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Meta-Metadata: Management of CDISC ADaM Metadata in Light of New Industry Documents – FDA Standard Safety Tables and Figures IG

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Meet the Speaker

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Active participant in several CDISC standards teams with a passion for standards management, currently focused on supporting submissions requirements for regulatory authorities. Experienced in CDISC SDTM, ADaM, metadata management, standards control, etc.

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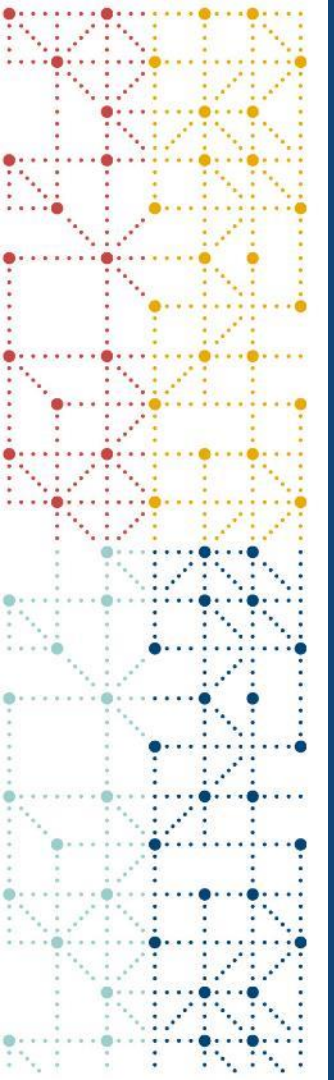
- *The author(s) have no real or apparent conflicts of interest to report.*

Agenda

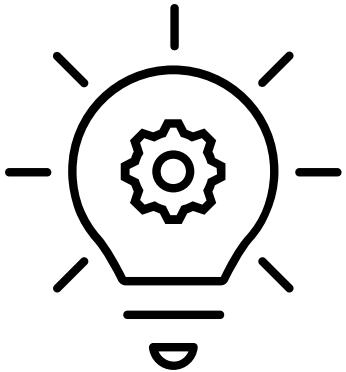
1. FDA Medical Queries - A Brand New Frontier
2. Overview - FDA Standard Safety Tables and Figures: Integrated Guide
3. Drug-Induced Liver Injury (DILI) - Why it Matters
4. Summary



FDA Medical Queries

A New Frontier for Adverse Events

What are FDA Medical Queries (FMQs)?



FDA published the *Standard Safety Tables and Figures: Integrated Guide* document in Aug 2022.

- Surprisingly, they created their own FDA Medical Queries.
- New concept impacts standards teams globally.

Questions have arisen such as:

- Do we want to include these new FMQ Tables in our metadata and data?

What are FDA Medical Queries (FMQs)?

FMQs - comprehensive list of AE PTs

FDA Developed to capture missed safety signals.

- Internal groupings
- Based on medical concepts

Are FMQs **really** needed?

FACT: Improper grouping of AEs can lead to missed safety signals.

- 104 FMQs.
- 4 *algorithmic* FMQs
- One SOC - **many different FMQs**.
- Classification: *Narrow* and *Broad.*

FMQs – Broad, Narrow and Algorithmic

2 basic types of FMQs:

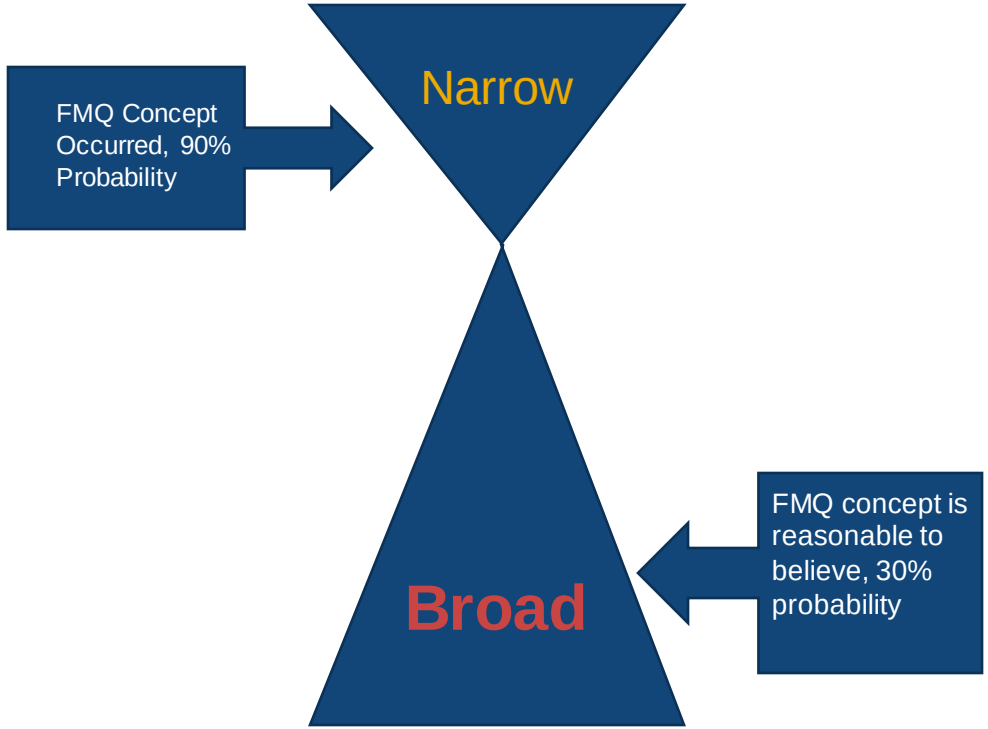
- **Medical concepts**
- **Algorithmic**

FACT: Broad FMQs include Narrow

- ❑ **Broad FMQs: 30% probability**
- ❑ **Narrow FMQs: 90% probability**

Algorithmic:

- 4 algorithmic FMQs, using different data



FMQs – Focus on Algorithmic

Potential question: ***Does my data indicate that I have a FMQ of Hypoglycemia?***

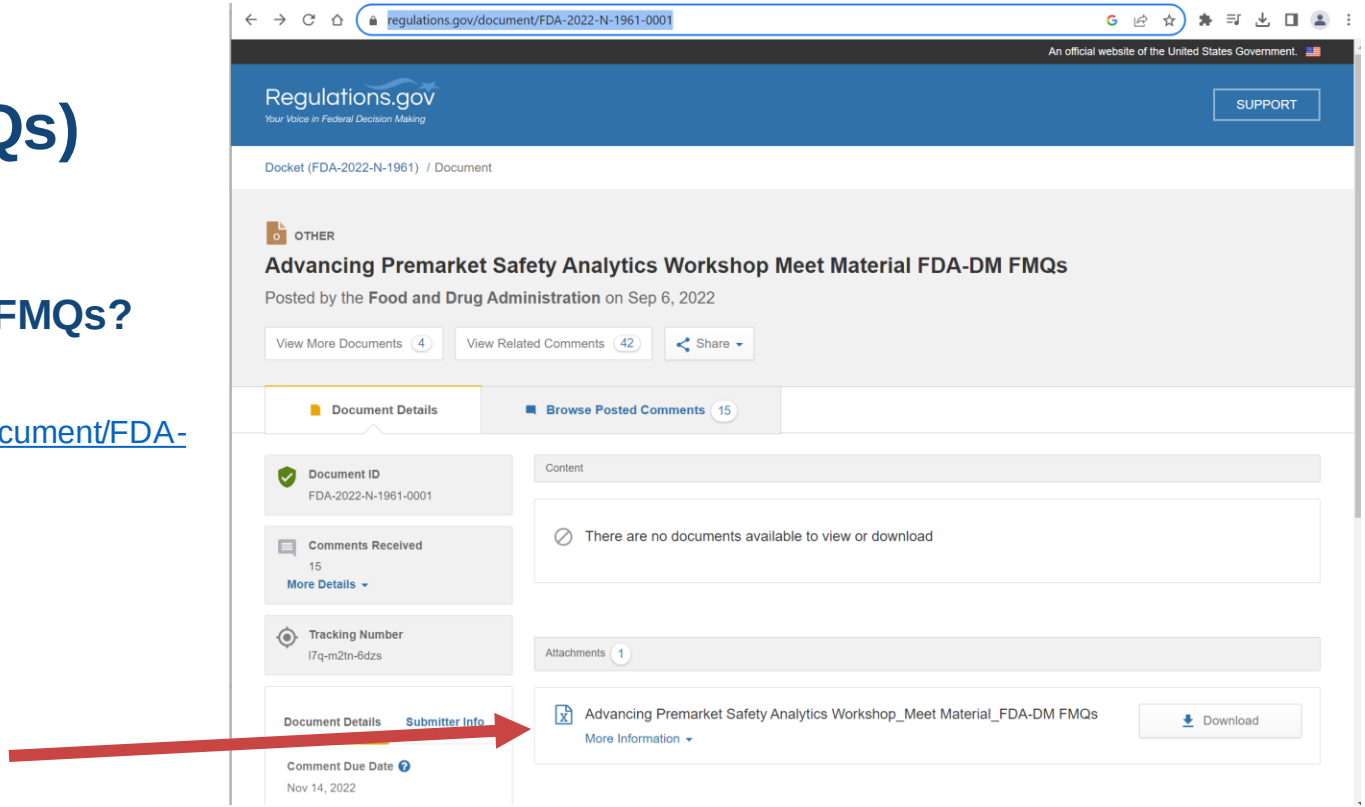
Criteria	Data Source
Any Hypoglycemia FMQ Narrow Term	Could be found in AE
Plasma Glucose <54 mg/dL	Could be found in LB
[Any Hypoglycemia FMQ Broad Term* OR Supplemental Term**] PLUS [Plasma Glucose <70 mg/dL] with start date within 1 week	Could be found in LB, DM and AE
[≥2 Occurrences of a Hypoglycemia FMQ Broad Term* OR Supplemental Term**] PLUS [≥2 Occurrences of Plasma Glucose <70 mg/dL]	Could be found in LB and AE

FDA Medical Queries (FMQs) continued…

Where can I find the FMQs?

Navigate to this link:

https://www.regulations.gov/document/FDA-2022-N-1961-0001



FDA Medical Queries (FMQs) continued…

Look to the comments to find out important information about the FMQ decision…

What do FMQs look like?

- Some FMQ groupings contain relevant comments or notes

For example, *Anaphylactic Reaction* contains the following notes.

PT	Final Classification
Amniotic fluid embolus	Narrow
Anaphylactic reaction	Narrow
Anaphylactic shock	Narrow
Anaphylactic transfusion reaction	Narrow
Anaphylactoid reaction	Narrow
Anaphylactoid shock	Narrow
Anaphylactoid syndrome of pregnancy	Narrow
Anaphylaxis treatment	Narrow
Kounis syndrome	Narrow
Acute circulatory failure	Broad
Chemokine abnormal	Broad
Chemokine increased	Broad
Circulatory collapse	Broad
Collapse	Broad
Dialysis membrane reaction	Broad
Drug hypersensitivity	Broad
First use syndrome	Broad
Hypersensitivity	Broad
Hypersensitivity type I NOS	Broad
Pharyngeal swelling	Broad
Reaction to excipient	Broad
Shock	Broad
Shock symptom	Broad
Type I hypersensitivity	Broad

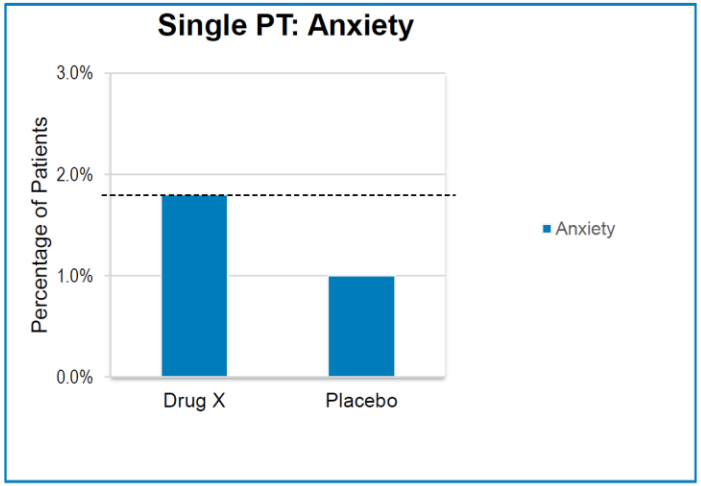
COMMENT: Preferred terms consistent with anaphylactoid reaction are included in this FMQ as anaphylaxis and anaphylactoid reactions are generally not distinguished clinically. The term "Dialysis membrane reaction" was included within Broad because this entity can present and be treated similarly to anaphylaxis.

Fig. 1 Advancing Premarket Safety Analytics Workshop_Meet Material_FDA-DM FMQs

FDA Medical Queries (FMQs) continued…

Question: How can adverse events be more accurately captured?

Answer: by considering FMQs when counting AEs, see below:



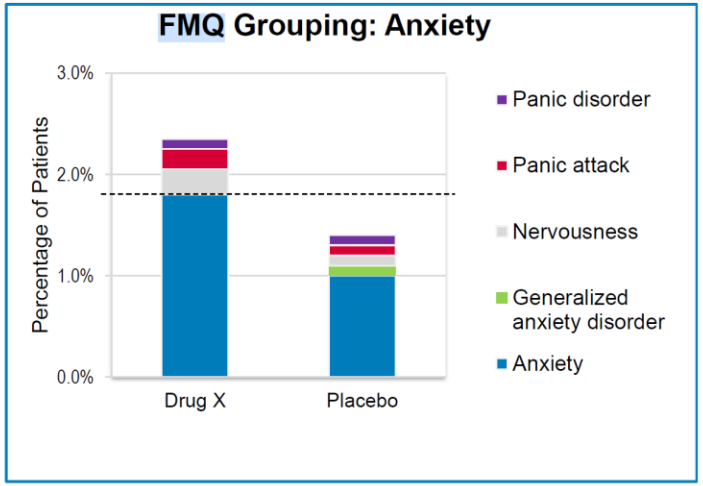


Fig 2. Slide 26 *Advancing Premarket Safety Analytics Final Slide Deck*

FDA Medical Queries – Labelling Impact

If FMQs are used in analysis, they may eventually show up in labelling.

ARs (Adverse Reactions): *reasonable belief/basis* between drug & AE.

Why? Grouping Adverse Reactions by FMQs may provide a *better safety signal* when grouping AEs compared to SMQs.

Overview - FDA Standard Safety Tables and Figures: Integrated Guide

FDA Standard Tables and Figures IG

In August 2022, FDA released a Standard TFL Guide (STFIG) for the first time ever.

- Standard set of safety tables and figures
  - Can be modified for treatment arms
  - Other changes for study analysis needs warranted

- Tables and Figures are not required for FDA submission
  - *Assists* in review of a data submission

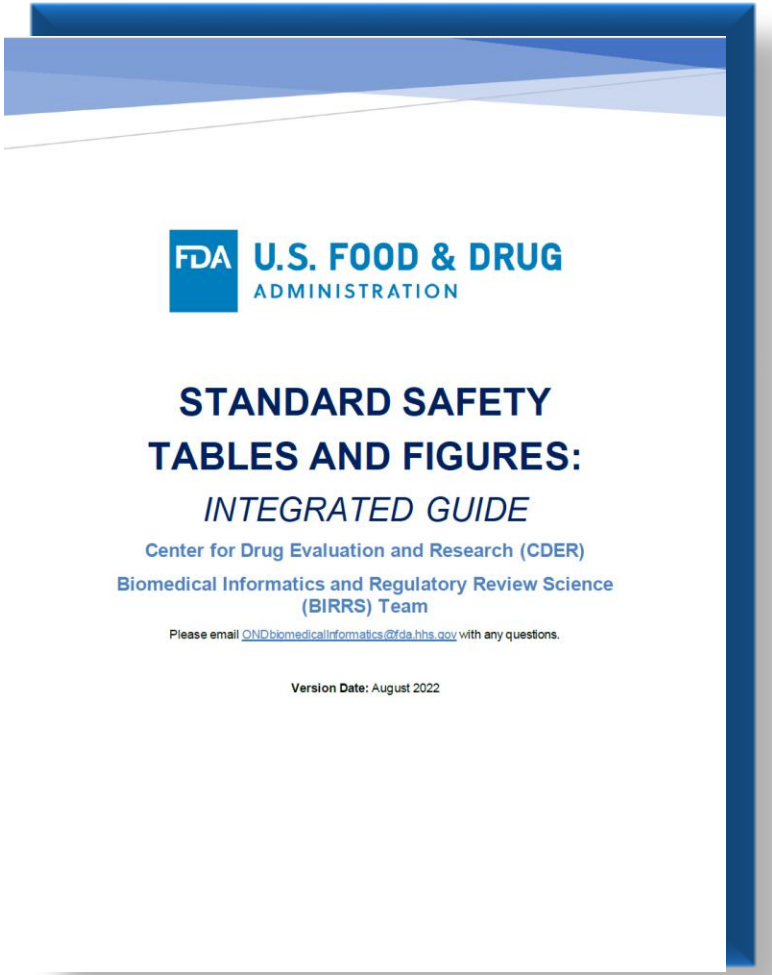


Fig 3. FDA Standard Tables and Figures Integrated Guide, Aug 2022

FDA Standard Tables and Figures IG

Basic Overview:

- 60 proposed Tables
- 35 proposed Figures
- Varied subjects which could be very helpful

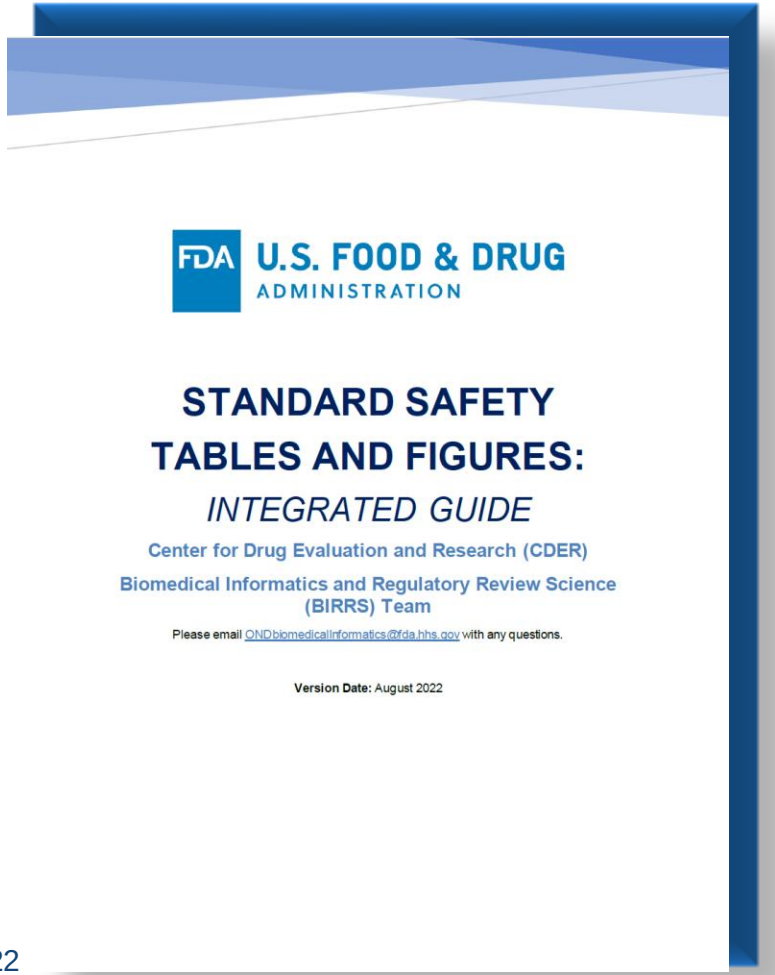


Fig 3. FDA Standard Tables and Figures Integrated Guide, Aug 2022

FDA Standard Tables and Figures IG

In this case, a cookie-cutter approach is best!

Why are they needed?

- Standardizing TF outputs introduces commonality
- Usage of different tables and figures creates variability across sponsors
- Improves efficiency in submissions

FDA Standard Tables and Figures IG

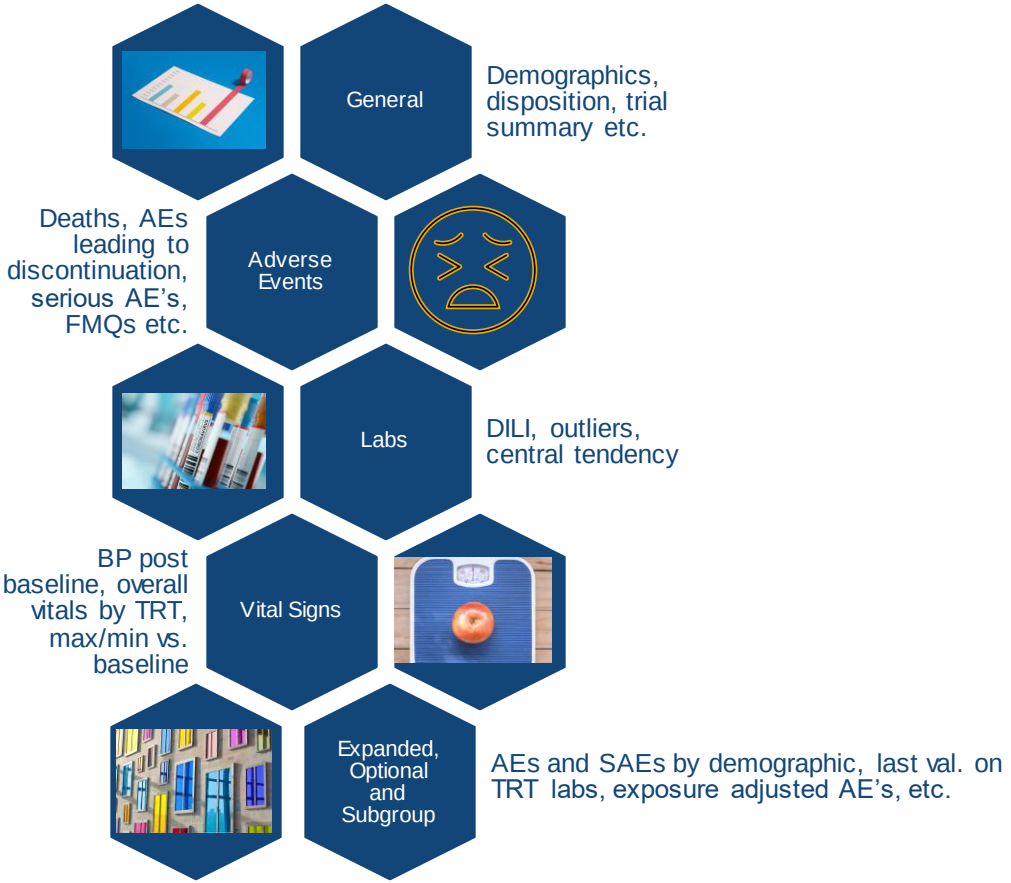
Simple Idea: Introduce *standard* outputs, reduce variability

But wait… do I have to use these?

- No, you do not have to submit your safety tables and figures using the FDA STFIG
- Using these potentially help the overall processing of your submission

FDA Standard Tables and Figures IG (STFIG)

What contents are covered?



FDA Standard Tables and Figures IG

What are the differences?

New table element: risk differences w/CI

Table 54. Exposure-Adjusted Incidence Rate Analysis, Safety Population, Pooled Analyses (or Trial X)

Preferred Term	Drug Name Dosage X PY[1]=xxx.x EAIR (Per 100 PY)	Placebo PY[1]=xxx.x EAIR (Per 100 PY)	Risk Difference (95% CI)[2,3]
PT1	EAIR (per 100 PY)	EAIR (per 100 PY)	X (Y, Z)
PT2	EAIR (per 100 PY)	EAIR (per 100 PY)	X (Y, Z)
PT3	EAIR (per 100 PY)	EAIR (per 100 PY)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
Treatment-emergent AE defined as [definition]. MedDRA version X. An asterisk (*) indicates a grouped term.
[1] Indicate method used to calculate the patient years.
[2] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
[3] Table display is ordered by the risk difference.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate; N, number of patients in treatment arm; n, number of patients with AE; PT, preferred term; PY, patient years

Fig 4. FDA Standard Tables and Figures Integrated Guide, Aug 2022

New table element: patient years

FDA Standard Tables and Figures IG

Side by side comparison – what are the differences?

New table elements:
Risk Differences w/CI

Table 1.2.3.4

Disposition of Participants
(ITT Population)

	Investigational Drug	Standard Treatment	Total
	n (%)	n (%)	n (%)
Participants in population	6	3	1
Status for Study Treatment in Trial			
Started	xx	xx	xx
Completed	x(xx.x)	x(xx.x)	x(xx.x)
Discontinued	1 (16.7)	0 (0.0)	0 (0.0)
Progressive Disease	1 (16.7)	0 (0.0)	0 (0.0)
Participants Ongoing	5 (83.3)	3 (100.0)	1 (100.0)
Status for Trial			
Discontinued	2 (33.3)	0 (0.0)	0 (0.0)
Death	2 (33.3)	0 (0.0)	0 (0.0)
Withdrawal By Participant			
Subsequently Died			
No Further Information			
Participants Ongoing	4 (66.7)	3 (100.0)	1 (100.0)
Database cutoff date: DDMMMYYYY.			

Table 4. Patient Disposition, Pooled Analyses[1,2]

	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]
Patients randomized	**n (%)**	**n (%)**	**n (%)**	**n (%)**	-
ITT/mITT population[3]	n (%)	n (%)	n (%)	n (%)	-
Safety population	n (%)	n (%)	n (%)	n (%)	-
Per-protocol population	n (%)	n (%)	n (%)	n (%)	-
Discontinued study drug	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
Adverse event	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Lack of efficacy	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Protocol deviation	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Death	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Withdrawal by subject	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Other	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Discontinued study	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**X (Y, Z)**
Death	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Lost to follow-up	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Withdrawal by subject	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Physician decision	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Protocol deviation	n (%)	n (%)	n (%)	n (%)	X (Y, Z)
Other	n (%)	n (%)	n (%)	n (%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[2] [Include route of administration for all treatment arms if different ROA were used in the drug development].
[3] Difference is shown between [treatment arms] (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; ITT, intention-to-treat; mITT, modified intention-to-treat; N, number of patients in treatment arm; n, number of patients in specified population or group

Fig 5. FDA Standard Tables and Figures Integrated Guide, Aug 2022

Some other differences:
- Randomized = ITT
- Wording changes

FDA Standard Tables and Figures IG

New Analysis for FMQ tables

There are 17 tables from the STFIG that use FMQs.

For Table 14, it's important to review the entire table and then decide the appropriate cutoff. For example, >5%, >2%, or >1% frequency may be an appropriate cutoff or none, depending on the data presented. Refer to Table 33 to view specific preferred terms under each FMQ by SOC.

Table 14. Patients With Adverse Events[1] by System Organ Class and FDA Medical Query, Safety Population, Pooled Analyses[2]

	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)
SOC3								
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)

Source: [include Applicant source, datasets and/or software tools used].
[1] Treatment-emergent adverse event 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] 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; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with at least one event; SOC, System Organ Class

Fig 6. FDA Standard Tables and Figures Integrated Guide, Aug 2022

FDA Standard Tables and Figures IG

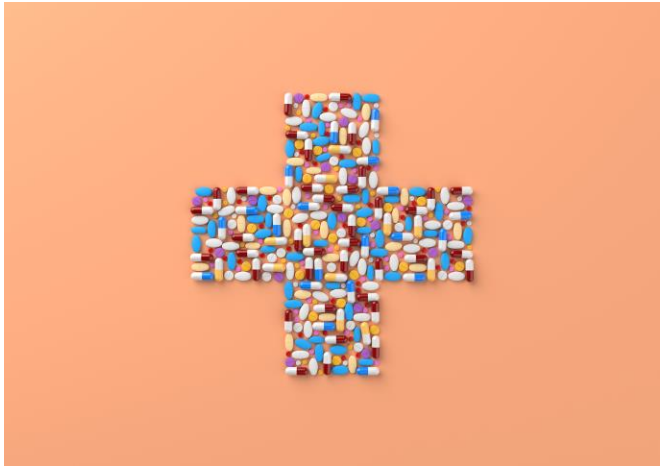
Without cut-off date

With cut-off date, therefore, end date is applicable

On-treatment vs. On-Study

Both impact TEAE Analysis

Both consider start day (of AE) as relevant



FDA Standard Tables and Figures IG

On-Study

With cut-off date – there is some discussion/concern from the FDA regarding the length of following the subjects prior to data cutoff.

- Per the FDA, most applicants use a 28- or 30-day cutoff window.
- Consideration should be given to the drug's half life.
- Example: monoclonals have a much longer half-life, so the cutoff day would be better served to be as long as 42-70 days, per the FDA

More Recommendations from the Webinar

Recommendation: to include contrast measure as an *additional* column

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

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Providing contrast to show the difference/ratio was mentioned as a recommended practice during the webinar.

Fig 7. Slide 26 *Advancing Premarket Safety Analytics Final Slide Deck*

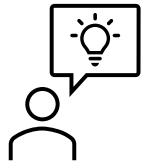
Drug-induced Liver Injury (DILI)

Drug-induced Liver Injury (DILI)

The FDA stated in their September 2022 webinar that DILI analysis is relevant to all trials.

- Wait, all trials?
- What does this mean for the industry?
- How do we become familiar with DILI?

DILI



- How can the standards community approach DILI as potentially relevant to *every submission*?
- *With no official guidance from CDISC yet, this spurred my idea to create an ADaM subteam to address DILI*
- *ADaM DILI subteam goal:*

> *"*To address the topic of Drug-induced Liver Injury (*DILI*) as it relates to CDISC SDTM & ADaM, as well as the needs set forth by the FDA in addition to the needs of the standards community and its consumers"

DILI Subteam

We began by assessing all the available guidance we could find

Fig. 7 & 8 https://www.fda.gov/science-research/bioinformatics-tools/liver-toxicity-knowledge-base-ltkb

This above page is a landing zone for DILI related information from the FDA.

Drug Induced Liver Injury Rank (DILIrank) Dataset | FDA

LTKBID	Compound Name	Severity Class	Label Section	vDILIConcern
LT00003	mercaptopurine	8	Warnings and precautions	vMost-DILI-Concern
LT00004	acetaminophen	5	Warnings and precautions	vMost-DILI-Concern
LT00006	azathioprine	5	Warnings and precautions	vMost-DILI-Concern
LT00009	chlorpheniramine	0	No match	vNo-DILI-Concern

DILIrank dataset consists of FDA-approved drugs that are divided into four classes according to their potential for causing DILI.

DILI Subteam Documents

DILIST_ID	CompoundName	DILIst Classification	Routs of Administration
1	mercaptopurine	1	Oral
2	acetaminophen	1	Oral
3	azathioprine	1	Oral
4	chlorpheniramine	0	Oral
5	clofibrate	1	Oral
6	cyclophosphamide	1	Oral
7	dopamine	0	Intravenous

Fig. 9 https://www.fda.gov/science-research/bioinformatics-tools/liver-toxicity-knowledge-base-ltkb

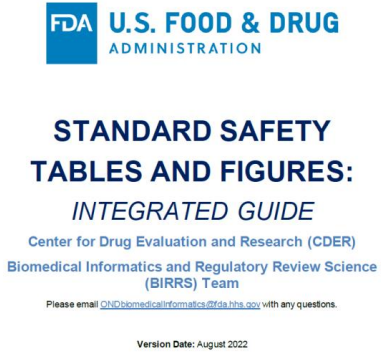
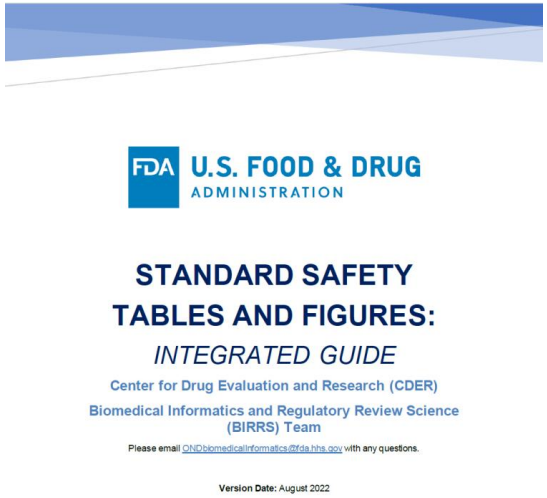


Fig 10. FDA Standard Tables and Figures Integrated Guide, Aug 2022

Then we have a DILI severity and toxicity (DILIst) dataset consisting of drugs that are divided into two classes according to their potential for causing DILI.

See page 58 for DILI content.

DILI Subteam Documents



U.S. FOOD & DRUG ADMINISTRATION

STANDARD SAFETY TABLES AND FIGURES:

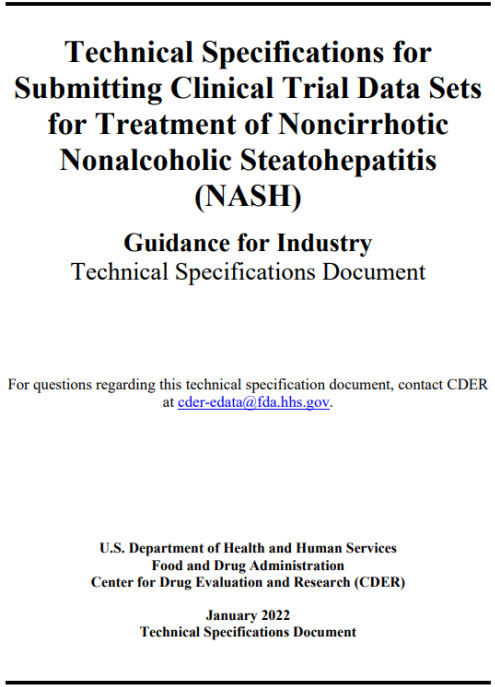
INTEGRATED GUIDE

Center for Drug Evaluation and Research (CDER)

Biomedical Informatics and Regulatory Review Science (BIRRS) Team

Please email CNDbiomedicalinformatics@fda.hhs.gov with any questions.

Version Date: August 2022



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

Guidance for Industry

Technical Specifications Document

For questions regarding this technical specification document, contact CDER at cder-edata@fda.hhs.gov.

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

January 2022
Technical Specifications Document

After comparing what available information we have in the NASH document, to the suggested figures in the STFIG, we are ready to form a plan.

DILI Subteam – Where are we now?

Currently, we are recruiting volunteers who are interested in joining this initiative.

- Differing data points impact DILI for a study.

We are working to identify helpful elements from the NASH document as a stepping stone to get us to an analysis DILI dataset.

- Prefer to name it something other than ADDILI
  - We want to differentiate from the NASH guidance.

Scope is to produce an example dataset, example variables etc. that can be used to create informative CDISC guidance.

Takeaway Summary

Summary Wrap Up

- The FDA STFIG has given those who work on analysis standards plenty of things to consider, such as:
  - Should we adopt these TFLs at my company?
  - Are they required outputs?
  - Do we need to use FMQs?
    - What is the impact if we do not use them?
  - If we use FMQs what will this look like for my ADaM metadata or data?
  - New elements shown in the STFIG – how can we apply it to internal standards?
  - What should we do about DILI?
  - CDISC guidance – is it available?

Summary Wrap Up

Forthcoming guidance/examples from CDISC can help, in the meantime discuss internally and consider getting involved in CDISC standards creation.

- FDA STFIG introduced many new elements and concepts to analysis standards; we can benefit from applying them to our internal processes
- Standardization is welcome, we all benefit knowing submission challenges, potential improvement areas
- FDA is considering FMQs when we provide our data to them, we should probably be considering it as well
- Important considerations include potential changes in cut-off date etc.

References

1. Figure 1, “Advancing Premarket Safety Analytics Workshop Meet Material FDA-DM FMQs” from https://www.regulations.gov/document/FDA-2022-N-1961-0001 Accessed 9/14/23
2. Figures 2, 7 & 5: “*Advancing Premarket Safety Analytics Final Slide Deck*” from https://healthpolicy.duke.edu/events/advancing-premarket-safety-analytics Accessed 9/20/23
3. Figures 3, 4, 5, 6, 10: https://www.regulations.gov/document/FDA-2022-N-1961-0002 Accessed 9/20/23
4. Figure 7, 8, 9 https://www.fda.gov/science-research/bioinformatics-tools/liver-toxicity-knowledge-base-ltkb Accessed 9/20/23
5. Figure 11, https://www.fda.gov/media/151864/download Accessed 9/20/23

Thank You!

Email: Amanda.johnson2@merck.com