, or other diagnostic test results reasonably suggestive of an FMQ, including PTs with ambiguous results such as “abnormal”
  - PT Blood Glucose Abnormal in FMQ Hyperglycemia
- PTs reasonably suggestive of the FMQ concept, but not required by the FMQ concept:
  - PT Bronchospasm in FMQ Hypersensitivity
- PTs that indicate a “carrier” status for FMQ concepts that specify an infectious disease
  - PT Bacterial Disease Carrier in FMQ Bacterial Infection

FMQ Ground Rules: PT's Excluded from FMQ

PTs Excluded from FMQs: terms that are too vague

- PTs that are neither a required component nor reasonably specific for the FMQ concept
  - PT Nausea would not be included in FMQ Migraine
- PTs that provide the names of laboratory, radiologic, or other diagnostic tests without a result
  - PT Clostridium Test
  - PTs that provide test names without a result, but that would only be performed in the presence of disease, should be included if they otherwise qualify (example: PT Antipsychotic Drug Level in FMQ Psychosis).

How FMQs were Constructed

- FDA review staff developed standard groupings of related AEs.
- Each FMQ represents a distinct medical concept (e.g., Anemia, Nausea, Vomiting, etc.) and stand on their own.
- Each preferred term was independently adjudicated by a subject matter expert reviewer; any discrepancies were adjudicated by the working group.
- FMQ "Ground Rules" were created and used to apply medical judgment in developing logical groupings
- Steering committee made final decisions when there were difference of opinions; ensured version control, systems development, up-versioning with each major MedDRA release, and change control
- Cumulative approach: includes current PTs, former PTs, misspelled terms.

Difference Between FMQs and SMQs

FMQs attempt to capture all instances of an AE, even if PT indicates a “non” drug-related cause:

FMQ Pancreatitis **SMQ Acute Pancreatitis**

(Does Contain) **(Does Not Contain)**

Alcoholic Pancreatitis
Autoimmune Pancreatitis
Obstructive Pancreatitis
Pancreatitis Viral

FMQs for which there are no SMQs

Abdominal pain	Dysgeusia	Myalgia
Abnormal uterine bleeding	Dyspepsia	Nasopharyngitis
Alopecia	Dyspnoea	Nausea
Amenorrhoea	Erectile dysfunction	Parasomnia
Anxiety	Erythema	Pruritus
Arthralgia	Excessive menstrual bleeding	Pyrexia
Back pain	Fatigue	Somnolence
Bacterial vaginosis	Gynaecomastia	Syncope
Constipation	Headache	Tremor
Cough	Hyperprolactinaemia	Urinary retention
Decreased appetite	Insomnia	Urticaria
Decreased menstrual bleeding	Irritability	Vertigo
Dizziness	Local administration reactions	Vomiting
Dry mouth	Mania	

71

FMQ version 2.1

1. Arthritis
2. Abdominal Pain
3. Abnormal Uterine Bleeding
4. Acute Coronary Syndrome
5. Acute Kidney Injury
6. Alopecia
7. Amenorrhea
8. Anemia
9. Anaphylactic Reaction
10. Angioedema
11. Anxiety
12. Arrhythmia
13. Arthralgia
14. Back Pain
15. Bacterial Infection
16. Bacterial Vaginosis
17. Bronchospasm
18. Cachexia
19. Cardiac Conduction Disturbance
20. Cholecystitis
21. Confusional State
22. Constipation
23. Cough
24. Decreased Appetite
25. Decreased Menstrual Bleeding
26. Depression
27. Diabetic Ketoacidosis
28. Diarrhea
29. Dizziness
30. Dry Mouth
31. Dysgeusia
32. Dyspepsia
33. Dyspnoea
34. Erectile Dysfunction
35. Erythema
36. Excessive Menstrual Bleeding
37. Fall
38. Fatigue
39. Fracture
40. Fungal Infection
41. Glaucoma
42. Gout
43. Gynaecomastia
44. Hemorrhage
45. Headache
46. Heart Failure
47. Hepatic Failure
48. Hepatic Injury
49. Hyperglycemia
50. Hyperprolactinaemia
51. Hypersensitivity
52. Hypoglycemia
53. Hypotension
54. Insomnia
55. Irritability
56. Invest Agent Abuse Potential
57. Leukopenia
58. Lipid Disorder
59. Local Administration Reactions
60. Malignancy
61. Mania
62. Myalgia
63. Myocardial Infarction
64. Myocardial Ischemia
65. Nasopharyngitis
66. Nausea
67. Opportunistic Infection
68. Osteoporosis
69. Palpitations
70. Pancreatitis
71. Paraesthesia
72. Parasomnia
73. Peripheral Oedema
74. Pneumonia
75. Pneumonitis
76. Pruritus
77. Psychosis
78. Purulent Material
79. Pyrexia
80. Rash
81. Renal & Urinary Tract Infection
82. Respiratory Depression
83. Respiratory Failure
84. Rhabdomyolysis
85. Seizure
86. Self-Harm
87. Sexual Dysfunction
88. Somnolence
89. Stroke-TIA
90. Syncope
91. Systemic Hypertension
92. Tachycardia
93. Tendinopathy
94. Thrombocytopenia
95. Thrombosis
96. Thrombosis (Arterial)
97. Thrombosis (Venous)
98. Tremor
99. Urinary Retention
100. Urticaria
101. Vertigo
102. Viral Infection
103. Volume Depletion
104. Vomiting

https://www.regulations.gov/docket/FDA-2022-N-1961/document

Algorithmic FDA Medical Queries

Scott Proestel, MD
Senior Medical Officer
Biomedical Informatics and Regulatory Review Science (BIRRS)
Office of New Drugs, CDER

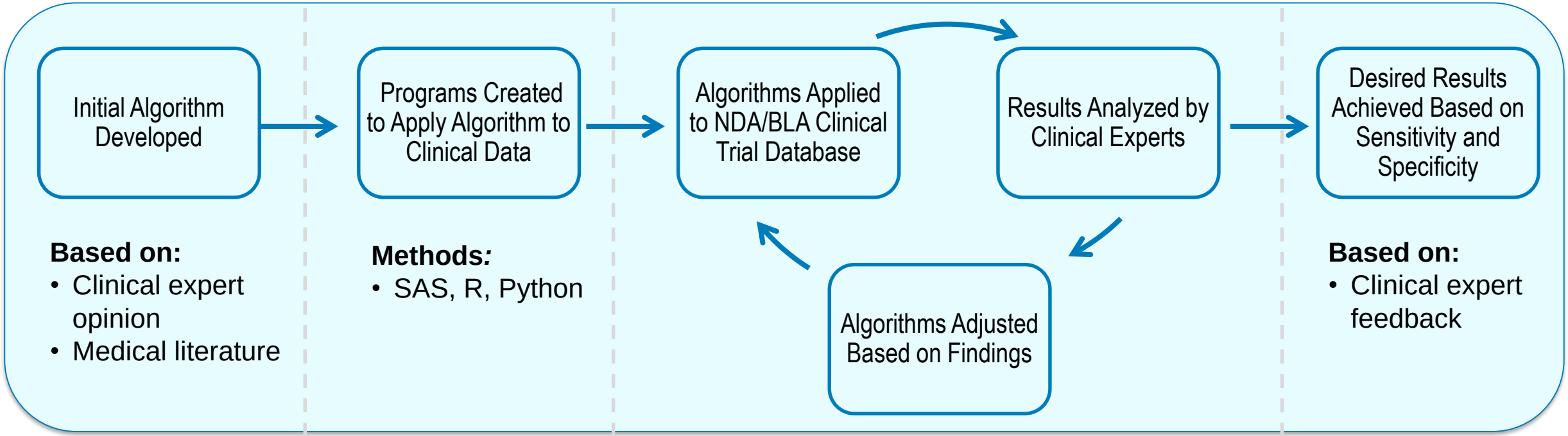
FMQ Components

- **Narrow** – contains PTs highly specific to the FMQ concept; indicates that the FMQ occurred.
- **Broad** – casts a wider net to capture additional cases of the FMQ concept.
- **Algorithmic** – an important step forward because multiple datasets are combined to leverage the available information, such as:
  - Adverse event datasets
  - Laboratory datasets
  - Concomitant meds datasets
  - Medical history datasets
  - Temporal relationships

Example Mock Algorithm:

1. PT + PT
2. Lab value >ULN
3. PT + Con Med within 3 days
4. PT + Medical History

FMQ Algorithm Development and Testing Process



Based on:
- Clinical expert opinion
- Medical literature

Methods:
- SAS, R, Python

- Trial database of over 10,000 studies
- Algorithm applied multiple ways:
  - *Large random trial selection*
  - *Targeted trials with known FMQ associations*
  - *Trials with high prevalence of FMQ terms*
- Revised algorithm based on:
  - *Total patients and safety signals identified*
  - *Individual case reports and data*

Based on:
- Clinical expert feedback

Rhabdomyolysis Algorithmic FMQ

Patients qualify for the algorithm if they meet any of the following criteria:

1. Any Rhabdomyolysis FMQ Narrow term
2. Urine myoglobin >ULN
3. CPK >5 x ULN **AND NO:**
   - CPK >ULN at baseline OR
   - CPK-MB/CPK >0.05 with start date within 3 days
4. [PT Myalgia + PT Muscular Weakness + (PT Myoglobin Urine Present OR PT Chromaturia)] with start date within 7 days of each other

ULN= Upper limit of normal, CPK = creatine phosphokinase

Hypoglycemia Algorithmic FMQ

Patients qualify for the algorithm if they meet any of the following criteria:

1. Any Hypoglycemia FMQ Narrow Term
2. Plasma Glucose <54 mg/dL
3. [Any Hypoglycemia FMQ Broad Term* OR Supplemental Term**] PLUS [Plasma Glucose <70 mg/dL] with start date within 1 week
4. [≥2 Occurrences of a Hypoglycemia FMQ Broad Term* OR Supplemental Term**] PLUS [≥2 Occurrences of Plasma Glucose <70 mg/dL]

* Includes Hypoglycemia FMQ Broad Terms only (while FMQ Broad analyses include both Narrow and Broad terms, this criterion only refers to the terms specifically identified as Broad).

** Supplemental Terms – Accident, Anxiety, Asthenia, Cold sweat, Coma, Confusional state, Fall, Fatigue, Hunger, Hyperhidrosis, Irritability, Loss of consciousness, Palpitations, Road traffic accident, Seizure, Tremor, Dysarthria, Balance disorder, Coordination abnormal, Headache, Vision blurred, and Visual impairment.

Hyperglycemia Algorithmic FMQ

Patients qualify for the algorithm if they meet any of the following criteria:

1. Any PT from Hyperglycemia FMQ Narrow
2. Fasting Plasma Glucose ≥126 mg/dL
3. ≥2 Plasma Glucoses >180 mg/dL
4. Any New Diabetes Concomitant Medication:
   - The medication must have been started following enrollment
   - CMINDC File
     - INCLUDE diab, mellitus, hyperglyc, glucose, dibet, dieb
     - EXCLUDE prophyla, prevent, insipidus, hyperglycerid, low blood glucose, low glucose, low blood sugar, low sugar, low afternoon blood glucose, low morning blood glucose
   - CMCLAS File
     - INCLUDE gliptin, glutide, diabet, glitaz, glucose lowering, glucosidas, dipeptidyl, sulfonyl, DPP, guanide, GLP, glucagon-like, metform, gliflozin, insulin, sodium-glucose, SGLT, thiazolid
     - EXCLUDE sex hormone
5. Post Baseline HbA1c ≥6.5%
6. HbA1c Increase ≥0.3% with Post Baseline HbA1c ≥5.7%
7. Change from Baseline Fasting Plasma Glucose ≥20 mg/dL with Post Baseline FPG >100 mg/dL

Hypersensitivity Algorithmic FMQ

A patient is included in the algorithm by having items from any of the following categories or combinations of categories with start dates within 7 days:

1. Category A
2. Category B + Category C
3. Category B + Category D
4. Category C + Category D

Category A (Narrow PTs)	Category B (Respiratory)	Category C (Skin)	Category D (Systemic Reactions)
Acute generalised exanthematous pustulosis	Allergic bronchitis	Administration related reaction	Acute circulatory failure
Administration site hypersensitivity	Allergic pharyngitis	Administration site dermatitis	Blood immunoglobulin E abnormal
Administration site recall reaction	Allergic respiratory symptom	Administration site pruritus	Blood pressure decreased
Administration site vasculitis	Asthma	Administration site rash	Blood pressure diastolic decreased
Allergic colitis...	Asthmatic crisis...	Administration site urticaria...	Blood pressure systolic decreased...

Acknowledgements: Core Workgroup Members*

Office of New Drugs

- Peter Stein (Executive Sponsor)
- Vaishali Popat* (Project lead)
- Ellis Unger*
- Scott Proestel* (Project co-lead)
- Vaishali Jarral*
- Aisha Summers*
- Preeti Venkatraman*
- Natalia Chalmers*
- Ramya Gopinath
- Joe Tonning
- Regina Zopf
- Bach Nhi Beasley
- Veronica Yang Pei
- Lourdes Villalba
- Stacy Chin
- Doug Warfield
- Tanvir Ahmed
- Jeffry Florian
- Sarah Olson
- Michelle Shen
- Jessica Voqui
- Lauren Choi
- Lesley-Anne Furlong
- Jeff Siegel

Office of Surveillance and Epidemiology

- Sonja Brajovic
- Manish Kalaria

Office of Translational Sciences

- Joy Li
- Alan Shapiro

Center for Biologics Evaluation and Research

- Patricia Rohan

*Steering Committee Members

Acknowledgements: Additional Contributors

- Ellen Fields
- Erika Torjusen
- Maria Allende
- Alma Davidson
- Shabnam Naseer
- Ana Szarfman
- Natalia Chalmers
- Elizabeth Hart
- Lara Dimick
- Ruby Mehta
- Stephanie Omokaro
- Suna Seo
- Dina Zand
- Frank Pucino
- Eric Bastings
- Melissa Reyes
- Shaz Siddiqi
- Kim Shimy
- Mahtab Niyyati
- Heather Fitter
- Laura Jawdizik
- Leonard P Kapcala
- Ranjit Mani
- Gerald Podskalny
- Philip Sheridan
- Michael Davis
- Gregory Dubitsky
- Michelle Horner
- Jean Kim
- Daniel Lee
- Martine Solages
- Zimri Yaseen
- Lori Ehrlich
- Candis Morrison
- Shanthi Marur
- Jordan Pomeroy
- Ann Miller
- Laleh Amiri Kordestani
- Shaily Arora
- Jamie Brewer
- Elaine Chang
- Jenny Gao
- Danielle Krol
- Candace Mainor
- Sarkar Wahby
- Sandra Casak
- Meredith Chuk
- Margit (Naomi) Horiba
- Steven Lemery
- Sangeeta Jain
- Jenni Lee
- Lauren Wood-Heickman
- David Mouser
- Peter Glass
- Sarah Rodgers

Including Grouped Term Information in the ADVERSE REACTIONS Section of the Prescribing Information

Eric Brodsky, M.D., Associate Director
Labeling Policy Team, Office of New Drug Policy, Office of New Drugs,
Center for Evaluation and Research, FDA

Disclaimer

- The views and opinions expressed in this presentation represent those of the presenter, and do not necessarily represent an official FDA position.
- The labeling examples in this presentation are provided only to illustrate concepts/challenges and should not be considered FDA recommended templates.

Overview of Presentation

- Discuss considerations on including group term (e.g., FMQ) information and component term information in the ADVERSE REACTIONS section of labeling

- Discuss updated prescription drug labeling resources

FMQs = FDA Medical Queries

Adverse Events vs. Adverse Reactions in Labeling

- **Adverse Events** (AEs): "Any untoward medical event associated with the use of a drug in humans, whether or not considered drug-related"[1]

- **Adverse Reactions** (ARs): "An undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all AEs observed during use of a drug, only those AEs for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the AE."[2]

[1] See guidance for industry: *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (January 2006) (referred to as the Adverse Reactions Section of Labeling Guidance)

[2] For PLR-formatted labeling, see 21 CFR 201.57(c)(7) and the Adverse Reactions Section of Labeling Guidance. For "old" (non-PLR) format labeling, the AR definition is different [21 CFR 201.80(g)]: *"an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence."*

Factors in Causality Assessment of AEs[1]

(helps determine if an AE is an AR and is appropriate for inclusion in the labeling)

- Increased frequency of reporting
- AE rate for the drug exceeds the placebo rate
- Dose-response relationship
- AE is consistent with the pharmacology of the drug
- Relationship between time of AE relative to the time of drug exposure
- Challenge and dechallenge cases
- AE is known to be caused by related drugs
- AE observed across studies
- AE led to higher discontinuation rate or serious adverse reactions in the drug-treated group

[1] AE = adverse event; AR = adverse reactions; See Adverse Reactions Section of Labeling Guidance

Including Group Term Information into *Clinical Trials Experience* Subsection of ADVERSE REACTIONS Section

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
9 DRUG ABUSE AND DEPENDENCE
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
13 NONCLINICAL TOXICOLOGY
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Common Adverse Reaction Table(s)

Example of Common Adverse Reaction Table[1,2] in the *Clinical Trials Experience* Subsection of ADVERSE REACTIONS Section

Table X: Common Adverse Reactions in Patients with Disease-X During the 24-week Treatment Period in Studies A, B, and C[1]

	DRUG-X N=XXX	Placebo N=XXX
Asthenia[2]	39%	17%
Musculoskeletal pain[3]	18%	7%
Vomiting	15%	11%
Upper respiratory tract infection	12%	3%
Thrombocytopenia	9%	2%
Anemia	9%	3%
Arthralgia	6%	3%
Headache	6%	4%
Herpes Zoster	5%	2%
Paresthesia	5%	3%

[1] Adverse reactions that occurred in ≥ 5% in DRUG-X-treated patients and ≥ 2% than placebo-treated patients

[2] Asthenia includes the terms fatigue and malaise

[3] Musculoskeletal pain includes back pain, neck pain, thigh pain, shoulder pain

[1] The *Clinical Trials Experience* subsection of the ADVERSE REACTIONS section "must list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database" – see 21 CFR 201.57(c)(7)(ii)(A)

[2] "To permit side-by-side comparison of adverse reaction rates, common adverse reactions are typically presented in a table" – see Adverse Reactions Section of Labeling Guidance

Merits of Grouping Related Terms

- Include an AR that was not initially apparent when reporting was spread across multiple related individual terms
- Provide a better estimate of the true magnitude of the AR; and
- Exclude an AE that is unrelated or unlikely related to the drug when analysis of grouped terms does not support determination that the AE is an AR

ARs = adverse reactions; AEs = adverse events

Classifying Adverse Reactions in the *Clinical Trials Experience Subsection* in the ADVERSE REACTIONS Section[1]

- AR that represent same phenomenon should ordinarily be grouped together as a single AR to avoid diluting or obscuring the true effect

- AR reported in more than one body system that appear to represent a common pathophysiologic AR should be grouped together to better characterize the AR

AR = adverse reactions; [1] See Adverse Reactions Section of Labeling Guidance.

Four Fictitious Labeling Examples

#1 Data Only Supports Including Anxiety FMQ Term (in Common AR Table in ADVERSE REACTIONS section)

FMQ Anxiety Analysis (this does not go into labeling)		
	DRUG-X N=XXX	Placebo N=XXX
FMQ Anxiety Grouped Term	**6.7%**	**2.7%**
Anxiety	3.3%	1.3%
Anxiety aggravated	1.5%	0.8%
Anxiety disorder	1.5%	0.7%
Anxiety disorder NEC	0.8%	0.1%

Table X: Common Adverse Reactions in Patients with Disease-X (48-week Studies 1 and 2)[1]		
	DRUG-X N=XXX	Placebo N=XXX
Vomiting	10%	2%
Diarrhea	9%	3%
Dermatitis	8%	3%
Anxiety[2]	7%	3%
Chills	5%	3%

[1] Adverse reactions that occurred in ≥ 5% in DRUG-X-treated patients and ≥ 2% than placebo-treated patients
2 Anxiety is composed of several similar terms

1. **FMQ Anxiety Grouped Term is an AR (included in table body)**
2. **Component terms represented in common AR table; however, they are not named because they are near-synonyms.**
3. **Footnote states that grouped term includes other related terms.**

#2 Include FMQ Grouped Term in Body of Table and Component Term(s) in Footnotes in Most Common AR Table in ADVERSE REACTIONS Section

FMQ Anxiety Analysis (this does not go into labeling)		
	DRUG-X N=XXX	Placebo N=XXX
FMQ Anxiety	**12.2%**	**2.2%**
Social phobia	5.1%	2.1%
Stress	2.1%	0.1%
Anxiety disorder	2.5%	0%
Anxiety disorder NEC	2.1%	0%
Anxiety	2.1%	0%

Table X: Common Adverse Reactions in Patients with Disease-X (48-week Studies 1 and 2)[1]

	DRUG-X N=XXX	Placebo N=XXX
Anxiety[2]	12%	2%
Vomiting	10%	2%
Diarrhea	9%	3%
Dermatitis	8%	3%

[1] Adverse reactions that occurred in ≥ 5% in DRUG-X-treated patients and ≥ 2% than placebo-treated patients

[2] Anxiety includes social phobia and stress and other related reactions

1. **FMQ Anxiety Grouped Term is an AR (included in table body)**
2. **Social phobia and stress included in grouped term and named in footnote because distinct clinical events and not near-synonyms**

#3.1 Include FMQ Grouped Term and Clinically Important Component Term(s) in Footnotes in Most Common AR Table in ADVERSE REACTIONS Section

FMQ Anxiety Analysis (this does not go into labeling)		
	DRUG-X N=XXX	Placebo N=XXX
FMQ Anxiety	**9.2%**	**2.2%**
Panic disorder	4.1%	2.1%
OCD	2.1%	0.1%
Anxiety disorder	1.4%	0%
Anxiety disorder NEC	1.3%	0%
Anxiety	1.2%	0%

OCD = obsessive compulsive disorder

Components in footnotes

Table X: Common Adverse Reactions in Patients with Disease-X (48-week Studies 1 and 2)[1]		
	DRUG-X N=XXX	Placebo N=XXX
Vomiting	10%	2%
Anxiety[2]	9%	2%
Dermatitis	8%	3%
Adverse reaction-a	x%	x%
Adverse reaction-b	x%	x%
Adverse reaction-c	x%	x%
Adverse reaction-d	x%	x%
Adverse reaction-e	x%	x%
Adverse reaction-f	x%	x%

[1] Adverse reactions that occurred in ≥ 5% in DRUG-X-treated patients and ≥ 2% than placebo-treated patients

[2] Anxiety includes panic disorder and obsessive compulsive disorder and other related reactions

1. **FMQ Anxiety Grouped Term is an AR (included in table body)**
2. **Panic disorder and OCD included in grouped term and in footnotes**

#3.2 Include FMQ Grouped Term and Clinically Important Component Term(s) in Body of Table in Most Common AR Table in ADVERSE REACTIONS Section

FMQ Anxiety Analysis (this does not go into labeling)		
	DRUG-X N=XXX	Placebo N=XXX
FMQ Anxiety	**9.2%**	**2.2%**
Panic disorder	4.1%	2.1%
OCD	2.1%	0.1%
Anxiety disorder	1.4%	0%
Anxiety disorder NEC	1.3%	0%
Anxiety	1.2%	0%

OCD = obsessive compulsive disorder

Components in body of table

Table X: Common Adverse Reactions in Patients with Disease-X (48-week Studies 1 and 2)[1]		
	DRUG-X N=XXX	Placebo N=XXX
Vomiting	10%	2%
Anxiety[2]	9%	2%
Panic disorder	4%	2%
Obsessive compulsive disorder	2%	< 1%
Dermatitis	8%	3%

[1] Adverse reactions that occurred in ≥ 5% in DRUG-X-treated patients and ≥ 2% than placebo-treated patients
[2] In addition to panic disorder and obsessive compulsive disorder, anxiety includes other related reactions

1. **FMQ Anxiety Grouped Term is an AR (included in table body)**
2. **Panic disorder and OCD included in grouped term and in table body because distinct clinical events and clinical importance**

#4 Data Only Supports Including ≥ 1 FMQ Component(s) in Common AR Table in ADVERSE REACTIONS Section

FMQ Anxiety Analysis (this table does not go into labeling)		
	DRUG-X N=XXX	Placebo N=XXX
FMQ Anxiety	**11.1%**	**2.7%**
Panic disorder	5.2%	0.4%
OCD	4.6%	0.1%
Nervousness	1.1%	0.9%
Anxiety disorder NEC	0.3%	0.1%
Anxiety aggravated	0.2%	0.2%
Anxiety postoperative	0%	1%

OCD = obsessive compulsive disorder

Table X: Common Adverse Reactions in Patients with Disease-X (48-week Studies 1 and 2)[1]		
	DRUG-X N=XXX	Placebo N=XXX
Vomiting	10%	2%
Diarrhea	9%	3%
Dermatitis	8%	3%
Panic disorder	5%	<1%
OCD	5%	<1%
[1] AR that occurred in ≥ 5% in DRUG-X treated patients and ≥ 2% than placebo-treated patients		

1. **Only panic disorder and OCD component terms meet AR definition and only apparent drivers of signal**
2. **Anxiety grouped term not included in table**

Summary of the FMQ Labeling Paradigm[1] (1 of 2)

1. FMQ grouped term(s) are included in common AR table if they meet the regulatory definition of an AR

2. If a grouped term and component term(s) meet the definition of an AR but the component term(s) are the only apparent driver(s) of the signal, only those component term(s) will be included in the body of the common AR table

[1] Labeling paradigm for your consideration applies to the common adverse reactions table(s) in the *Clinical Trials Experience* subsection in the ADVERSE REACTIONS section

Summary of the FMQ Labeling Paradigm[1] (2 of 2)

3. Component terms that contribute to a grouped term are represented in the common AR table by being part of the group term incidence.

If the component terms are:

- Near synonyms of the grouped term, they are not mentioned in the body or footnotes in the table
  - Footnote will state that the grouped term includes related terms
- Distinct clinical events and not near synonyms of grouped term, they are mentioned in footnotes OR in the body of the table.

[1] Labeling paradigm for your consideration applies to the common adverse reactions table(s) in the *Clinical Trials Experience* subsection in the ADVERSE REACTIONS section

FDA's Labeling Resources for Human Prescription Drugs

FDA's Labeling Resources for Human Prescription Drugs

For Industry

Share | Tweet | Linkedin | Email | Print

FDA's labeling resources for human prescription drugs are primarily directed to industry staff who develop human prescription drug* labeling. Human prescription drug labeling (1) contains a summary of the essential scientific information needed for the safe and effective use of the drug; and (2) includes the Prescribing Information, FDA-approved patient labeling (Medication Guides, Patient Package Inserts, and/or Instructions for Use), and/or carton and container labeling.

If you are a healthcare professional, patient, or caregiver, visit Frequently Asked Questions about Labeling for Prescription Medicines.

- **Searchable Labeling Databases**
- **How May "Current" Labeling Be Different Than "FDA-Approved" Labeling**
- **Searchable Product Databases**
- **Imported-Drug Specific Labeling Resources**
- **Resources for Promotional Labeling and Other FDA-Regulated Products**

[1] FDA's Labeling Resources for Human Prescription Drugs webpage available at https://www.fda.gov/drugs/laws-acts-and-rules/fdas-labeling-resources-human-prescription-drugs

Prescribing Information Resources

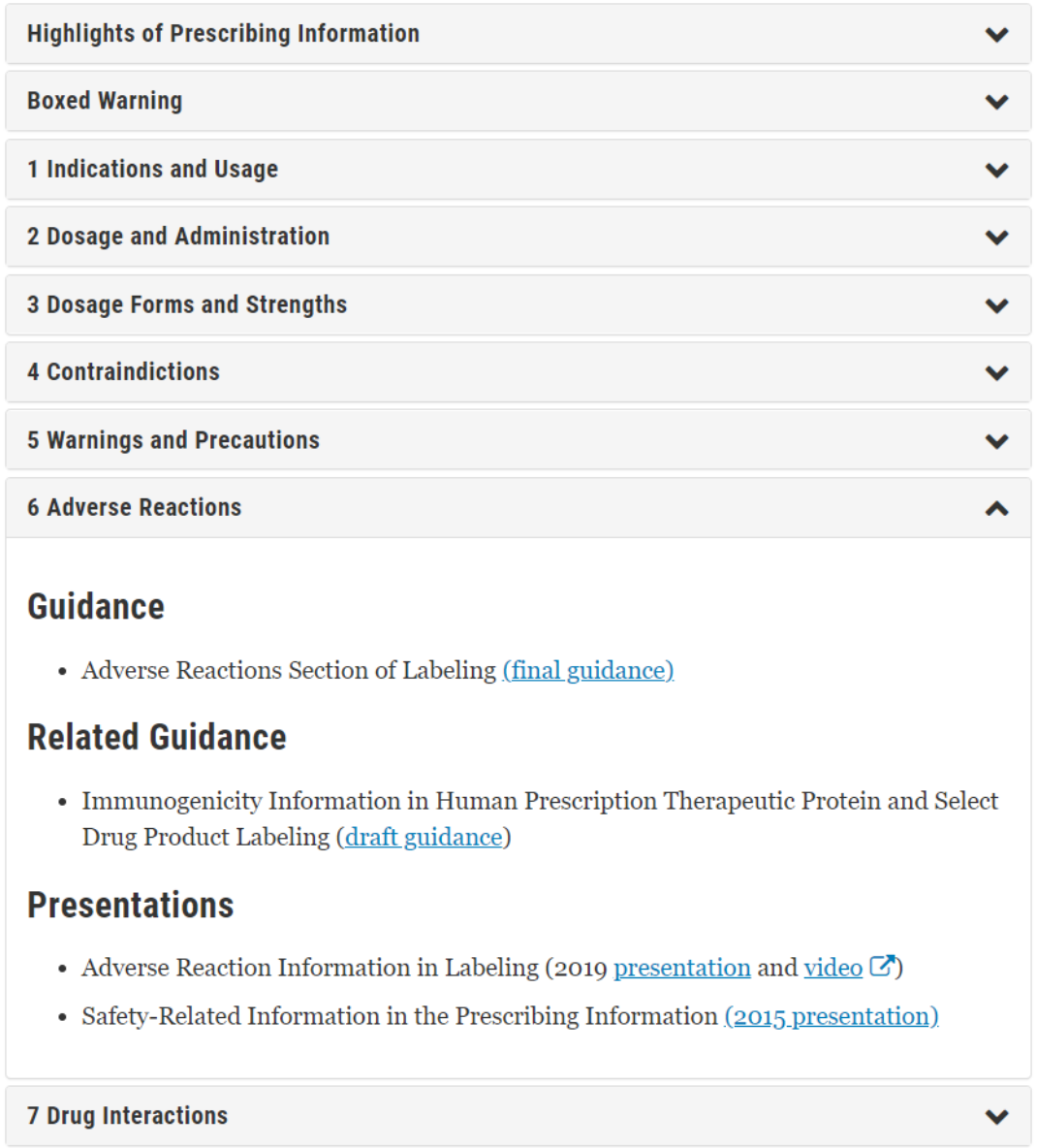
for Industry

Share | Tweet | Linkedin | Email | Print

- Highlights of Prescribing Information
- Boxed Warning
- 1 Indications and Usage
- 2 Dosage and Administration
- 3 Dosage Forms and Strengths
- 4 Contraindictions
- 5 Warnings and Precautions
- 6 Adverse Reactions
- 7 Drug Interactions

[1] Prescribing Information Resources webpage available at https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/prescribing-information-resources

Prescribing Information Resources



[1] Prescribing Information Resources webpage available at https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/prescribing-information-resources

Frequently Asked Questions about Labeling for Prescription Medicines

For Healthcare Professionals and Patients

Frequently asked questions about labeling for prescription drugs (medicines) on this webpage are primarily directed to healthcare professionals (for example, doctors, nurse practitioners, physician assistants, pharmacists, nurses) and patients and their caregivers. For information about prescription drug labeling resources primarily directed to industry such as those for the Prescribing Information, FDA-approved patient labeling, carton and container labeling, biological product labeling, generic drug labeling, labeling databases, and product databases visit FDA's Labeling Resources for Prescription Drugs.

Labeling for prescription medicines is FDA's primary tool for communicating drug information to healthcare professionals, and patients and their caregivers. Labeling for prescription medicines includes:

- Prescribing Information (labeling for healthcare professionals),
- Carton and container labeling (cartons and containers are outside packaging that contain information about prescription medicines), and
- Labeling for patients or caregivers (e.g., Medication Guides, Patient Package Inserts,

[1] FAQs about Labeling for Prescription Medications is available at https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/frequently-asked-questions-about-labeling-prescription-medicines

Discussion

What questions or comments do you have about the FDA Medical Queries?

Contact us at ONDbiomedicalinformatics@fda.hhs.gov


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Stakeholder Perspectives Exploring Premarket Adverse Event Grouping

Moderator: **Scott Proestel,** U.S. Food and Drug Administration

Panelists:

Ellis Unger, Hyman, Phelps & McNamara

Greg Ball, Novavax (PHUSE)

Barbara Hendrickson, Abbvie (DIA-ASA Interdisciplinary Safety Evaluation Working Group)

Duke-Margolis-FDA Public Workshop:

"Advancing Premarket Safety Analytics"

September 14, 2022

Ellis F. Unger, M.D.

Principal Drug Regulatory Expert
Hyman, Phelps & McNamara PC
Washington, D.C.

Disclaimers

- These are my opinions.
- I have no financial or intellectual conflicts of interest to report.
- I am not suggesting that the US Government take any particular course of action here.

Why Do We Collect Safety Data?

- To determine what drugs ***do*** and communicate this information in labeling
- To help make benefit-risk assessments
- To help make regulatory decisions

The Current State of Affairs

- Adverse events are recorded by investigators using their own language (verbatim terms), e.g., ‘Fall with R hip Fx.’
- Verbatim terms are translated to standard preferred terms (>20,000 of these) for analyses.
- Preferred terms are tabulated using various approaches.
- Companies may (or may not) perform:
  - Standard MedDRA queries (SMQs)
  - Custom queries on adverse events of special interest (AESIs)

Essentially Identical Preferred Terms are Reported Separately (1)

- Upper respiratory tract infection
- Viral upper respiratory tract infection
- Lower respiratory tract infection
- Respiratory tract infection
- Respiratory tract infection viral
- Upper respiratory tract congestion

- Do you really think these is a difference between these preferred terms?
- <u>These preferred terms are functionally the same!</u>

Essentially Identical Preferred Terms are Reported Separately (2)

- cardiac failure
- cardiac failure, acute
- cardiac failure, chronic
- cardiac failure, congestive
- cardiopulmonary failure
- left ventricular failure
- ventricular failure

- <u>These preferred terms are all important and all functionally the same!</u>

Why Would any Rational Person Separate ‘Pulmonary Oedema’ from…

Sleep Apnoea Syndrome	47	(0.7)	50	(0.7)
Asthma	61	(0.9)	46	(0.7)
Rhinorrhoea	32	(0.5)	34	(0.5)
Rhinitis Allergic	39	(0.6)	30	(0.4)
Pulmonary Hypertension	34	(0.5)	29	(0.4)
Dysphonia	16	(0.2)	27	(0.4)
Wheezing	25	(0.4)	26	(0.4)
Sinus Congestion	22	(0.3)	24	(0.3)
Bronchitis Chronic	8	(0.1)	22	(0.3)
Respiratory Tract Congestion	31	(0.4)	22	(0.3)
Nasal Congestion	31	(0.4)	21	(0.3)
Respiratory Failure	14	(0.2)	19	(0.3)
Pulmonary Oedema	27	(0.4)	15	(0.2)
Bronchospasm	12	(0.2)	14	(0.2)
Hypoxia	8	(0.1)	13	(0.2)

‘Acute Pulmonary Oedema?’

Obstructive Airways Disorder	4 (<0.1)	8 (0.1)
Pulmonary Embolism	11 (0.2)	8 (0.1)
Acute Pulmonary Oedema	7 (<0.1)	7 (<0.1)
Nasal Polyps	2 (<0.1)	7 (<0.1)
Pleurisy	7 (<0.1)	7 (<0.1)
Dyspnoea Paroxysmal Nocturnal	12 (0.2)	6 (<0.1)
Hiccups	6 (<0.1)	6 (<0.1)
Lung Disorder	5 (<0.1)	6 (<0.1)
Pulmonary Mass	5 (<0.1)	6 (<0.1)

- These terms are the same. (Not many patients walk around with “chronic” pulmonary edema.)
- One should not separate ‘acute pulmonary oedema’ from ‘pulmonary oedema!’

And Amazingly, Some Preferred Terms with Essentially Identical Meaning are Split Across System-Organ-Classes

- ‘Acute Pulmonary Oedema’ and ‘Pulmonary Oedema’ are in the Respiratory, Thoracic and Mediastinal Disorders System-Organ-Class

- ‘Cardiac Failure,’ ‘Cardiac Failure, Acute,’ etc. are in the Cardiac Disorders System-Organ-Class

But pulmonary edema generally is heart failure (unless it is non-cardiogenic pulmonary edema).

And Segregating Preferred Terms from the ‘Investigations’ SOC is Also a Problem

- Hyperkalaemia (Metabolism and nutrition disorders)
- Blood potassium increased (Investigations)

Why would anyone want to separate these?

The Problem

- Some companies run no adverse event queries at all.
- Even if queries are run for adverse events of special interest (AESI), they are generally not run for adverse events not designated as AESI.
- When similar, related preferred terms are reported only separately, important adverse drug reactions can go undetected.

An Interim Solution – Not Ideal

- As a medical officer at FDA, I always wanted to look for particular adverse events, e.g., heart failure, arrhythmias, renal dysfunction, falls, fractures, dyspnea, pneumonia, urinary tract infections, depression, insomnia, seizures, nausea, bacterial infections, viral infections, etc. These analyses required queries.
- I developed >300 queries and ran them myself. My safety reviews were based on these analyses.

So What's the Problem with MedDRA Standard Queries?

- Per MedDRA: "SMQs are tools developed to facilitate retrieval of MedDRA-coded data as a first step in investigating drug safety issues in pharmacovigilance and clinical development."
- Much of the use of SMQs is for pharmacovigilance.

What's the Solution?

- The FDA MedDRA queries (FMQs) have been developed by FDA medical officers with extensive experience in drug safety assessment.
- Some 80 medical officers have been involved.
- The expertise brought to bear in the development of FMQs is unmatched and truly impressive!
- Broader use of FMQs will represent an important advance in the safety assessment of new drugs and drug labeling.

Thanks for listening!

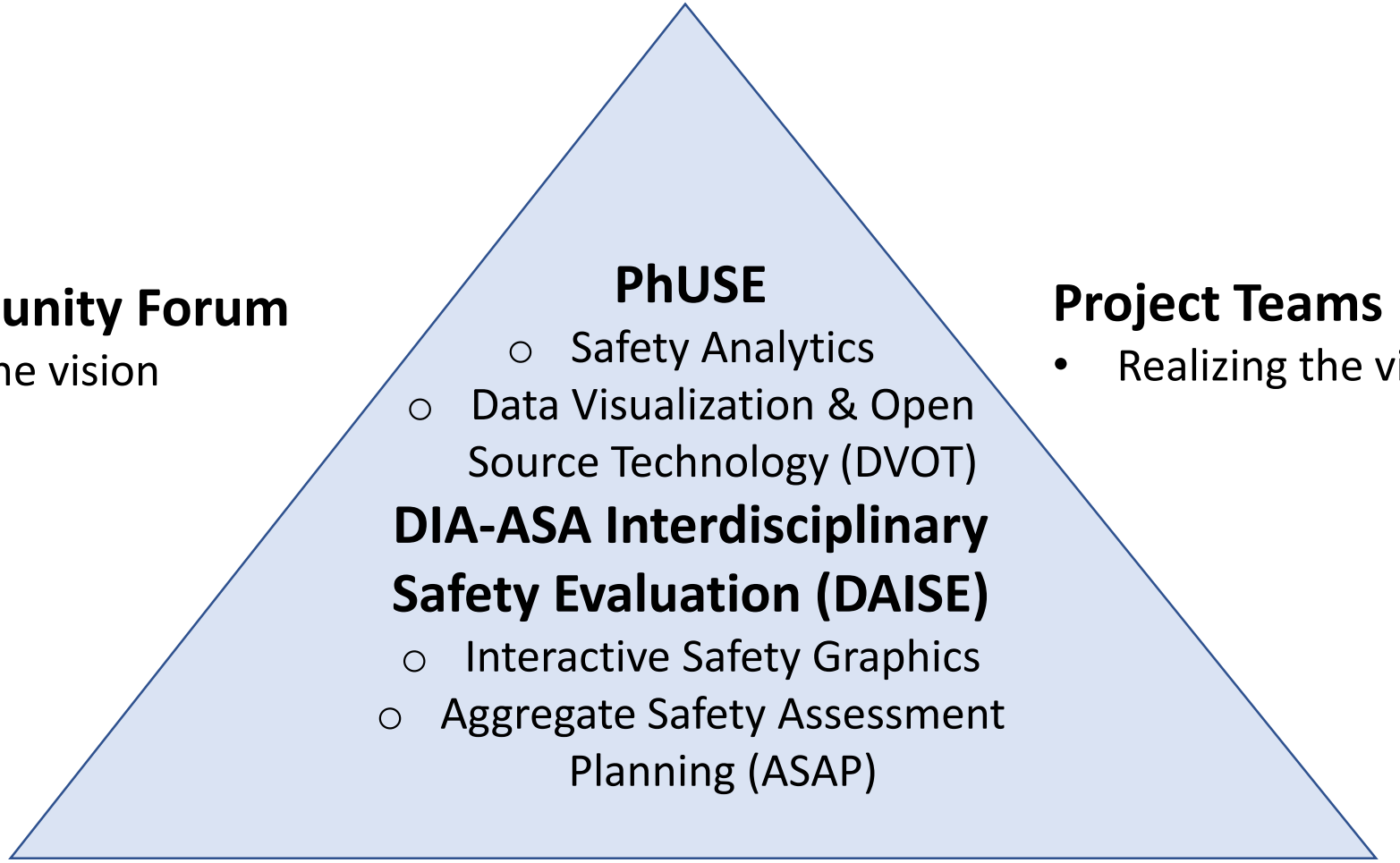
Preparing the Ecosystem for FMQs

Greg Ball, PhD
Head of Safety Statistics
Global Vaccine Safety, Novavax

Reimagining a Safety Submission

PhUSE Community Forum

- Developing the vision



Project Teams

- Realizing the vision

Safety Graphics Consortium

- Networking together

Motivation

“Far better an approximate answer to the right question, which is often vague, than an exact answer to the wrong question, which can always be made precise.

– John Tukey (1962)

Challenges and Opportunities

- Complex challenges exist for evaluating the relationship of study drug with AEs
  - Accounting for duration of exposure time, patient-level covariates and other clinical considerations
  - Specific safety issues, such as dose response and subgroup differences
- Could benefit from the expanded interest and participation by clinical safety professionals and statisticians working closely together
- Opportunities for sponsors and academia to partner with regulatory authorities for developing interdisciplinary safety evaluation procedures

O'Neill R. Stat Med. 1995;14(9-10):117-127.

The Spirit of the IND Safety Reporting Final Rule

“The important thing is to have a thoughtful process;
a system in place to look for clinically important imbalances,
applying the best clinical and quantitative judgment,
while maintaining trial integrity.

– Jacqueline Corrigan-Curay (2018)

The Spirit of the IND Safety Reporting Final Rule

- Scientific evaluation of accumulating program-level safety information throughout drug development, leveraging the scientific expertise and medical judgment of multidisciplinary teams
  - A multidisciplinary approach
  - Assessments customized for the specific product
  - Quantitative frameworks for measuring evidence of association
  - Decisions that incorporate medical judgment

Ball G, Hendrickson BA, Freedman AL, Gordon R, Crowe B, Veenhuizen MF Buchanan J (2021). Interdisciplinary Safety Evaluation for Learning and Decision-Making. *Therapeutic Innovation & Regulatory Science,* 55:705-716.

Space Shuttle Challenger Disaster

- Looking only at the quantitative data supported NASA's decision to proceed with the launch
  - There was other important information the engineers presented
  - But it was not quantitative, so NASA managers did not accept it
- An engineer, asked to quantify his concerns, couldn't
  - 75-degree flight: Very thin streak of light gray soot beyond an O-ring in the joint
  - 53-degree flight: Jet-black soot fanned out across a large swath of the joint
- He had no data to quantify it
  - But he did say he knew that it was "away from goodness"

Epstein D (2019). Range: Why generalists triumph in a specialized world. Riverhead books.

A Learning and Decision-Making Approach

- Transitioning from a 3-tier approach: Classify endpoints by analysis
  - Tier 1: Events with a priori questions (report *P*-values regardless of having a stated hypothesis)
  - Tier 2: Events not identified a priori, and not “rare” (confidence intervals)
  - Tier 3: Rare events not identified a priori (descriptive statistics)

- To a 2-part approach: Classify endpoints by clinical interest
  - Part 1 (for learning): All events are summarized in the overall safety assessment with descriptive statistics and graphical displays (CIs may be provided but no inferential statistics are included)
  - Part 2 (for decision-making): Safety topics of interest are explored using more in-depth analyses and/or specific groupings of events that help to further characterize their occurrence (*P*-values are only provided for safety endpoints with explicit hypotheses)

PhUSE: AE Groupings in Safety (AEGiS)

- AEs that are too specific can result in underestimation of an event
- The PhUSE Safety Analytics working group is launching a new cross-disciplinary project team:
  - To develop points to consider when deciding whether to use a MedDRA-defined grouping of PTs versus creating a custom grouping
  - To provide recommendations on process/implementation
- Note: this project team will not be creating any custom groupings

- PhUSE/FDA Computational Science Symposium: 19-22 September
  - Plenary Session: FDA OND Public Review on Standard Tables and Figures, Standard Adverse Event Groupings and Queries for Evaluation of Biologic/New Drug Applications
  - Vaishali Popat, FDA

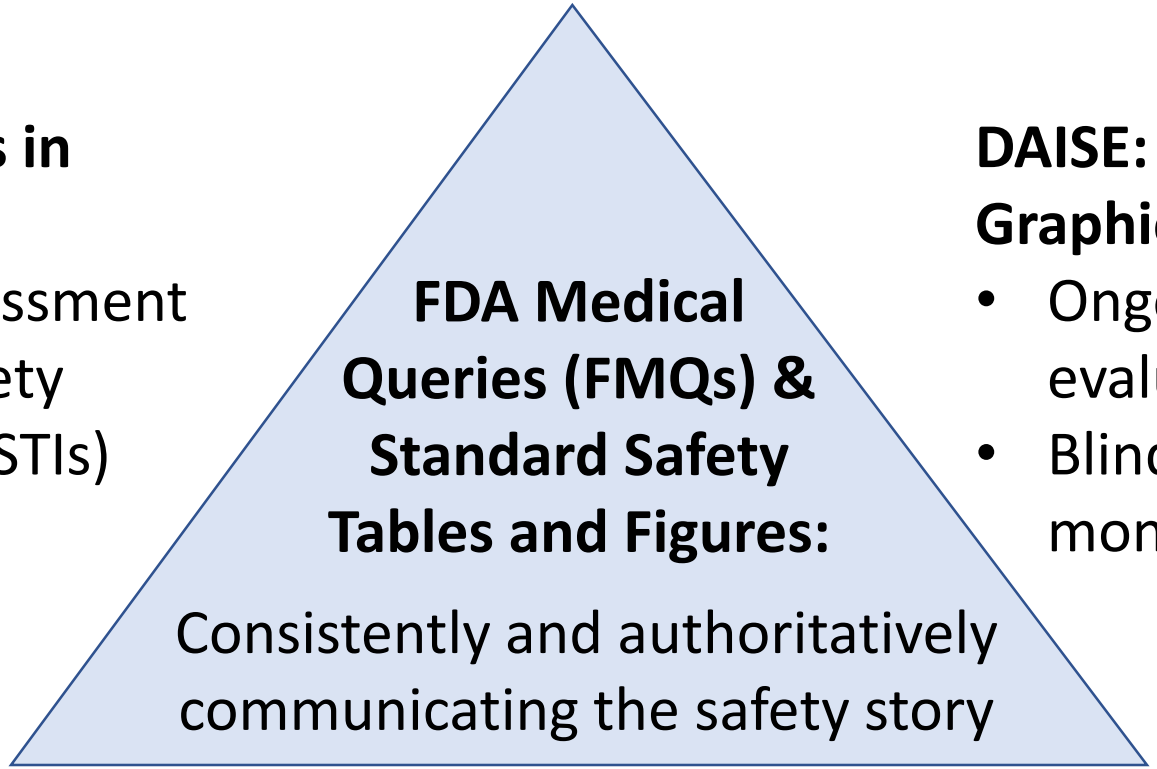
DAISE: Aggregate Safety Assessment Planning (ASAP)

- Proactive and systematic planning for product-level, ongoing aggregate safety assessments
  - Prioritization of safety topics of interest, pooling strategy, and characterization of emerging safety profile
  - Planning and execution for ongoing aggregate monitoring (including for blinded trials), focused on these topics
  - Preparation for regulatory filing activities and responses to regulatory queries
- Consistent and authoritative communication of the safety story in scientific evaluations and public disclosures

Reimagining a Safety Submission

PhUSE: AE Groupings in Safety (AEGiS):

- Overall safety assessment
- Assessment of safety topics of interest (STIs)



DAISE: Interactive Safety Graphics (ISG):

- Ongoing aggregate safety evaluation (OASE)
- Blinded safety monitoring procedures

DAISE: Aggregate Safety Assessment Planning (ASAP) process:

- Scientific evaluation of program-level safety data (Rolling ISS)
- Proactive safety assessments to enable effective risk management

John Tukey and Joe Heyse

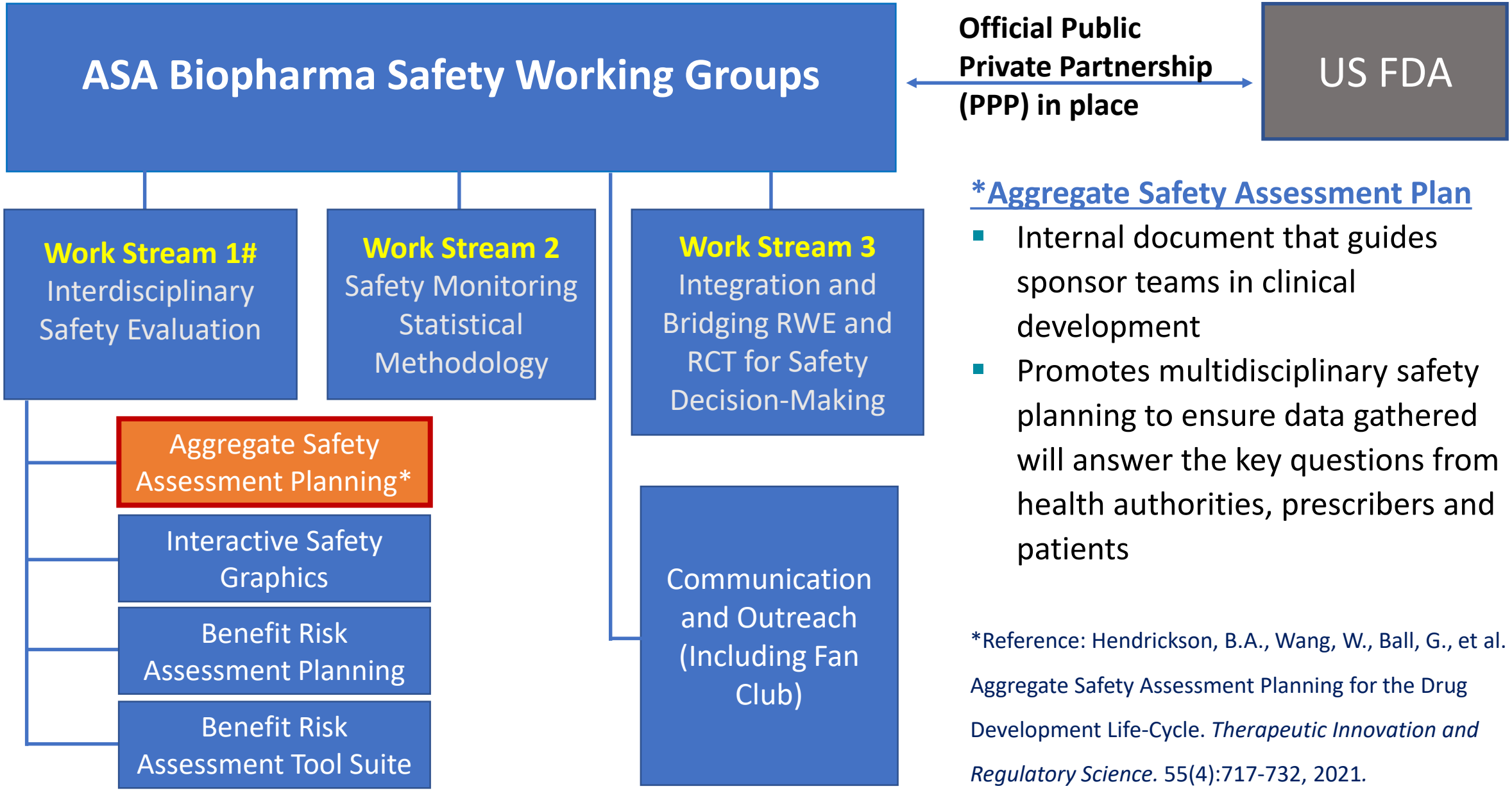
Weisberg H. Willful Ignorance: The Mismeasure of Uncertainty. Hoboken, NJ: John Wiley & Sons, Inc; 2014.

Aggregate Safety Assessment Planning (ASAP) in Clinical Development

Barbara Hendrickson, MD
Immunology Therapeutic Area Head
Pharmacovigilance and Patient Safety, AbbVie

Disclaimer Content

- The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to the Drug Information Association, Inc. (DIA), American Statistical Association (ASA), communities or affiliates, or any organization with which the presenter is employed or affiliated.



#Joint collaboration between DIA Communities and ASA Biopharma: DIA-ASA Interdisciplinary Safety Evaluation (DAISE) working group

*Aggregate Safety Assessment Plan

- Internal document that guides sponsor teams in clinical development
- Promotes multidisciplinary safety planning to ensure data gathered will answer the key questions from health authorities, prescribers and patients

*Reference: Hendrickson, B.A., Wang, W., Ball, G., et al. Aggregate Safety Assessment Planning for the Drug Development Life-Cycle. *Therapeutic Innovation and Regulatory Science*. 55(4):717-732, 2021.

Key Features of the Aggregate Safety Assessment Plan (ASAP)

- Promotes proactive safety planning, including specifying the safety topics of interest (STOI) and relevant event search criteria
- Supports systematic characterization of the emerging product safety profile
- Drives consistency in collection and assessment of the safety data across the program, including analysis conventions and data pooling approaches
- Describes ongoing signal detection and evaluation activities
- Facilitates earlier recognition of safety knowledge gaps
- Helps prepare for safety communications and regulatory submissions
  (serves as a foundation for the Integrated Summary of Safety Statistical Analysis Plan)

Safety Topics of Interest

Have the potential to impact the product's benefit:risk profile

- **Important Identified Risks**

(Sufficient clinical data to conclude a causal association with the product)

- **Important Potential Risks**
- **Other Safety Topics of Interest**

- Product clinical trial data
- Preclinical findings or reported risks of products of the same class
- Theoretical concerns based on the product's mechanism of action
- Traditional regulatory concerns (e.g. drug induced liver injury)
- Events of high interest based on epidemiology of the patient population

Safety Topics of Interest (STOI)	Basis for Inclusion	Identification of Events*	Use of event adjudication	Special data collection (form or study)	Relevant restrictions/risk minimiation#
Identified Risks					
Serious hypersensitivity reactions	Reports in clinical trials	Hypersensitivity Standardised MedDRA Query (SMQ) (Narrow)	External expert Adjudication (see Charter for details)	Supplemental event CRF (all studies): • SAEs and AEs leading to D/C	Exclusion criteria: History of anaphylactic reaction
Potential Risks					
Herpes zoster (HZ)	Possible increased risk for immunomodulatory products	????	????	Supplemental event CRF (all studies): • Dermatomal/Organ involvement • Event details; Vaccine history	Exclusion criteria: History of disseminated HZ
Other STOI					
A. Drug Induced Liver Injury	Traditional regulatory concern for all products	Drug related hepatic disorder – comprehensive (narrow)	None	Supplemental CRF (all studies) – SAEs, AEs leading to D/C, potential Hy's Law cases, ALT/AST>8xULN	Exclusion criteria: ALT/AST>2.5xULN; protocol specified discontinuation criteria

~e.g. Preferred Term (PT), specified PT grouping, HLT, SMQ Broad/Narrow. Laboratory, Vital sign or ECG Value outliers

e.g. protocol exclusion criteria limiting data on certain patient populations

Example of Herpes Zoster Events

In completing the Safety Topics of Interest Table:

SMT* realizes

- There is no SMQ for Herpes Zoster (HZ); the medical concept of which is reflected by multiple MedDRA Preferred Terms (PTs).
- SMT creates a PT Grouping with relevant PTs

Solution

- This PT grouping can be used across the program to identify HZ events
- SMT decides to include all investigator reported events without adjudication since HZ is often a visual diagnosis by a physician without confirmatory testing

ASAP Benefit

- **Uniform approach to identifying events across program**

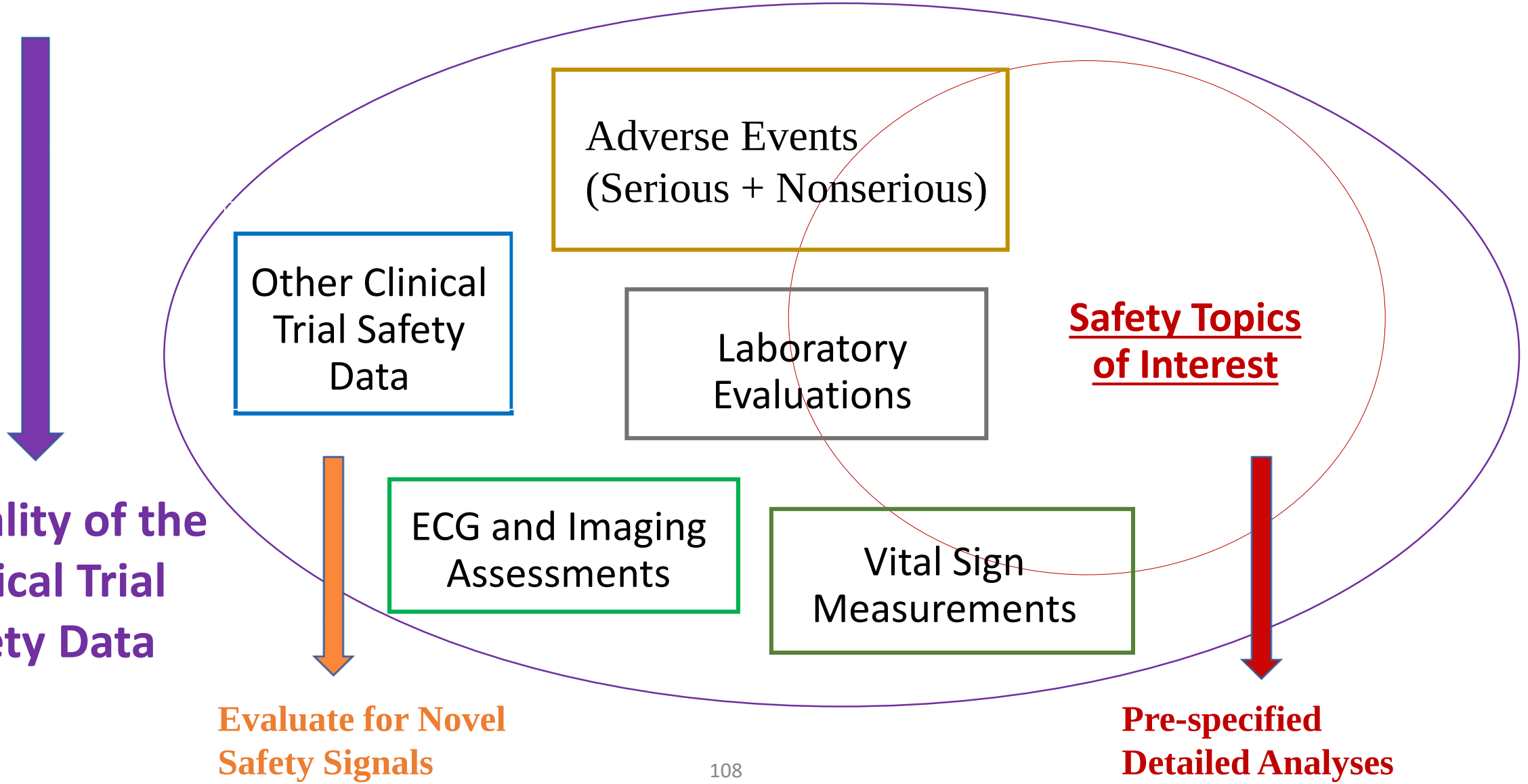
*SMT = Safety Management Team of the Clinical Trial Sponsor

Developing New MedDRA Queries to Assess Product Data

For signal detection purposes, search criteria ideally should be standardized across the clinical program.

- Define medical concept of interest
- Review relevant literature and published event queries, if any
- Specify inclusion/exclusion criteria (“guiding principles”) for PT grouping
- Confirm with subject matter experts
- Finalize Standardized PT grouping
- Assess impact of MedDRA upgrades on the PT grouping

ASAP SIGNAL DETECTION ACTIVITIES (Completed and Ongoing Clinical Trials)



ASAP Support of Adverse Reaction Labelling

- Delineated aggregate analyses help identify events for which there is evidence to conclude a causal association (adverse reaction)
- Facilitates further characterization of the identified and potential risks
- Specifies MedDRA PT groupings used to calculate event rates across treatment groups (*search criteria to identify events for rate calculations may become narrower as the nature of the adverse reaction is better understood*)
- Describes how the occurrence of expected adverse reactions will be monitored in future clinical trials (for example in novel patient populations) to determine if the rate is higher than noted in the current reference safety information

ASAP – Concluding Thoughts

- Guide for methodical product safety planning, data generation, risk assessment and communications, alignment on safety topics of interest
- Proactively developed by multidisciplinary Clinical Trial Sponsor SMTs
- Promotes systematic evaluation of the safety data from ongoing clinical trials and earlier signal detection
- Lays the foundation for the future integrated summary of safety, determination of the important identified risks and product adverse reactions
- Acknowledges important safety knowledge gaps to be addressed in future

Discussion Questions

1. Does your institution group adverse events? If so, what criteria do you use?
    a) What is the process of implementation and validation?
    b) Please share challenges and successes, and lessons learned.
2. What have been your challenges when including group and component terms in labeling?
3. What new approaches can help enhance querying of adverse events in clinical trials?
    a) Especially when PTs alone are not adequate?
    b) Other approaches to identify and characterize safety signals using AE datasets?

Break

We will be back momentarily.

The next session will begin at 2:40 p.m. (U.S. Eastern Time)

Overview of the Standard Safety Tables and Figures Integrated Guide

Vaishali Popat, Mat Soukup, Nhi Beasley, Veronica Pei

U.S. Food and Drug Administration

Standard Safety Tables and Figures (ST&F)

Vaishali Popat MD, MPH
Associate Director
Biomedical Informatics and Regulatory Review Science (BIRRS)
Office of New Drugs, FDA

Today's Presenters

Vaishali Popat, MD, MPH
Associate Director
Biomedical Informatics and Regulatory Review Science (BIRRS), Office of New Drugs

Mat Soukup, PhD
Deputy Director
Division of Biometrics VII, Office of Biostatistics

Nhi Beasley, Pharm.D
ADBMI for Office of Cardiology Nephrology, Hematology, and Endocrinology

Yang "Veronica" Pei, MD, MEd, MPH
ADBMI for Division of Gastroenterology (DG) and Division of Hepatology and Nutrition (DHN)

ADBMI = Associate Directors for Biomedical Informatics

Agenda

- Background
- Treatment-emergent Adverse Events
- Statistical Considerations in Adverse Event Analyses
- Standard Laboratory Analyses
- Drug-induced Liver Injury

Why Standard Safety Tables & Figures?

Inconsistent Standards

- Tables and figures not produced in a standard manner across Divisions/ Teams/Applicants.
- Significant variability in similar safety signal evaluation related tables and figures

A Collective Way Forward

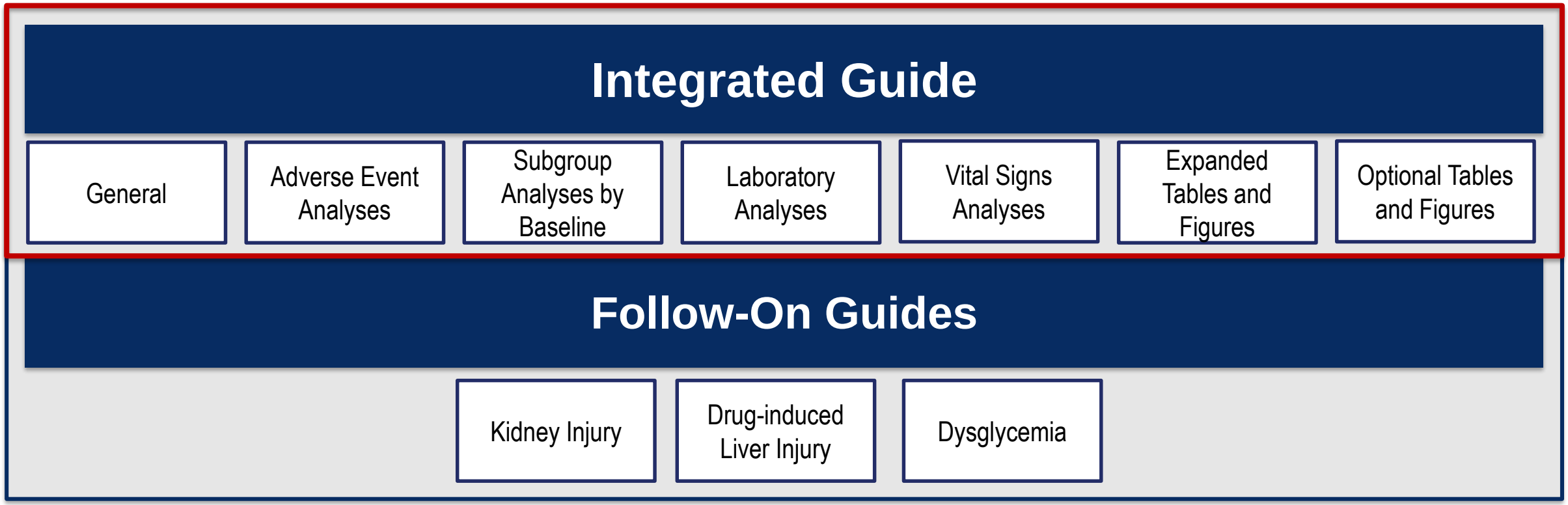
- Develop standard safety analyses in a consistent format to facilitate safety evaluation
- Create uniform data presentation & visualization that reflect formatting standards used in major medical journals

An OND Standard

- Launched standardized safety analyses
- Created a set of standard safety analyses considered important for premarket clinical safety evaluation
- Established formatting standards that create consistency in analyses produced

OND=Office of New Drugs

Standard Safety Tables & Figures Organization



Standard Safety Tables & Figures Integrated Guide: Components

Integrated Guide

General

- Clinical Trials Summary
- Demographic and Clinical Characteristics
- Patient Disposition
- Duration of Exposure

Adverse Event Analyses

- Overview of Adverse Events
- Deaths
- Serious Adverse Events
- Adverse Events Leading to Discontinuation
- FDA Medical Queries (FMQs)

Subgroup Analyses

- Overview of certain AEs or SAEs across demographic characteristics

Laboratory Analyses

- Analyses of Central Tendency
- Analyses of Abnormalities and Outliers
- DILI Screening subsection:
  - Missing Data Analysis
  - Potential Hy's Law Screening Plot

Vital Signs Analyses

- VS distribution by Treatment Group
- Baseline vs. Max/Min by Treatment Group
- Blood Pressure Post-Baseline Data

Expanded Tables and Figures

- Expanded AE Analyses
  - SAEs
  - TEAEs
- Expanded Laboratory Analyses
  - Change Over Time
  - Outlier Criteria
  - Last Value on Treatment

Optional Tables and Figures

- Optional AE Analyses
  - Exposure-Adjusted Analyses
  - Relatedness Analyses
  - Additional FMQ Tables
- Optional Laboratory and Vital Signs Analyses
  - Median and Interquartile Range Plots

Standardization of Data Presentation: Tables

Table 6. Overview of Adverse Events[1], Safety Population, Pooled Analyses[2]

Event	Drug Name Dosage X N=XXX n (%)	Drug Name Dosage Y N=XXX n (%)	Active Control N=XXX n (%)	Placebo N=XXX n (%)	Risk Difference (%) (95% CI)[3]
SAE	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SAEs with fatal outcome	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Life-threatening SAEs	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SAEs requiring hospitalization	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SAEs resulting in substantial disruption of normal life functions	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Congenital anomaly or birth defect	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Other	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
AE leading to permanent discontinuation of study drug	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
AE leading to dose modification of study drug	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
AE leading to interruption of study drug	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
AE leading to reduction of study drug	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
AE leading to dose delay of study drug	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Other	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Any AE[4]	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Severe	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Moderate	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Mild	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Note the order of the treatment columns: drug arms followed by active control, and placebo

Bolded column headers

Subtext is indented

10 pt. Arial font for all table text (including headers)

Only horizontal borders in the table for easier side by side comparisons

Footnotes provide important definitions and context

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

[1] Treatment-emergent AE defined as [definition]. MedDRA version X.

is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).

[4] Se[2] Duration = [e.g., X-week double-blind treatment period or, median and a range indicating pooled trial durations].

[3] Difference verity as assessed by the investigator

Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event

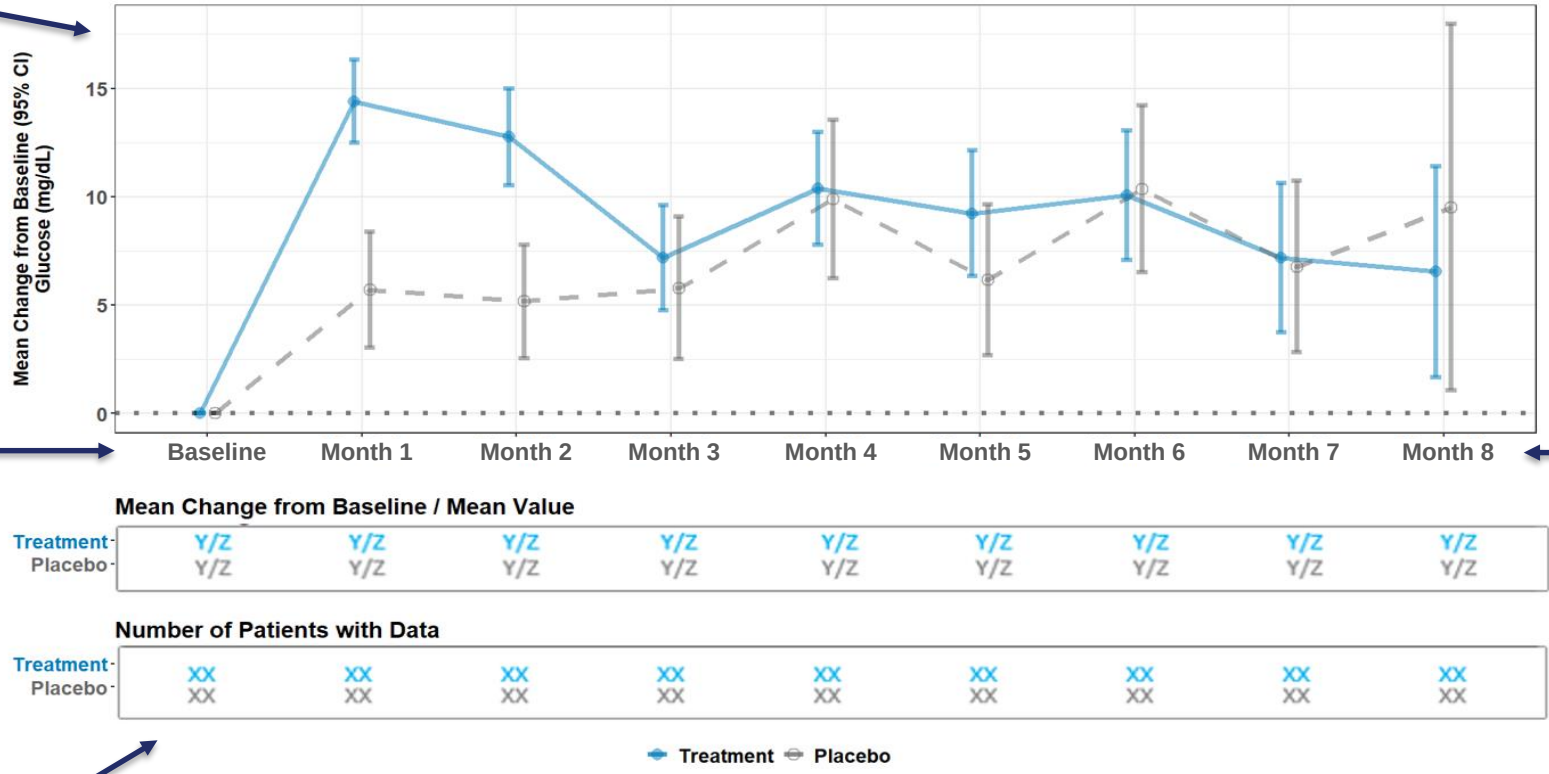
Standardization of Data Presentation: Figures

To ensure standardization, all generated figures follow the below formatting principles.

Figure X. Mean Laboratory (Chemistry) Data Change from Baseline Over Time by Treatment Arm, Safety Population, Trial X

The y-axis is scaled appropriately

Colors, symbol, and line types can be used to distinguish between series in a graph.



When the x-axis is used to represent time, labeled by **protocol specified visit** schedule

When displaying data over time, total "n's" are presented per time period at the bottom of the figure

Standardized color selection and consistency across trials.

Adverse Event Analyses

- Provides analysis of AEs including:
  - Serious AEs (SAEs)
  - AEs leading to discontinuation
  - FDA Medical Queries (FMQs)
  - AEs of special interest (AESIs)
- All AE tables and figures present treatment-emergent adverse events (TEAEs) as a default
  - Consider the definition of TEAE that occur on-study (OSAE) vs. on-treatment (OTAE)

Overview of Adverse Events

SAE determination includes all AEs that met individual SAE criteria

Table 6. Overview of Adverse Events[1], Safety Population, Pooled Analyses[2]

Event	Drug Name Dosage X N=XXX n (%)	Drug Name Dosage Y N=XXX n (%)	Active Control N=XXX n (%)	Placebo N=XXX n (%)	Risk Difference (%) (95% CI)[3]
SAE	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SAEs with fatal outcome	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Life-threatening SAEs	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SAEs requiring hospitalization	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SAEs resulting in substantial disruption of normal life functions	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Congenital anomaly or birth defect	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Other	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
AE leading to permanent discontinuation of study drug	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
AE leading to dose modification of study drug	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
AE leading to interruption of study drug	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
AE leading to reduction of study drug	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
AE leading to dose delay of study drug	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Other	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Any AE[4]	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Severe	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Moderate	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Mild	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

TEAE definition and MedDRA version is also included in footnotes.

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

[1] Treatment-emergent AE defined as [definition]. MedDRA version X.

[2] Duration = [e.g., X-week double-blind treatment period or, median and a range indicating pooled trial durations].

[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo). [4] Severity as assessed by the investigator

Serious Adverse Events - FMQs

Adverse Event Tables also include FDA Medical Queries (FMQs) arranged by System Organ Class (SOC). FMQs are standardized groupings of adverse event terms developed by FDA reviewers.

In displays of FMQ data, tables are arranged by SOC, and within the SOC if there are multiple FMQs, FMQs are ordered by decreasing RD.

Table 10. Patients with Serious Adverse Events[1] by SOC and FDA Medical Query (Narrow), Safety Population, Pooled Analyses[2]

System Organ Class[4] FMQ (Narrow)	Drug Name Dosage X N=XXX n (%)	Drug Name Dosage Y N=XXX n (%)	Active Control N=XXX n (%)	Placebo N=XXX n (%)	Risk Difference (%) (95% CI)[3]
SOC1					
FMQ1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
SOC2					
FMQ3	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ4	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source and/or Software tools used]

[1] Defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].

[3] Difference is shown between [treatment arms]. (e.g., Difference is shown between Drug Name Dosage X vs. Placebo)

[4] Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Abbreviations: CI, confidence interval; FMQ, FDA Medical Query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, System Organ Class

Expanded section: FMQs with PT and Drill Down Tables

Table 34. Patients With Serious Adverse Events[1] by System Organ Class, FDA Medical Query (Narrow) and Preferred Term, Safety Population, Pooled Analysis (or Trial X)[2]

System Organ Class[5] FMQ (Narrow)[3]	Drug Name Dosage X N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[4,6]
SOC1			
FMQ1	n (%)	n (%)	X (Y , Z)
PT1	n (%)	n (%)	X (Y , Z)
PT2	n (%)	n (%)	X (Y , Z)
FMQ2	n (%)	n (%)	X (Y , Z)
PT1	n (%)	n (%)	X (Y , Z)
PT2	n (%)	n (%)	X (Y , Z)
SOC2			
FMQ1	n (%)	n (%)	X (Y , Z)
PT1	n (%)	n (%)	X (Y , Z)
PT2	n (%)	n (%)	X (Y , Z)
FMQ2	n (%)	n (%)	X (Y , Z)
PT1	n (%)	n (%)	X (Y , Z)
PT2	n (%)	n (%)	X (Y , Z)

Optional Tables: FMQs with PT and Drill Down Tables

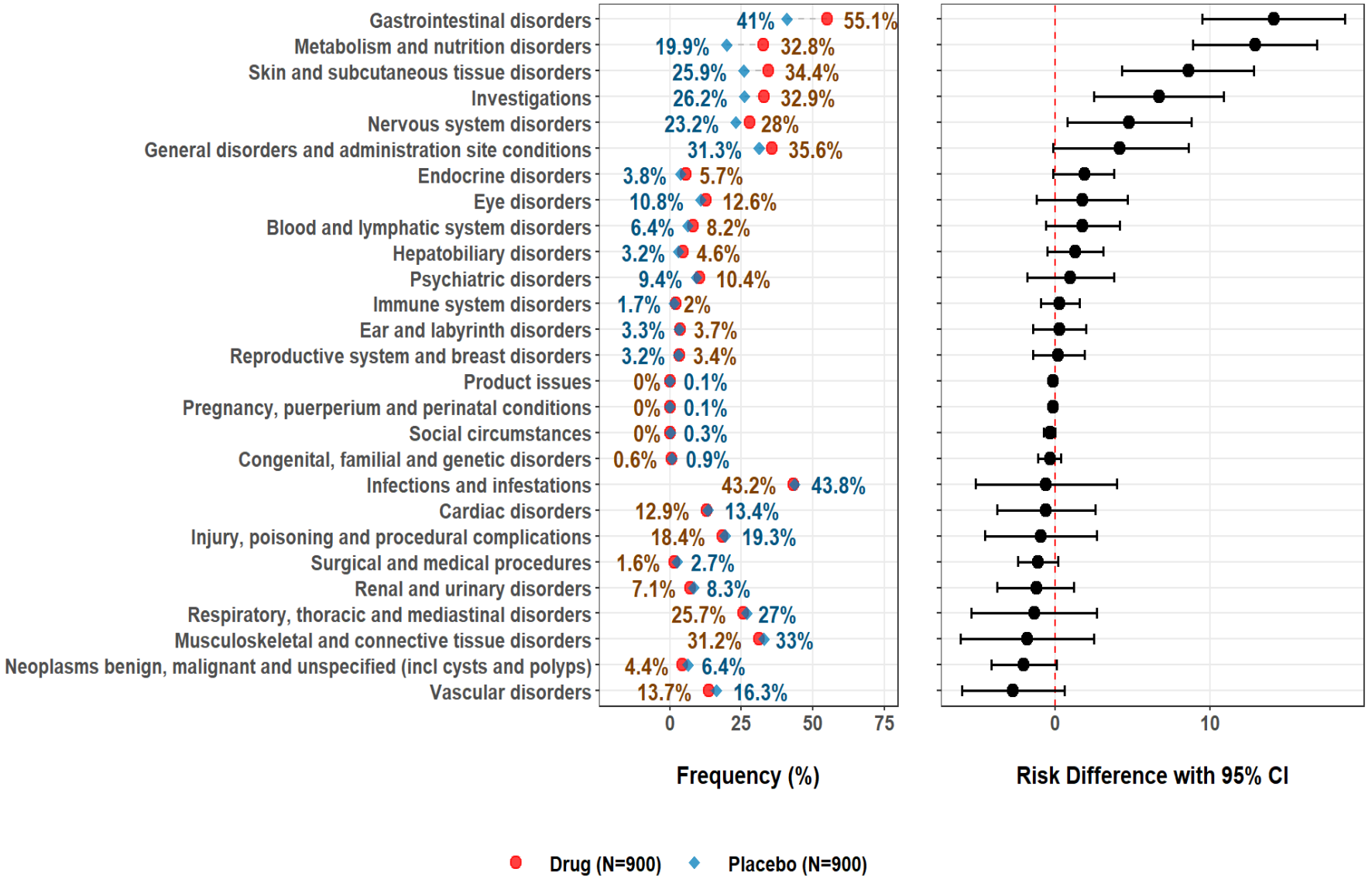
Table 56. Selected Narrow FDA Medical Queries[1], Safety Population, Pooled Analyses (or Trial X)

FMQ Patient ID	Age	PT	Verbatim Term	Serious	AE Discontinuation	Severity	Study Day of Onset	Action Taken	Outcome
FMQ1 (Drug)									
Patient ID1									
Patient ID2									
FMQ1 (Control)									
Patient ID1									
Patient ID2									
FMQ2 (Drug)									
Patient ID1									
Patient ID2									
FMQ2 (Control)									
Patient ID1									
Patient ID2									

Source: [include Applicant source, datasets and/or software tools used].
[1] Treatment-emergent AE defined as [definition].
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
Abbreviations: AE, adverse event; FMQ; FDA Medical Query; PT, preferred term

Treatment Emergent Adverse Events (TEAE)

Figure 5. Patients With Adverse Events[1] by System Organ Class, Safety Population, Pooled Analyses



Treatment Emergent Adverse Events

Table X. Patients with Common Adverse Events Occurring at ≥ X% Frequency, Safety Population, Pooled Analyses

Preferred Term[3]	Drug Name Dosage X N=XXX n (%)	Drug Name Dosage Y N=XXX n (%)	Active Control N=XXX n (%)	Placebo N=XXX n (%)	Risk Difference (%) (95% CI)[4,5]
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT3	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Table X. Patients With Adverse Events by System Organ Class and FDA Medical Query, Safety Population, Pooled Analyses

	Narrow FMQs				Broad FMQs			
System Organ Class[4] FMQ	Drug Name N=XXX n (%)	Active Control N=XXX n (%)	Placebo N=XXX n (%)	Risk Difference (%) (95% CI)[3]	Drug Name N=XXX n (%)	Active Control N=XXX n (%)	Placebo N=XXX n (%)	Risk Difference (%) (95% CI)[3]
SOC1								
FMQ1	n (%)	n (%)	n (%)	X (Y, Z)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ2	n (%)	n (%)	n (%)	X (Y, Z)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ3	n (%)	n (%)	n (%)	X (Y, Z)	n (%)	n (%)	n (%)	X (Y, Z)
SOC2								
FMQ1	n (%)	n (%)	n (%)	X (Y, Z)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ2	n (%)	n (%)	n (%)	X (Y, Z)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ3	n (%)	n (%)	n (%)	X (Y, Z)	n (%)	n (%)	n (%)	X (Y, Z)

Adverse Events of Special Interest (AESI)

The information included may vary depending on the AESI and may combine observations across different datasets to provide a complete picture of the AESI (e.g., laboratory and adverse event datasets).

Table 20. Adverse Events of Special Interest Assessment, Safety Population, Pooled Analysis (or Trial X)

AESI Assessment	Drug Name Dosage X N=XXX n (%)	Drug Name Dosage Y N=XXX n (%)	Active Control N=XXX n (%)	Placebo N=XXX n (%)	Risk Difference (%) (95% CI)[2]
AE Grouping Related to AESI	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
PT1	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
PT2	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Maximum severity					
Severe	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Moderate	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Mild	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Serious	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
Deaths	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Resulting in discontinuation	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
Relatedness	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
Laboratory Assessment[5]	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**

Treatment Emergent AE
On Study vs. On-treatment AE

Treatment-emergent Adverse Events: Key Issues and Considerations

Safety analyses focus on treatment-emergent adverse event (TEAE).

Definition: Occurrence of an AE or worsening of an existing AE after the first dose of investigational product (IP) administration.

There are two approaches to TEAE analyses:

- On-study analysis
  - Occurrence of an AE or worsening of an existing AE after the first dose of investigational product (IP) administration without a cut-off date.
- On-treatment analysis
  - Occurrence of AEs within a specified time-frame after study drug discontinuation, so it includes a cut-off date, beyond which AEs are not included in the analyses.

Treatment Emergent AE: Key Issues and Considerations

- Start day: On-study analysis and On-treatment analysis
  - AEs reported on day of start of investigational product (IP) administration
  - Any adverse event that starts before the IP administration and gets worse in severity or relatedness after the IP administration, is included in TEAE analysis.
  - If start date is missing (which may suggest poor data quality), then the AE is included in the TEAE analysis

- End-date: only applicable to on-treatment AE analysis
  - There are several approaches to determine the cut-off date.
  - Most Applicants use 28 or 30 days as cut-off dates.
  - However, for drugs with long half-life, the cut-off date should be longer – for example, a monoclonal with a 14-day half-life, should include a longer cutoff (e.g., 42-70 days).

Clinical considerations for when to use On-Study analysis vs. On-Treatment analysis?

On- Study Approach

If there is an AE that occurs only after a lag period

- valvulopathies, cataracts, fractures from drug-induced osteoporosis
- if study drug discontinuation is linked to the risk or occurrence of the event.

Limitation

- If there are many patients who have discontinued study drug and AE collection has continued, this may "dilute" finding of pharmacologically-related AEs.
- Patients off of study drug may be started on other therapies; AEs associated with these therapies will then be "swept in" to the AE analysis

On-Treatment Approach

When events that are pharmacodynamic responses to drug

- bleeding in study of anticoagulant drug
- falls for a drug associated with sedation or orthostatic hypotension.

Limitation

- If there is imbalanced study drug discontinuation (especially if discontinuation that may result in informative censoring), this approach may lead to inappropriate comparisons.

When there is limited study drug discontinuation, particularly in trials that are not of long duration (e.g.,<6 months), these two analysis approaches (i.e., using a cut-off date vs "all AEs") usually have minimal differences.

Conclusion

- Reliable evaluation requires protocol design and conduct approaches to ensure comprehensive follow-up of all randomized subjects for events through end of trial. Need to have data for all AEs!
- It is important to identify in the SAP what analyses were conducted
- In most cases, on-study approach for TEAE analysis is appropriate. If needed, both analyses can be provided
- Alternatively, if the approach using a cut-off date (e.g., AEs within 30 days) is the primary analysis, presenting a report of the number of AEs not included is helpful

Statistical Considerations in Adverse Event Analyses

Mat Soukup, PhD
Deputy Director
Division of Biometrics VII, Office of Biostatistics

Presentation Focus

- Statistical considerations that move towards tailored, statistically appropriate analyses of adverse event data
- Integrated Guide is important step to moving towards such a safety assessment
  - Some considerations presented today go beyond methods in the Integrated Guide

Example AE Table

Patients with Adverse Events by MedDRA System Organ Class and Preferred Term, Pooled Analysis

System Organ Class Preferred Term	**Drug** **N = XXX**	**Control** **N = XXX**	**Contrast (95% CI)**
SOC 1			
PT1			
PT2			
PT3			
SOC 2			
PT1			
PT2			
PT3			

General Notes on Safety Analysis

- Analysis approach for a specified summary measure (within-arm and between-arm) should align with trial design(s) and any other factor (e.g. extent of dropout)
- Analysis approach should align with analysis purpose (e.g. signal detection vs. signal refinement)
- Collaboration of clinicians, data scientists, and statisticians critical

Example AE Table

Patients with Adverse Events by MedDRA System Organ Class and Preferred Term

System Organ Class Preferred Term	**Drug** **N = XXX**	**Control** **N = XXX**
SOC 1	n (X.X)	n (X.X)
PT1	n (X.X)	n (X.X)
PT2	n (X.X)	n (X.X)
PT3	n (X.X)	n (X.X)
SOC 2	n (X.X)	n (X.X)
PT1	n (X.X)	n (X.X)
PT2	n (X.X)	n (X.X)
PT3	n (X.X)	n (X.X)

Recommendation: Provide an appropriate within-arm summary measure of the risk

Typical Within-arm Summary Measures

- Cumulative incidence proportion
  - Measures the proportion of the population that experience at least one event in a given time period
  - Example: cumulative incidence of major bleed within 1 year of drug exposure is 0.02 (i.e., 2%)
- Incidence rate*
  - Measures the number of incidence (first) events in the population per unit of person time at-risk
  - Example: Incidence rate of serious infections in the drug population is 5 events per 100 PY

* Integrated Guide refers to this as exposure adjusted incidence rate

Cumulative Incidence Considerations

- Cumulative incidence in given period (e.g., 1 year) focuses on snapshot of risk through single time point
  - May not be sensitive to differences at early or late time points
  - Can look at incidence over time to help address this (e.g., use Kaplan-Meier plots)
- Beware of crude proportions (i.e. n/N) to estimate cumulative incidence
  - Not appropriate when subjects are followed for different lengths of time (e.g. time-to-event trials); reliable estimation in such settings requires more complex methods (e.g. Aalen-Johansen estimator)

Incidence Rate Considerations

- Incidence rate interpreted easily only under assumption of constant event rate over time
  - Assumption likely plausible in trials with relatively short duration
- Estimation by ratio of number of incident events over the total at-risk time for the event in the population is reliable whether subjects are followed for the same or different lengths of time

Example AE Table

Patients with Adverse Events by MedDRA System Organ Class and Preferred Term

System Organ Class Preferred Term	**Drug** **N = XXX**	**Control** **N = XXX**	**Contrast**
SOC 1	n (X.X)	n (X.X)	X.X
PT1	n (X.X)	n	
PT2	n (X.X)	n	
PT3	n (X.X)	n	
SOC 2	n (X.X)	n	
PT1	n (X.X)	n (X.X)	X.X
PT2	n (X.X)	n (X.X)	X.X
PT3	n (X.X)	n (X.X)	X.X

Recommendation: Include a contrast measure to provide a comparative summary between drug and control

Between-Arm Comparisons of Risk

- **Concept**: Provide a contrast of the within-arm summary measures of risk to provide a comparative estimate of the risk of two treatment arms
  - Contrast is either a difference or ratio of the within-arm treatment effects
- In randomized trials, the comparison can provide an appropriate causal estimate of the risk of treating with the investigational drug product

Between-Arm Comparisons of Risk

- Relative metrics (i.e. ratios)
  - Examples: relative risk (cumulative incidence ratio), incidence rate ratio, odds ratio, hazard ratio
  - Reasons to use: Mathematical reasons (e.g., better precision) and treatment effects tend to be more stable on relative scales across populations with different background risks
- Absolute difference
  - Examples: risk difference (cumulative incidence difference; also known as attributable risk), incidence rate difference
  - Most meaningful for evaluating public health impact and benefit-risk

Importance of Presenting Key Results on Absolute Difference Scale (1)

- Relative to control
  - Drug X prevents hip fracture
    - Relative risk=0.5
  - Drug X causes heart attacks
    - Relative risk=2.0
- Do the benefits outweigh the risks?

Importance of Presenting Key Results on Absolute Difference Scale (2)

- Relative to control
  - Drug X prevents hip fracture
    - IR (Control vs. Drug X) = 40 vs 20 fractures per 1000 PY
    - IRD = 20 fractures prevented per 1000 PY
  - Drug X causes heart attacks
    - IR (Control vs Drug X) = 1 vs 2 heart attacks per 1000 PY
    - IRD = 1 additional heart attacks per 1000 PY
- Do the benefits outweigh the risks?

IR = incidence rate, IRD = incidence rate difference

Example AE Table

Patients with Adverse Events by MedDRA System Organ Class and Preferred Term

System Organ Class Preferred Term	Drug N = XXX	Control N = XXX	Contrast (95% CI)
SOC 1	n (X.X)	n (X.X)	X.X (X.X, X.X)
PT1	n (X.X)	n (X.X)	X.X (X.X, X.X)
PT2	n (X.X)	n	
PT3	n (X.X)	n	
SOC 2	n (X.X)	n	
PT1	n (X.X)	n (X.X)	X.X (X.X, X.X)
PT2	n (X.X)	n (X.X)	X.X (X.X, X.X)
PT3	n (X.X)	n (X.X)	X.X (X.X, X.X)

Recommendation: Include statistical uncertainty for comparative assessments

Importance of Comparisons and Uncertainty

- Risk of MI: 4% on drug versus 2% on control
  - RD: 2%
  - What do you conclude?

Importance of Comparisons and Uncertainty

- Risk of MI: 4% on drug versus 2% on control
  - RD: 2%
  - What do you conclude?
- Risk of MI: 4% on drug versus 2% on control
  - RD (95% CI): 2% **(-6%, 10%**)
  - What do you conclude?

Importance of Comparisons and Uncertainty

- Risk of MI: 4% on drug versus 2% on control
  - RD: 2%
  - What do you conclude?
- Risk of MI: 4% on drug versus 2% on control
  - RD (95% CI): 2% **(-6%, 10%**)
  - What do you conclude?
- Risk of MI: 4% on drug versus 2% on control
  - RD (95% CI): 2% (**1.5%, 2.5%)**
  - What do you conclude?

Example AE Table

Patients with Adverse Events by MedDRA System Organ Class and Preferred Term, **Pooled Analysis**

System Organ Class Preferred Term	Drug N = XXX	Control N = XXX	Contrast (95% CI)
SOC 1	n (X.X)	n (X.X)	X.X (X.X, X.X)
PT1	n (X.X)		
PT2	n (X.X)		
PT3	n (X.X)		
SOC 2	n (X.X)	n (X.X)	X.X (X.X, X.X)
PT1	n (X.X)	n (X.X)	X.X (X.X, X.X)
PT2	n (X.X)	n (X.X)	X.X (X.X, X.X)
PT3	n (X.X)	n (X.X)	X.X (X.X, X.X)

Recommendation: Ensure appropriate integrated analysis (i.e. stratify analysis by trial)

Appropriate Integrated Analyses

- For a comparison of interest (e.g., drug vs. placebo), typically analysis 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 extension data with only drug arm) subject to confounding and bias
- Stratify analyses by trial
  - **CAUTION!** Unstratified analyses of multiple trials may be subject to confounding (see next slide)
  - **Stratified analyses are always appropriate**

Simpson's Paradox and Need to Stratify

Trial	Drug	Control
1	8/100 (8%)	4/100 (4%)
2	10/200 (5%)	8/200 (4%)
3	75/250 (30%)	130/500 (26%)
Proportion from crude pooling	**16.9%**	**17.8%**
Relative risk (95% CI) based on crude pooling	**0.95 (0.75, 1.21)**	

What do you conclude?

Simpson's Paradox and Need to Stratify

Trial	Drug	Control
1	8/100 (8%)	4/100 (4%)
2	10/200 (5%)	8/200 (4%)
3	75/250 (30%)	130/500 (26%)
Proportion from crude pooling	16.9%	17.8%
Study-size adjusted percentage	**19.3%**	**16.2%**
Relative risk (95% CI) based on crude pooling	0.95 (0.75, 1.21)	
Relative risk (95% CI) based on stratified analysis	**1.18 (0.94, 1.49)**	

What do you conclude?

Example AE Table

Patients with Adverse Events by MedDRA System Organ Class and Preferred Term, Pooled Analysis

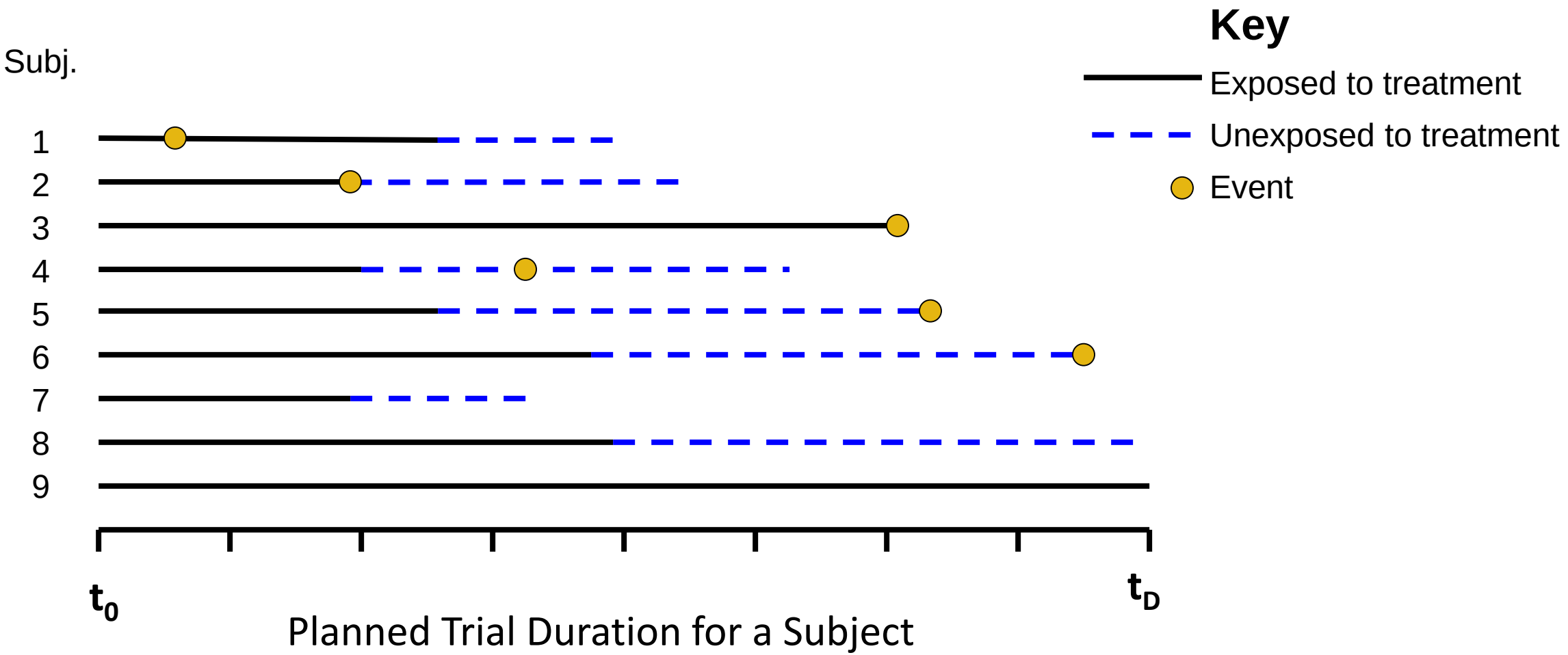
System Organ Class Preferred Term	Drug N = XXX	Control N = XXX	Contrast (95% CI)
SOC 1	n (X.X)	n (X.X)	X.X (X.X, X.X)
PT1	n (X.X)		
PT2	n (X.X)		
PT3	n (X.X)		
SOC 2	n (X.X)		
PT1	n (X.X)	n (X.X)	X.X (X.X, X.X)
PT2	n (X.X)	n (X.X)	X.X (X.X, X.X)
PT3	n (X.X)	n (X.X)	X.X (X.X, X.X)

Recommendation: Ensure analyses appropriately address time at risk (i.e. on-treatment vs. on-study analyses)

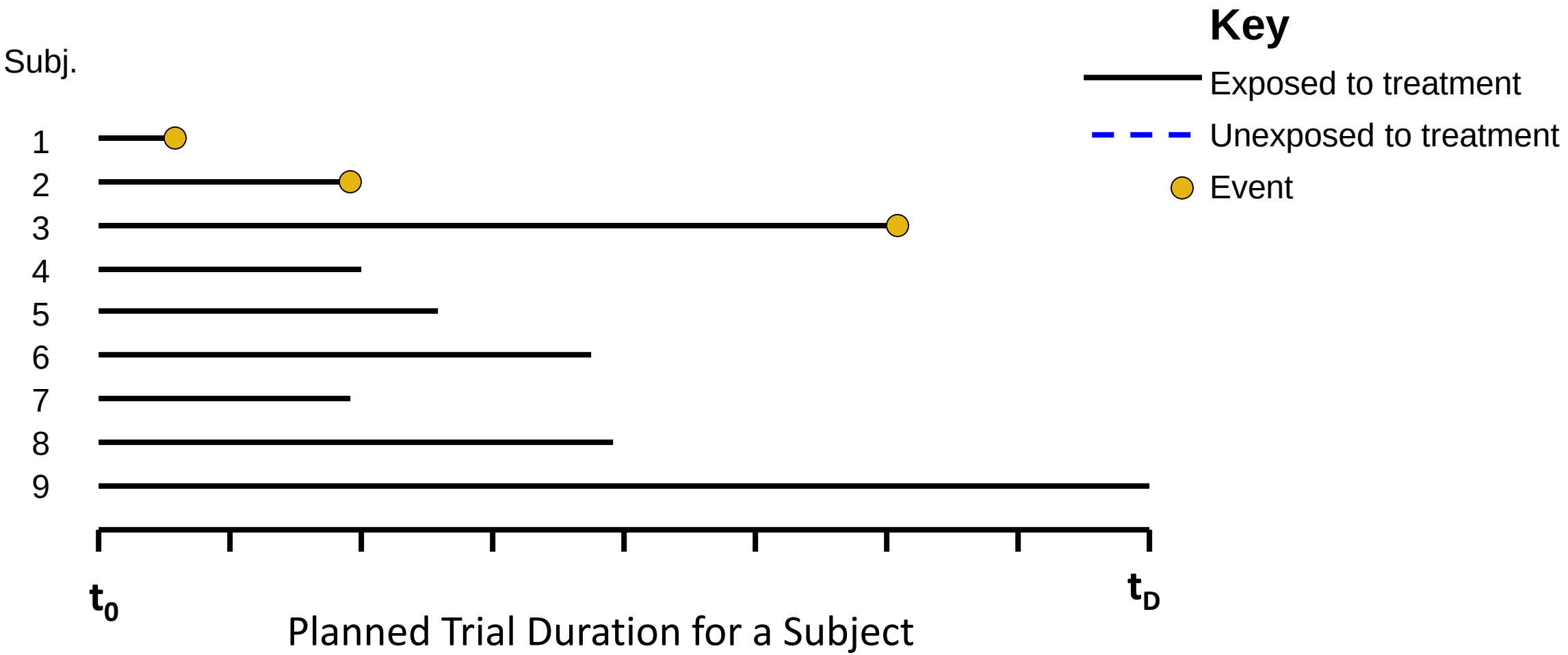
Event Ascertainment

- Ascertainment window: defines the period of time for which a subject is at risk of the event
  - Captures time at risk for an individual subject and whether or not an event occurred within the ascertainment window
- Analyses of safety typically considers two ascertainment windows
  - On-treatment (OT) analysis
    - Typically defined as time from randomization to treatment discontinuation plus some period of time thereafter (e.g., OT + 7 days)
  - On-study analysis
    - Typically defined as time from randomization until trial discontinuation – includes events that occur while on treatment and off treatment

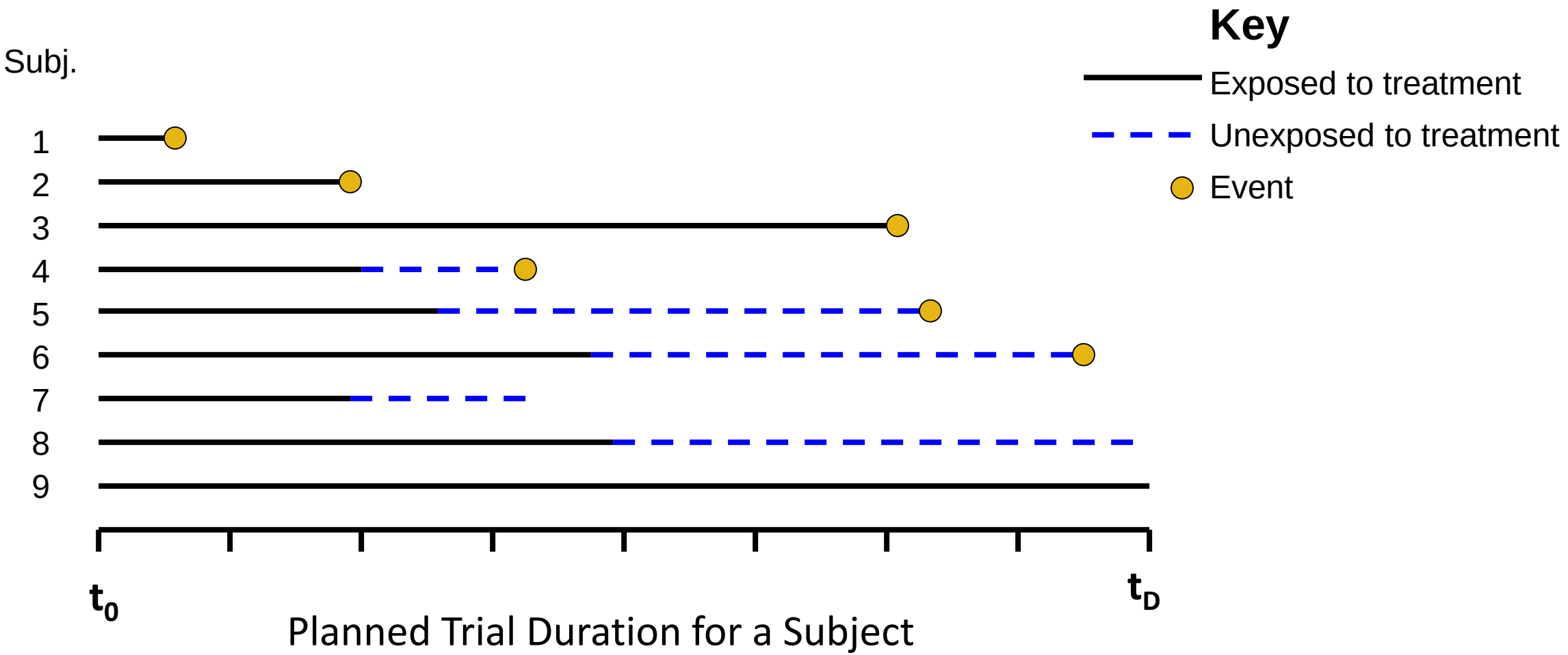
Illustration



On-Treatment Analysis of Incidence



On-Study Analysis of Incidence



On-Treatment Analysis Considerations

- Cutoff date may depend on drug (e.g., half-life)
- May be more useful for events thought to be pharmacodynamic responses (e.g., bleeding for anticoagulant drug)
- **Major limitation** is that comparison breaks integrity of randomization and may be subject to bias
  - May be differences between arms in extent of treatment discontinuation (can be “corrected” with incidence rates or Kaplan-Meier estimates)
  - May be differences between arms in types of patients who stop treatment, e.g., more susceptible patients may discontinue drug (cannot be easily “corrected” in analyses)

On-Study Analysis Considerations

- Suitable for events that may have long latency period (e.g., fractures)
- Reliable evaluation requires design and conduct approaches to ensure comprehensive follow-up of all randomized subjects for events through end of trial
- Preserves integrity of randomization
  - Can reflect real-world use under conditions: (1) control represents a valid treatment option and (2) appropriate rescue therapy
- **Limitation**: May be less sensitive to detecting true adverse effects, especially in case of a lot of treatment discontinuation or use of rescue medication that can increase risk

Example AE Table

Patients with Adverse Events by MedDRA System Organ Class and Preferred Term, Pooled Analysis

System Organ Class Preferred Term	Drug N = XXX	Control N = XXX	Contrast (95% CI)
SOC 1	n (X.X)	n (X.X)	X.X (X.X, X.X)
PT1	n		
PT2	n		
PT3	n		
SOC 2	n		
PT1	n		
PT2	n (X.X)	n (X.X)	X.X (X.X, X.X)
PT3	n (X.X)	n (X.X)	X.X (X.X, X.X)

In Summary: Calculations of all the "X.X" values in the table need to be tailored to the trial set and collaboration among clinicians, statisticians, and data scientists are instrumental to doing this correctly.

Acknowledgements

- Greg Levin, Associate Director for Statistical Science and Policy, CDER/OTS/OB
- Office of Biostatistics Safety and Benefit-Risk Working Group
  - Sue-Jane Wang, Susan Duke, Cesar Torres, Therri Usher, Sirisha Mushti, Lisa Rodriguez, Bo Li, Taehyun (Ryan) Jung, Sai Dharmarajan, Matilde Kam

Standard Laboratory Analyses

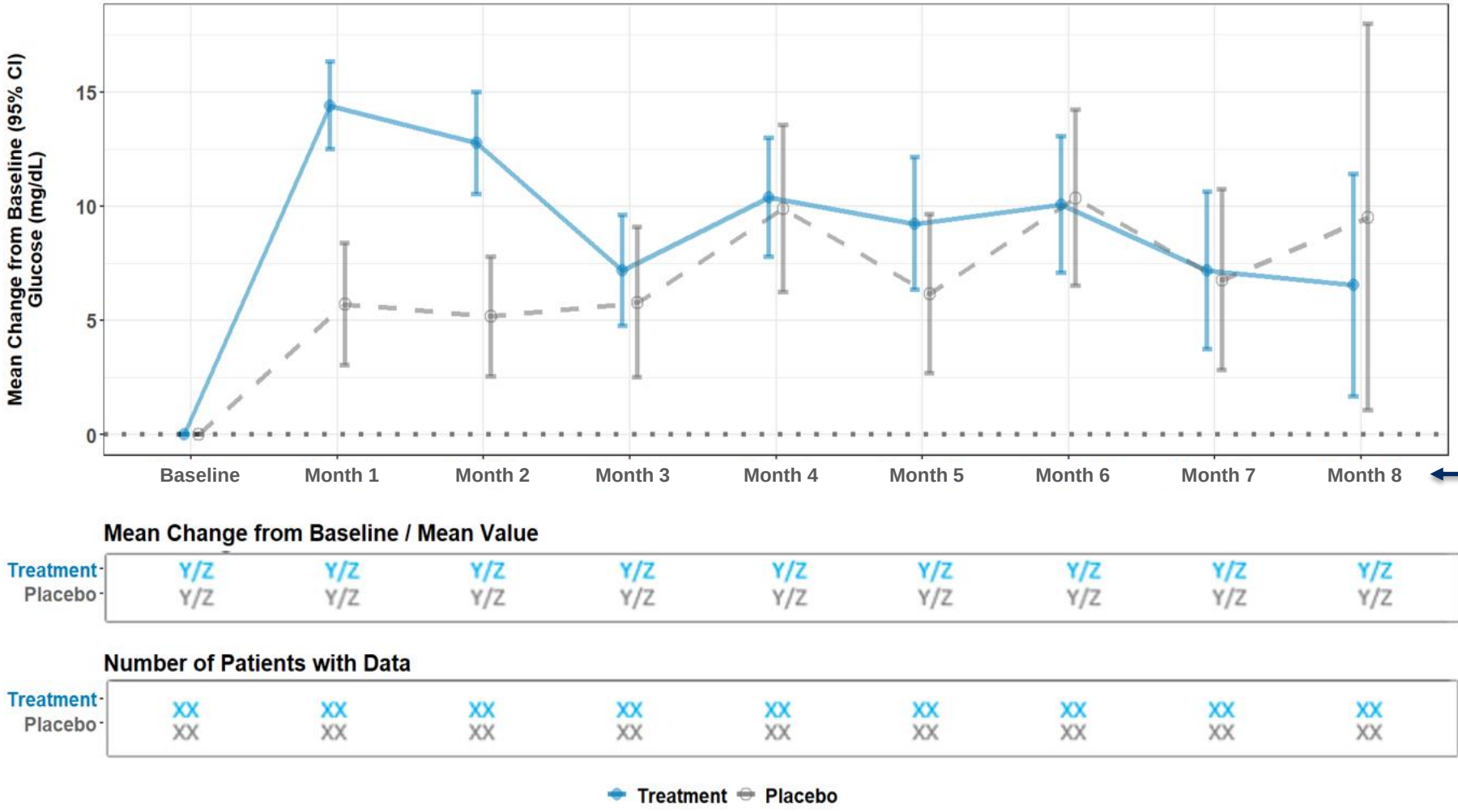
B. Nhi Beasley, PharmD
Associate Directors for Biomedical Informatics
Biomedical Informatics and Regulatory Review Science (BIRRS)

Standard Laboratory Analyses

- Provides an analysis of routine laboratory parameters including:
  - Missing and existing data analyses
  - Measures of central tendency
  - Outlier analyses
- Additional analyses can be found in the Standard Expanded Safety Tables and Figures section (referred to as Expanded Section)
  - Specific outlier criteria and analyses
  - Last value on-treatment analyses
  - Alternate tabulations and visualizations

Laboratory Analyses Over Time

Figure X. Mean Laboratory (Chemistry) Data Change from Baseline Over Time by Treatment Arm, Safety Population, Trial X



X-axis shows scheduled visits per protocol

Mean change from baseline and mean value

Figure truncated when less than 5-10% of subjects with data remain in trial

Laboratory Analyses Over Time – Expanded Section

95% CI

Risk difference 95% CI

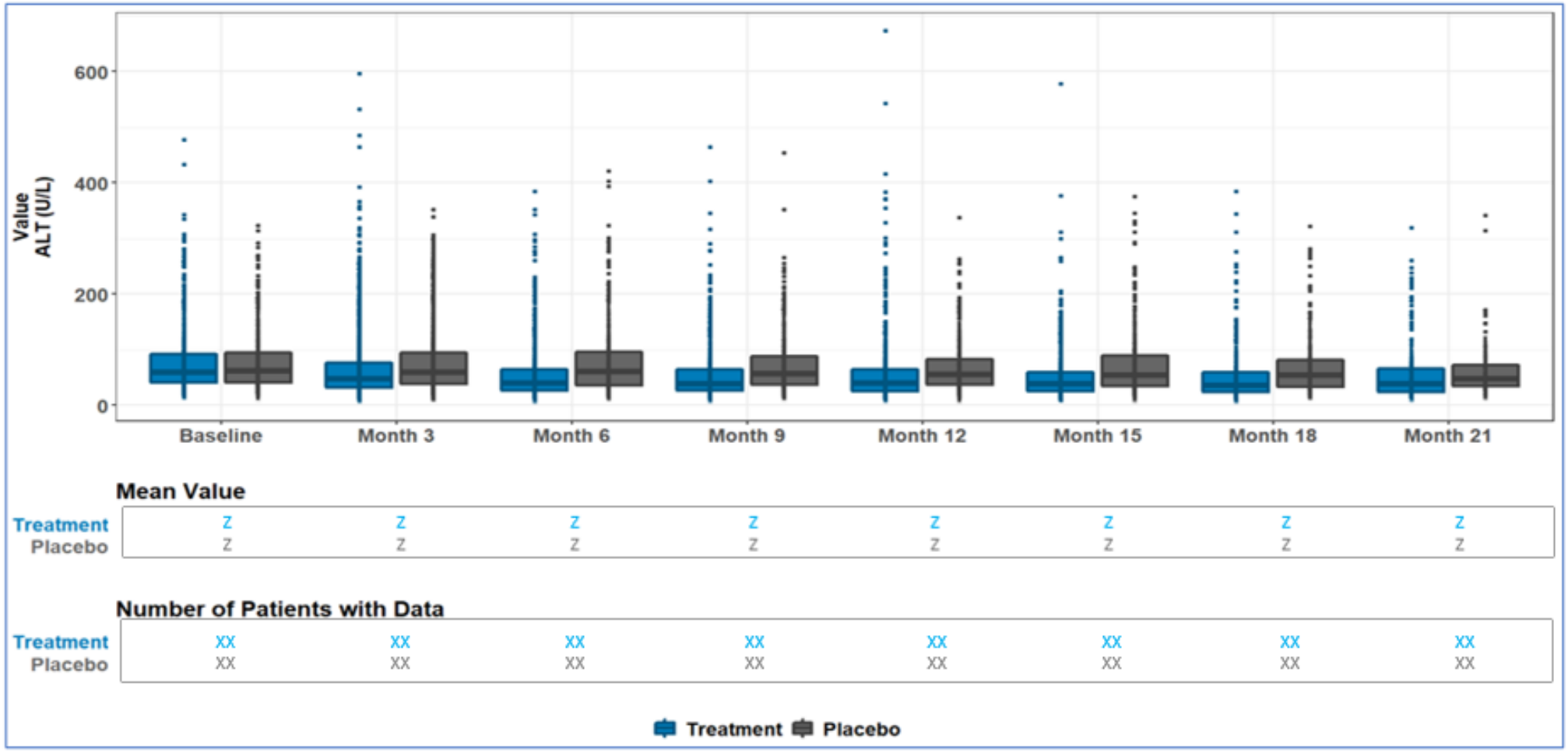
Table 45. Mean Change From Baseline for General Chemistry Data Over Time by Treatment Arm, Safety Population, Pooled Analysis (or Trial X)

Parameter	Study Visit time[1] (Study Day/Week/Month)	Treatment Arm (N = X) n (%) at Visit	Treatment Arm (N = X) Mean (95% CI)	Treatment Arm (N = X) Mean Change From Baseline (95% CI)	Control Arm (N = X) n (%) at Visit	Control Arm (N = X) Mean (95% CI)	Control Arm (N = X) Mean Change From Baseline (95% CI)	Difference in Mean Change (95% CI)[2]
Sodium (mEq/L)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
Potassium (mEq/L)	Baseline	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week X	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)
	Week Y	n (%)	X (Y,Z)	X (Y,Z)	n (%)	X (Y,Z)	X (Y,Z)	X (Y,Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit # is used as the study visit (+/- protocol-defined # days).
[2] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria

Laboratory Analyses Over Time – Optional Section
Median and interquartile (includes unscheduled visits)

Figure 29. Median and Interquartile Range[1] of Alanine Aminotransferase Over Time by Treatment Arm, Safety Population Pooled Analyses (or Trial X)[2]



Laboratory Outlier Analyses

- Tables generally separated clinically (e.g., kidney, liver, lipids, hematology)
- Cutoff criteria defined in Table 59, follow a cumulative format

Table 25. Patients with One or More Kidney Function Analyte Values Exceeding Specified Levels,[1] Safety Population, Trial XXX[2]

	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3]
Creatinine, high (mg/dL)				
Level 1 (≥1.5 x baseline)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (≥2.0 x baseline)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (≥3.0 x baseline)	n (%)	n (%)	n (%)	X (Y, Z)
eGFR, low (mL/min/1.73 m^2)				
Level 1 (≥25% decrease)	n (%)	n (%)	n (%)	X (Y, Z)
Level 2 (≥50% decrease)	n (%)	n (%)	n (%)	X (Y, Z)
Level 3 (≥75% decrease)	n (%)	n (%)	n (%)	X (Y, Z)

Lab parameter followed by "high" or "low"

Source: [include Applicant source, datasets and/or software tools used].
[1] Threshold Levels 1, 2, and 3 as defined by Table 59.
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; N, number of patients in treatment arm; n, number of patients meeting criteria

Laboratory Outlier Analyses – Cutoff Thresholds

- Thresholds created to identify outliers across all therapeutic areas and based on expert opinions
- Considered multiple published grading strategies, but many not applicable to all therapeutic areas

Table 59. Abnormality Level Criteria[1] for Chemistry Laboratory Results

Parameter	Level 1	Level 2	Level 3
General Chemistry			
Sodium, low (mEq/L)	<132	<130	<125
Sodium, high (mEq/L)	>150	>155	>160
Potassium, low (mEq/L)	<3.6	<3.4	<3.0
Potassium, high (mEq/L)	>5.5	>6	>6.5
Chloride, low (mEq/L)	<95	<88	<80
Chloride, high (mEq/L)	>108	>112	>115
Bicarbonate, low (mEq/L)	<20	<18	<15
Bicarbonate, high (mEq/L)	N/A	N/A	>30
Blood urea nitrogen, high (mg/dL)	>23	>27	>31
Glucose, low (mg/dL)	<70	<54	
Glucose, high (mg/dL)			
Fasting or	≥100	≥126	
Random	N/A	≥200	

Glucose levels close to ADA criteria

Last Value On-Treatment – Expanded Section

- Last value on-treatment defined as last lab value obtained within a specific timeframe (e.g. three half-lives) following treatment intervention discontinuation, regardless of reason for discontinuation

Table 52. Patients With Last On-Treatment[1] Chemistry Value ≥ Level 2 Criteria[2] by Treatment Arm, Safety Population, Pooled Analyses[3]

Parameter	Drug Name N = XXX n (%)	Control N = XXX n (%)	Risk Difference (%) (95% CI)[4]
General Chemistry			
Sodium, low (<130mEq/L)	n (%)	n (%)	X (Y, Z)
Sodium, high (>155 mEq/L)	n (%)	n (%)	X (Y, Z)
Potassium, low (<3.4 mEq/L)	n (%)	n (%)	X (Y, Z)
Potassium, high (>6 mEq/L)	n (%)	n (%)	X (Y, Z)
Chloride, low (<88 mEq/L)	n (%)	n (%)	X (Y, Z)
Chloride, high (>112 mEq/L)	n (%)	n (%)	X (Y, Z)
Bicarbonate, low (<18 mEq/L)	n (%)	n (%)	X (Y, Z)
Bicarbonate, high (>30 mEq/L)	n (%)	n (%)	X (Y, Z)
Blood urea nitrogen, high (>27 mg/dL)	n (%)	n (%)	X (Y, Z)
Glucose, low (<54 mg/dL)	n (%)	n (%)	X (Y, Z)
Glucose, high Fasting (≥126 mg/dL) or Random (≥200 mg/dL)	n (%)	n (%)	X (Y, Z)

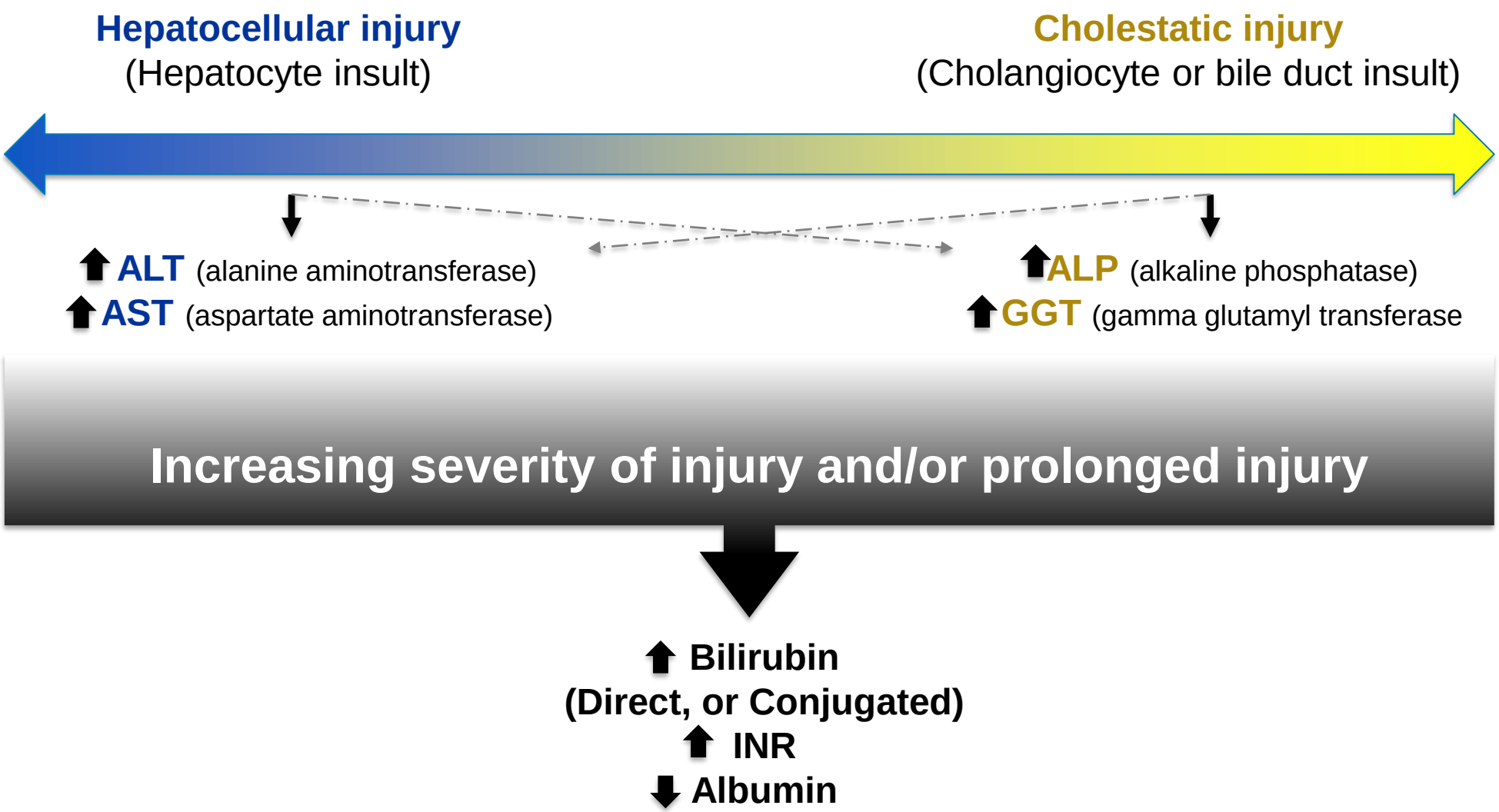
Drug-Induced Liver Injury

Y. Veronica Pei, MD, MEd, MPH
Associate Directors for Biomedical Informatics
Biomedical Informatics and Regulatory Review Science (BIRRS)

Potential DILI Evaluation

1. Evaluation of potential DILI is complex
2. Initial screening analyses intended to identify patients at high risk of potential hepatocellular and cholestatic DILI
3. Additional patient-level analyses may be needed

Review of Liver Biochemistries



Reproduced with permission from Dr. Paul (Skip) Hayashi

Standard Tables & Figures
Integrated Guide and DILI Screening Analyses

Integrated Guide (IG)

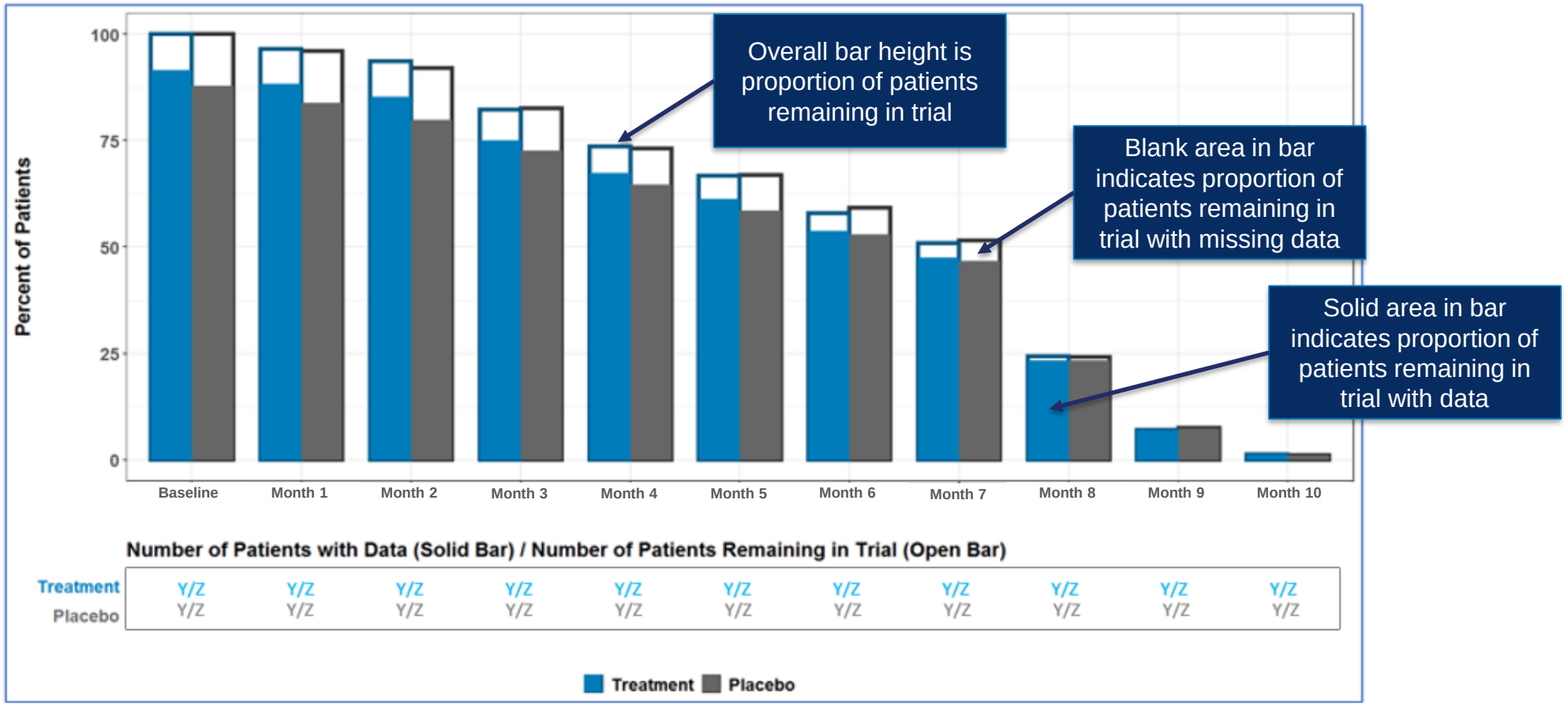
DILI Screening Analyses

1. Missing Data
2. Hepatocellular Screening Plot
3. Cholestatic Screening Plot
4. Comparison of Patients with Maximal Treatment-emergent Liver Test Abnormalities

*The DILI Follow-on Guide is produced upon request by reviewer

Missing Data Analyses

Figure 11. Proportion of Patients Remaining in Trial X with Missing Y (e.g., ALT, AST, etc.) Data Records, Safety Population

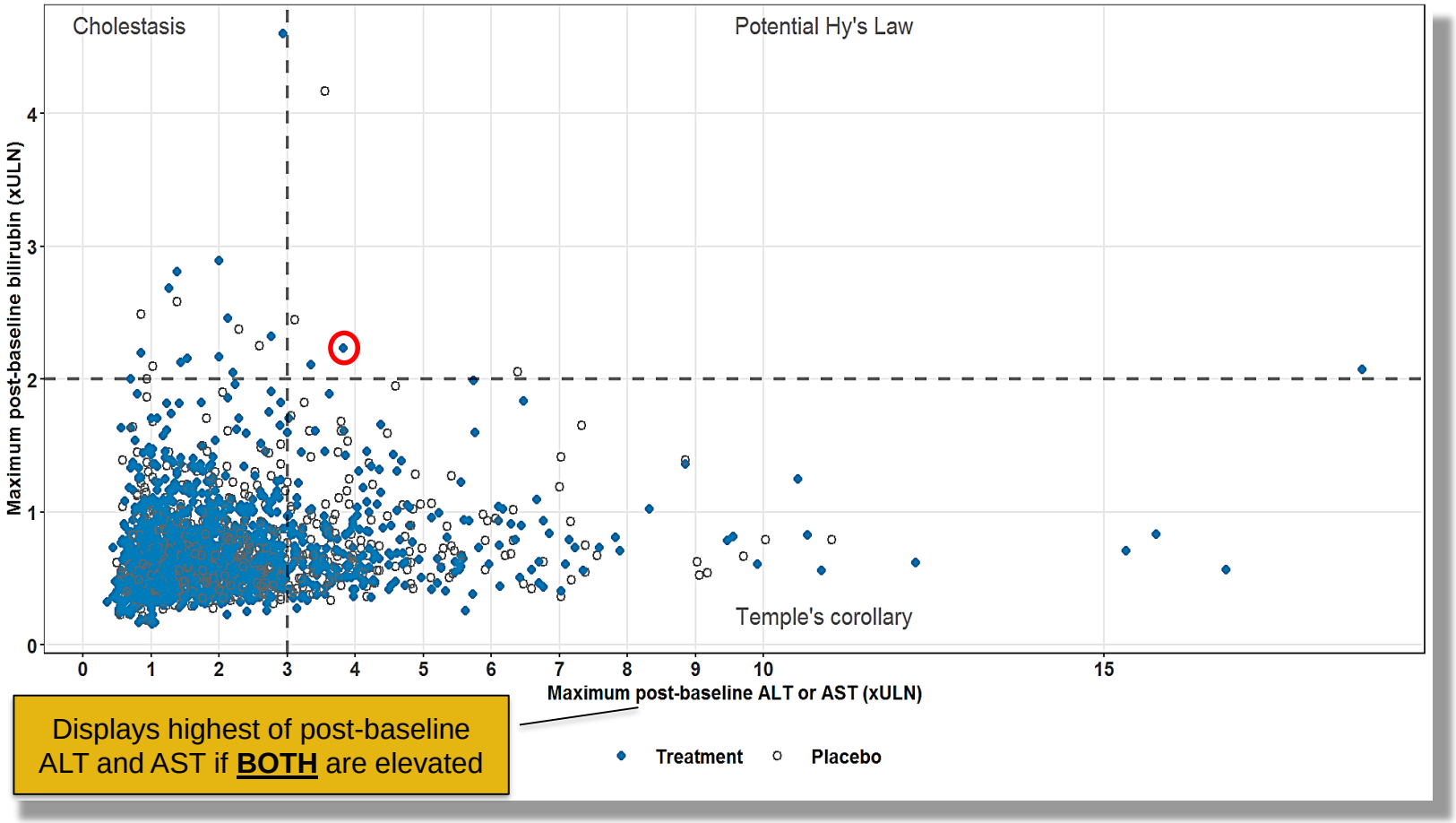


Source: [include Applicant source, datasets and/or software tools used].
Note: The frequency of laboratory measurements presented here is based on actual data collected.
Note: The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit # is used as the study visit (+/- protocol-defined # days).

Hepatocellular DILI Case Screening Plot

Note: Default cut-offs are TB ≥ 2xULN and ALT or AST ≥ 3x ULN

Figure 12. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analyses



Displays highest of post-baseline ALT and AST if **BOTH** are elevated

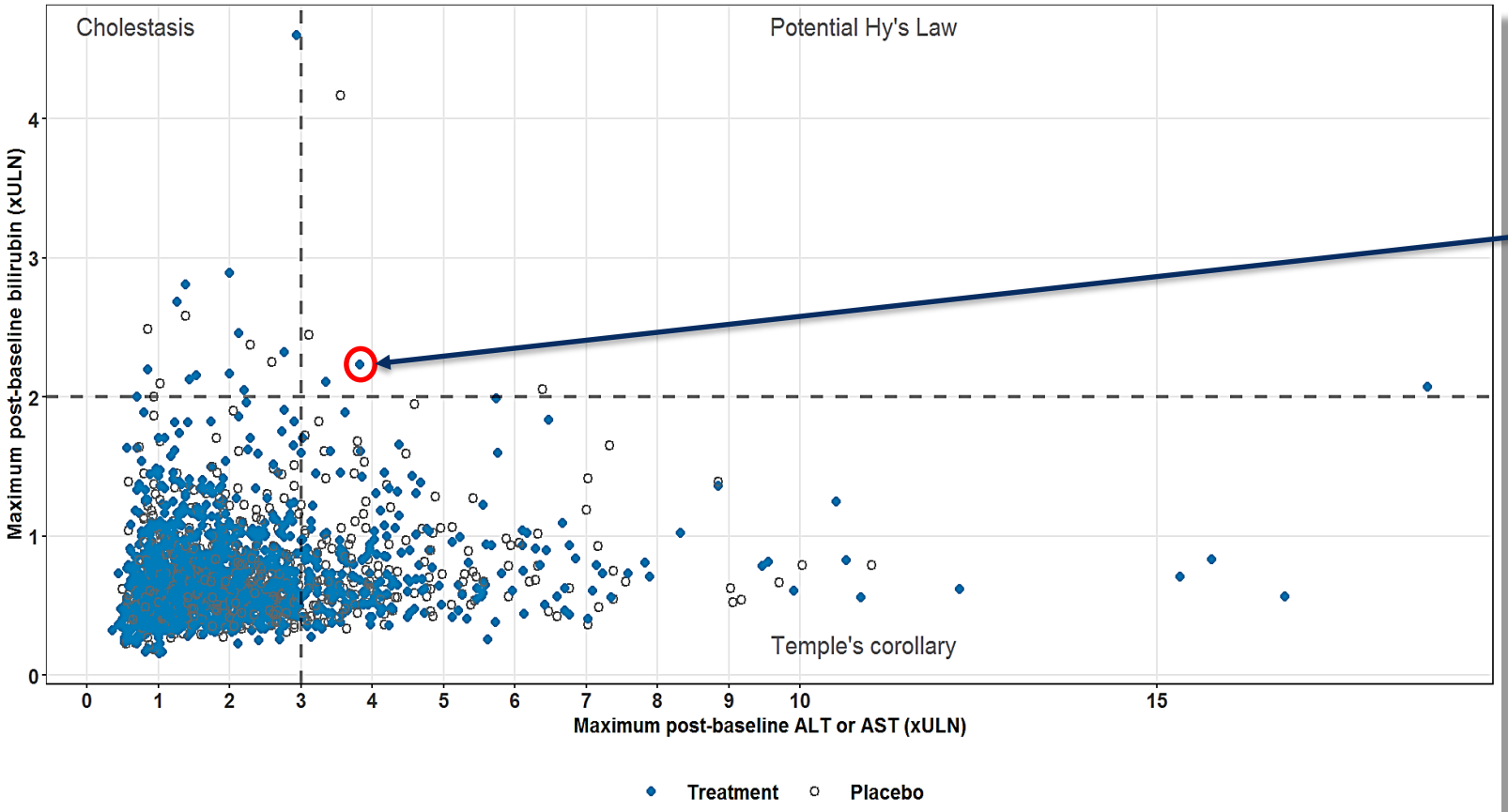
Each data point represents a patient plotted by their maximum ALT or AST versus their maximum TB values in the postbaseline period.

Source: Include source dataset(s) and tools used; Software:
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI= total bilirubin; ULN = upper limit of normal; ALP= alkaline phosphatase.
Note: The Hy's Law Screening Plot is generated using maximum treatment-emergent liver test abnormalities.

Hepatocellular DILI Case Screening Plot

Note: Default cut-offs are TB ≥ 2xULN and ALT or AST ≥ 3x ULN

Figure 12. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analyses



Red circle indicates this patient meets timing and ALP criteria:

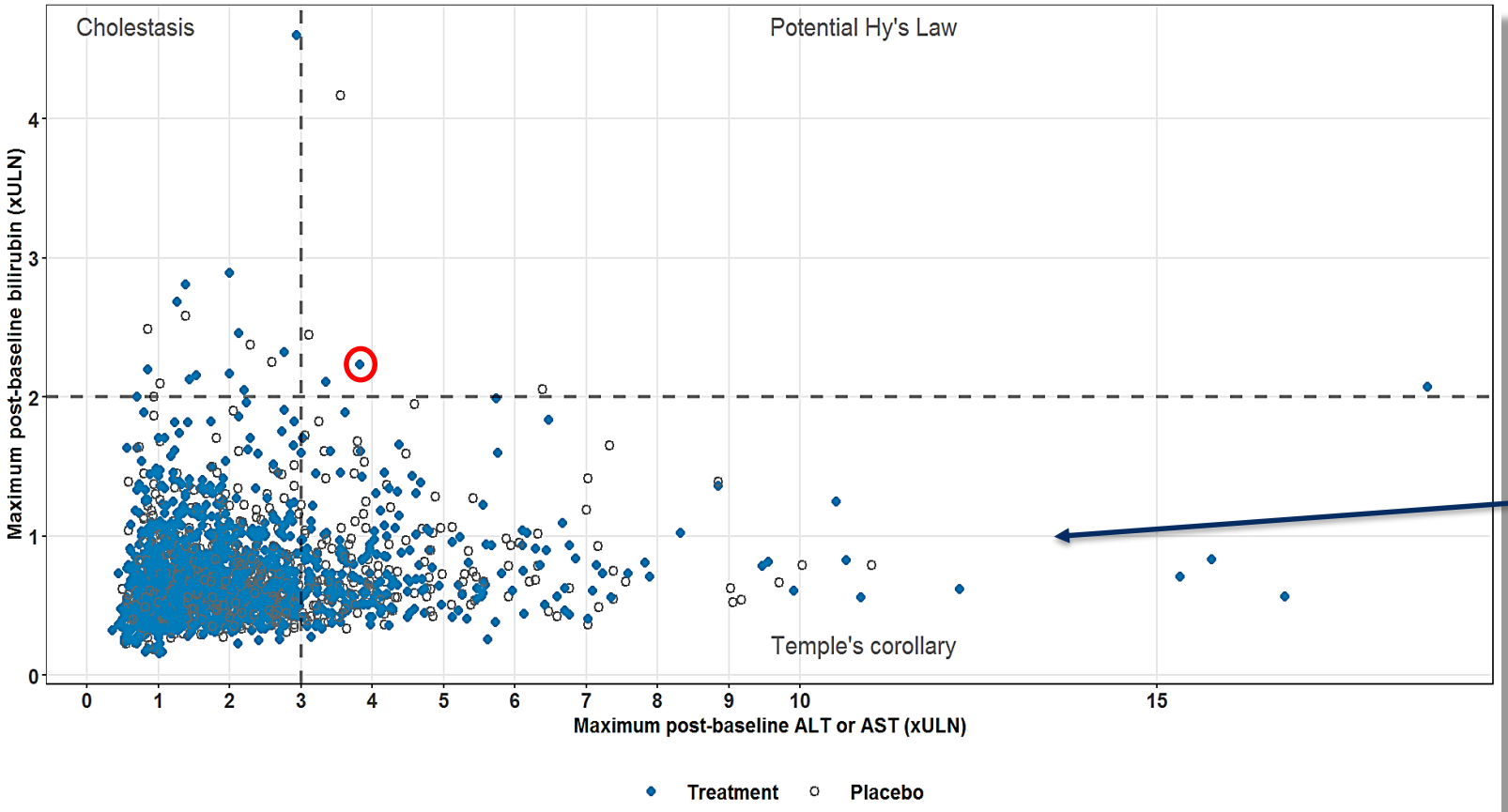
1. ***Any postbaseline TB ≥2x ULN within 30 days after a postbaseline ALT or AST ≥3x ULN***
2. ***ALP <2x ULN***

Source: Include source dataset(s) and tools used; Software:
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI= total bilirubin; ULN = upper limit of normal; ALP= alkaline phosphatase.
Note: The Hy's Law Screening Plot is generated using maximum treatment-emergent liver test abnormalities.

Hepatocellular DILI Case Screening Plot

Note: Default cut-offs are TB ≥ 2xULN and ALT or AST ≥ 3x ULN

Figure 12. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analyses



Temple's Corollary: Moderate to severe ALT or AST elevation and TB is <2x ULN.

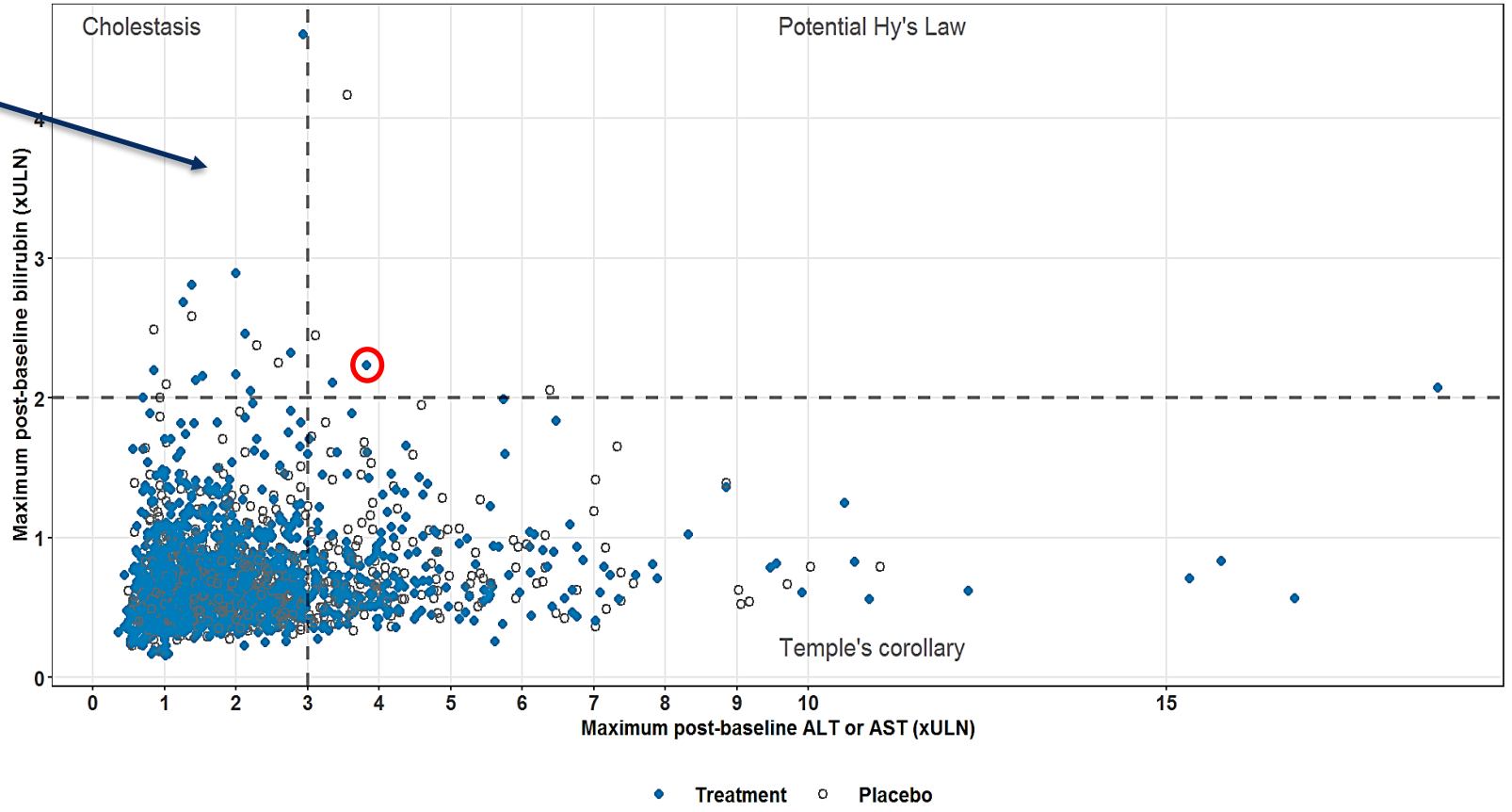
Source: Include source dataset(s) and tools used; Software:
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI= total bilirubin; ULN = upper limit of normal; ALP= alkaline phosphatase.
Note: The Hy's Law Screening Plot is generated using maximum treatment-emergent liver test abnormalities.

Hepatocellular DILI Case Screening Plot

Note: Default cut-offs are TB ≥ 2xULN and ALT or AST ≥ 3x ULN

TB ≥2x ULN with no more than minimal elevation in ALT or AST

Figure 12. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analyses

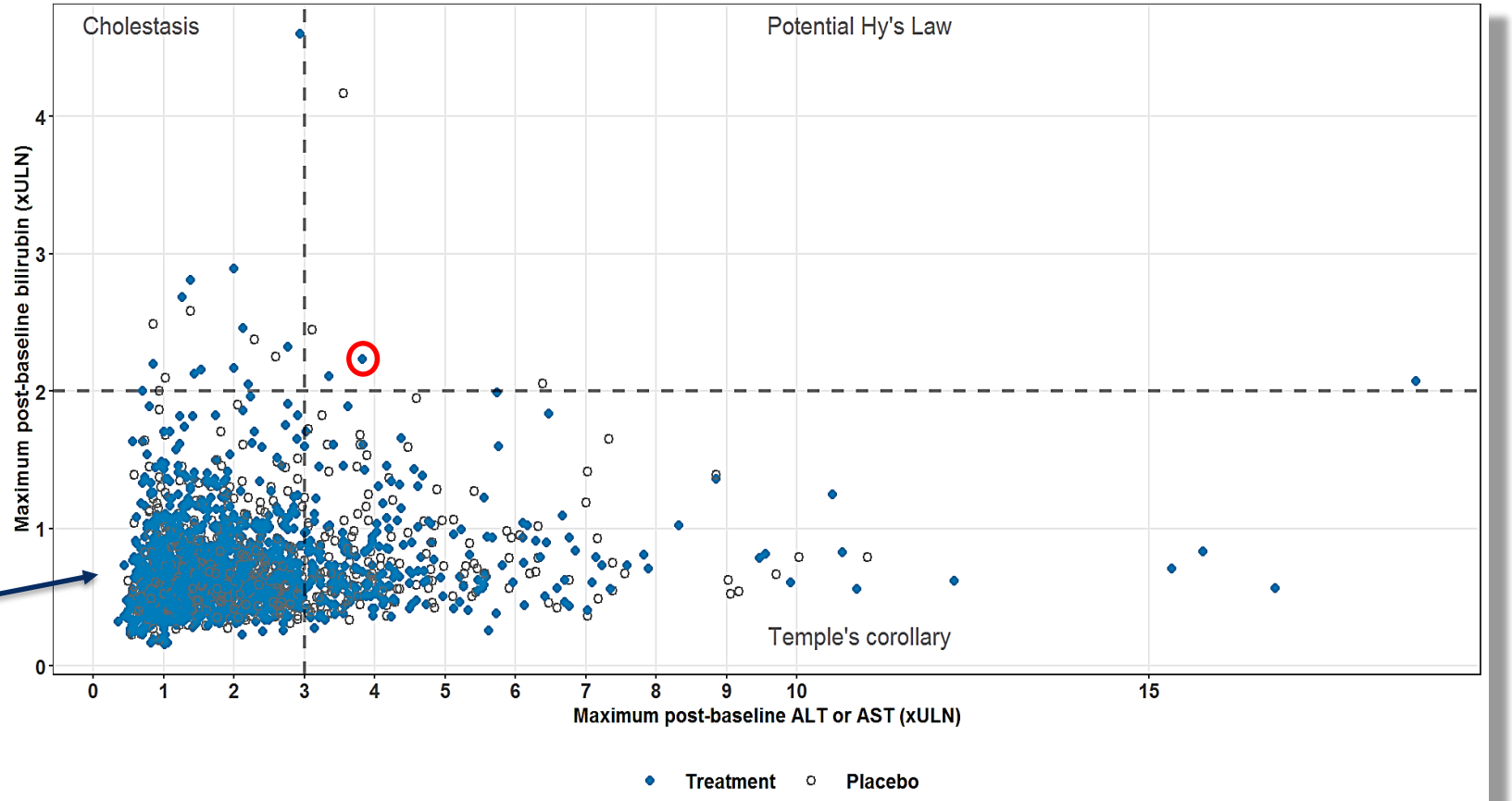


Source: Include source dataset(s) and tools used; Software:
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI= total bilirubin; ULN = upper limit of normal; ALP= alkaline phosphatase.
Note: The Hy's Law Screening Plot is generated using maximum treatment-emergent liver test abnormalities.

Hepatocellular DILI Case Screening Plot

Note: Default cut-offs are TB ≥ 2xULN and ALT or AST ≥ 3x ULN

Figure 12. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analyses



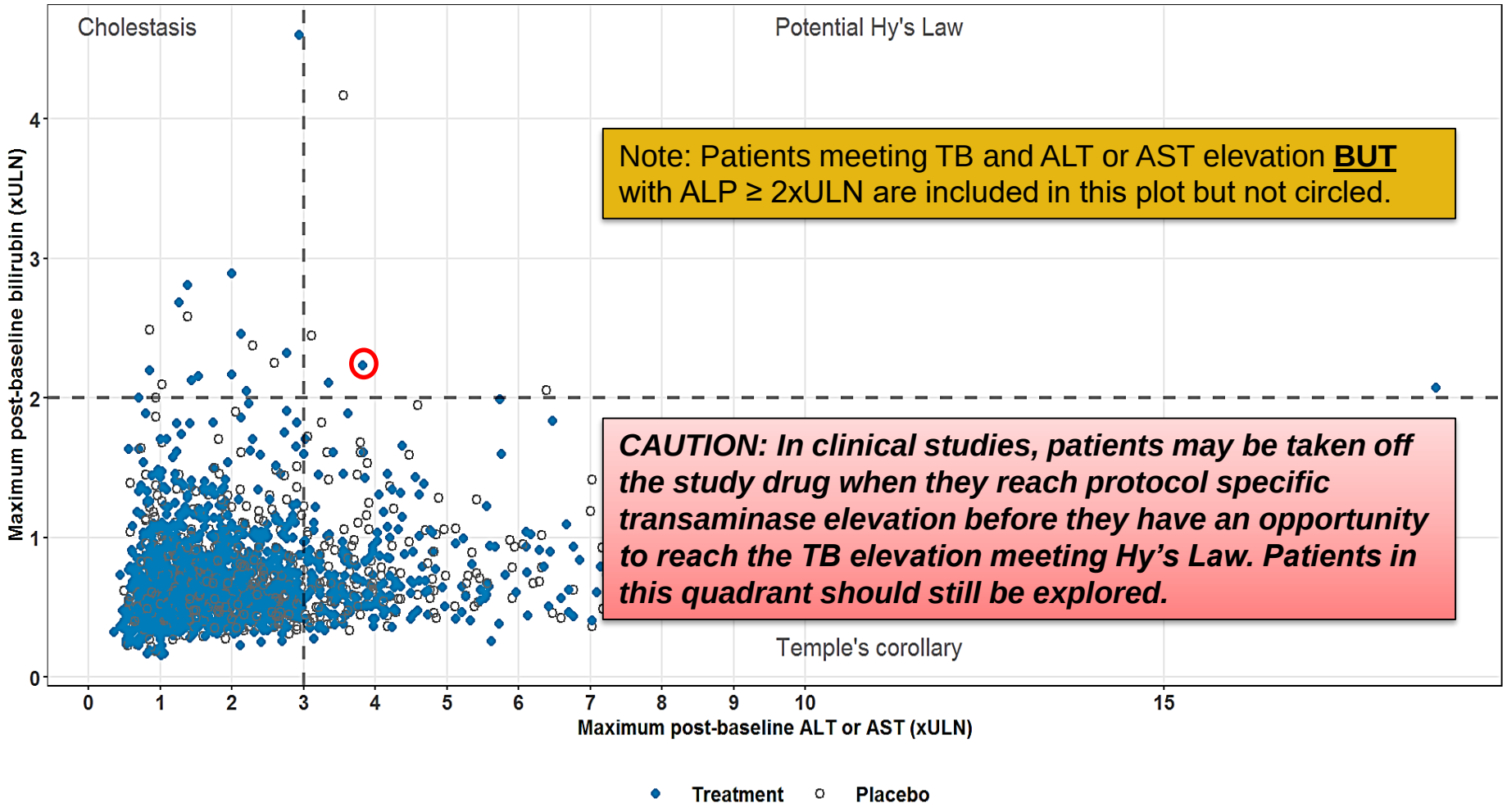
Risk of severe DILI is unlikely

Source: Include source dataset(s) and tools used; Software:
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI= total bilirubin; ULN = upper limit of normal; ALP= alkaline phosphatase.
Note: The Hy's Law Screening Plot is generated using maximum treatment-emergent liver test abnormalities.

Hepatocellular DILI Case Screening Plot

Additional Considerations

Figure 12. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analyses

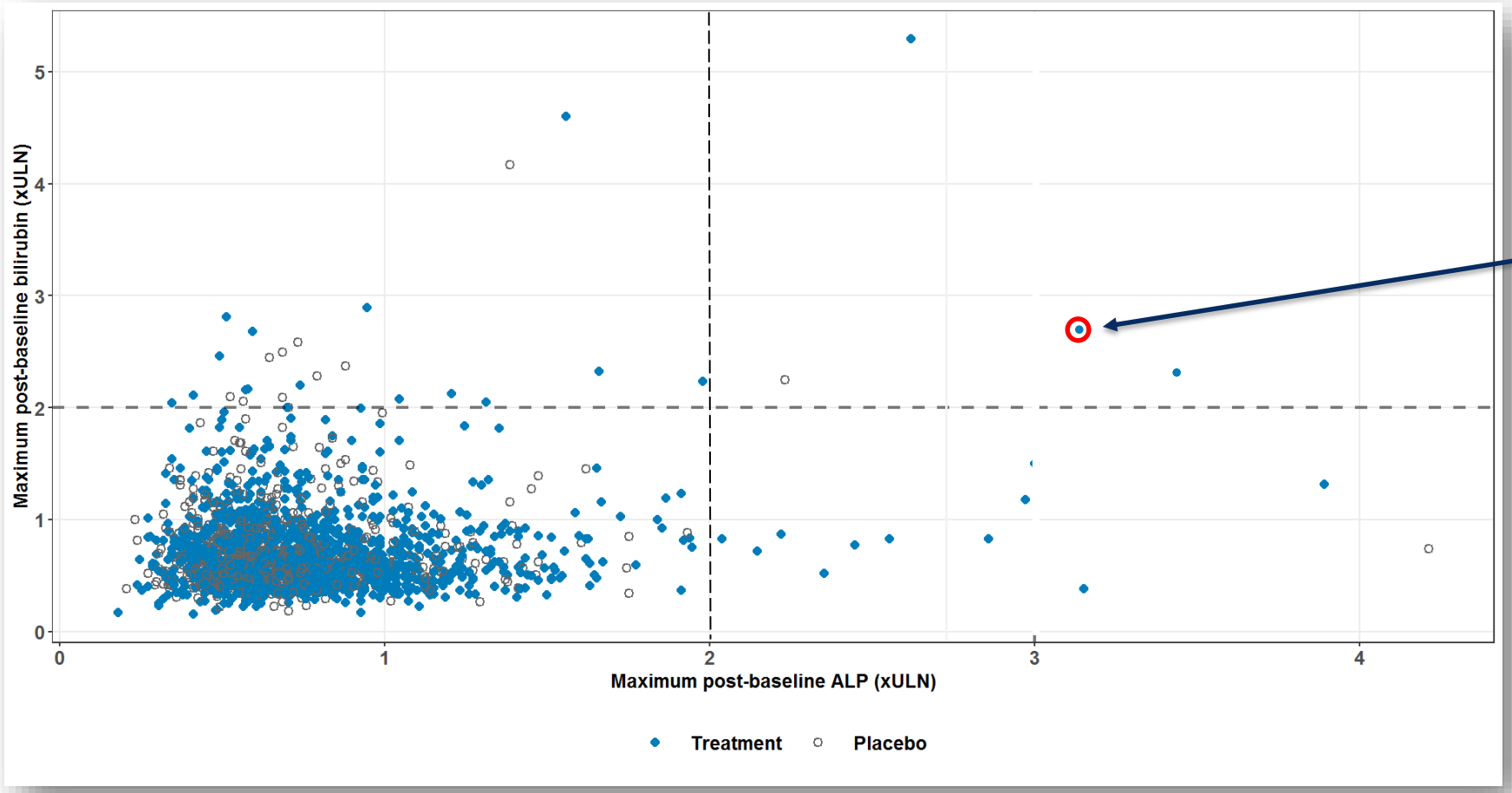


Source: Include source dataset(s) and tools used; Software:
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = total bilirubin; ULN = upper limit of normal; ALP = alkaline phosphatase.
Note: The Hy's Law Screening Plot is generated using maximum treatment-emergent liver test abnormalities.

Cholestatic Liver Injury Screening Plot

Note: Default cut-offs are TB ≥ 2xULN and ALP ≥ 2x ULN

Figure 13. Cholestatic Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analyses



Red circle indicates this patient meets timing criteria:

Maximum postbaseline TB ≥2x ULN within 30 days after postbaseline ALP became ≥2x ULN.

Source: Include source dataset(s) and tools used; Software:
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = total bilirubin; ULN = upper limit of normal; ALP = alkaline phosphatase.
Note: The Hy's Law Screening Plot is generated using maximum treatment-emergent liver test abnormalities.

Comparison of Patients with Maximal Treatment-emergent Liver Test Abnormalities

Table 1. Number of Patients with Potential DILI in Active Group versus Comparator by Treatment Group, Safety Population, Pooled Analyses

Quadrant	**Active (N=XXX) n (%)**	**Comparator (N=XXX) n (%)**
Potential Hy's Law (right upper)		
Cholestasis (left upper)		
Temple's corollary (right lower)		
Total		

Note: The DILI Screening Plot and this table are generated using Maximum Treatment-Emergent Liver Test Abnormalities.

Similar table is provided for the Cholestatic DILI Screening plot

Patient Level Analyses: Critical Elements for Diagnosing DILI

- Baseline data (PMHx including underlying liver disease)
- Timing of drug exposure, liver injury and course
  - Latency: Time from drug start to injury onset
  - Washout: Recovery from liver injury
- Competing causes for liver injury (differential diagnosis)

Potential DILI Narrative Critical Elements

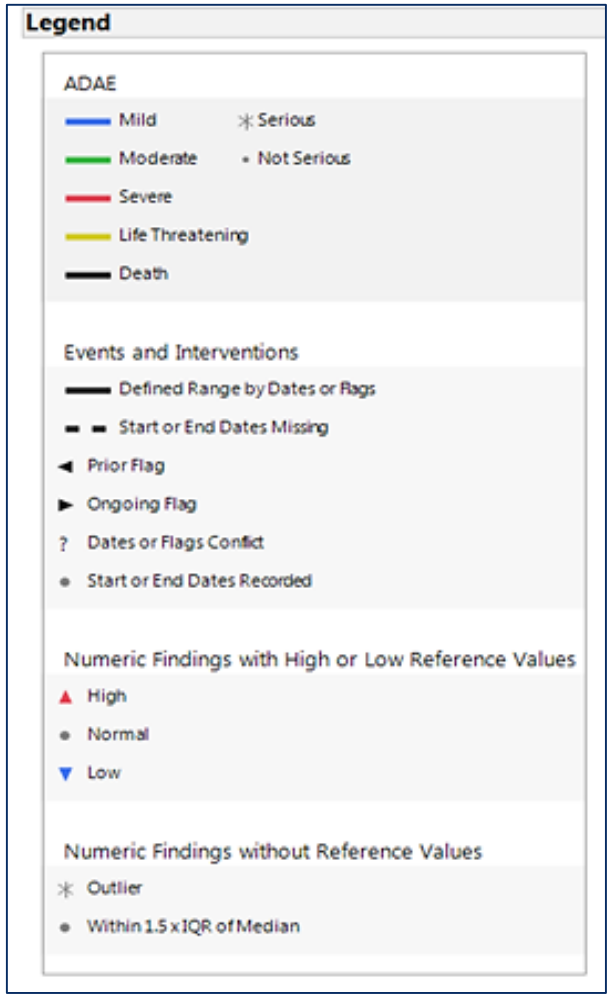
- Timing
  - Drug start, stop and any interruptions
- Liver biochemistries
  - Baseline, onset of injury day and levels, peak day and levels
  - Injury pattern and severity
  - Washout
- Symptoms
- Concomitant medications
- Evaluation for other causes
  - Viral serologies
  - Imaging of the liver
  - Autoimmune hepatitis markers
  - Biopsy, if done.

Example Case-level Summary (from Narrative)

Table X. Hepatotoxicity Work-up Case-level Summary for Patient ID XXXXXXX

	Test Performed (Yes/No)	Date of Test	Result Summary	Hyperlink to Report (If available)
Serum Serology				
Hepatitis A IgM antibody				
Hepatitis B surface antigen				
Hepatitis B anti-HB core IgM antibody				
Hepatitis C antibody				
Hepatitis C RNA				
Hepatitis E IgM antibody				
ANA (anti-nuclear antibody)				
ASMA (anti-smooth muscle antibody)				
Immunoglobulin G (IgG) level				
CMV (cytomegalovirus) antibody IgM				
EBV (Epstein Barr Virus) heterophile antibody				
EBV capsid antibody IgM				
EBV early antigen IgG				
Imaging/Biopsy/Diagnoses				
Abdominal or liver ultrasound				
Abdominal CT scan				
Abdominal MRI scan				
MRCP or MRC (magnetic resonance cholangiopancreatography or MR cholangiography)				
Cholangiogram (e.g., ERCP, percutaneous)				
Liver histology				

Timeline: Graphical Patient Profile



Relevant Guidance

Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of Noncirrhotic Nonalcoholic Steatohepatitis (NASH)

Guidance for Industry

Technical Specifications Document

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-specifications-submitting-clinical-trial-data-sets-treatment-noncirrhotic-nonalcoholic

Concluding Remarks

- Development of Standard Safety Tables and Figures can streamline the data used for generating analyses, foster consistency in the visualizations utilized, and aid FDA clinical review staff in the interpretation of analyses.
- Clinical judgement is very important, as safety analyses are exploratory in nature, and collaboration with data scientists, and statisticians is essential.
- Refinement of analyses with feedback to further finalize standard tables and figures is important.
- We look forward to future collaboration with external stakeholders.

Acknowledgement: OND Standard Tables and Figures Working Group and subject matter experts who provided input for their therapeutic area specific visualizations.

Acknowledgement: Standard Safety Tables and Figures Working group

- Peter Stein (Executive Sponsor)
- Vaishali Popat (Project lead)
- Alan Shapiro
- Anne Bunner
- Benjamin Schick
- Chenoa Conley
- Douglas Warfield
- Ellen Wertheimer
- Ellis Unger
- Frank Anania
- Frank Pucino
- Gregory Levin
- Hyo Sook Song
- James Smith
- Jinzhong Liu
- Jizu Zhi
- Matilde Kam
- Katharine Bradley
- Kerry Jo Lee
- Kim Shimy
- Larissa Stabinski
- Mahtab Niyyati
- Mat Soukup
- Matthew Guerra
- McKinley DeAngelo
- Michelle Carey
- Nhi Beasley
- Paul Hayashi
- Preeti Venkataraman
- Qunshu Zhang
- Ramya Gopinath
- Rhonda Hearns-Stewart
- Rituparna Moitra
- Robert Temple
- Sarah Connelly
- Sarah Rodgers
- Sarita Boyd
- Scott Proestel
- Susan Duke
- Terrence Autry
- Yang Veronica Pei

Discussion

- What questions or comments do you have about the Standard Safety Tables and Figures?
- Contact us at ONDbiomedicalinformatics@fda.hhs.gov


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Examining Strategies for Premarket Adverse Event Analysis

Moderator: **Vaishali Popat,** U.S. Food and Drug Administration

Panelists:

Mary Nilsson, Eli Lilly (PHUSE)

Bess LeRoy, Clinical Data Interchange Standards Consortium

Jeremy Wildfire, Gilead (DIA-ASA Interdisciplinary Safety Evaluation Working Group)

Standard Safety Tables and Figures – PHUSE Initiatives

Mary Nilsson

14 September 2022

Duke-Margolis Public Workshop on Advancing Premarket Safety Analytics

Outline

- Background of FDA/PHUSE collaboration
- Summary of PHUSE deliverables related to Safety Analytics
  - Final deliverables
  - Ongoing projects
- Next steps

FDA/PHUSE Collaboration

www.phuse.global
Working Groups

- Started 2012
- Platform for academia, regulators, industry, and technology providers to address computational science needs in support of regulatory review
- Supported by PHUSE, the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER)

Projects on Standard Safety Tables and Figures

- Multiple projects teams have produced deliverables related to standard safety tables and figures
  - Mostly from the Standard Analyses and Code Sharing Working Group (2012-June 2020), and Safety Analytics Working Group (June 2020+)

Safety Analytics Working Group Description: A cross-disciplinary collaboration working to improve the content and implementation of clinical trial safety analysis for medical research, leading to better data interpretations and increased efficiency in the clinical drug development and review processes.

Example PHUSE Deliverables

- 2013 Labs, vital signs, ECGs analyses and displays central tendency white paper (WP)
- 2015 Labs, vital signs, ECGs analyses and displays outlier/shift WP
- 2017 Adverse event analyses and displays WP
- 2017 Study-size adjusted % educational video
- 2018 Demographics, disposition, medications displays (version 2) WP
- 2019 Safety Analytics Workshop Part 1
- 2019 Interactive volcano plot (adverse events) proof-of-concept and pilot
- 2020 Adverse event collection, treatment-emergent definition survey results WP
- 2020 Safety Analytics Workshop Part 2 (Integrated Analyses)
- 2021 Analysis and display of safety topics of interest WP
- 2021 Data listings in clinical study reports WP
- 2022 Labs analyses and displays (updated recommendations) WP

Finding PHUSE Deliverables

www.phuse.global

Ongoing Projects

PHUSE Safety Analytics Working Group

Listings in Clinical Study Reports
- Mercy Navarro
- Nancy Brucken

Hepatotoxicity Analyses and Displays
- Terry Walsh
- Melvin Munsaka

Lab Analyses and Displays
- Wei Wang
- Charles Beasley

Adverse Event Collection
- Aimee Basile
- Mary Nilsson

Treatment Emergent Definition
- Bill Palo
- Mary Nilsson

Safety Analytics Education
- Bill Palo

NEW: Adverse Event Groupings in Safety (AEGiS)
- Greg Ball
- Mary Nilsson

PLANNED: Gather comments on FDA's Safety Tables and Figures Integrated Guide

Next Steps

- FDA/PHUSE discussions at PHUSE CSS (Sept 19-21)
- PHUSE project team to provide comments to the Standard Safety Tables and Figures Integrated Guide
  - Target October 31st to provide consolidated feedback
  - Will include a comparison with existing PHUSE white papers
- Discuss plans for potentially updating adverse event, labs, and vitals white papers

CDISC Perspective on Standards for Analysis Results

Bess LeRoy, MPH

Head of Standards Development, CDISC

Background

- Unnecessary variation in analysis results reporting
- Limited CDISC standards to support analysis results and associated metadata
- CDISC has been working towards creating standards to support, consistency, traceability, and reuse of results data
- We anticipate that the CDISC work will support sponsor submissions of analysis results in a standard format that aligns with the FDA effort

Analysis Results Current State

- Static results created for Clinical Study Report
- May be hundred of tables in PDF format, often difficult to navigate
- Variability between sponsors
- Expensive to generate and only used once, no or limited reusability

Analysis Ready ADaM Dataset

Table 3.1.1: ADHYPO Analysis Dataset

Row	STUDYID	USUBJID	MIDS	CEDECOD	WASAEYN	ASTDTM
1	XYZ	000001	HYPO 1	Hypoglycemia	Y	07Sep2012 22:29:00
2	XYZ	000001	HYPO 2	Hypoglycemia	N	10Sep2012 09:12:00
3	XYZ	000001	HYPO 3	Hypoglycemia	N	10Sep2012 23:05:00
4	XYZ	000001	HYPO 4	Hypoglycemia	N	11Sep2012 15:24:00
5	XYZ	000001	HYPO 5	Hypoglycemia	N	18Sep2012 11:39:00
6	XYZ	000002	HYPO 1	Hypoglycemia	N	22Oct2012 13:28:00
7	XYZ	000002	HYPO 2	Hypoglycemia	N	25Oct2012 13:59:00
8	XYZ	000002	HYPO 3	Hypoglycemia	N	17Nov2012 05:01:00

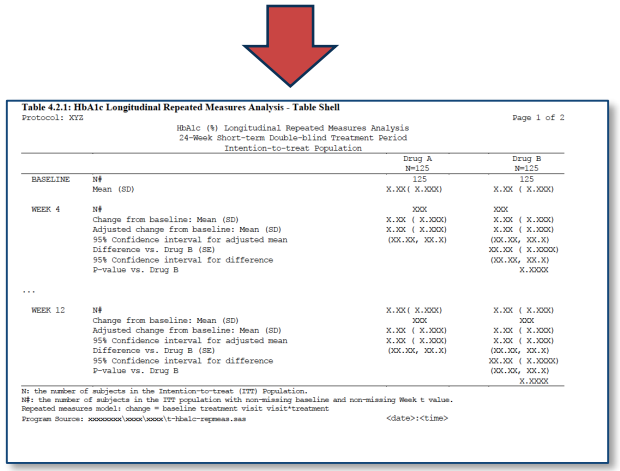


Table 4.2.1: HbA1c Longitudinal Repeated Measures Analysis - Table Shell

Protocol: XYZ — Page 1 of 2

HbA1c (%) Longitudinal Repeated Measures Analysis
24-Week Short-term Double-blind Treatment Period
Intention-to-treat Population

		Drug A N=125	Drug B N=125
BASELINE	N#	125	125
	Mean (SD)	X.XX(X.XXX)	X.XX (X.XXX)
WEEK 4	N#	XXX	XXX
	Change from baseline: Mean (SD)	X.XX (X.XXX)	X.XX (X.XXX)
	Adjusted change from baseline: Mean (SD)	X.XX (X.XXX)	X.XX (X.XXX)
	95% Confidence interval for adjusted mean	(XX.XX, XX.X)	(XX.XX, XX.X)
	Difference vs. Drug B (SE)		XX.XX (X.XXXX)
	95% Confidence interval for difference		(XX.XX, XX.X)
	P-value vs. Drug B		X.XXXX
...			
WEEK 12	N#	X.XX(X.XXX)	X.XX (X.XXX)
	Change from baseline: Mean (SD)	XXX	XXX
	Adjusted change from baseline: Mean (SD)	X.XX (X.XXX)	X.XX (X.XXX)
	95% Confidence interval for adjusted mean	X.XX (X.XXX)	X.XX (X.XXX)
	Difference vs. Drug B (SE)	(XX.XX, XX.X)	(XX.XX, XX.X)
	95% Confidence interval for difference		XX.XX (X.XXXX)
	P-value vs. Drug B		(XX.XX, XX.X)
			X.XXXX

N: the number of subjects in the Intention-to-treat (ITT) Population.
N#: the number of subjects in the ITT population with non-missing baseline and non-missing Week t value.
Repeated measures model: change = baseline treatment visit visit*treatment
Program Source: xxxxxxxx\xxxx\xxxx\t-hba1c-repmeas.sas — <date>:<time>

Static Display

Analysis Results Current State

Table 3.1.1: ADHYPO Analysis Dataset

Row	STUDYID	USUBJID	MIDS	CEDECOD	WASAEYN	ASTDTM
1	XYZ	000001	HYPO 1	Hypoglycemia	Y	07Sep2012 22:29:00
2	XYZ	000001	HYPO 2	Hypoglycemia	N	10Sep2012 09:12:00
3	XYZ	000001	HYPO 3	Hypoglycemia	N	10Sep2012 23:05:00
4	XYZ	000001	HYPO 4	Hypoglycemia	N	11Sep2012 15:24:00
5	XYZ	000001	HYPO 5	Hypoglycemia	N	18Sep2012 11:39:00
6	XYZ	000002	HYPO 1	Hypoglycemia	N	22Oct2012 13:28:00
7	XYZ	000002	HYPO 2	Hypoglycemia	N	25Oct2012 13:59:00
8	XYZ	000002	HYPO 3	Hypoglycemia	N	17Nov2012 05:01:00

ADaM Dataset

Table 4.2.1: HbA1c Longitudinal Repeated Measures Analysis - Table Shell

Protocol: XYZ — Page 1 of 2

HbA1c (%) Longitudinal Repeated Measures Analysis
24-Week Short-term Double-blind Treatment Period
Intention-to-treat Population

		Drug A N=125	Drug B N=125
BASELINE	N‡	125	125
	Mean (SD)	X.XX(X.XXX)	X.XX (X.XXX)
WEEK 4	N‡	XXX	XXX
	Change from baseline: Mean (SD)	X.XX (X.XXX)	X.XX (X.XXX)
	Adjusted change from baseline: Mean (SD)	X.XX (X.XXX)	X.XX (X.XXX)
	95% Confidence interval for adjusted mean	(XX.XX, XX.X)	(XX.XX, XX.X)
	Difference vs. Drug B (SE)		XX.XX (X.XXXX)
	95% Confidence interval for difference		(XX.XX, XX.X)
	P-value vs. Drug B		X.XXXX
...			
WEEK 12	N‡	X.XX(X.XXX)	X.XX (X.XXX)
	Change from baseline: Mean (SD)	XXX	XXX
	Adjusted change from baseline: Mean (SD)	X.XX (X.XXX)	X.XX (X.XXX)
	95% Confidence interval for adjusted mean	X.XX (X.XXX)	X.XX (X.XXX)
	Difference vs. Drug B (SE)	(XX.XX, XX.X)	(XX.XX, XX.X)
	95% Confidence interval for difference		XX.XX (X.XXXX)
	P-value vs. Drug B		(XX.XX, XX.X)
			X.XXXX

N: the number of subjects in the Intention-to-treat (ITT) Population.
N‡: the number of subjects in the ITT population with non-missing baseline and non-missing Week t value.
Repeated measures model: change = baseline treatment visit visit*treatment
Program Source: xxxxxxxx\xxxx\xxxx\t-hba1c-repmeas.sas <date>:<time>

Static Display

ARM for Define-XML

Table 4.2.2: HbA1c Longitudinal Repeated Measures Analysis Results Metadata

Metadata Field	Metadata
DISPLAY IDENTIFIER	Table 4.2.1/Figure 4.2.1
DISPLAY NAME	Mean Change from Baseline in HbA1c (Percent) Longitudinal Repeated Measures Analysis, 24-Week Short-term Double-blind Treatment Period, Intention-to-treat Population
RESULT IDENTIFIER	Treatment difference results (LSMean, confidence interval, p-value)
PARAM	HbA1c (%)
PARAMCD	HBA1C
ANALYSIS VARIABLE	CHG (Change from baseline)
ANALYSIS REASON	SPECIFIED IN SAP
ANALYSIS PURPOSE	PRIMARY OUTCOME MEASURE
ANALYSIS DATASET	ADHBA1C

ARM v1

cdisc

Analysis Results Current State

- ARM v1.0 describes *metadata* about analysis displays and results (at a high level), no formal analysis and results model or results data
- Lack of features to drive automation
- Limited regulatory use cases
- Limited traceability

Table 4.2.2: HbA1c Longitudinal Repeated Measures Analysis Results Metadata

Metadata Field	Metadata
DISPLAY IDENTIFIER	Table 4.2.1/Figure 4.2.1
DISPLAY NAME	Mean Change from Baseline in HbA1c (Percent) Longitudinal Repeated Measures Analysis, 24-Week Short-term Double-blind Treatment Period, Intention-to-treat Population
RESULT IDENTIFIER	Treatment difference results (LSMean, confidence interval, p-value)
PARAM	HbA1c (%)
PARAMCD	HBA1C
ANALYSIS VARIABLE	CHG (Change from baseline)
ANALYSIS REASON	SPECIFIED IN SAP
ANALYSIS PURPOSE	PRIMARY OUTCOME MEASURE
ANALYSIS DATASET	ADHBA1C

Shifting the Paradigm

Table 3.1.1: ADHYPO Analysis Dataset

Row	STUDYID	USUBJID	MIDS	CEDECOD	WASAEYN	ASTDTM
1	XYZ	000001	HYPO 1	Hypoglycemia	Y	07Sep2012 22:29:00
2	XYZ	000001	HYPO 2	Hypoglycemia	N	10Sep2012 09:12:00
3	XYZ	000001	HYPO 3	Hypoglycemia	N	10Sep2012 23:05:00
4	XYZ	000001	HYPO 4	Hypoglycemia	N	11Sep2012 15:24:00
5	XYZ	000001	HYPO 5	Hypoglycemia	N	18Sep2012 11:39:00
6	XYZ	000002	HYPO 1	Hypoglycemia	N	22Oct2012 13:28:00
7	XYZ	000002	HYPO 2	Hypoglycemia	N	25Oct2012 13:59:00
8	XYZ	000002	HYPO 3	Hypoglycemia	N	17Nov2012 05:01:00

ADaM Dataset

Shifting the Paradigm

Table 3.1.1: ADHYPO Analysis Dataset

Row	STUDYID	USUBJID	MIDS	CEDECOD	WASAEYN	ASTDTM
1	XYZ	000001	HYPO 1	Hypoglycemia	Y	07Sep2012 22:29:00
2	XYZ	000001	HYPO 2	Hypoglycemia	N	10Sep2012 09:12:00
3	XYZ	000001	HYPO 3	Hypoglycemia	N	10Sep2012 23:05:00
4	XYZ	000001	HYPO 4	Hypoglycemia	N	11Sep2012 15:24:00
5	XYZ	000001	HYPO 5	Hypoglycemia	N	18Sep2012 11:39:00
6	XYZ	000002	HYPO 1	Hypoglycemia	N	22Oct2012 13:28:00
7	XYZ	000002	HYPO 2	Hypoglycemia	N	25Oct2012 13:59:00
8	XYZ	000002	HYPO 3	Hypoglycemia	N	17Nov2012 05:01:00

ADaM Dataset

Table 4.2.2: HbA1c Longitudinal Repeated Measures Analysis Results Metadata

Metadata Field	Metadata
DISPLAY IDENTIFIER	Table 4.2.1/Figure 4.2.1
DISPLAY NAME	Mean Change from Baseline in HbA1c (Percent) Longitudinal Repeated Measures Ana Period, Intention-to-treat Population
RESULT IDENTIFIER	Treatment difference results (LSMean, confidence interval, p-value)
PARAM	HbA1c (%)
PARAMCD	HBA1C
ANALYSIS VARIABLE	CHG (Change from baseline)
ANALYSIS REASON	SPECIFIED IN SAP
ANALYSIS PURPOSE	PRIMARY OUTCOME MEASURE
ANALYSIS DATASET	ADHBA1C

ARM v1

ARM Extension Technical Specification

Shifting the Paradigm

Table 3.1.1: ADHYPO Analysis Dataset

Row	STUDYID	USUBJID	MIDS	CEDECOD	WASAEYN	ASTDTM
1	XYZ	000001	HYPO 1	Hypoglycemia	Y	07Sep2012 22:29:00
2	XYZ	000001	HYPO 2	Hypoglycemia	N	10Sep2012 09:12:00
3	XYZ	000001	HYPO 3	Hypoglycemia	N	10Sep2012 23:05:00
4	XYZ	000001	HYPO 4	Hypoglycemia	N	11Sep2012 15:24:00
5	XYZ	000001	HYPO 5	Hypoglycemia	N	18Sep2012 11:39:00
6	XYZ	000002	HYPO 1	Hypoglycemia	N	22Oct2012 13:28:00
7	XYZ	000002	HYPO 2	Hypoglycemia	N	25Oct2012 13:59:00
8	XYZ	000002	HYPO 3	Hypoglycemia	N	17Nov2012 05:01:00

ADaM Dataset

Table 4.2.2: HbA1c Longitudinal Repeated Measures Analysis Results Metadata

Metadata Field	Metadata
DISPLAY IDENTIFIER	Table 4.2.1/Figure 4.2.1
DISPLAY NAME	Mean Change from Baseline in HbA1c (Percent) Longitudinal Repeated Measures Ana Period, Intention-to-treat Population
RESULT IDENTIFIER	Treatment difference results (LSMean, confidence interval, p-value)
PARAM	HbA1c (%)
PARAMCD	HBA1C
ANALYSIS VARIABLE	CHG (Change from baseline)
ANALYSIS REASON	SPECIFIED IN SAP
ANALYSIS PURPOSE	PRIMARY OUTCOME MEASURE
ANALYSIS DATASET	ADHBA1C

ARM v1

ARM Extension Technical Specification

Automation

qb:Observation	qb:Table	dim.population	dim.treatment	dim.parameter	dim.sex	dim.agecat	dim.statistic	analysisResult
1001	dm.summary	enrolled	Treatment.A	param.subjects	sex.ALL	agecat.ALL	stat.freq	100
1002	dm.summary	enrolled	Treatment.A	param.subjects	sex.F	agecat.ALL	stat.freq	60
1003	dm.summary	enrolled	Treatment.A	param.subjects	sex.F	agecat.ALL	stat.percent	60
1004	dm.summary	enrolled	Treatment.A	param.subjects	sex.M	agecat.ALL	stat.freq	40
1005	dm.summary	enrolled	Treatment.A	param.subjects	sex.M	agecat.ALL	stat.percent	40
1006	dm.summary	enrolled	Treatment.B	param.subjects	sex.ALL	agecat.ALL	stat.freq	50
1007	dm.summary	enrolled	Treatment.B	param.subjects	sex.F	agecat.ALL	stat.freq	30
1008	dm.summary	enrolled	Treatment.B	param.subjects	sex.F	agecat.ALL	stat.percent	60
1009	dm.summary	enrolled	Treatment.B	param.subjects	sex.M	agecat.ALL	stat.freq	20
1010	dm.summary	enrolled	Treatment.B	param.subjects	sex.M	agecat.ALL	stat.percent	40
1011	dm.summary	enrolled	Treatment.ALL	param.subjects	sex.ALL	agecat.ALL	stat.freq	150
1012	dm.summary	enrolled	Treatment.ALL	param.subjects	sex.F	agecat.ALL	stat.freq	90
1013	dm.summary	enrolled	Treatment.ALL	param.subjects	sex.F	agecat.ALL	stat.percent	60
1014	dm.summary	enrolled	Treatment.ALL	param.subjects	sex.M	agecat.ALL	stat.freq	60
1015	dm.summary	enrolled	Treatment.ALL	param.subjects	sex.M	agecat.ALL	stat.percent	40
1016	dm.summary	itt	Treatment.A	param.age	sex.ALL	agecat.ALL	stat.freq	100
1017	dm.summary	itt	Treatment.A	param.age	sex.ALL	agecat.ALL	stat.mean	40.7
1018	dm.summary	itt	Treatment.A	param.age	sex.ALL	agecat.ALL	stat.stdev	10.7
1019	dm.summary	itt	Treatment.A	param.age	sex.ALL	agecat.ALL	stat.median	37.0
1020	dm.summary	itt	Treatment.A	param.age	sex.ALL	agecat.ALL	stat.min	21.0
1021	dm.summary	itt	Treatment.A	param.age	sex.ALL	agecat.ALL	stat.max	66.0
1022	dm.summary	itt	Treatment.B	param.age	sex.ALL	agecat.ALL	stat.freq	50
1023	dm.summary	itt	Treatment.B	param.age	sex.ALL	agecat.ALL	stat.mean	41.2
1024	dm.summary	itt	Treatment.B	param.age	sex.ALL	agecat.ALL	stat.stdev	10.3
1025	dm.summary	itt	Treatment.B	param.age	sex.ALL	agecat.ALL	stat.median	36.0
1026	dm.summary	itt	Treatment.B	param.age	sex.ALL	agecat.ALL	stat.min	23.0
1027	dm.summary	itt	Treatment.B	param.age	sex.ALL	agecat.ALL	stat.max	67.0
1028	dm.summary	itt	Treatment.ALL	param.age	sex.ALL	agecat.ALL	stat.freq	150
1029	dm.summary	itt	Treatment.ALL	param.age	sex.ALL	agecat.ALL	stat.mean	40.9
1030	dm.summary	itt	Treatment.ALL	param.age	sex.ALL	agecat.ALL	stat.stdev	10.4
1031	dm.summary	itt	Treatment.ALL	param.age	sex.ALL	agecat.ALL	stat.median	37.0
1032	dm.summary	itt	Treatment.ALL	param.age	sex.ALL	agecat.ALL	stat.min	21.0
1033	dm.summary	itt	Treatment.ALL	param.age	sex.ALL	agecat.ALL	stat.max	67.0

Analysis Results Dataset

Reuse

Traceability

Table 4.2.1: HbA1c Longitudinal Repeated Measures Analysis - Table Shell

Protocol: XYZ — Page 1 of 2

HbA1c (%) Longitudinal Repeated Measures Analysis
24-Week Short-term Double-blind Treatment Period
Intention-to-treat Population

		Drug A N=125	Drug B N=125
BASELINE	N#	125	125
	Mean (SD)	X.XX(X.XXX)	X.XX (X.XXX)
WEEK 4	N#	XXX	XXX
	Change from baseline: Mean (SD)	X.XX (X.XXX)	X.XX (X.XXX)
	Adjusted change from baseline: Mean (SD)	X.XX (X.XXX)	X.XX (X.XXX)
	95% Confidence interval for adjusted mean	(XX.XX, XX.X)	(XX.XX, XX.X)
	Difference vs. Drug B (SE)		XX.XX (X.XXXX)
	95% Confidence interval for difference		(XX.XX, XX.X)
	P-value vs. Drug B		X.XXXX
...			
WEEK 12	N#	X.XX(X.XXX)	X.XX (X.XXX)
	Change from baseline: Mean (SD)	XXX	XXX
	Adjusted change from baseline: Mean (SD)	X.XX (X.XXX)	X.XX (X.XXX)
	95% Confidence interval for adjusted mean	X.XX (X.XXX)	X.XX (X.XXX)
	Difference vs. Drug B (SE)	(XX.XX, XX.X)	(XX.XX, XX.X)
	95% Confidence interval for difference		XX.XX (X.XXXX)
	P-value vs. Drug B		(XX.XX, XX.X)
			X.XXXX

N: the number of subjects in the Intention-to-treat (ITT) Population.
N#: the number of subjects in the ITT population with non-missing baseline and non-missing Week t value.
Repeated measures model: change = baseline treatment visit visit*treatment
Program Source: xxxxxxxx\xxxx\xxxx\t-hba1c-repmeas.sas <date>:<time>

Display

cdisc

Analysis Results Desired Future State

- Formal model for describing analyses and results as data
- Facilitate automated generation of results
- From static to machine readable results
- Improved navigation and reusability of analyses and results
- Support storage, access, processing and reproducibility of results
- Traceability to Protocol/SAP and to input ADaM data
- Open-source tools to design, specify, build and generate analysis results

Analysis Results Standards Goals

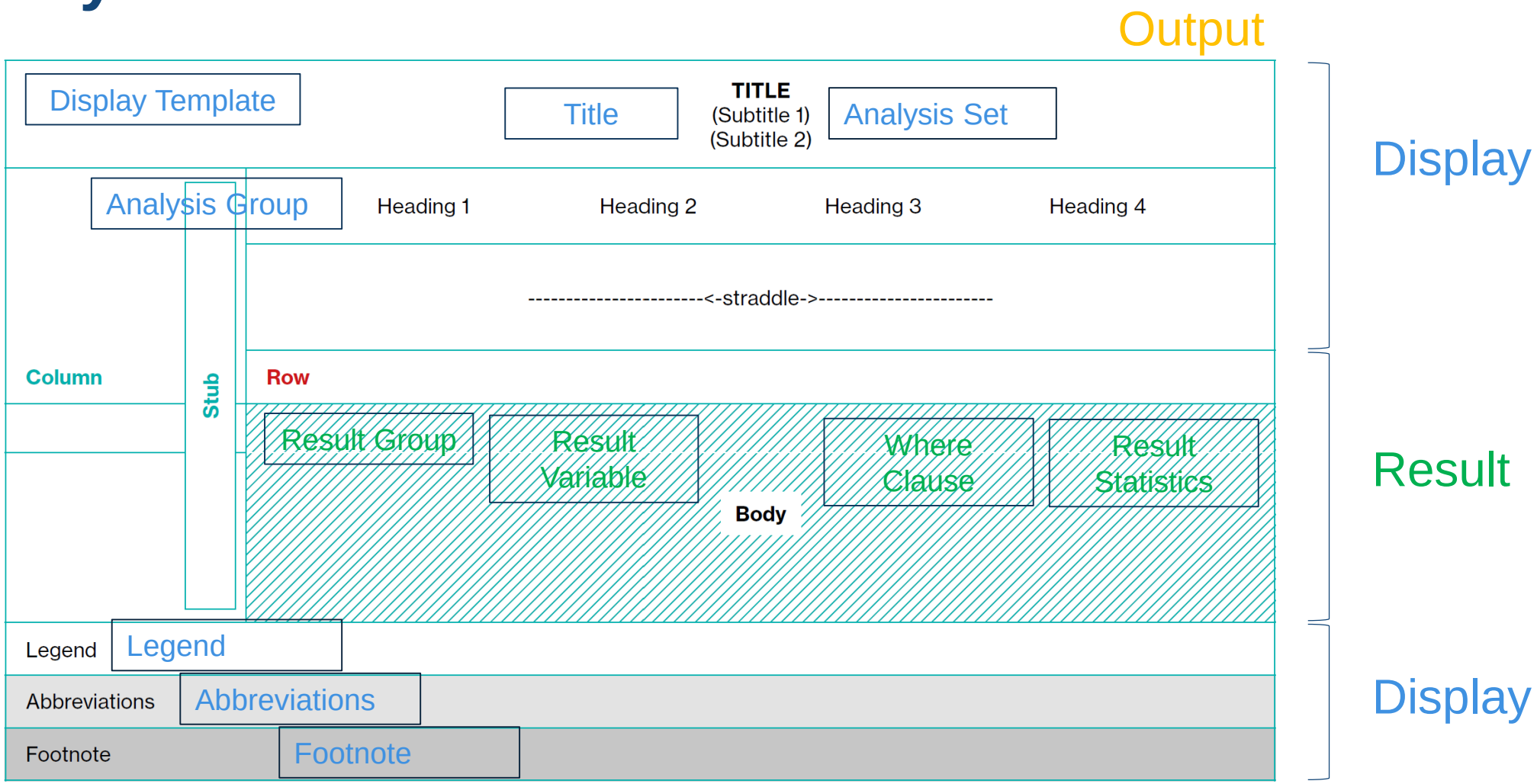
Analysis Results Metadata Technical Specification (ARM-TS), to support automation, traceability, and creation of data displays

Define an Analysis Results Data (ARD) structure, to support reuse and reproducibility of results data

Illustrate and exercise ARD and ARM-TS with a set of machine-readable common safety displays

cdisc

Key Metadata Elements of a Table



Reference: PHUSE White Paper "*General Output Tips and Considerations*", Doc ID: WP-034, Version 1.0, Aug 2020

Demographics Analysis Results and Metadata

Display Template | Title | Analysis Set

Table 2. Baseline Demographic and Clinical Characteristics, Safety Population, Pooled Analyses (or Trial X)

Characteristic	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Placebo N = XXX n (%)	Active Control N = XXX n (%)	Total Population N = XXX n (%)
Sex, n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Male	n (%)	n (%)	n (%)	n (%)	n (%)
Female	n (%)	n (%)	n (%)	n (%)	n (%)
Age, years	**X.X (Y.Y)**	**X.X (Y.Y)**	**X.X (Y.Y)**	**X.X (Y.Y)**	**X.X (Y.Y)**
Mean (SD)	X.X (Y.Y)	X.X (Y.Y)	X.X (Y.Y)	X.X (Y.Y)	X.X (Y.Y)
Median (min, max)	X.X (Y.Y, Z.Z)	X.X (Y.Y, Z.Z)	X.X (Y.Y, Z.Z)	X.X (Y.Y, Z.Z)	X.X (Y.Y, Z.Z)
Age groups (years), n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
≥17 to <65	n (%)	n (%)	n (%)	n (%)	n (%)
≥65	n (%)	n (%)	n (%)	n (%)	n (%)
≥65 to <75	n (%)	n (%)	n (%)	n (%)	n (%)
≥75	n (%)	n (%)	n (%)	n (%)	n (%)
Race, n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
American Indian or Alaska Native Asian	n (%)	n (%)	n (%)	n (%)	n (%)
Black or African American	n (%)	n (%)	n (%)	n (%)	n (%)
Native Hawaiian or Other Pacific Islander	n (%)	n (%)	n (%)	n (%)	n (%)
White	n (%)	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)	n (%)

Analysis Group

Result Group | Result Variable | Where Clause | Result Statistics

Source: [include Applicant source, datasets and/or software tools used].
[1] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: N, number of patients in treatment arm; n, number of patients with given characteristic; SD, standard deviation

Footnote | Abbreviations | Legend

cdisc

Analysis Results Dataset Example: Demographics

Identifiers		Analysis Group			Result Variable			Results Statistic		
Name	Title	Dataset	Variable	Value	Variable	Value	Label	Value	Name	Label
Table 2	Baseline Demographics and Clinical Characteristics, Safety Population	ADSL	TR01X	Drug Name Dosage X	SEX	M	Male	53	Count	n
Table 2	Baseline Demographics and Clinical Characteristics, Safety Population	ADSL	TR01X	Drug Name Dosage X	SEX	M	Male	61.6	Percent	%
Table 2	Baseline Demographics and Clinical Characteristics, Safety Population	ADSL	TR01X	Drug Name Dosage X	SEX	F	Female	33	Count	n
Table 2	Baseline Demographics and Clinical Characteristics, Safety Population	ADSL	TR01X	Drug Name Dosage X	SEX	F	Female	38.4	Percent	%

Analysis Results Dataset Example: Demographics

Identifiers		Analysis Group			Result Variable			Results Statistic		
Name	Title	Dataset	Variable	Value	Variable	Value	Label	Value	Name	Label
Table 2	Baseline Demographics and Clinical Characteristics, Safety Population	ADSL	TR01X	Drug Name Dosage X	SEX	M	Male	53	Count	n
Table 2	Baseline Demographics and Clinical Characteristics, Safety Population	ADSL	TR01X	Drug Name Dosage X	SEX	M	Male	61.6	Percent	%
Table 2	Baseline Demographics and Clinical Characteristics, Safety Population	ADSL	TR01X	Drug Name Dosage X	SEX	F	Female	33	Count	n
Table 2	Baseline Demographics and Clinical Characteristics, Safety Population	ADSL	TR01X	Drug Name Dosage X	SEX	F	Female	38.4	Percent	%

Traceability to the underlying ADaM dataset

cdisc

Machine Readable TFL Shells

```xml
<?xml version="1.0" encoding="UTF-8"?>
<TableShell>
    <ID>TEAE.01</ID>
    <Ordinal>1</Ordinal>
    <Type>Table</Type>
    <Name>TEAE-Overall</Name>
    <Title>Overall Summary of Treatment Emergent Adverse Events</Title>
    <Population>Safety Population</Population>
    <ColDefs>
        <TreatmentVar Name="TRT01" Num="4" StatOID="ST.01"/>
        <ComputeCols>
            <ComputeCol Name="Overall" StatOID="ST.01"/>
        </ComputeCols>
    </ColDefs>
    <ResultGroupDef OID="EAE.01.GRP.01" OrderNumber="1"> [3 lines]
    <ResultGroupDef OID="TEAE.01.GRP.02" OrderNumber="2"> [2 lines]
    <ResultDef OID="TEAE.01.GRP.01.RES.01"> [4 lines]
    <ResultDef OID="TEAE.01.GRP.01.RES.02">
        <Label>Subjects with a related AE</Label>
        <StatRef StatOID="ST.01"/>
        <StatRef StatOID="ST.02"/>
    </ResultDef>
    <ResultDef OID="TEAE.01.GRP.02.RES.01">
        <Label>Number of AEs</Label>
        <StatRef StatOID="ST.01"/>
    </ResultDef>
    <StatDef OID="ST.01" Name="N">
        <Label>Number of Subjects</Label>
        <Format>XX</Format>
    </StatDef>
    <StatDef OID="ST.02" Name="PCT">
        <Label>Percentage of Subjects</Label>
        <Format>(XX.X%)</Format>
    </StatDef>
</TableShell>
```

Adverse Events

Table 35. Patients With Adverse Events[1] by System Organ Class, Safety Population, Pooled Analysis (or Trial X)[2]

System Organ Class	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3,4]
Blood and lymphatic system	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Cardiac disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Ear and labyrinth disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Endocrine disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Eye disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Gastrointestinal disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Hepatobiliary disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Immune system disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Infections and infestations	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Injury, poisoning and procedural complications	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

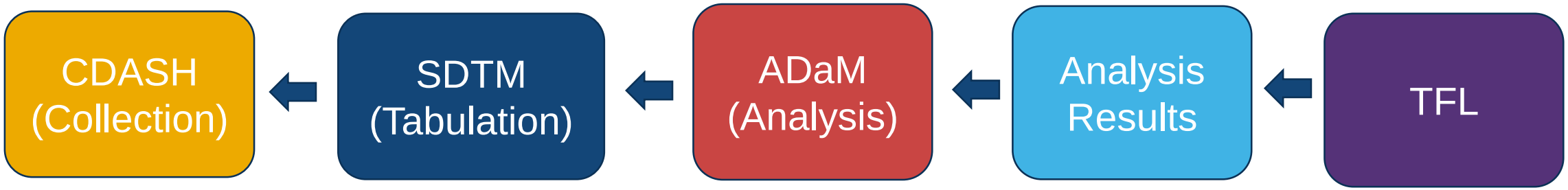
Source: [include Applicant source, datasets and/or software tools used].
[1] Treatment-emergent adverse event defined as [definition].
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
[4] Table display is ordered by the risk difference.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event

Develop schema for machine readable TFL shells

cdisc

End Goal: Reducing Unnecessary Variability

Standardized Metadata



Adverse Events

Table 35. Patients With Adverse Events[1] by System Organ Class, Safety Population, Pooled Analysis (or Trial X)[2]

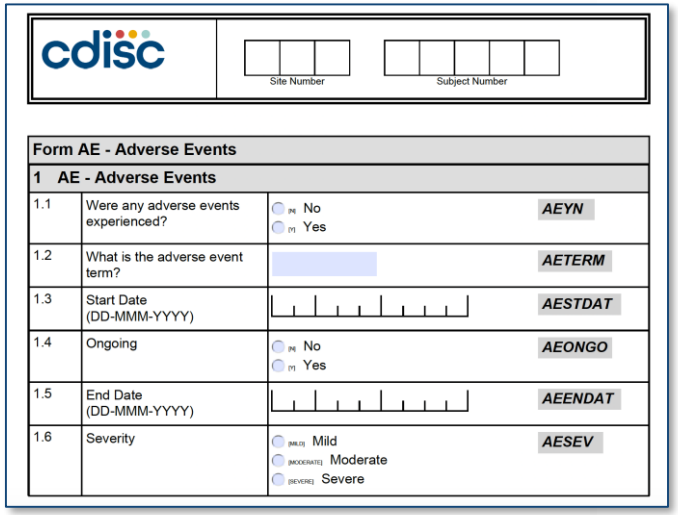
System Organ Class	Drug Name Dosage X N = XXX n (%)	Drug Name Dosage Y N = XXX n (%)	Active Control N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[3,4]
Blood and lymphatic system	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Cardiac disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Ear and labyrinth disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Endocrine disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Eye disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Gastrointestinal disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Hepatobiliary disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Immune system disorders	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Infections and infestations	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Injury, poisoning and procedural complications	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Treatment-emergent adverse event defined as [definition].
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
[4] Table display is ordered by the risk difference.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event

End Goal: Reducing Unnecessary Variability

Standardized Metadata

CDASH (Collection) → SDTM (Tabulation) → ADaM (Analysis) → Analysis Results → TFL



cdisc

Site Number | Subject Number

Form AE - Adverse Events			
1 AE - Adverse Events			
1.1	Were any adverse events experienced?	(N) No (Y) Yes	AEYN
1.2	What is the adverse event term?		AETERM
1.3	Start Date (DD-MMM-YYYY)		AESTDAT
1.4	Ongoing	(N) No (Y) Yes	AEONGO
1.5	End Date (DD-MMM-YYYY)		AEENDAT
1.6	Severity	(MILD) Mild (MODERATE) Moderate (SEVERE) Severe	AESEV

Support for FDA Standard Safety Tables and Figures

- For a selection of FDA tables and figures, create packages containing
  - Machine readable displays
  - Associated analysis results metadata
  - Analysis results dataset examples
  - Underlying ADaM datasets

- Make packages freely available on the CDISC website

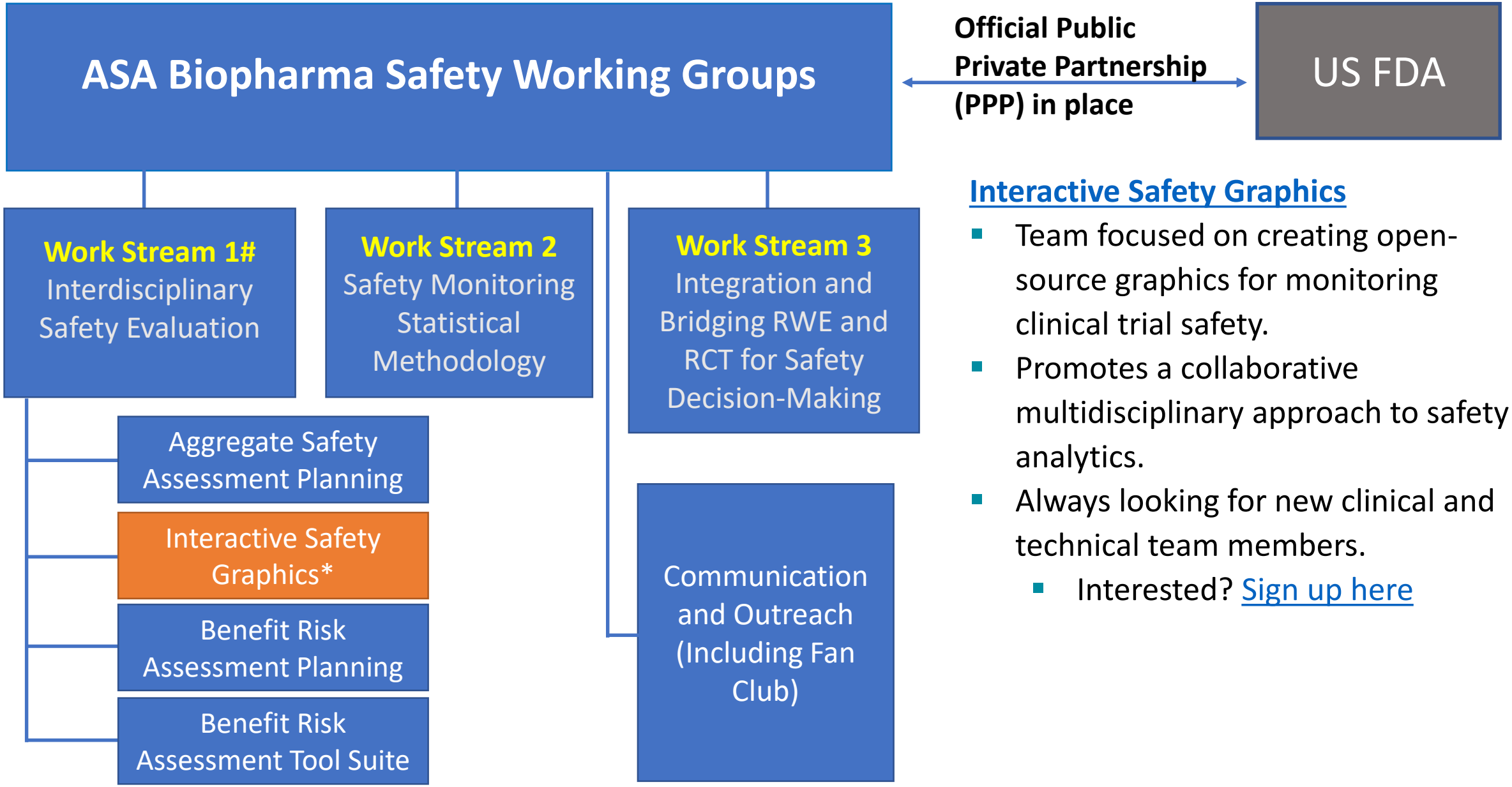
- Create schema for TFL shells

Interactive Safety Graphics: Innovative Approaches to Safety Analytics

Jeremy Wildfire

14 September 2022

Duke-Margolis Public Workshop on Advancing Premarket Safety Analytics



#Joint collaboration between DIA Communities and ASA Biopharma: DIA-ASA Interdisciplinary Safety Evaluation (DAISE) working group

Interactive Safety Graphics

- Team focused on creating open-source graphics for monitoring clinical trial safety.
- Promotes a collaborative multidisciplinary approach to safety analytics.
- Always looking for new clinical and technical team members.
  - Interested? Sign up here

safetyGraphics R Package

An open-source framework for evaluation of clinical trial safety

Links: CRAN | GitHub | Demo

DIA

Therapeutic Innovation & Regulatory Science
1–5
© The Author(s) 2018
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/2168479018754846
tirs.sagepub.com

Safety Explorer Suite: Interactive Safety Monitoring for Clinical Trials

Jeremy Wildfire, MS[1], Ryan Bailey, MA[1], Rebecca Z. Krouse, MS[1], Spencer Childress, BS[1], Britt Sikora, MS[1], Nathan Bryant, BS[1], Shane Rosanbalm, MS[1], Emily Wilson, BS[1], and Jack G. Modell, MD[1]

Abstract

Background: Frequent and thorough monitoring of patient safety is a requirement of clinical trials research. Safety data are traditionally reported in a tabular or listing format, which often translates into many pages of static displays. This poses the risk that clinically relevant signals will be obscured by the sheer volume of data reported. Interactive graphics enable the delivery of the vast scope of information found in traditional reports, but allow the user to interact with the charts in real time, focusing on signals of interest. *Methods:* Clinical research staff, including biostatisticians, project managers, and a medical monitor, were consulted to guide the development of a set of interactive data visualizations that enable key safety assessments for participants. The resulting "Safety Explorer" is a set of 6 interactive, web-based, open source tools designed to address the shortcomings of traditional, static reports for safety monitoring. *Results:* The Safety Explorer is freely available on GitHub as individual JavaScript libraries: Adverse Event Explorer, Adverse Event Timelines, Safety Histogram, Safety Outlier Explorer, Safety Results Over Time, and Safety Shift Plot; or in a single combined framework: Safety Explorer Suite. The suite can also be utilized through its R interface, the safetyexploreR package. *Conclusions:* The Safety Explorer provides interactive charts that contain the same information available in standard displays, but the interactive interface allows for improved exploration of patterns and comparisons. Medical Monitors, Safety Review Boards, and Project Teams can use these tools to effectively track and analyze key safety variables and study endpoints.

Keywords

safety reporting, medical monitoring, interactive graphics, JavaScript, R

Introduction

Data visualizations and statistical graphics have a well-established history in the conduct of clinical trials, but traditional methods are focused on static displays of data. In recent years, web-based interactive graphics have increased in popularity and usage,[1] including many innovative scientific data visualizations.[2-4] The clinical research industry seems poised to tap into this trend, as companies like SAS and Tableau now offer interactive online charting tools for clinical research and organizations such as PhUSE[5] and CTSPedia[6] encourage the application of innovative data visualization methods in clinical trials.

Statistical graphics are especially useful for safety oversight and risk-based monitoring.[7-9] The appeal of these tools for clinical investigators comes from the need to constantly monitor data and quickly identify concerns while trials are in progress. Interactive monitoring tools offer a promising alternative to traditional reporting approaches, which are characterized by the tedious review of pages of text-based listings.[7,10] Such methods are not merely inefficient but also problematic, as the sheer volume of data reported threatens to obscure clinically relevant signals.

Interactive reports give researchers an intuitive and streamlined workflow for data analysis by combining a summary view of a given data domain with on-demand access to data listings for observations of special interest.[11] This approach can cover the broad scope of information found in traditional safety reports, while improving the signal-to-noise ratio and eliminating the need to sort through pages of static listings. Using these principles of interactive data visualization, we created the Safety Explorer, a set of open-source interactive graphics designed specifically for safety monitoring in clinical trials.

While other interactive data visualization tools for clinical research exist, they are generally packaged as add-ons to expensive clinical trial analytics environments and cannot be

[1] Rho, Chapel Hill, NC, USA

Submitted 4-Oct-2017; accepted 20-Dec-2017

Corresponding Author:
Ryan Bailey, MA, Rho, ORCiD# 0000-0001-8223-5302, 6330 Quadrangle Drive, Chapel Hill, NC 27517, USA.
Email: ryan_bailey@rhoworld.com

The Safety Explorer Suite: Interactive Safety Monitoring for Clinical Trials, Wildfire et al. 2018
Paper - Repo

Therapeutic Innovation & Regulatory Science
https://doi.org/10.1007/s43441-021-00319-3

DIA

ORIGINAL RESEARCH

A New Paradigm for Safety Data Signal Detection and Evaluation Using Open-Source Software Created by an Interdisciplinary Working Group

James Buchanan, PharmD[1] · Mengchun Li, MD[2] · Xiao Ni, PhD[3] · Jeremy Wildfire, PhD[4]

Received: 4 February 2021 / Accepted: 18 June 2021

Abstract

Techniques to evaluate large amounts of safety data continue to evolve based on a greater understanding of how the brain processes visual information and the advancement of programing tools. The Interactive Safety Graphics Task Force of the American Statistical Association Biopharmaceutical Safety Working Group has assembled a multidisciplinary team of experts in a variety of domains to develop the next generation of open-source visual analytical tools for safety data based on these advances. The multidisciplinary approach resulted in the rapid development of the first tool, a novel interactive version of the familiar Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) graphic along with a unique clinical workflow to guide the reviewer through the data analysis. This now serves as the model for the team to expand the open-source platform into a suite of other interactive safety analysis tools.

Keywords Drug safety · Pharmacovigilance · Interactive graphics

Background

Safety monitoring during clinical trials is an essential component in drug development. Thorough reviews of medical safety data at regular intervals are critical to characterize the drug safety profile as early as possible to protect patient safety and, eventually, public health. Traditionally, safety data were only comprehensively reviewed at the end of trials. Safety data from ongoing studies, when available, are typically presented in long tedious listings, which are time-consuming to review and less intuitive to inform critical insights. Hence, a thorough review is difficult to conduct on an ongoing basis. As analytical tools became available, comprehensive safety data could be reviewed in using static graphics, usually at certain planned time points. While an improvement on the less informative listings, static graphics are still of limited utility since they do not allow patient-level data exploration, nor population-level ad hoc analyses related to questions arising during the review process. With these inefficient methods, safety data reviews during clinical trials are less frequent and less comprehensive than they ideally should be performed. The result is that safety signals are not identified promptly, and the evaluation of these signals is delayed leading to unnecessary risk in the study patient population. Obviously, this is not in the best interest of any of the various stakeholders during clinical development.

An interactive graphical tool would facilitate ongoing, timely, and flexible safety data exploration to identify safety signals as well as offer capabilities to evaluate events of interest at a population level and the cases of interest at a patient level. Yet, interactive safety displays also have limitations; many such tools do not guide the user as to how to best utilize their features to resolve the important clinical questions when evaluating a safety signal. Graphical display tools are most powerful when paired with an appropriate medical approach to interrogate the data for evidence for or against a causal association between the safety finding and the study drug. Thus, the development of a medically valid clinical workflow with suggested evaluations and guidance as to their interpretation greatly improves the utility of the interactive tool, while also encouraging

✉ James Buchanan
jbuchanan@covilance.com

[1] Covilance, LLC, 2723 Sequoia Way, Belmont, CA 94002, USA
[2] TB Alliance, New York, NY, USA
[3] Sarepta, Inc., Boston, MA, USA
[4] Gilead Sciences, Foster City, CA, USA

Published online: 19 July 2021

Springer

A New Paradigm for Safety Signal Detection and Evaluation Using Open-Source Software Created by an Interdisciplinary Working Group. 2021 Buchanan
Paper – Repo

Contemporary Clinical Trials 98 (2020) 106154

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Data monitoring committees for clinical trials evaluating treatments of COVID-19

Tobias Mütze[a], Tim Friede[b,c,*]

[a] Statistical Methodology, Novartis Pharma AG, Basel, Switzerland
[b] Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany
[c] DZHK (German Center for Cardiovascular Research), partner site Göttingen, Göttingen, Germany

ARTICLE INFO

Keywords:
Data safety monitoring boards
SARS-CoV-2
Pandemic
Randomized controlled trials
Adverse events

ABSTRACT

The first cases of coronavirus disease 2019 (COVID-19) were reported in December 2019 and the outbreak of SARS-CoV-2 was declared a pandemic in March 2020 by the World Health Organization. This sparked a plethora of investigations into diagnostics and vaccination for SARS-CoV-2, as well as treatments for COVID-19. Since COVID-19 is a severe disease associated with a high mortality, clinical trials in this disease should be monitored by a data monitoring committee (DMC), also known as data safety monitoring board (DSMB). DMCs in this indication face a number of challenges including fast recruitment requiring an unusually high frequency of safety reviews, more frequent use of complex designs and virtually no prior experience with the disease. In this paper, we provide a perspective on the work of DMCs for clinical trials of treatments for COVID-19. More specifically, we discuss organizational aspects of setting up and running DMCs for COVID-19 trials, in particular for trials with more complex designs such as platform trials or adaptive designs. Furthermore, statistical aspects of monitoring clinical trials of treatments for COVID-19 are considered. Some recommendations are made regarding the presentation of the data, stopping rules for safety monitoring and the use of external data. The proposed stopping boundaries are assessed in a simulation study motivated by clinical trials in COVID-19.

1. Introduction

The first clusters of Coronavirus disease 2019 (COVID-19) cases were reported in December 2019 and January 2020 [1–4]. On 11 March 2020, the World Health Organization declared the outbreak of SARS-CoV-2 a pandemic [5]. As of 18 July 2020, over 14 million cases and over 600,000 deaths of COVID-19 were confirmed according to the Center for Systems Science and Engineering at Johns Hopkins University [6,7].

A search in clinicaltrials.gov for studies targeting the conditions "COVID-19", "COVID", or "SARS-CoV-2" shows that the first studies surrounding COVID-19 were registered in late January 2020 and until July 2020 over 2500 studies were registered. Clinical trials studying interventions for COVID-19 primarily focus on short-term endpoints assessing mortality, morbidity, the requirement for mechanical ventilation or ICU care. For instance, the primary endpoint in the RECOVERY trial (ClinicalTrials.gov Identifier: NCT04381936) is all-cause mortality at 28 days [8], the primary endpoint in the Adaptive COVID-19 Treatment Trial (ACTT; ClinicalTrials.gov Identifier: NCT04280705) was time to recovery within 28 days after enrollment [9], and the primary endpoint in the GS-US-540-5773 trial (ClinicalTrials.gov Identifier: NCT04292899) was the clinical status on day 14, assessed on a 7-point ordinal scale [10].

Well-conducted double-blind randomized controlled trials are considered the gold standard for clinical trials and there have been calls for their rigorous application in COVID-19 [11]. However, conducting a clinical trial for a pandemic disease to established standards in the midst of an evolving pandemic poses a number of challenges [12]. For instance, the location of areas with high numbers of infections changes over time. Therefore, clinical trial sites might need to pause or even stop recruitment which in turn means that new sites have to be opened in different locations. Sites in locations severely affected by the pandemic might be able to screen, randomize and treat a large number of subjects within a short period of time, however, this brings challenges for on-site trial personnel to properly document the cases and enter the data in a timely manner into the study database. Moreover, due to the seriousness of COVID-19, standard of care or best available therapy instead of placebo are included as comparator in many trials, at least as of Summer 2020, but what constitutes standard of care or best available therapy is changing rapidly due to efficacious treatments being

* Corresponding author at: Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany.
E-mail address: tim.friede@med.uni-goettingen.de (T. Friede).

https://doi.org/10.1016/j.cct.2020.106154
Received 13 August 2020; Accepted 15 September 2020
Available online 19 September 2020
1551-7144/

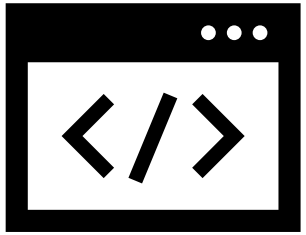
Data Monitoring committees for clinical trials evaluating treatments of COVID-19. Tobias Mütze and Tim Friede. 2020 - Paper

ISG Guiding Principles

https://safetygraphics.github.io/

Open Source

Highly Collaborative

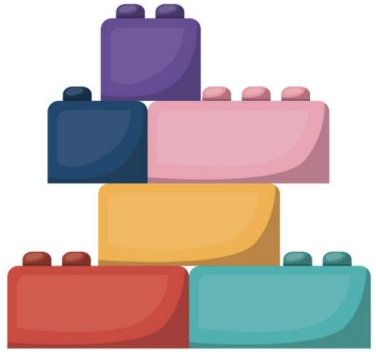


Interactive

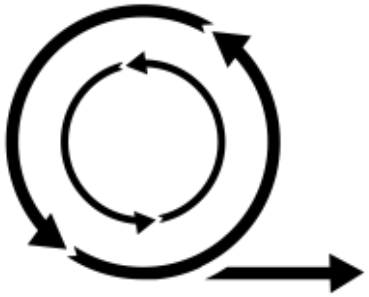
Easy to use

cdisc

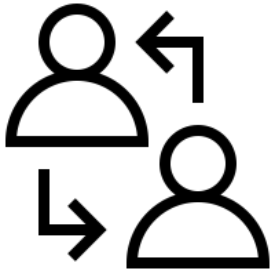
Data Standard Compliant



Extensible Data Model

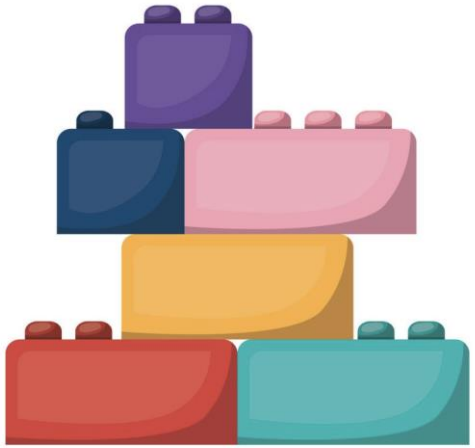


Agile



Engaging

- Across Companies
- Across Functional Areas
- Across Technologies
- Across Biotech Sectors
- Public/Private Partnership with CDER



Study-Specific Inputs

- Study Data - Domain-level Study Data
- Data Mapping - List identifying the key columns/fields in your data

General Inputs used across multiple studies

- Charts Specifications – Metadata and code defining the charts used in the app.
- Chart Mapping – List of key data elements required for each chart.

Study Data

Chart Specs

Data + Chart Mappings

Web Application

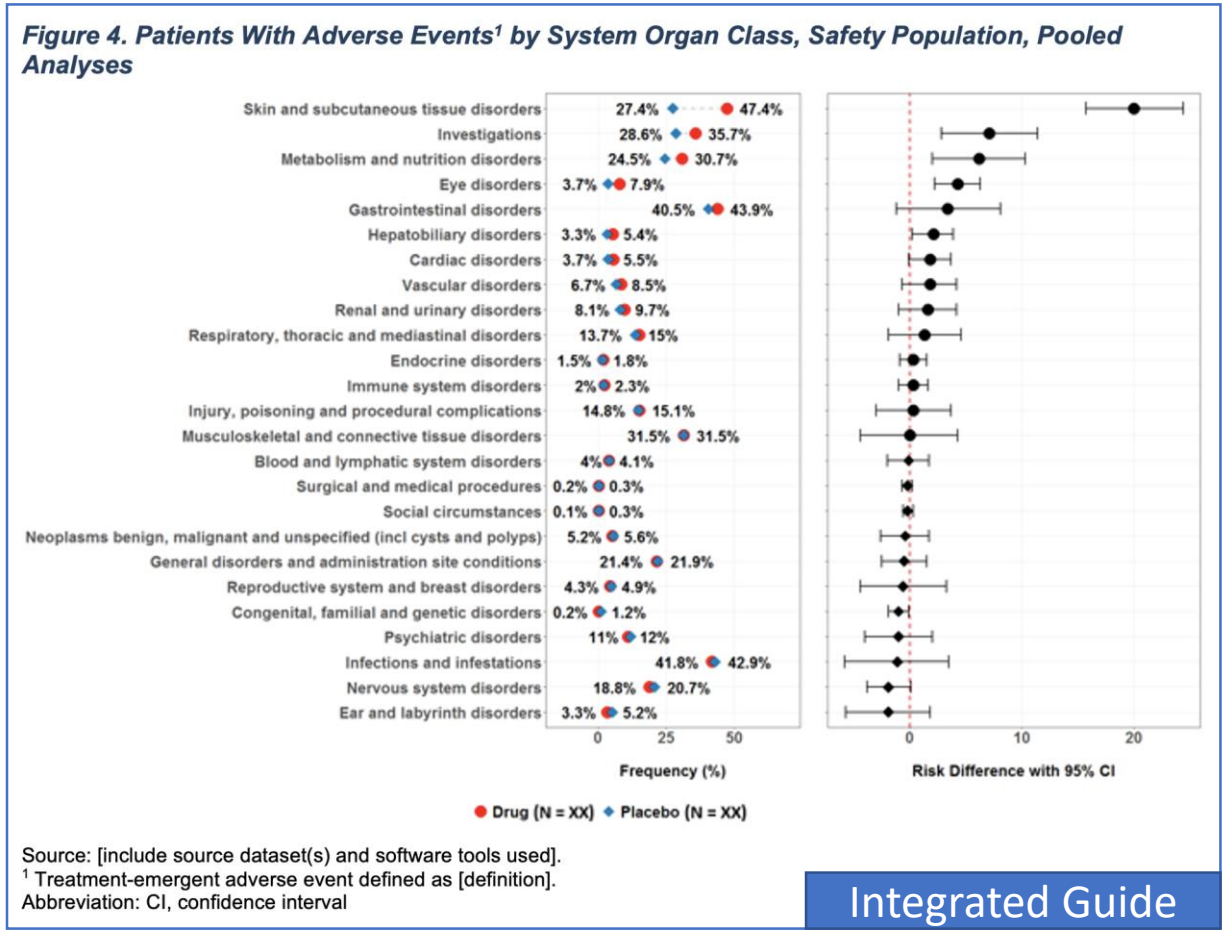
Stand-alone Reports

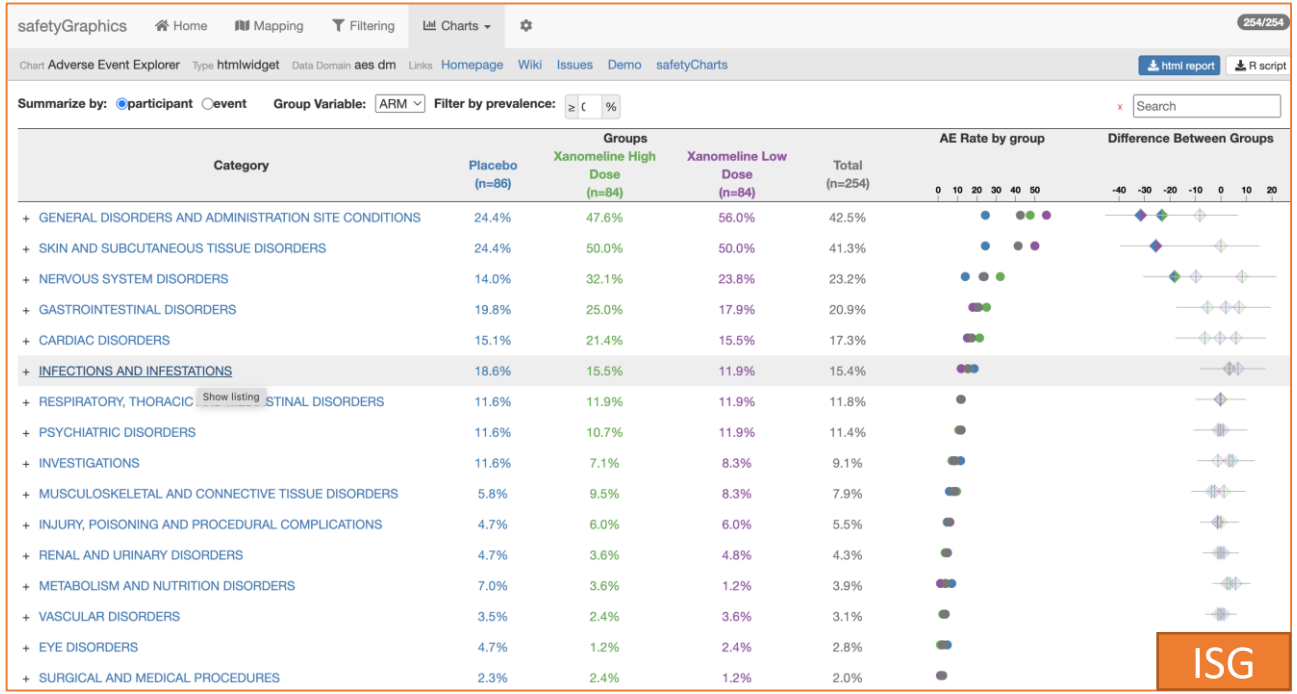
Chart Code

Application Code

Synergy with the Integrated Guide

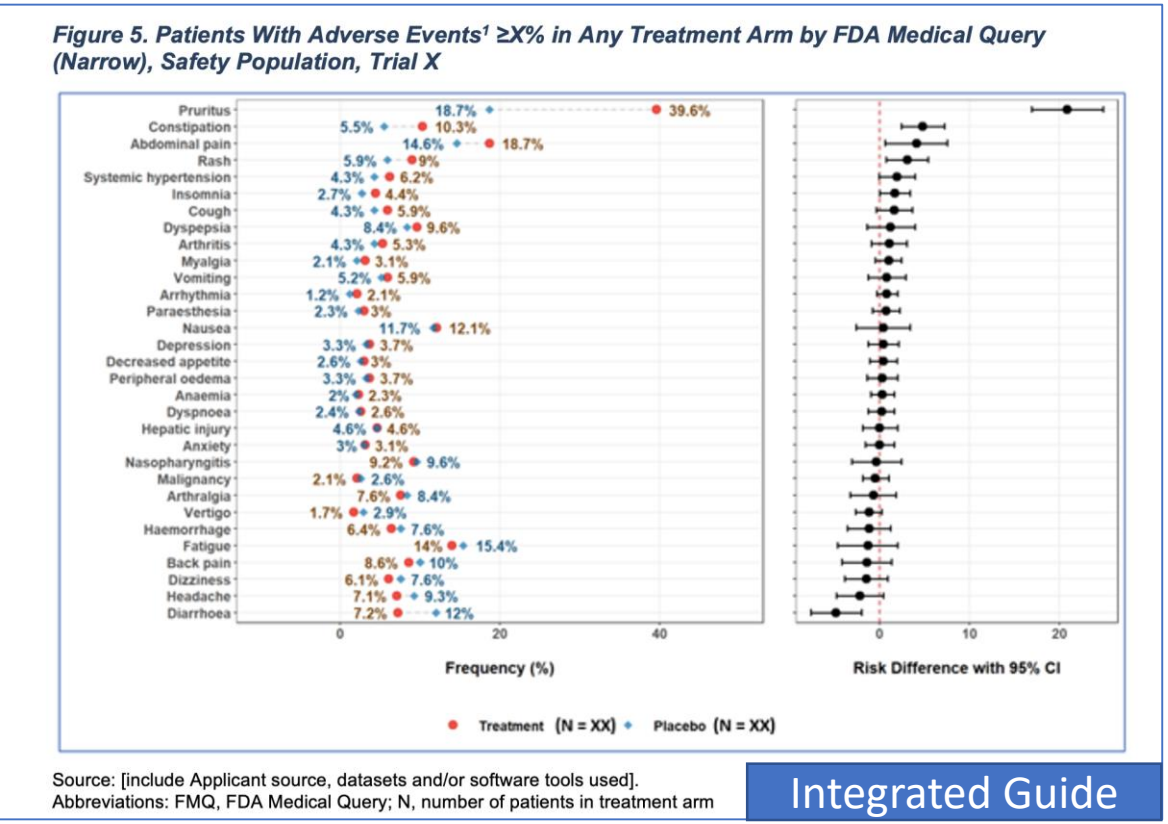
Figure 4. Adverse Events by System Organ Class





Synergy with the Integrated Guide

Figure 5. Adverse Events by FDA Medical Query



Source: [include Applicant source, datasets and/or software tools used].
Abbreviations: FMQ, FDA Medical Query; N, number of patients in treatment arm

Integrated Guide

Filter by Prevalence

Summarize by: participant event Group Variable: ARM Filter by prevalence: ≥ 10 %

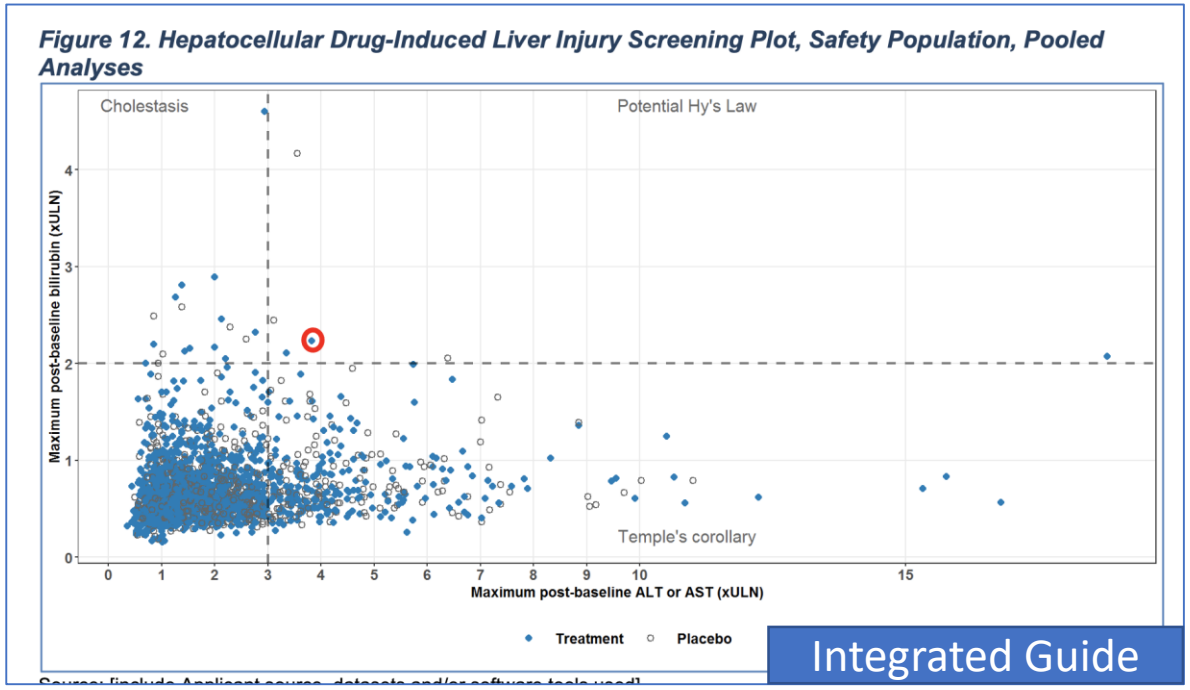
Category	Placebo (n=86)	Groups: Xanomeline High Dose (n=84)	Xanomeline Low Dose (n=84)	Total (n=254)	AE Rate by group	Difference Between Groups
- GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	24.4%	47.6%	56.0%	42.5%		
APPLICATION SITE PRURITUS	7.0%	26.2%	26.2%	19.7%		
APPLICATION SITE ERYTHEMA	3.5%	17.9%	14.3%	11.8%		
APPLICATION SITE DERMATITIS	5.8%	8.3%	10.7%	8.3%		
APPLICATION SITE IRRITATION	3.5%	10.7%	10.7%	8.3%		
- SKIN AND SUBCUTANEOUS TISSUE DISORDERS	24.4%	50.0%	50.0%	41.3%		
PRURITUS	9.3%	31.0%	27.4%	22.4%		
ERYTHEMA	10.5%	16.7%	17.9%	15.0%		
RASH	5.8%	13.1%	15.5%	11.4%		
- NERVOUS SYSTEM DISORDERS	14.0%	32.1%	23.8%	23.2%		
DIZZINESS	2.3%	14.3%	9.5%	8.7%		
- GASTROINTESTINAL DISORDERS	19.8%	25.0%	17.9%	20.9%		
DIARRHOEA	10.5%	4.8%	6.0%	7.1%		
+ CARDIAC DISORDERS	15.1%	21.4%	15.5%	17.3%		
+ INFECTIONS AND INFESTATIONS	18.6%	15.5%	11.9%	15.4%		
+ RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	11.6%	11.9%	11.9%	11.8%		
+ PSYCHIATRIC DISORDERS	11.6%	10.7%	11.9%	11.4%		

ISG

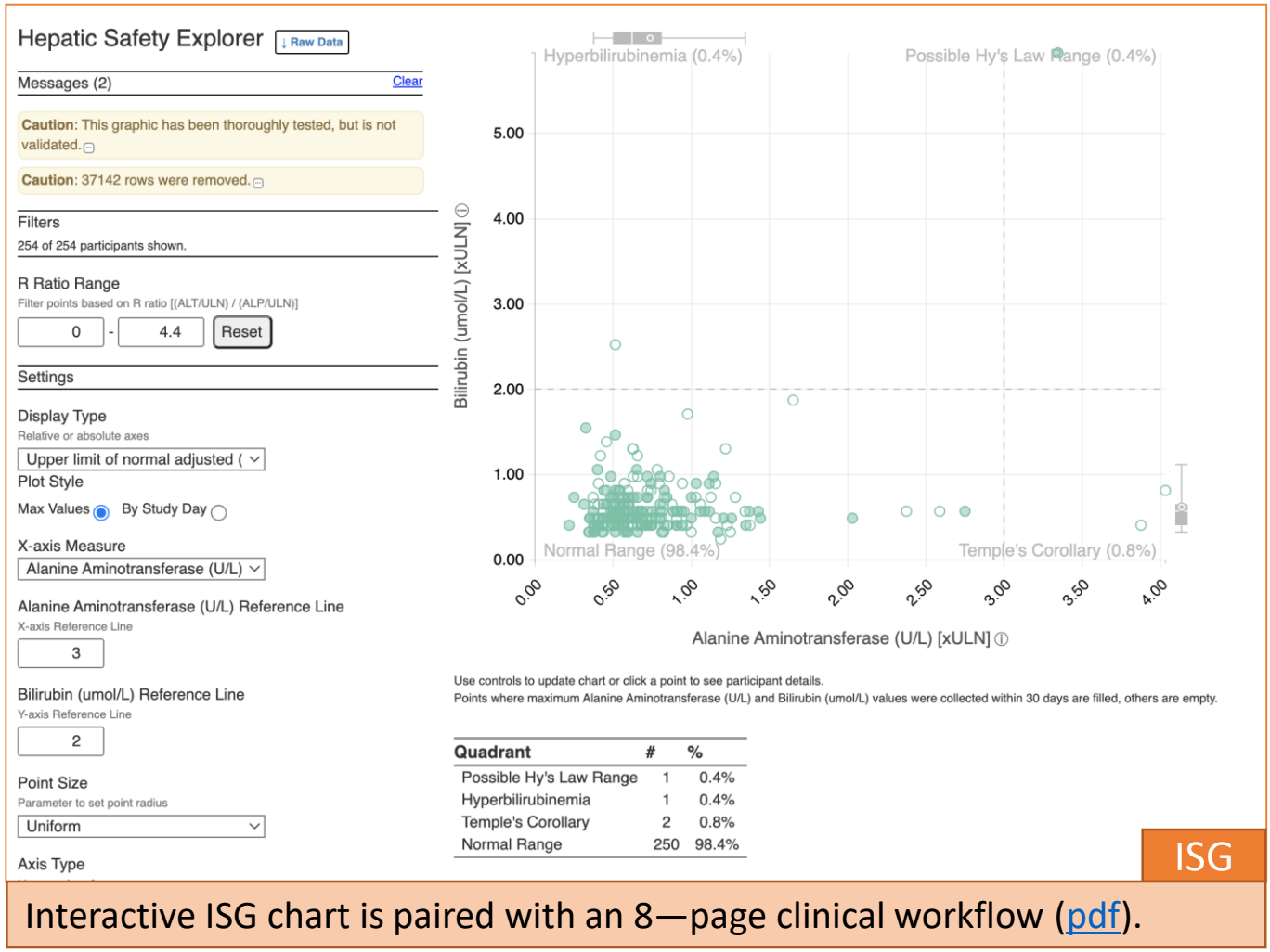
Drill down to Med Query

Synergy with the Integrated Guide

Figure 12. Hepatocellular Drug-induced Liver Injury



Integrated Guide

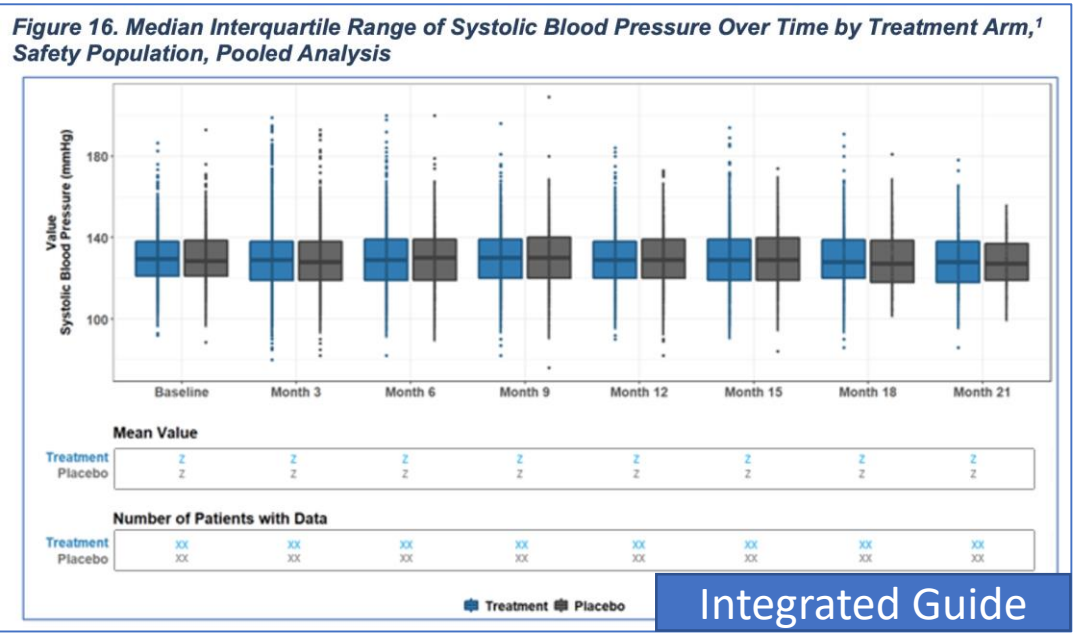


ISG

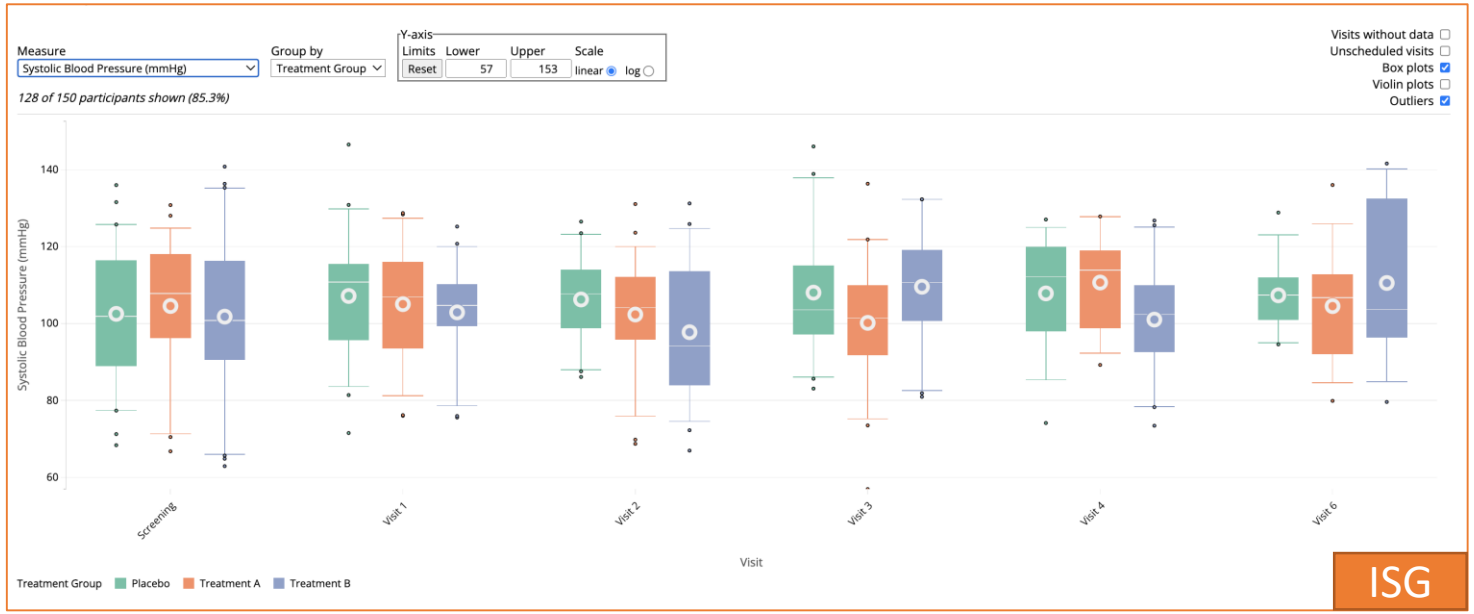
Interactive ISG chart is paired with an 8—page clinical workflow (pdf).

Synergy with the Integrated Guide

Figure 16. IQR of Systolic BP over time



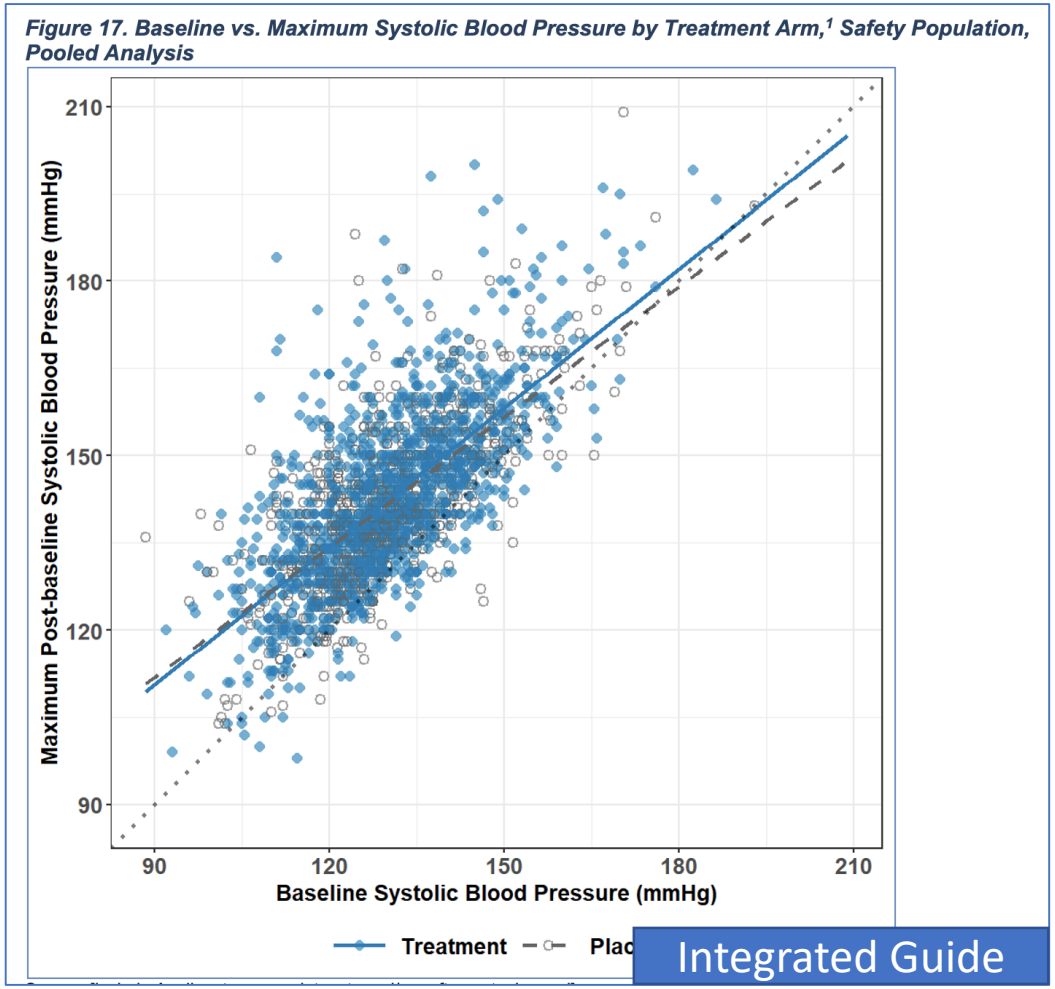
Integrated Guide



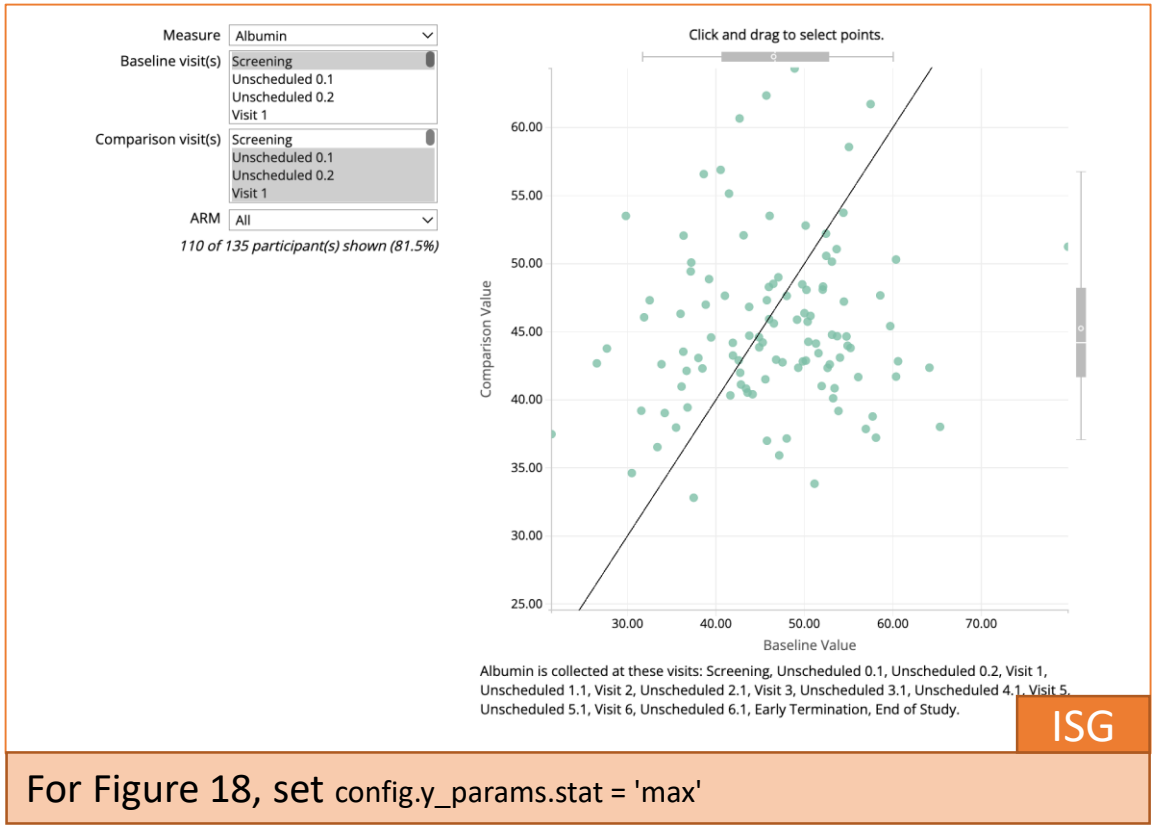
ISG

Synergy with the Integrated Guide

Figure 17/18. Baseline vs. Min/Max Systolic BP



Integrated Guide



ISG

For Figure 18, set config.y_params.stat = 'max'

Next Steps

- Further Synchronize ISG with outputs from the Integrated Guide
  - Update default configuration in existing charts to match IG
  - Automatically generate static charts using IG specifications
  - Add option to create a stand-alone report including charts + source code
- Extend Exploratory Capabilities to new Safety Domains
  - Nephrotoxicity
  - ECG/QT
  - Patient Profile
  - Benefit-Risk

Discussion Questions

1. What are the strengths of the Integrated Guide and how can the Integrated Guide be improved?
2. What promising practices exist for presenting safety data into tables and figures? How are these practices implemented and validated? What are the major obstacles to overcome?
3. Please share your thoughts on the definition of treatment emergent adverse event presented by the FDA?
4. What new approaches or technologies or methods can help enhance identification of premarket safety signals in clinical trials?
5. What metadata elements and additional materials are needed to ensure reproducibility of safety graphics?

Closing Remarks

Marianne Hamilton Lopez, PhD, MPA

Senior Research Director, Duke-Margolis Center for Health Policy

Thank You!

Contact Us

healthpolicy.duke.edu

Subscribe to our monthly newsletter at
dukemargolis@duke.edu

1201 Pennsylvania Avenue, NW, Suite 500
Washington, DC 20004

DC office: 202-621-2800
Durham office: 919-419-2504

Follow Us

DukeMargolis

@DukeMargolis

@DukeMargolis

Duke Margolis