

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 PHUSE 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 program in the office of New Drugs/CDER/FDA since 2015
- As an AD for Biomedical informatics and regulatory review science, I lead 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

Two Important Safety Analytics Initiatives



The FDA medical
Queries Project



Standard Safety Tables
and Figures Project



Why FDA Medical Queries?

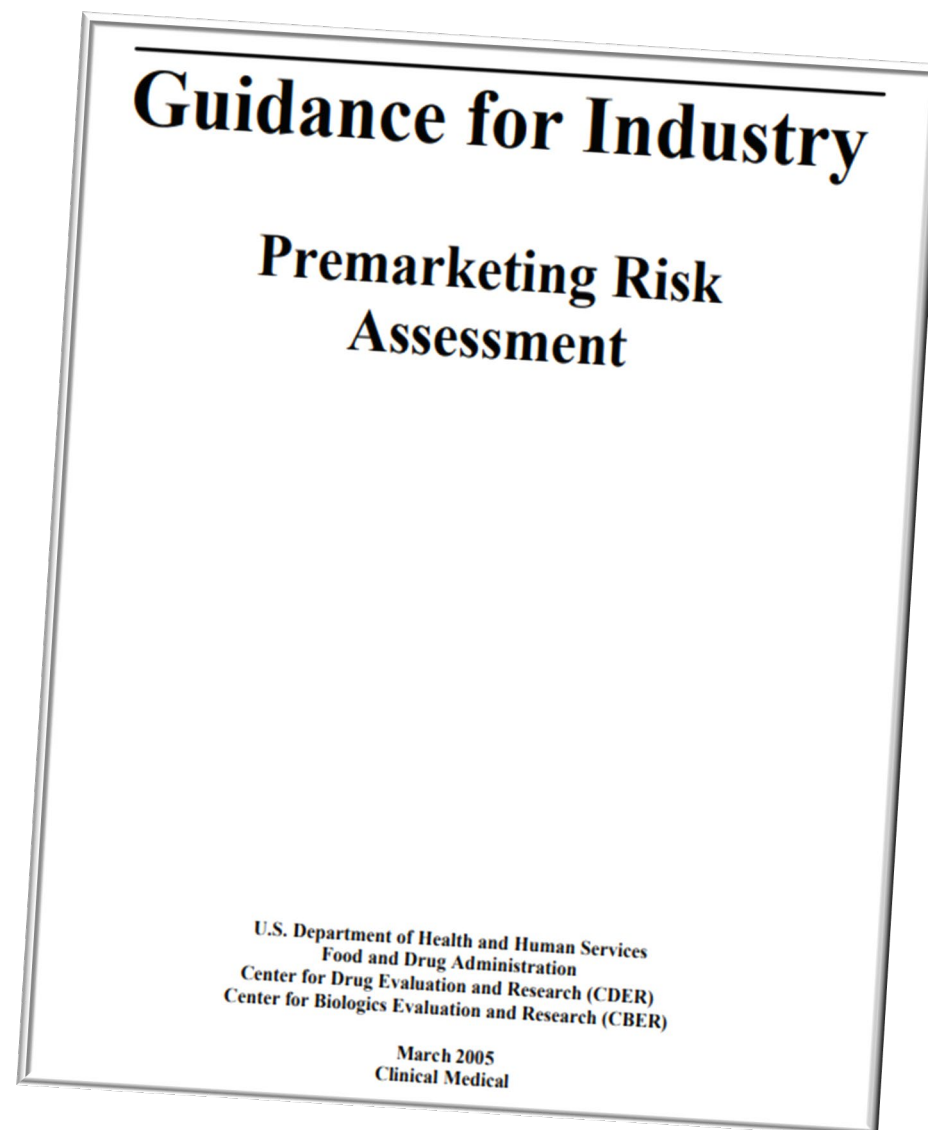
Inconsistent Standards

- Investigators' verbatim terms are coded into Preferred Terms (PTs) differently.
 - A patient complaining of abdominal pain may be reported using 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 FDA Medical Queries (FMQs)?

- Standardized groupings of related PTs being developed by review staff primarily in FDA/CDER.
 - MedDRA PTs are highly granular with >24000 PTs
 - Not grouping terms can lead to missed safety signals
- Each grouping represents a medical concept. “Initial insomnia,” “middle insomnia,” “early morning awakening,” need to be combined to represent “insomnia.”
- Goal is to improve safety signal detection in clinical trial datasets.
- Standardized approach to increase efficiency and consistency.

Importance of Grouping Similar PTs Not a New Concept



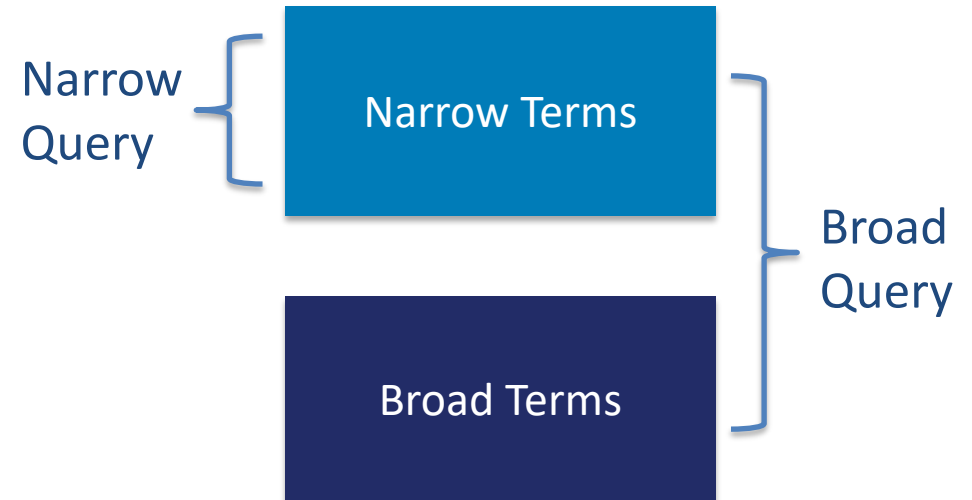
FMQ Concept

- **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*
4. PTs that indicate a “carrier” status for FMQ concepts that specify an infectious disease: Ex: *PT Bacterial Disease Carrier* in FMQ *Bacterial Infection*

PTs that are EXCLUDED from FMQs:

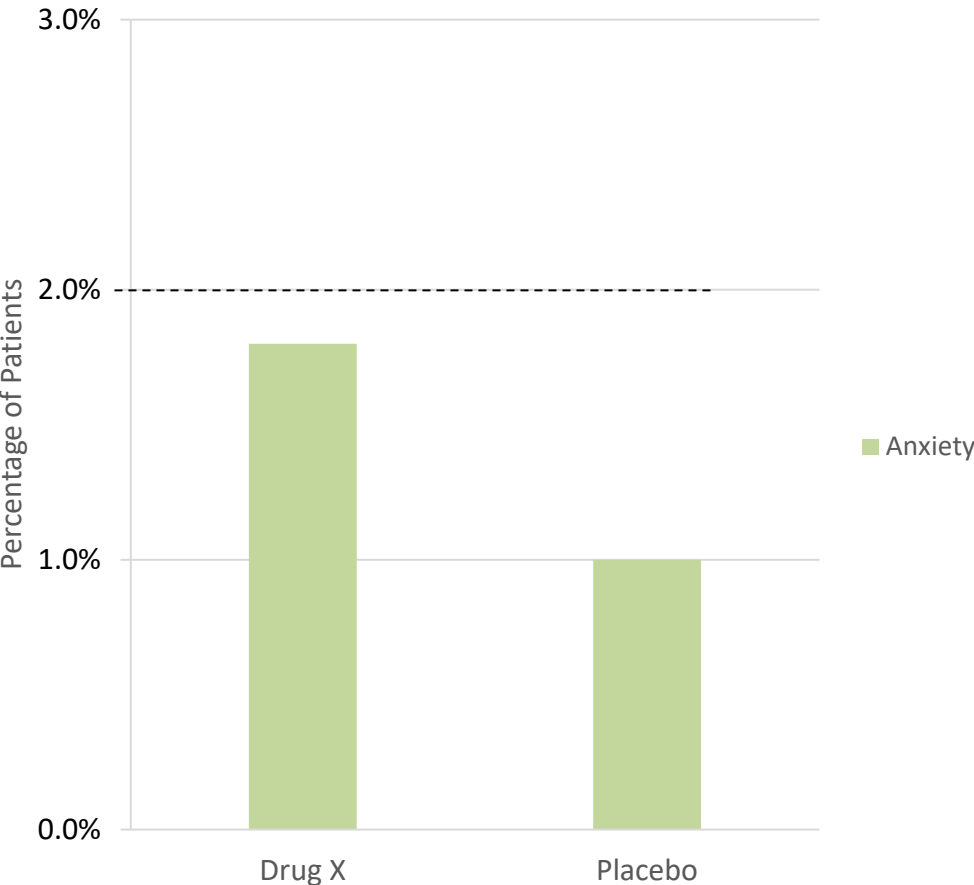
PTs that are neither a required component nor reasonably specific for the FMQ concept.

- Ex: PT Nausea would not be included in *FMQ Migraine*

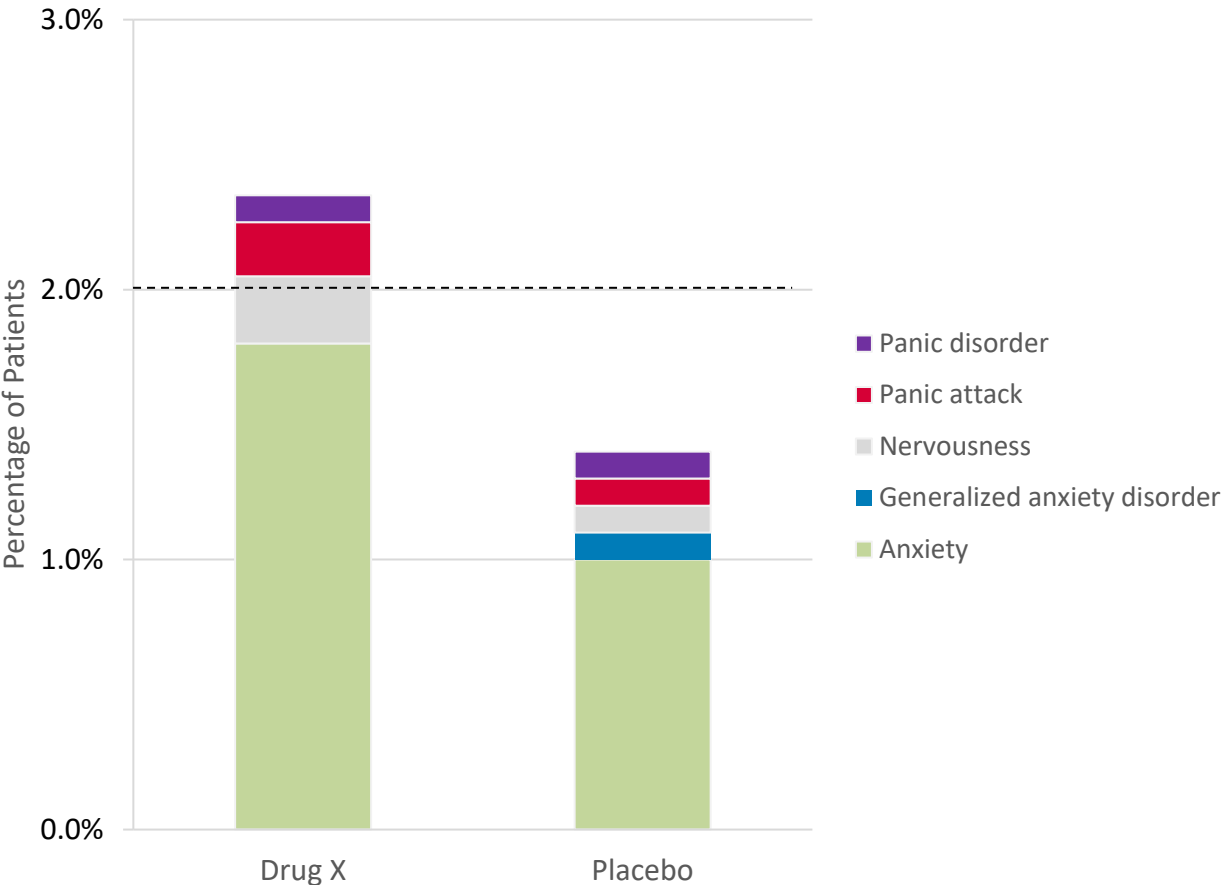
PTs that are laboratory or radiologic tests without a result. - Ex: PT Clostridium Test

Example: Individual PT Analysis vs. FMQ

Anxiety PT



FMQ Categorization of Anxiety



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

FDA Medical Queries

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

Acknowledgments: Core Workgroup Members*



Office of New Drugs FMQ steering committee, who organized and coordinated inter-office working group and multiple sub-groups with ~80 reviewers and staff participation.

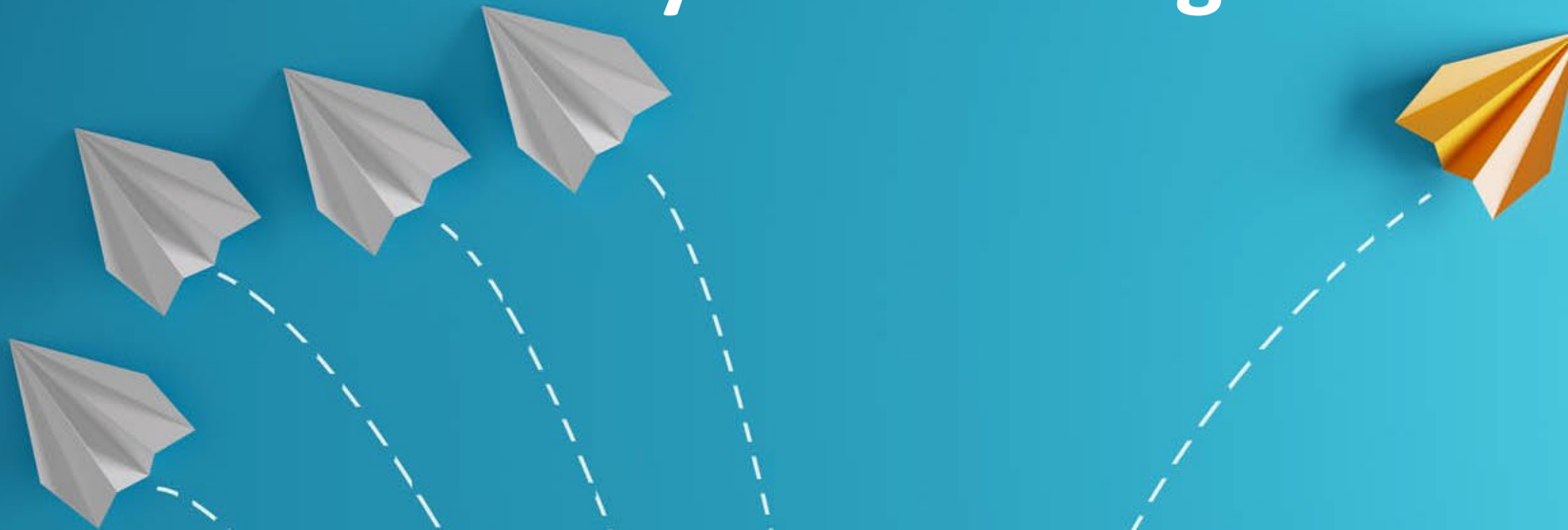
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Why Standard Safety Tables & Figures?



Inconsistent Standards

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

A Collective Way Forward

- Develop standard safety analyses in a consistent format to facilitate safety evaluation
- Generate standardized ST&F for safety analyses for the Reviewers
- 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

Standard Tables & Figures Organization



Integrated Guide

General/Core
Analyses

Adverse Event
Analyses

Laboratory
Analyses

Vital Sign
Analyses

Follow-On Guides

Kidney Injury

Drug Induced Liver
Injury

Dysglycemia

Instruction Manual

Formatting Principles

General
Instructions/Definitions

Standardization of Data Presentation: Tables

Table 6. Overview of Adverse Events¹, Safety Population, Pooled

Analyses²

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 AE⁴	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

Subtext is indented

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

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 Se² Duration = [e.g., X-week double-blind treatment period or, median and a range indicating pooled trial durations].

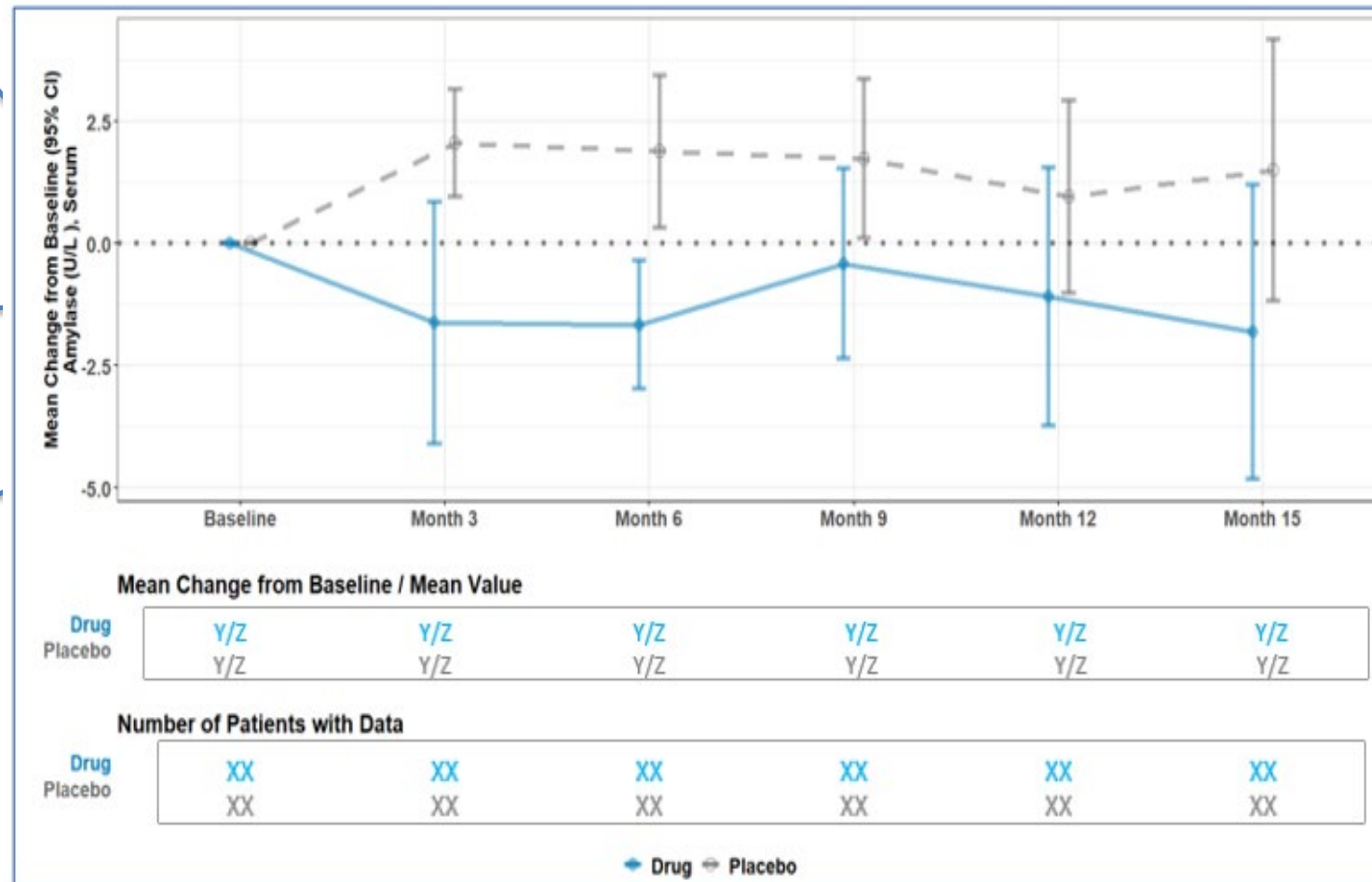
³ Difference verity as assessed by the investigator

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.

Standardized color selection and consistency across trials.

When the x-axis is used to represent time, it is scaled uniformly and labeled by protocol specified visit schedule

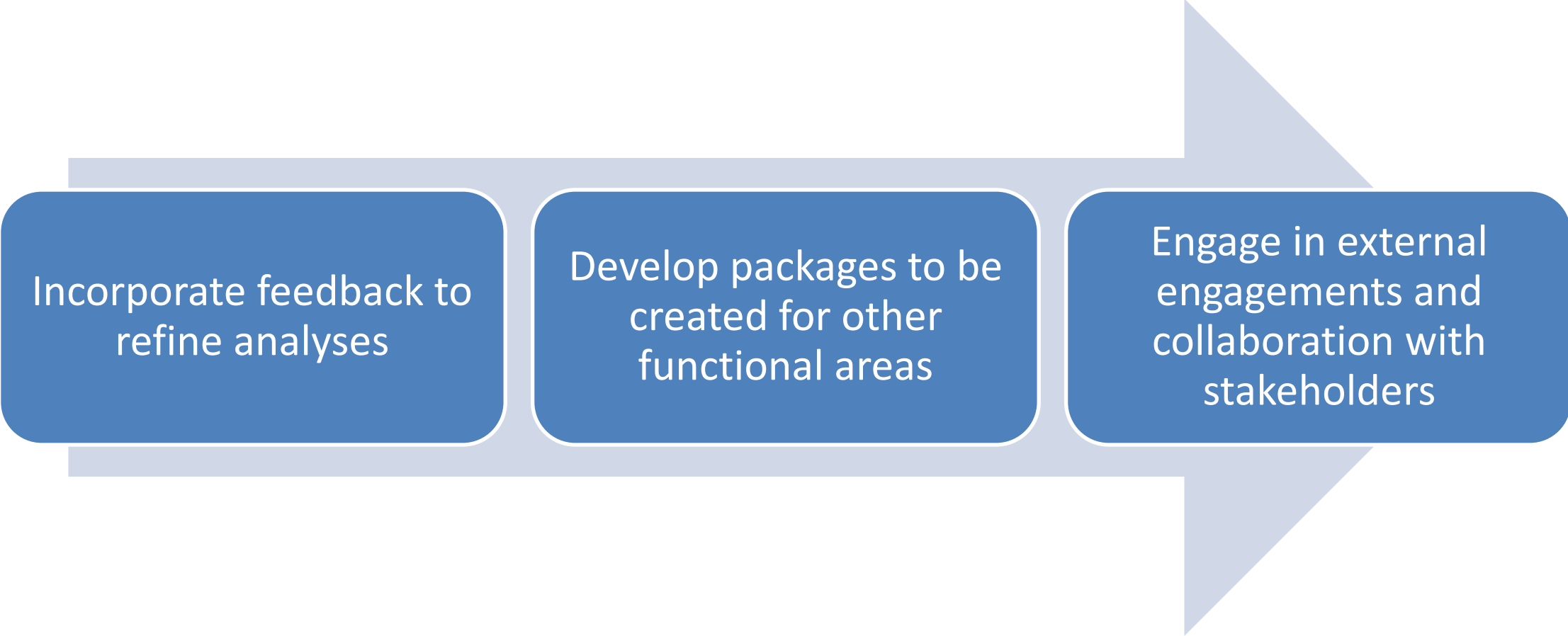
When displaying data over time, total "n's" are presented per time period at the bottom of the figure

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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

- **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>