Safety Analytics in the Office of New Drugs, CDER/FDA

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Disclaimer

- This presentation reflects the views of the presenter and should not be construed to represent FDA's or CDISC views or policies.

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- Board certified in Internal Medicine, Endocrinology and Clinical Informatics.
- Joined Office of New Drugs in 2008 and worked as a reviewer for 7 years, and now a founding director of the Biomedical Informatics team in the office of New Drugs/CDER/FDA since 2015
- As an AD for Biomedical informatics and regulatory review science, she leads safety analytics and informatics including data standards, data integrity/data quality, and Clinical reviewer training & mentoring activities in OND
- Co-Chair of the CDER Safety analytic control board, the FDA Medical Queries working group and chair of the Office of New Drugs Safety Standard tables and Figures Working Group.

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.

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

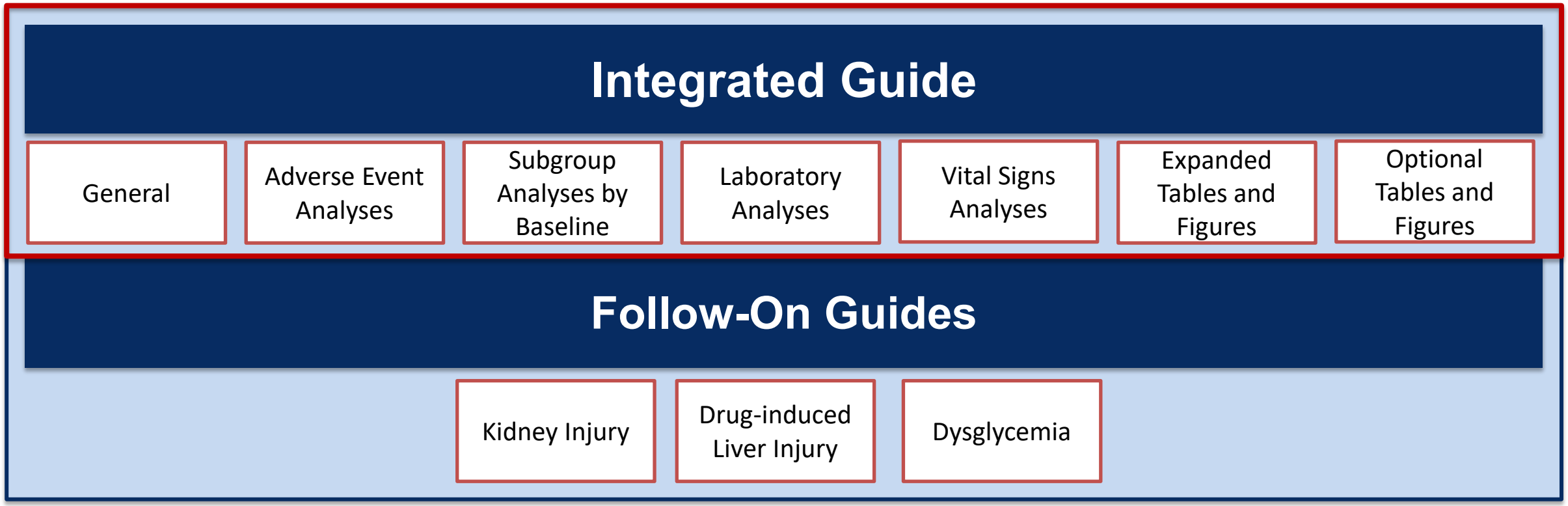
- Develop standard safety analyses in a consistent format to facilitate safety evaluation
- Create uniform data presentation & visualization that reflect formatting standards used in major medical journals

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)

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

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

Subtext is indented

Footnotes provide important definitions and context

Bolded column headers

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

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

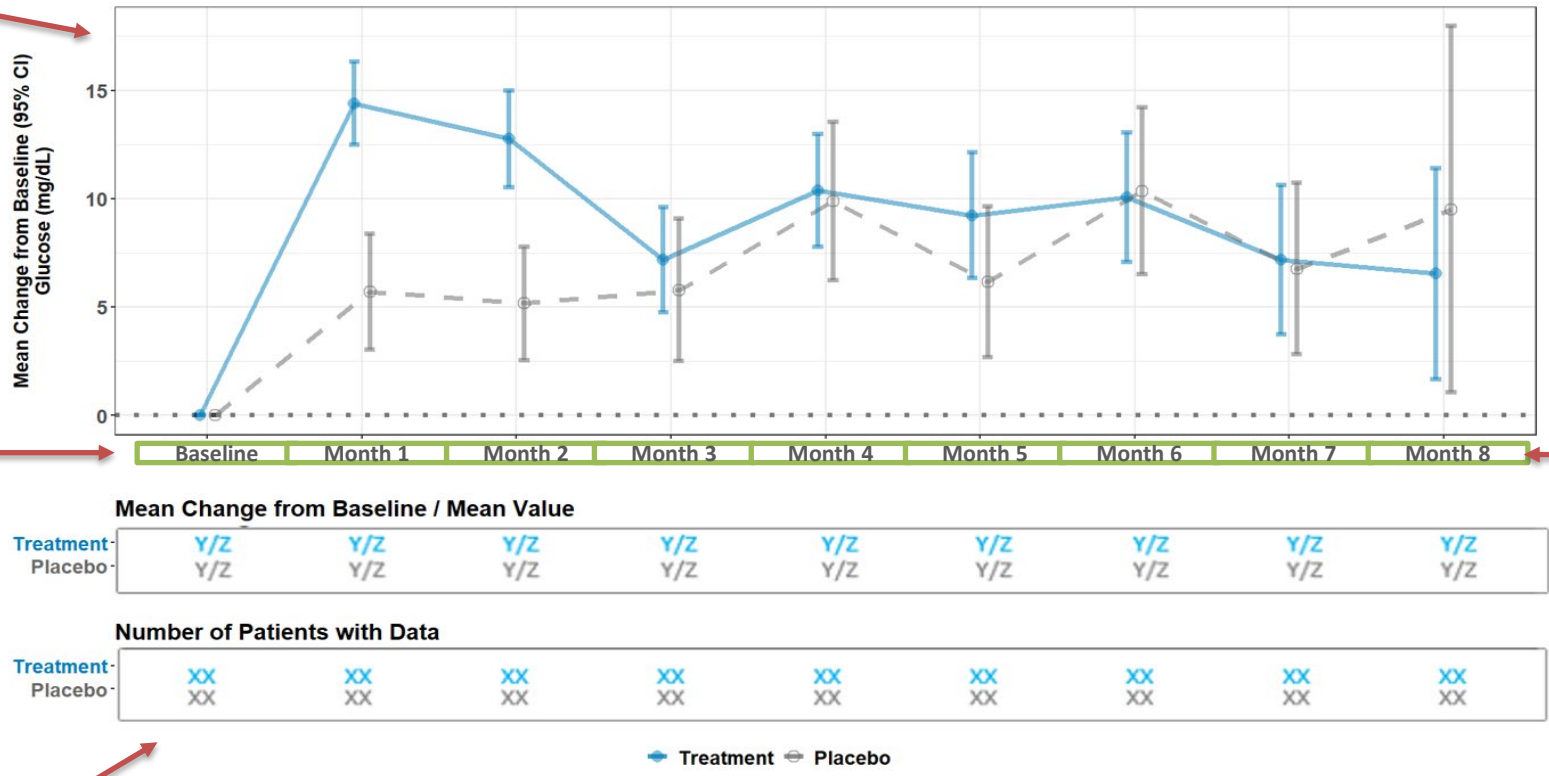
Standardization of Data Presentation: Figures

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]
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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)
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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)
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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

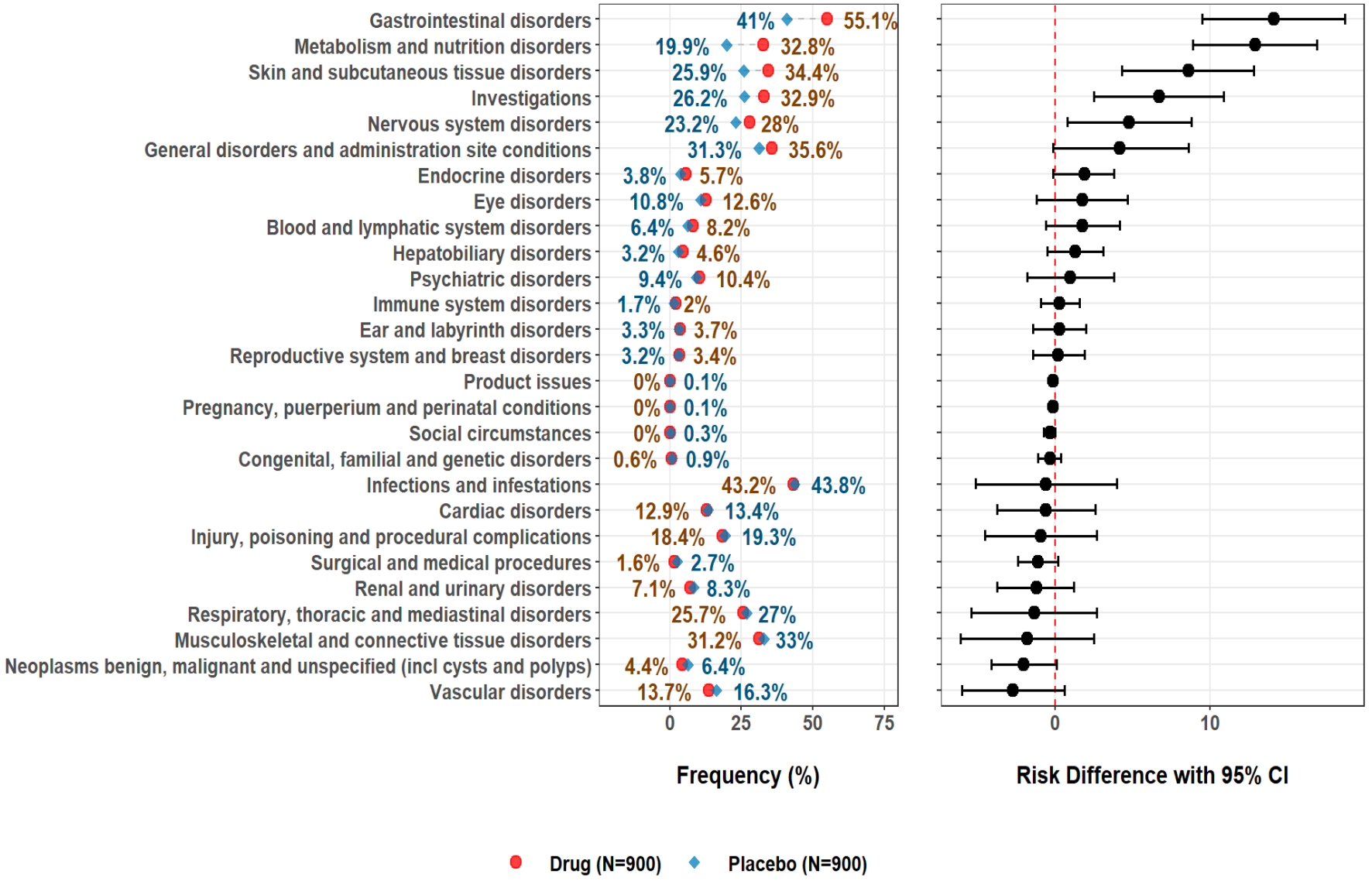
Table 56. Selected Narrow FDA Medical Queries[1], Safety Population, Pooled Analyses (or Trial X)

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)

	Drug Name Dosage X N=XXX	Drug Name Dosage Y N=XXX	Active Control N=XXX	Placebo N=XXX	Risk Difference (%)
AESI Assessment	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**(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)**

Acknowledgement: Standard Safety Tables and Figures Working group

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- Scott Proestel
- Susan Duke
- Terrence Autry
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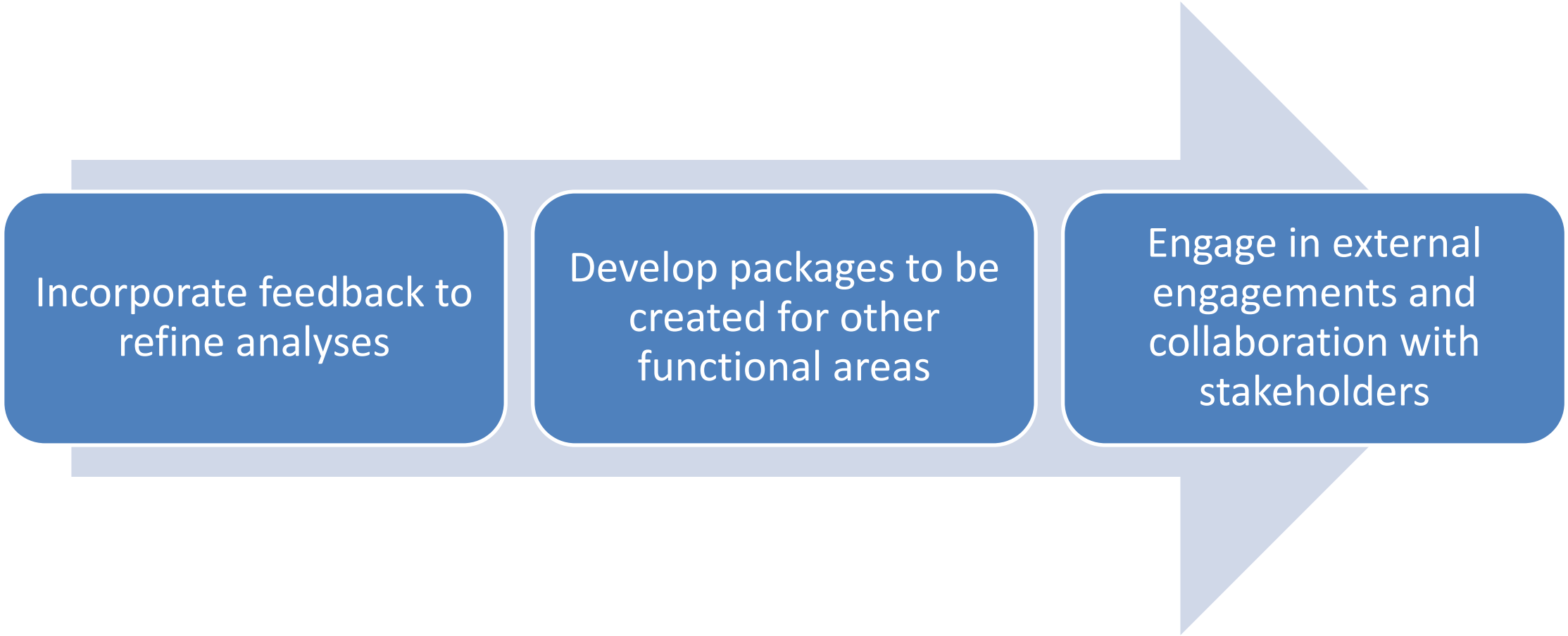
Next Steps


Incorporate feedback to refine analyses
Develop packages to be created for other functional areas
Engage in external engagements and collaboration with stakeholders

Concluding Remarks

- Development of standardized grouping of terms and 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 due to exploratory nature of the safety analysis.
- Refinement of analyses with feedback is important to further finalize standard tables and figures.
- 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.

Advancing Premarket Safety Analytics

- 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.
- 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
- **Public Workshop** https://healthpolicy.duke.edu/events/advancing-premarket-safety-analytics
- **Advancing Premarket Safety Analytics Workshop Meeting Material Standard Safety Tables and Figures Integrated Guide**
- https://www.regulations.gov/document/FDA-2022-N-1961-0002