Biomedical Informatics and Safety Analytics in the Office of New Drugs, CDER/FDA – A 2021 Update

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Disclaimer

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

Pre-Market Safety Analytics Program

- New Drug Review Modernization initiatives are being developed and implemented to create efficient, standardized processes and analyses that can leverage new technologies in the review process for premarketing safety assessments.

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 FDA Medical Queries?

Inconsistent Standards

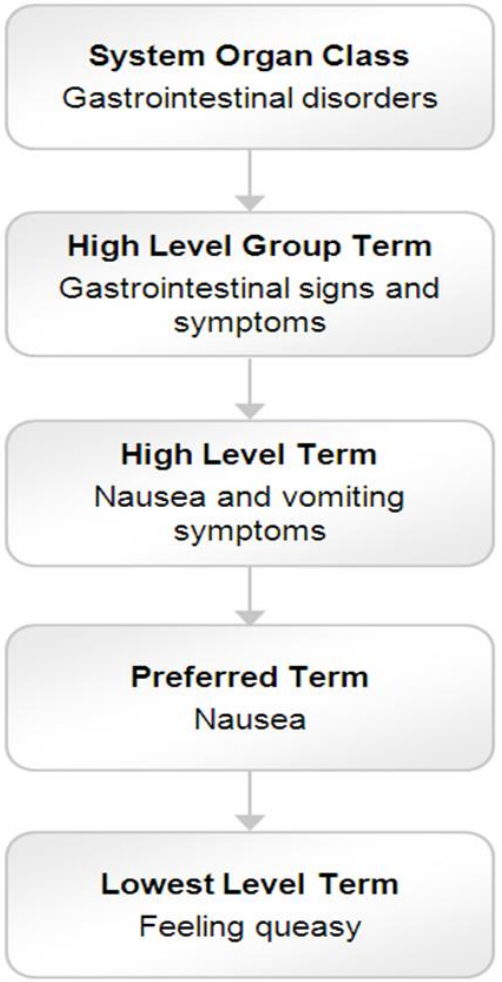
- Investigators code verbatim terms into Preferred Terms (PTs) differently.
  - A patient complaining of abdominal pain may be reported using verbatim terms coding to abdominal pain, abd. pain lower, abd. pain upper, gastrointestinal pain, visceral pain, abdominal discomfort, among others
- Adverse Events (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-popular 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.

What are FMQs?

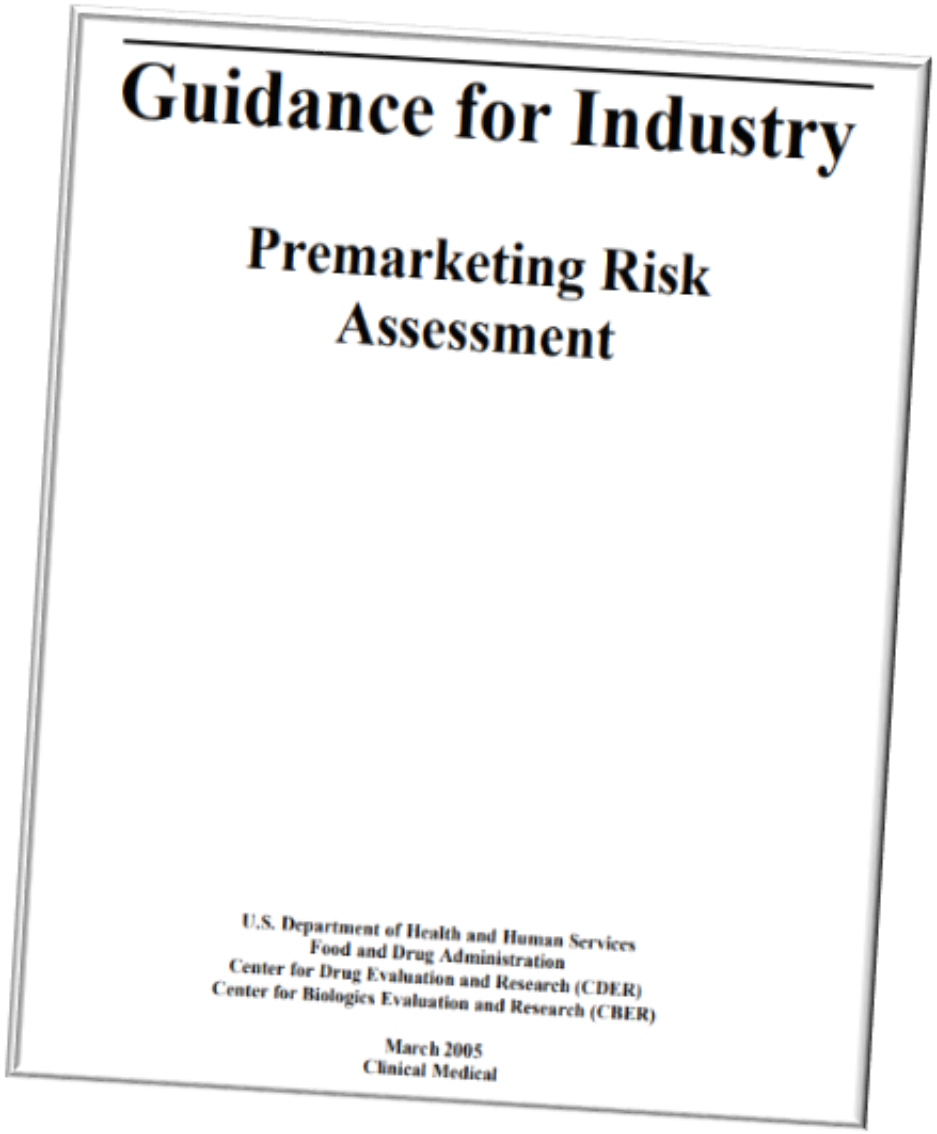
- Standardized groupings of related PTs being developed by review staff primarily in FDA/CDER.
- Each grouping represents a medical concept. “Initial insomnia,” “middle insomnia,” “early morning awakening,” need to be combined to consider “insomnia.”
- Goal is to improve safety signal detection in clinical trial datasets.
- Standardized approach to increase efficiency and consistency.
- "Ground Rules” used to apply medical judgment to develop logical groupings.

MedDRA Background

- Medical Dictionary for Regulatory Activities
- Hierarchical system for categorizing AEs in clinical trial datasets
- Highly granular with >24000 PTs
- Not grouping terms can lead to missed safety signals



Importance of Grouping Similar PTs Not a New Concept



Guidance for Industry

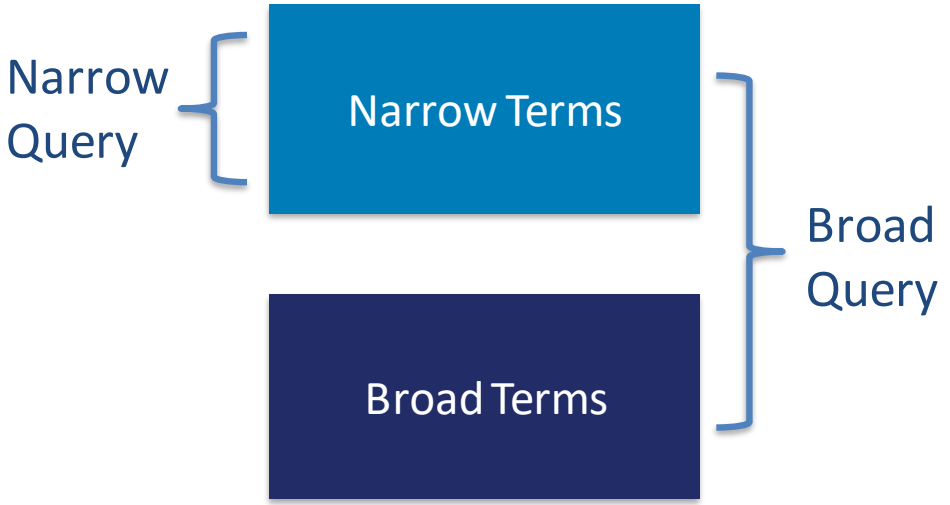
Premarketing Risk Assessment

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2005
Clinical Medical

FMQ Concept

- **Narrow FMQ terms:**
  - Specific for the medical concept.
  - Indicate that the FMQ occurred.
- **Broad FMQ terms:**
  - Casts a wider net than narrow query terms for signal detection.
  - Less specific; more sensitive.
  - Provide reasonable assurance FMQ occurred (at least ~30-50% probability).



FMQ Ground Rules

Narrow

1. PTs that are near-synonyms of FMQ
   Ex: *Abd Discomfort* in FMQ *Abd Pain*
2. PTs that are subgroups of FMQ
   Ex: *Anaemia Neonatal* in FMQ *Anaemia*
3. PTs that specify an etiology for the FMQ
   Ex: *Uremic Pruritus* in FMQ *Pruritus*
4. PTs that uniformly lead to the FMQ
   Ex: *Aortic Rupture* in FMQ *Haemorrhage*

Broad

1. PTs that may result from FMQ but are not equivalent to the FMQ
   Ex: *HTN Cardiomyopathy* in FMQ *Systemic HTN*
2. PTs that are lab or radiologic tests with vague result
   Ex: *Blood Glucose Abn* in FMQ *Hyperglycaemia*
3. PTs reasonably suggestive for an FMQ, but not required for FMQ
   Ex: Bronchospasm in FMQ *Hypersensitivity*

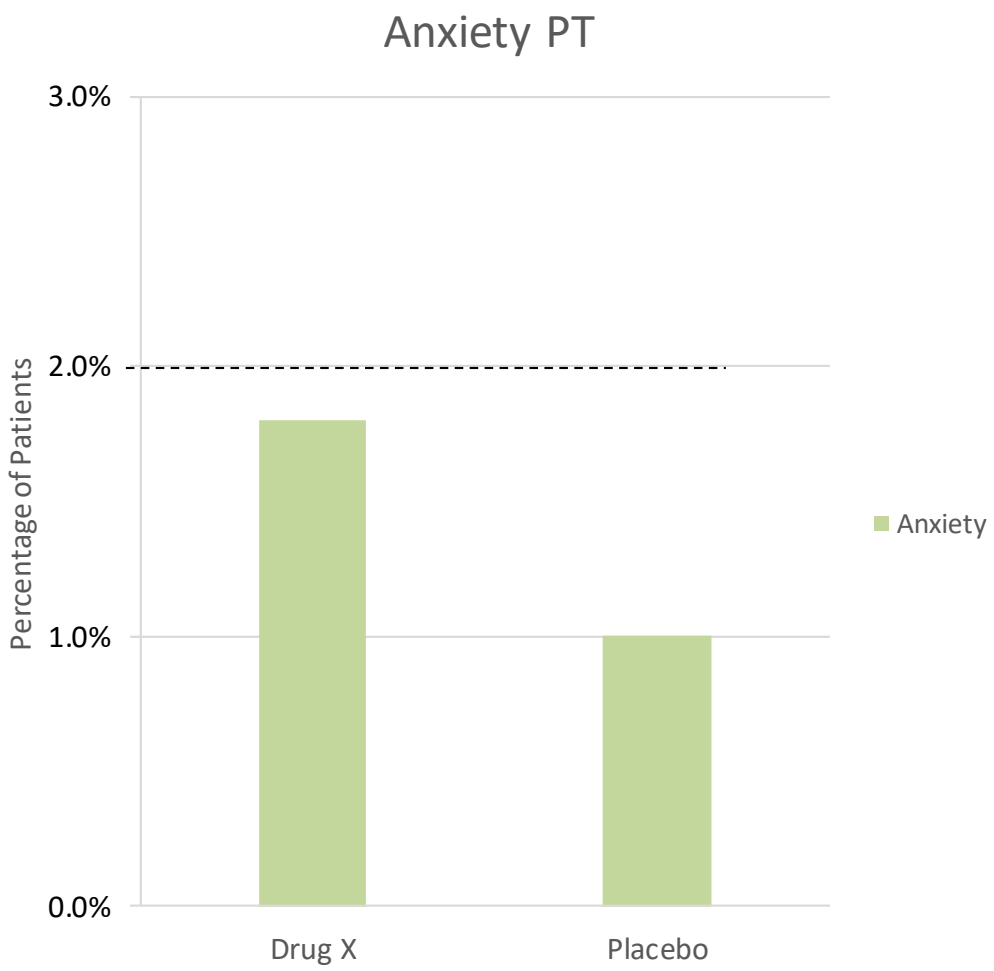
PTs that are EXCLUDED from FMQs:

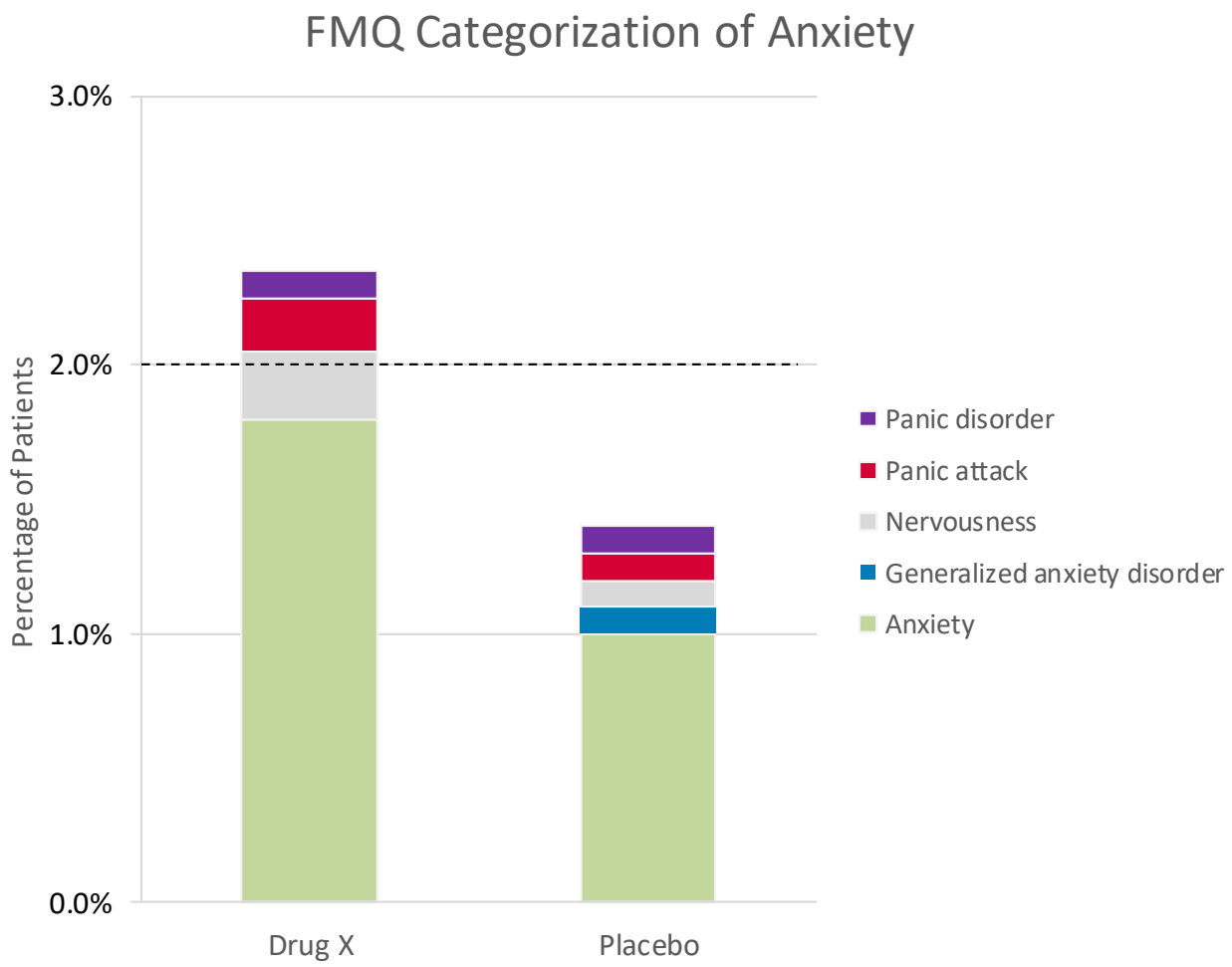
PTs that are neither a required component nor reasonably specific for the FMQ concept.
- Ex: PT Nausea would not be included in *FMQ Migraine*

PTs that are laboratory or radiologic tests without a result. - Ex: PT Clostridium Test

PTs that represent congenital disorders including familial and genetic syndromes. - Ex: Down Syndrome

Example: Individual PT Analysis vs. FMQ





Acknowledgments

- Office of New Drugs FMQ steering committee, who organized and coordinated inter-office working group and multiple sub-groups (~70 reviewers and staff participation).

Standard Tables & Figures

Why Standard Tables & Figures?

- Significant variability across divisions for similar safety signal evaluation related tables and figures
- Uniform data presentation & visualization.
- Reflect formatting standards used in major medical journals.
- Ensures standardized analyses across Divisions.

Purpose & Objectives

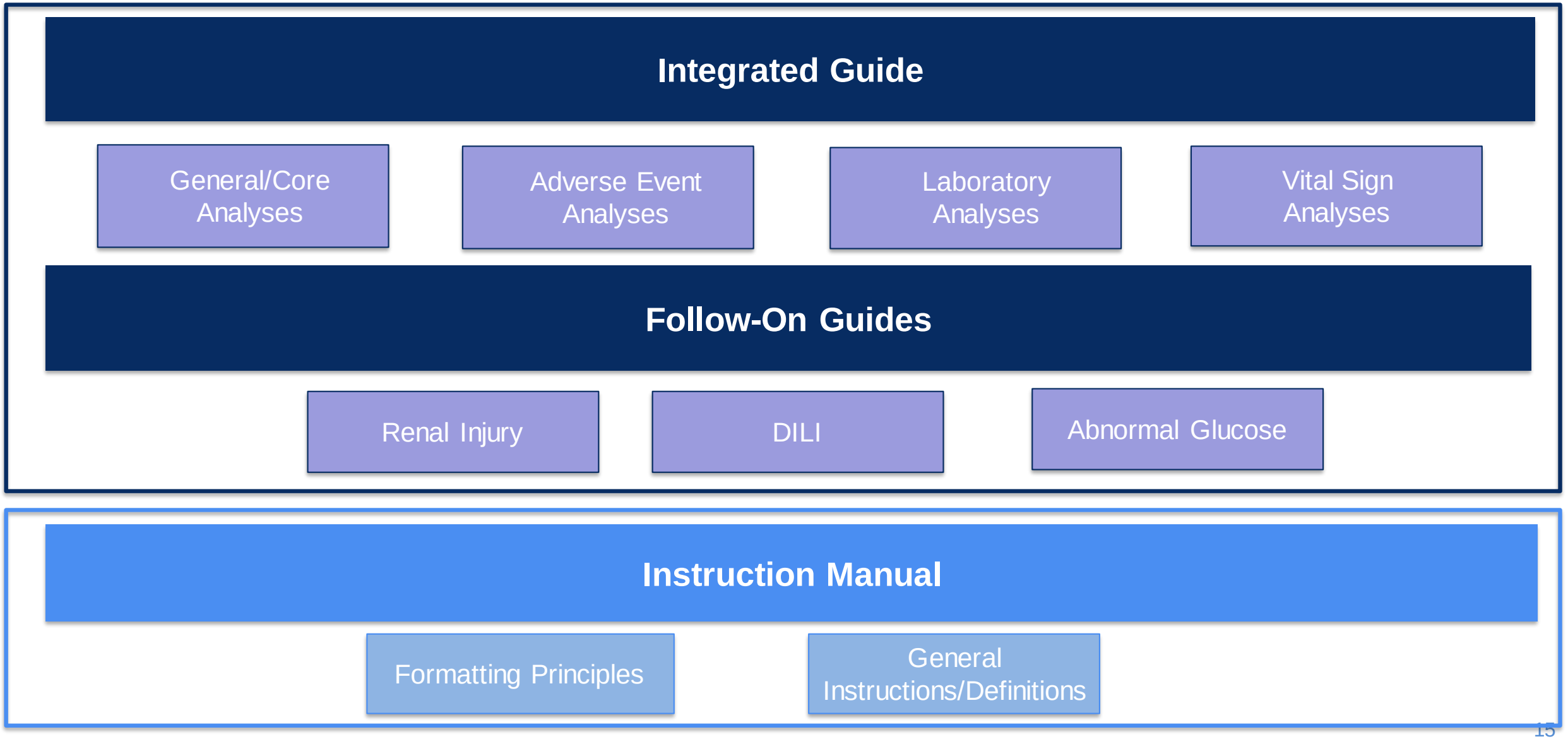
Purpose

To develop standardized tables and figures to streamline the **data used** for generating analyses, the **interpretation of analyses**, and the **visualizations utilized**.

Objectives

- Uniform strategy for data presentation & visualization
- Improve ability to create standardized analyses
- Reflect formatting standards used in major medical journals
- Provide templates for common tables in clinical reviews

Standard Tables & Figures Organization



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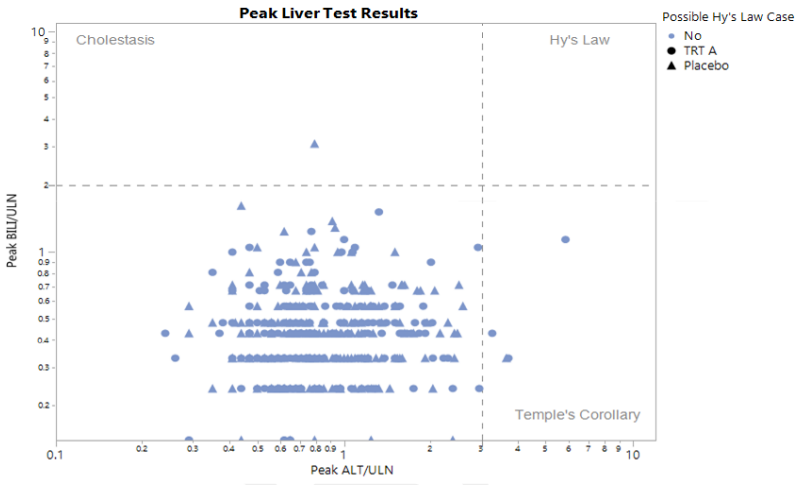
Standard Tables & Figures
Follow-On Guides

Produced upon request by the reviewer, if a signal is identified.

Follow-On Guides

Renal Injury



DILI

- Analyses of Hepatic TEAE and Early Discontinuation
- Analyses of Liver Biochemistry Studies
- Patient-Level Analyses

Abnormal Glucose

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Table 28. Adverse Events Leading to Discontinuation by Descending Difference (>0.1%) Order, Safety Population, High CV Risk Pool, Trials 040 and 047

Adverse Event[1,2]	Bempedoic Acid N=2009 n (%)	Placebo N=999 n (%)	Risk Difference (95% CI)
Patients with at least one AE leading to discontinuation	219 (10.9)	75 (7.5)	3.4 (1.3, 5.5)
Diarrhea[3]	10 (0.5)	1 (0.1)	0.4 (0.0, 0.8)
Pain in extremity	6 (0.3)	0 (0.0)	0.3 (0.1, 0.5)
Muscle spasms	11 (0.5)	3 (0.3)	0.2 (-0.2, 0.7)
Myocardial infarction	7 (0.3)	1 (0.1)	0.2 (-0.1, 0.6)
Elevated liver enzymes[4]	7 (0.3)	1 (0.1)	0.2 (-0.1, 0.6)
Abdominal pain[5]	6 (0.3)	1 (0.1)	0.2 (-0.1, 0.5)
Headache	9 (0.4)	3 (0.3)	0.1 (-0.3, 0.6)
Nausea	6 (0.3)	2 (0.2)	0.1 (-0.3, 0.5)
Dyspnoea	5 (0.2)	1 (0.1)	0.1 (-0.1, 0.4)
Anaemia	3 (0.1)	0 (0.0)	0.1 (-0.0, 0.3)
Gastroesophageal reflux disease	3 (0.1)	0 (0.0)	0.1 (-0.0, 0.3)
Vomiting	3 (0.1)	0 (0.0)	0.1 (-0.0, 0.3)
Musculoskeletal pain	3 (0.1)	0 (0.0)	0.1 (-0.0, 0.3)
Angina unstable	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Visual impairment	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Blood uric acid increased	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
International normalised ratio increased	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Decreased appetite	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Hyperkalaemia	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Osteoarthritis	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Lung neoplasm malignant	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Prostate cancer	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)
Cough	2 (0.1)	0 (0.0)	0.1 (-0.0, 0.2)

Source: Reviewer's analysis [adae.xpt; Software: Python]
[1] Coded as MedDRA preferred terms
[2] Terms included are those that occurred more often in the treatment than comparator group
[3] Includes diarrhea and frequent bowel movements
[4] Includes aspartate aminotransferase increased and alanine aminotransferase increased
[5] Includes abdominal pain upper and abdominal pain lower
Abbreviations: AE, adverse event; CI, confidence interval; CV, cardiovascular; N, number of subjects in group; n, number of subjects with adverse event

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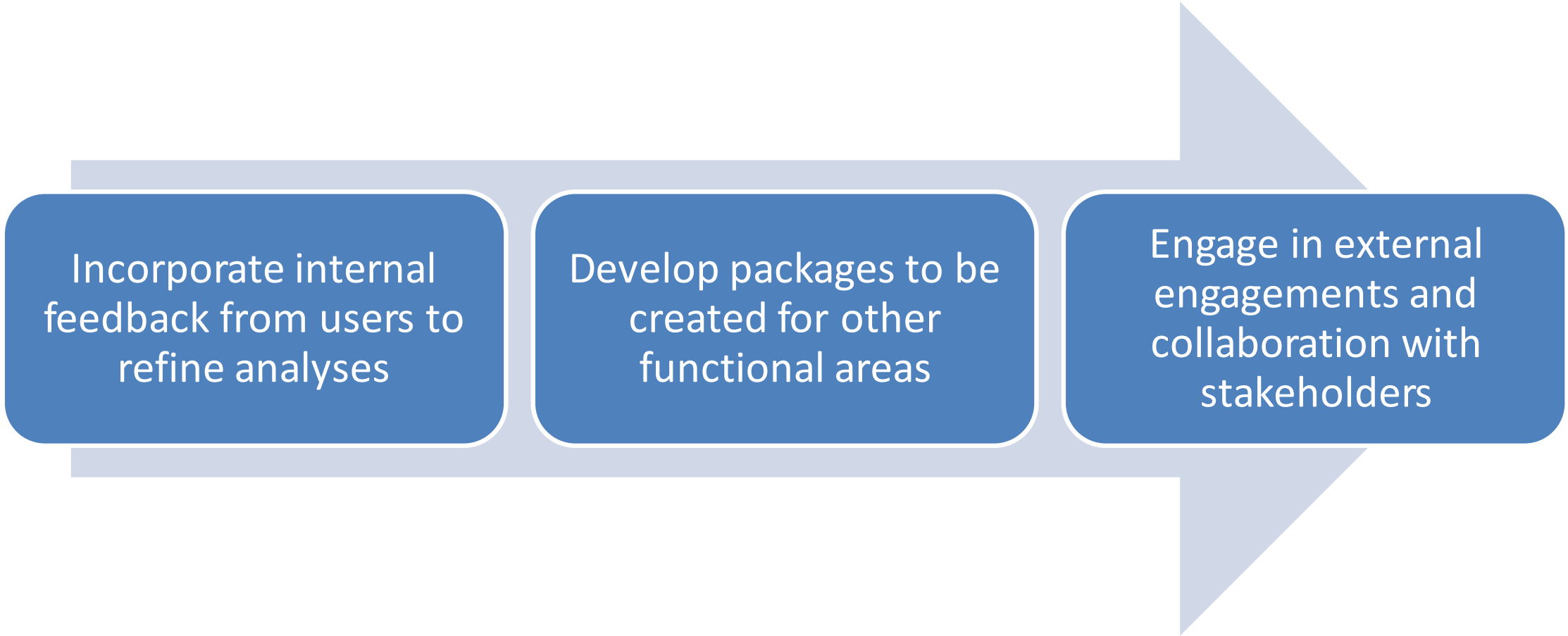
Next Steps


Incorporate internal feedback from users 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.
- Refinement of analyses with feedback from internal review staff to further finalize standard tables and figures.
- We look forward to future collaboration with external stakeholders who are also working in this space.

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

Back up Slides

Differences between FMQs and SMQs

Some SMQs lack specificity:

SMQ Acute Central Respiratory Depression **CONTAINS** *Breath sounds abnormal*

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FMQ Respiratory Depression **OMITS** *Breath sounds abnormal*

Some SMQs lack sensitivity:

FMQ Pancreatitis **CONTAINS** *Cytomegalovirus pancreatitis* **AND** *Pancreatitis mumps*

↓

SMQ Acute Pancreatitis **DOES NOT CONTAIN** *Cytomegalovirus pancreatitis* **OR** *Pancreatitis* mumps