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US 2020

The Computational Science Symposium

September 21st–23rd

Session Chair: Vaishali Popat, MD, MPH

- Scott Proestel, MD: The FDA Medical Queries Project
- Preeti Venkataraman, MD: The Standard Tables and Figures Visualization Project
- Vaishali Popat, MD,MPH: Data Quality/Integrity
- B. Nhi Beasley, PharmD: Type C meeting – Safety Analysis Strategy Planning

- *The views expressed during this presentation are those of the presenter and do not represent those of the US Food and Drug Administration.*

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.

Safety Analysis and Review Support

Goal: Establish best practices for safety analyses for consistency, transparency and efficiency

This program includes several initiatives including

1. FDA Medical Queries (FMQ) Project
2. Standard Tables and Figures visualization working group
3. Clinical Data Acceptance (Data Integrity/Data Quality Fit-for Review)
4. Type C Safety ISS meeting

FDA Medical Queries (FMQs)

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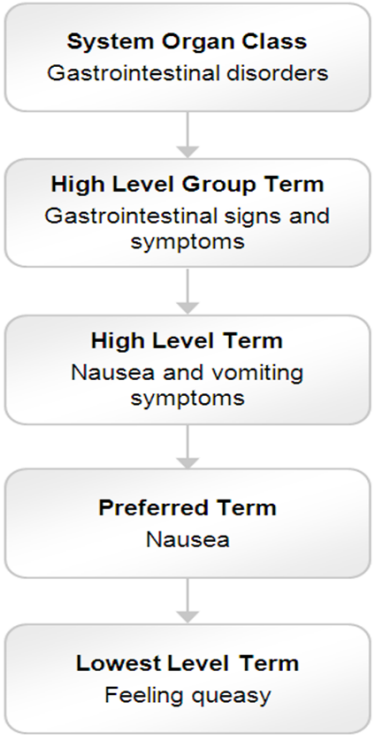
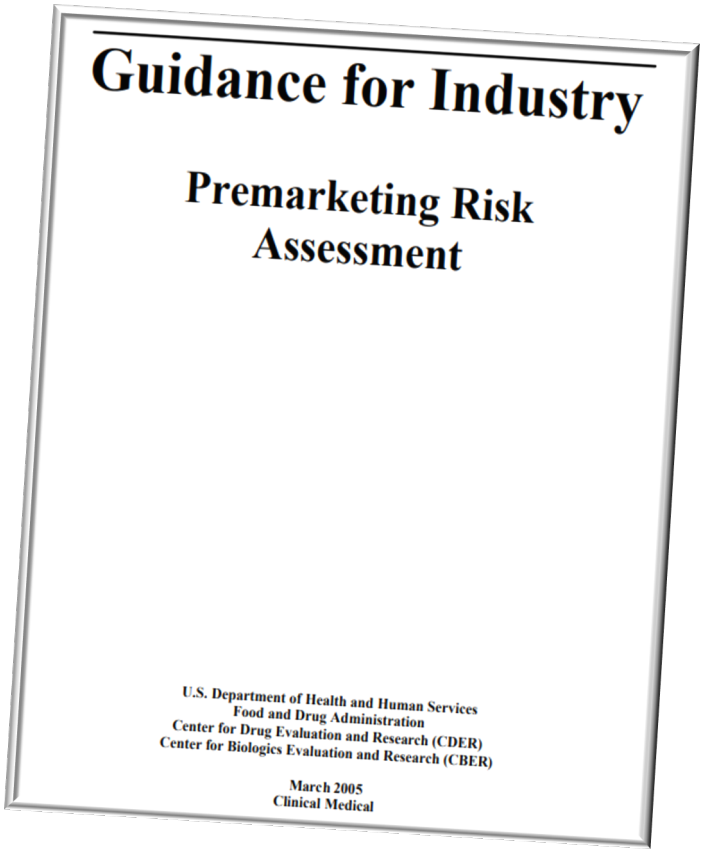
MedDRA Background

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



Importance of Grouping Similar PTs Not a New Concept



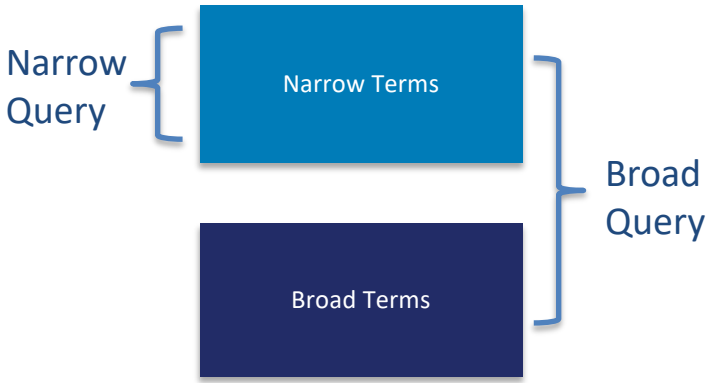
What are FMQs?

- 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.

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 ~50% probability).



FMQ Ground Rules

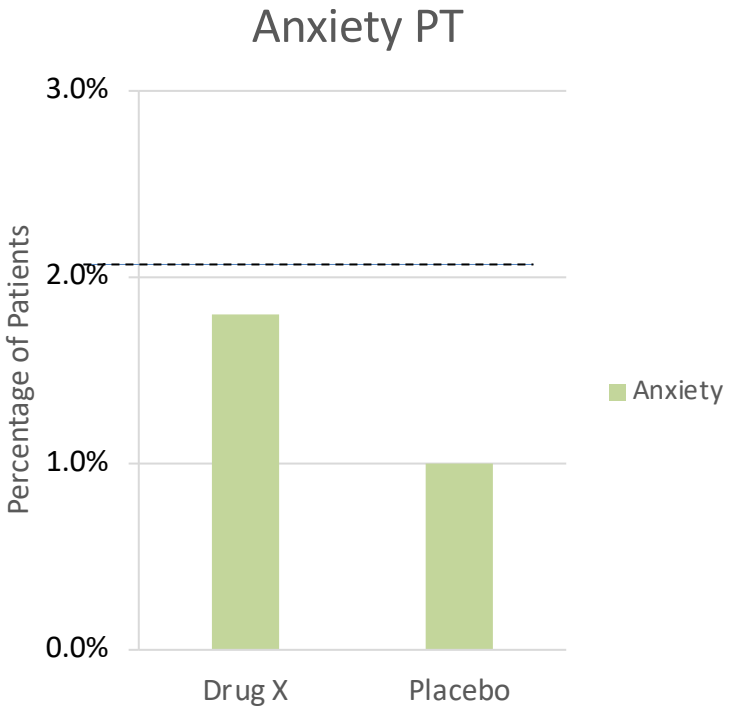
Narrow

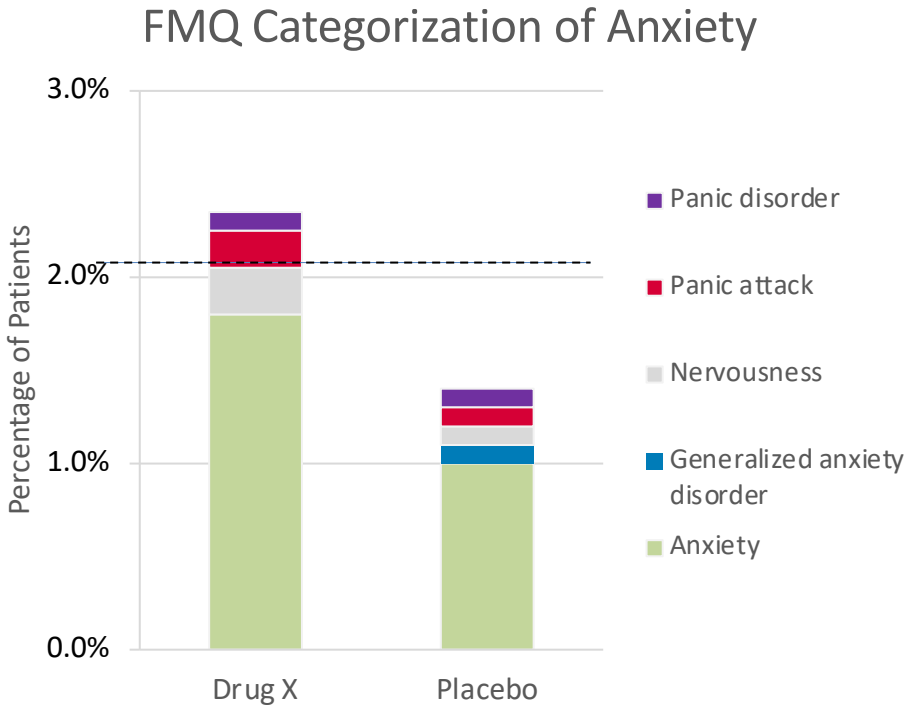
1. PTs that are near-synonyms of FMQ
   Ex: *Abd Discomfort* in FMQ *Abd Pain*
2. PTs that are subgroups of FMQ
   Ex: *Anaemia Neonatal* in FMQ *Anaemia*
3. PTs that specify an etiology for the FMQ
   Ex: *Uremic Pruritus* in FMQ *Pruritus*
4. PTs that ensure the occurrence of the FMQ
   Ex: Aortic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

Example: Individual PT Analysis vs. FMQ





Why Not Use the MedDRA Hierarchy?

- MedDRA PTs - symptoms, signs, diagnoses, therapeutic indications, investigations, product quality issues, medical procedures, and medical/social family history characteristics
- PTs cover broader range than just AEs
- Hierarchy combines PTs using multiple strategies - anatomy, pathology, physiology, etiology, manifestation site, purpose, and function
- Purpose of FMQs more narrow - combining only AEs to create clinically meaningful groupings

Example: Abdominal Pain FMQ

~~HLT Gastrointestinal and~~ abdominal pains (excl oral and throat)

- Abdominal migraine
- Abdominal pain
- Abdominal pain lower
- Abdominal pain upper
- Abdominal rebound tenderness
- Abdominal rigidity
- Abdominal tenderness
- Gastrointestinal pain
- Infantile colic
- **Oesophageal pain**
- **Visceral pain**

HLT Gastrointestinal signs and symptoms NEC

- Abdominal discomfort
- Abdominal symptom
- Acute abdomen
- **Anal incontinence**
- **Bradyphagia**
- **Breath odour**
- **Bruxism**
- Cullen's sign
- Dumping syndrome
- Dysphagia
- Dysphagia lusoria
- Early satiety
- **Encopresis**
- Fixed bowel loop
- **Foetor hepaticus**
- Gastrocardiac syndrome
- Gastrointestinal somatic symptom disorder
- **Gastrointestinal wall thickening**
- **Gastrointestinal wall thinning**
- **Hiccups**
- **Hyperphagia**
- **Hypophagia**
- **Incontinence**
- **Intestinal calcification**
- Intestinal congestion
- Malignant dysphagia
- **Mastication disorder**
- Merycism
- Myochosis
- Oesophageal discomfort
- Oesophageal food impaction
- Pelvic discomfort
- Pelvic pain
- Peripancreatic fluid collection
- Peristalsis visible
- **Pharyngeal dystonia**
- Portal venous gas
- Post cholecystectomy syndrome
- Radiation dysphagia
- Radiation sickness syndrome
- **White nipple sign**
- **Wischnewsky spots**

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

Alcoholic Pancreatitis
Autoimmune Pancreatitis
Obstructive Pancreatitis
Pancreatitis Viral

Example: Depression FMQ

Narrow

- Agitated depression
- Childhood depression
- Depression
- Depression postoperative
- Depression suicidal
- Major depression
- Menopausal depression
- Perinatal depression
- Persistent depressive disorder

Broad

- Apathy
- Crying
- Decreased interest
- Dysphoria
- Feeling guilty
- Feeling of despair
- Feelings of worthlessness
- Helplessness
- Self-injurious ideation
- Suicidal behaviour
- Suicidal ideation
- Suicide attempt

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 and Figures Visualization Project

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September 2020

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Purpose & Objectives

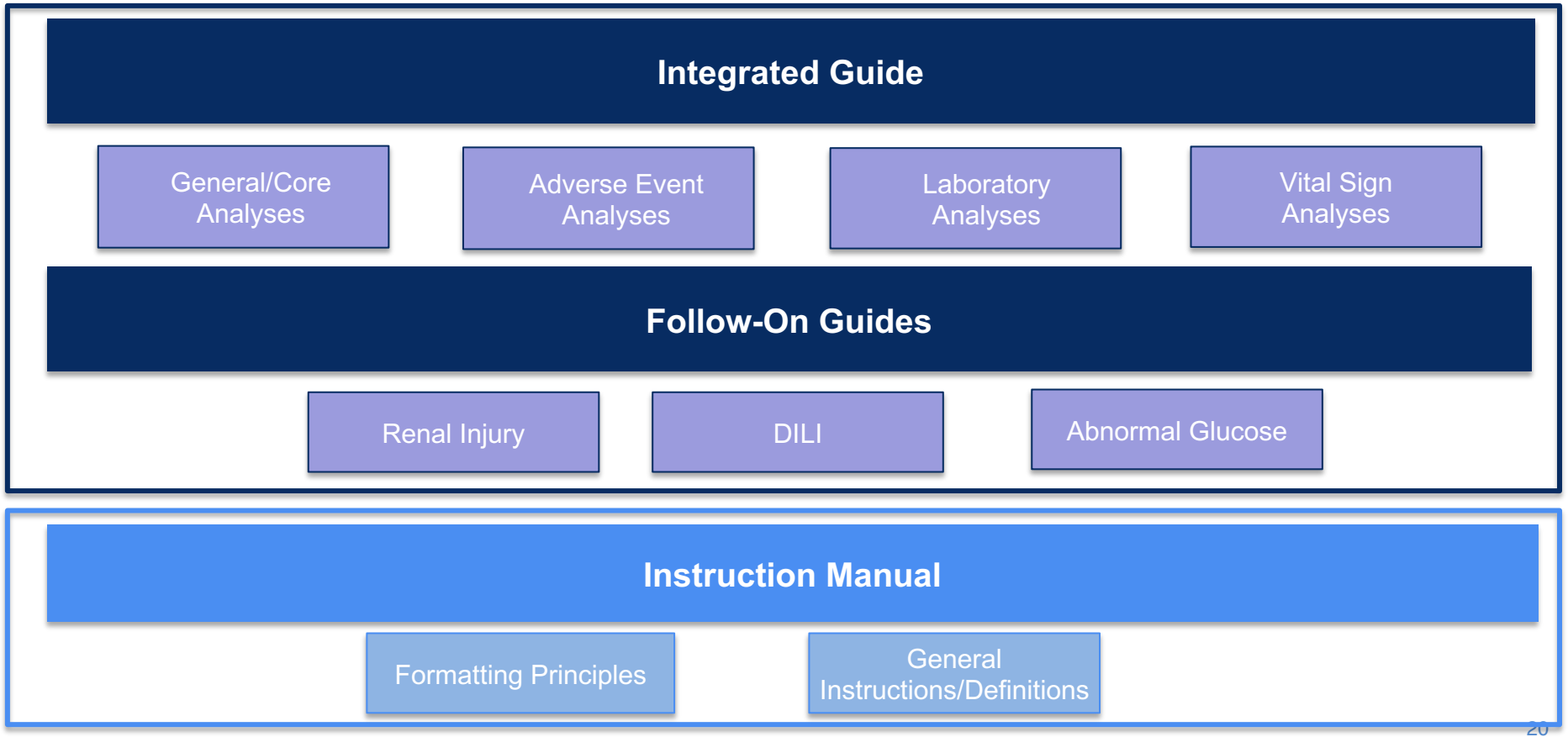
Purpose

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



Standard Tables & Figures Integrated Guide

Produced for every application under Integrated Assessment for Marketing Applications.

Integrated Guide

General Analyses

- Clinical Trials Summary
- Demographic and Clinical Characteristics
- Patient Disposition

Adverse Event Analyses

- Duration of Exposure
- Overview of Adverse Events
- Deaths
- Non-fatal Serious Adverse Events
- Adverse Events Leading to Discontinuation
- Incorporation of FDA Medical Queries (FMQs)

Laboratory Analyses

- Analyses of Central Tendency
- Analyses of Abnormalities and Outliers by Level and Treatment Arm
- DILI Screening subsection:
  - Missing Data Analysis
  - Potential Hy's Law Screening Plot
  - Cholestatic Injury Screening Plot

Vital Signs Analyses

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

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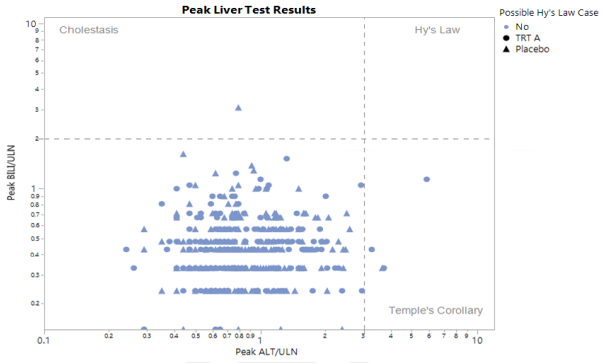
Standard Tables & Figures
Follow-On Guides

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

Follow-On Guides

Kidney Injury



DILI

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

Abnormal Glucose

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Standard Tables & Figures
Instruction Manual

Instruction Manual

Formatting Principles

- General guidelines for font, title, footnotes
- For tables: Order of treatment groups when comparing data across columns, alignment, lines, units
- For figures: annotation, axes, line and symbol style, colors, techniques

General Instructions/Definitions

- Important definitions, e.g., TEAE, baseline, last value on treatment
- Approach for presentation of data from unscheduled vs scheduled visits
- Groupings of clinically relevant parameters

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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 training and communication plan with timelines for internal outreach
- Develop packages to be created for other functional areas
- Engage in external engagements and collaboration with stakeholders

Concluding Remarks

- OND development of standardized 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.

Data Quality/Integrity (Fit-for-Review)

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Data Quality/Integrity (Fit-for-Review)

Objectives

1. Learn more about data quality issues reviewers have encountered while reviewing NDAs/BLAs.
2. Understand the steps that were taken to identify the data quality issue(s) and determine any trends.

Survey Overview

The survey was sent to ~410 individuals. 95 individuals responded

ADBMI Pilot

Who: ADBMIs
What: Survey Pilot
How: Multiple email blasts
Why: To pilot the survey and gain early insight into data quality issues

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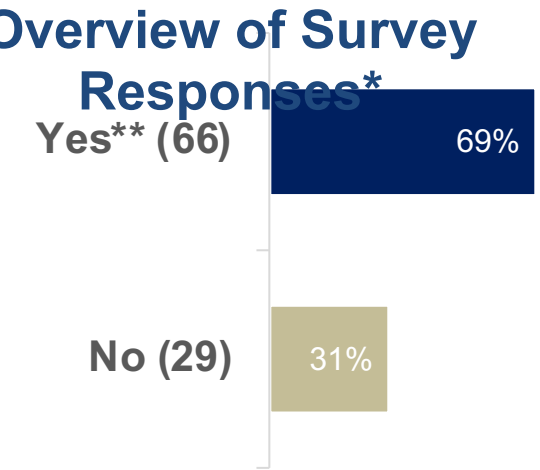
OND Wide Launch

Who: OND Medical Officers & Office of Biostatistics
What: Survey Full-Launch
How: Multiple email blasts
Why: To gain high volume responses for insight into data quality issues



*Out of 95 Responses, **48% (i.e., 46 participants) were incomplete responses

Process for Identifying Data Quality Issues

Q2d: Please detail your process for identifying data quality issues.
Q3: Please list the analyses performed to identify the data quality related issue(s).

- Respondents used multiple tools; however, some did manual comparison.
- Assessing data by region is an analysis approach for identifying data quality issues.
- Open ended responses did not identify any additional processes the group needs to consider.

Q3. Open-Ended Responses

Please list the analyses performed to identify the data quality related issue(s).

"Multiple sensitivity analyses, IRs to request clarification, recoding of data"

"Summary and descriptive analysis on SDTM and ADAM data to compare key attributes related to primary endpoint"

"Evaluation of safety and efficacy by region"

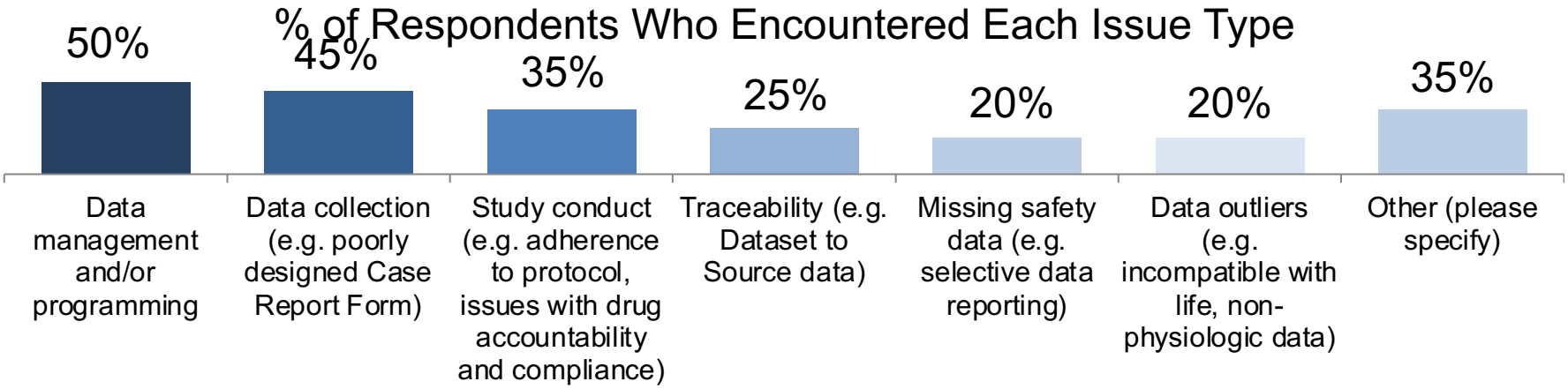
"This statistical approach to central monitoring is based on a large number of statistical tests performed on all variables collected in the database, in order to identify centers that differ from the others."

"Region specific safety (AE, SAE, AE leading to DC) and region specific pregnancy data (Pearl Index-the primary end-point)"

Key Takeaways

A variety of different analyses were used by respondents to identify data quality issues

Types of Data Quality Issues



Key Takeaways

Data Quality issues varied across respondents, but top issues relate to data management, data collection and study.

Data inconsistency and NDA format are additional data quality issues captured in open ended responses.

Sources: Q6: Please indicate the type of data quality issue(s) you encountered. Select all that apply.
Q2c: Please provide a brief description of the data quality issue(s) you encountered. Open Ended Response.

Q2c. Open-Ended responses

Please provide a brief description of the data quality issue(s) you encountered

"Poorly constructed case report forms, errors in data entry, inconsistent formatting"

"Poorly designed case report forms, incorrectly coded outcomes, no/poor quality control"

"Uninterpretable, inconsistent datasets"

"We had aggregated data and we wanted to trace the data back to patient level data to allow for verification of the analysis results."

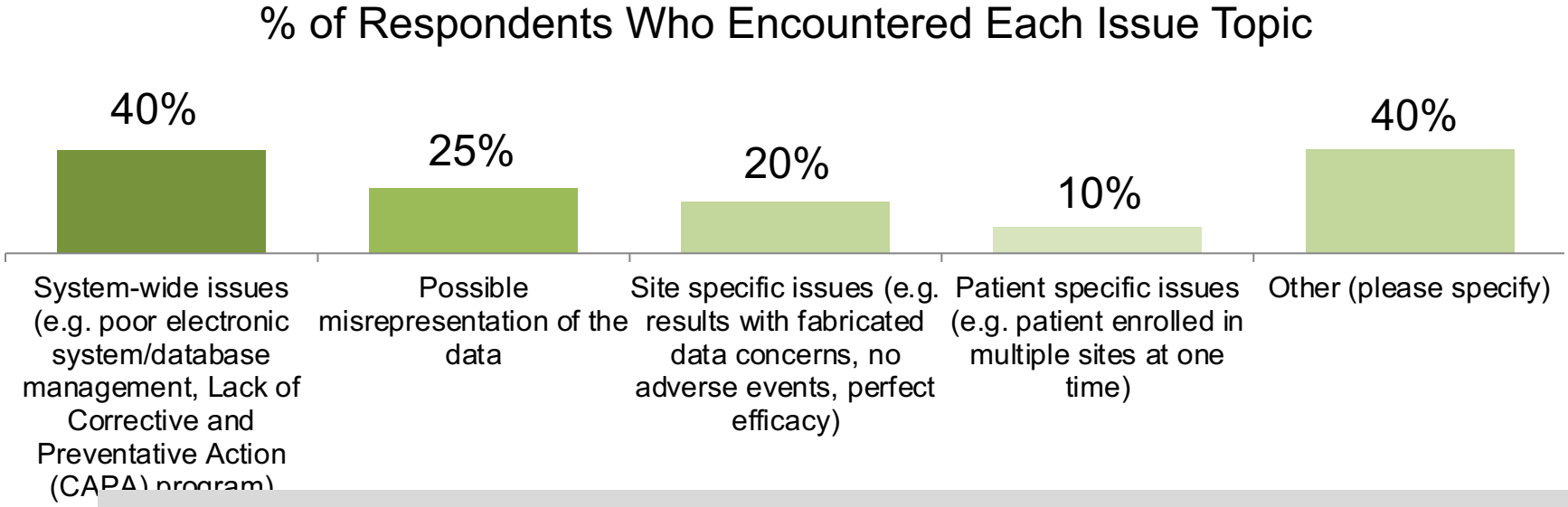
"Incomplete, incorrect, or missing analyses/datasets/domains"

Key Takeaways

Issues were either related to data collection and management or the structure of the NDA report

Incomplete or missing data is also a major driver of data quality issues

Data Quality Issue Related Topics

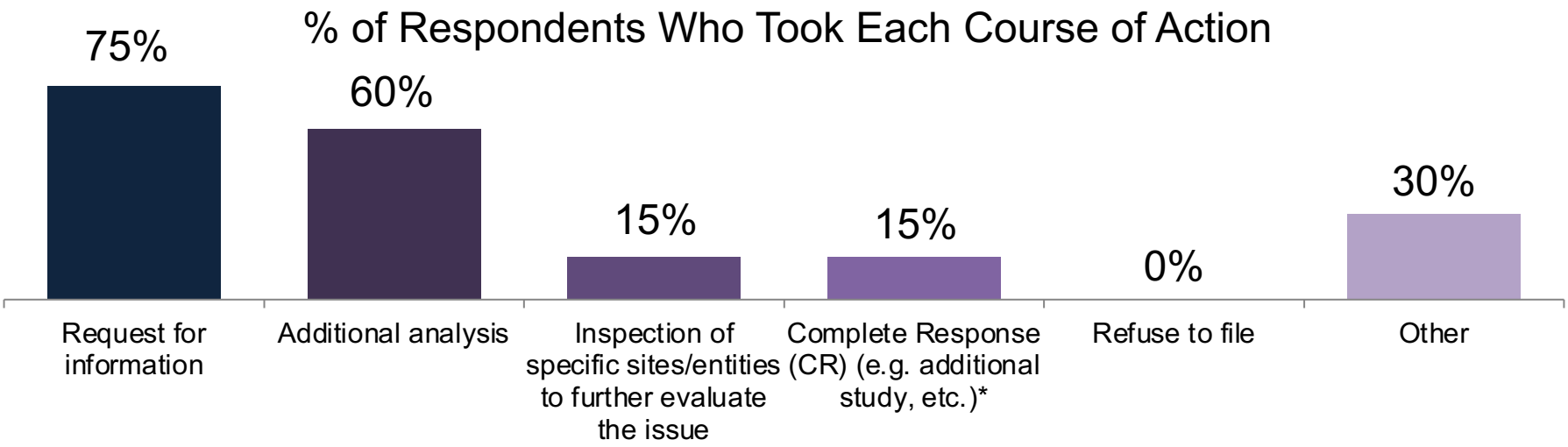


Key Takeaways

Data Quality issues are primarily related to system-wide issues like poor system/database management and CAPA program issues.

Sources: Q7: Please indicate what the data quality issue(s) were related to. Select all that apply.
Q2c: Please provide a brief description of the data quality issue(s) you encountered. Open Ended Response.

Course of Action Taken



Key Takeaways

Over half of respondents Request Information or Perform Additional Analyses after discovering a data quality issue.

T-Con is another next step taken by reviewers, as captured in the open-ended responses.

Q4. Other, please specify

What course of action did you take as a result of finding the data quality issue(s)?

"Tcon with sponsor to educate on how to submit the files correctly."

"Raised the problem during t-con"

"Above issues contributed to triggering a major amendment"

"Incomplete submission"

Key Takeaways

T-con is a commonly used method for addressing data quality issues

Major amendments are cited as a possible outcome of identifying data quality issues

Source: Q4: What course of action did you take as a result of finding the data quality issue(s)? Select all that apply.

Concluding remarks

- Data quality issue vary, but **data management, report structure** and **study conduct** are most frequent issues

- **No singular data quality issue themes identified**
- **Issues typically stem from system-wide issues like poor database management**

- **Request for Information** and **Additional analyses** are most common next steps by reviewers to address data issues.
- Paying attention to quality of data will help the efficiency by avoiding rounds of information requests and additional analyses.

Acknowledgement: OND Clinical Data Acceptance Working Group and the reviewers who responded to the survey.

Type C meeting: Safety Analysis Strategy for the Integrated Summary of Safety

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Type C Meeting to Discuss Safety Analysis Strategy

***Objective*: Gain *earlier* alignment on pooling and other principal safety analyses**

- **Type C meeting to "Discuss Safety Analysis Strategy for the ISS"** ← Cover letter
  - Held after have analytic plan for ISS and prior to programming work for pooled or other safety analyses planned for inclusion in ISS
  - This meeting, *if held*, would precede the Pre-NDA meeting.
  - This meeting is optional; the issues can instead be addressed at the pre-NDA meeting.
- **Process**
  - Language in EOP2 meeting minutes offer~~ings~~ sponsor an opportunity to request a Type C meeting
  - Request about a year prior to NDA filing
  - Meeting within 75 days of FDA receipt of written meeting request
  - Package submitted at least 4 weeks before meeting

Discussion Topics

- Safety Analysis Strategy
  - Study pooling
  - Specific queries for pooled databases
  - Specific safety analyses for ISS or clinical studies
    - Specific tables or figures
    - Specific AE analyses, AE groupings
- Sample clinical dataset submission
  - Opportunity to review conformance to standards, structure and format
- Data standards
- preNDA data requests

Meeting Package

- Description of all trials to be included in the ISS.
- ISS statistical analysis plan, including proposed pooling strategy
  - Rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs
- For a phase 3 program that includes trial(s) with multiple periods, submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Safety issues to be evaluated
  - Planned analytic strategy including any specific queries of AE terms with rationale for use

Summary

- FDA is encouraging Sponsors to request Type C meeting to discuss safety analysis strategy for the ISS to gain earlier alignment on pooling and other important safety analyses
- Optional meeting held
  - After initiation of all Phase 3 trials
  - After devised an analytic plan for ISS
  - Prior to programming work for pooled or other safety analyses planned for inclusion in ISS.
  - Prior to preNDA meeting
- Offers an opportunity to discuss how to analyze, report, and submit safety data
- Early identification of key risks and how to evaluate will aid in evaluation of benefit-risk

FYI - Type C Meeting Language in EOP2 Minutes

"DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request."