How to Avoid More Flags than the United Nations when Creating ADaM Data Sets

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September 13, 2013

Agenda

- Introduction
- Review of ADAE Metadata
- Overview of Flags
- Closer Look at ADAE: ADaM Data Structure for Adverse Event Analysis
- Explore AOCCzzFL: ADAE Occurrence Flags
- Exercise Time!
  - Real World Example
  - Challenge

Challenge "Sneak Preview"

Will Revisit Later

- Given mock AE analysis tables
- Given a standard for ADAE (metadata)
- Create study specifications for one or more ADAE data set structures – **Occurrence FLAG Variables Only**

Introduction

- Emphasis on Pros & Cons of Occurrence Flags in an ADAE Structure

- Hand out flags ☺
  - Questions
  - Challenge
  - Voting

- Audience Experience with Defining Metadata – Informal Survey (Show of Flags)

Review of Metadata

Table Level Metadata
Example

- Data set definitions
- Description of data set structure
- Sort order – KEYS (variables that make unique records)

Dataset	Label	Structure	Class	Documentation/Rules
ADSL	Subject-Level Analysis	One record per subject	ADSL	To include all randomized subjects
ADAE	Adverse Event Analysis Dataset	One record per subject per each AE	ADAE	ADaM.ADAE Uses Dictionary MedDRA V11.1
ADVS	Vital Signs Analysis	One or more subject per vital sign per visit	BDS	To support change from baseline analysis

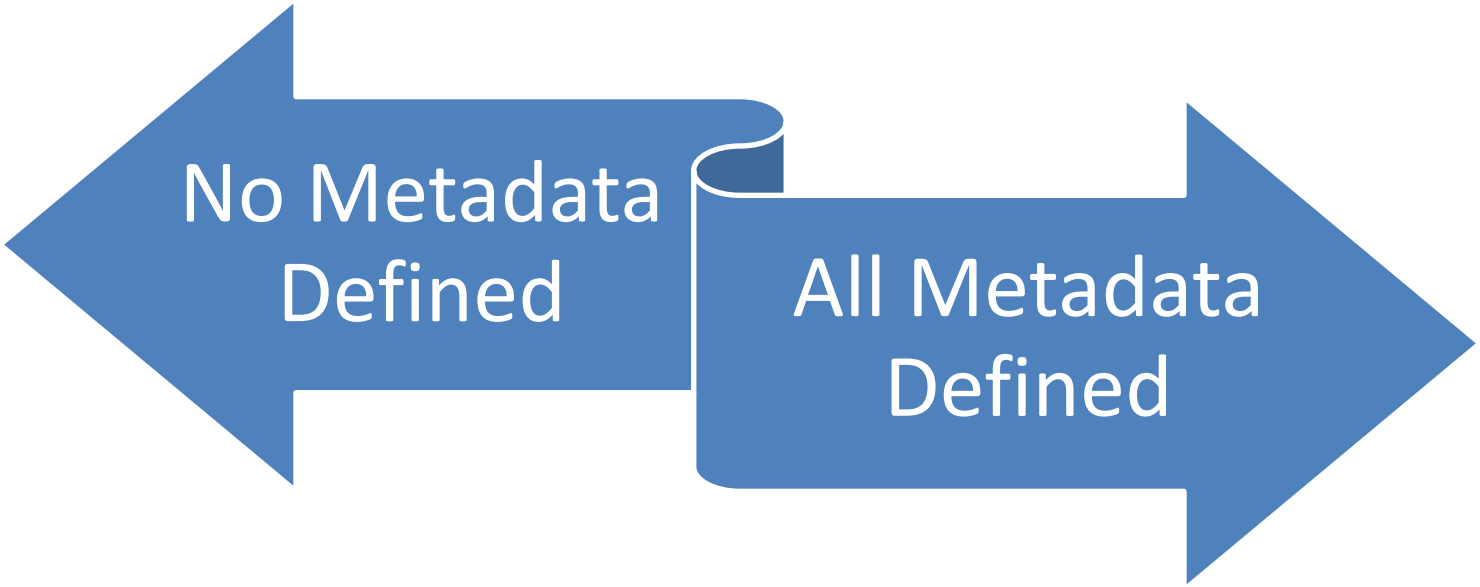
Variable Level Metadata
Example

- Variable descriptions
  - Variable Name
  - Label
  - Length
  - Source
  - Type (text/integer/float)
  - Significant Digits (for float)
  - Display Format
  - Analysis Algorithm

Dataset	Variable	Label	Type	Length	Algorithm/Source
ADAE	USUBJID	Unique Subject Identifier	text	12	ADaM.ADSL
ADAE	AETERM	Reported Term for the AE	text	200	AE.AETERM
ADAE	ASTDT	Analysis Start Date	integer	8	Create date9. date from AE.AESTDTC

ADaM Metadata
Where do you fall on the continuum?

- Resources used for creating ADaM data sets?
  - ADaMIG only?
  - Generic ADaM template?
  - Completed study specifications?
  - Sponsor defined criteria and pre-defined standard metadata?



Standards

ADaM Linked to SDTM

Variable	Label	Type	Code List	Length	Algorithm
USUBJID	Unique Subject Identifier	text		12	ADSL.USUBJID
AESEQ	Sequence Number	integer		8	**AE.AESEQ**
AETERM	Reported Term for the AE	text		200	**AE.AETERM**
AEREL	Causality	text	CT.AEREL	40	**AE.AEREL**
AEOUT	Outcome of Adverse Event	text	CT.AEOUT	40	**AE.AEOUT**
TRTP	Planned Treatment	text	CL.TRT	40	TRTP = ADSL.TRT01P
TRTPN	Planned Treatment (N)	integer	CL.TRTN	8	TRTPN = ADSL.TRT01PN

Variable Level Metadata

Re-usable Metadata

Variable	Label	Type	Code List	Len	Algorithm
AOCCFL	1st Occurrence of Any AE Flag	text	CL.YES	1	Subset by TRTEMFL="Y" Sort by USUBJID ASTDT AESEQ and flag first record
AOCCSFL	1st Occurrence of SOC Flag	text	CL.YES	1	Subset by TRTEMFL="Y" Sort by USUBJID AEBODSYS ASTDT AESEQ and flag first record
AOCCPFL	1st Occurrence of PT Flag	text	CL.YES	1	Subset by TRTEMFL="Y" Sort by USUBJID AEBODSYS AEDECOD ASTDT AESEQ and flag first record
AOCCzzFL	1st Occurrence of *<fill in>*	text	CL.YES	1	*<fill in>*

All Metadata Pre-Defined

Metadata Before Programming

Pros

- Tables level metadata defined
- Variable level metadata defined
- Re-usable metadata
- ADaM Standards linked to SDTM Standards

Cons

- More time up front
- Some inflexibility depending on Standards

Overview of Flags

Population Flags Example
Y/N = Yes/No

- All subject-level population flags must be present in ADSL
  - **SAFFL**
  - ITTFL
  - RANDFL

- At least one population flag in data sets used for analysis

Data set	Var.	Label	Type	Code List	Len	Algorithm
ADSL	**SAFFL**	Safety Population Flag	text	Y/N	1	Meets SAP definition of ITT
ADSL	SAFFN	Safety Population Flag (N)	integer	1/0	8	One-to-one mapping of ITTPFL

BDS Flags Example

Y/null = Yes/null

Metadata

Data set	Var.	Label	Type	Code List	Len	Algorithm
ADVS	ABLFL	Baseline Record Flag	text	Y/null	1	Set to "Y" when AVISIT = "Baseline"
ADVS	ABLFN	Baseline Record Flag (N)	integer	1/null	8	One-to-one mapping of ABLFL

Data

PARAM	PARAMCD	AVISIT	ABLFL	ABLFLN	AVAL	BASE
Weight (kg)	WEIGHT	Screening			99	100
Weight (kg)	WEIGHT	Baseline	Y	1	100	100
Weight (kg)	WEIGHT	Week 1			96	100

Flags Values
Ending in FL or FN

- Populations Flags ending in *FL & *FN
  - **N = No, 0 = N**
  - **Y = Yes, 1 = Y**
- Other Flags ending in *FL & *FN
  - **Y = Yes, 1 = Y**
  - **null**

ADAE Flags Example

- At least one population flag in data sets used for analysis
- True for ADAE? SAFFL?

Note: A population flag may not be appropriate in ADAE if ADAE does not contain all subjects

Incidence of Treatment Emergent Adverse Events **Safety Population**	
System Organ Class Preferred Term	Total (N = xxx) n (%)
Any Adverse Event	xxx (xx %)
SOC Term 1	xxx (xx %)
PT Term 1	xxx (xx %)
PT Term 2	xxx (xx %)
...	
Note: denominator of percentage is the number of subjects in the column	

United Nations Fun Facts

Flags

- The name "United Nations“ was coined by President Franklin D. Roosevelt
- Founded on October 24, 1945
- Official languages: Arabic, Chinese, English, French, Russian, and Spanish
- 193 Members States – Flags arranged alphabetically

Closer Look at ADAE

What is ADAE?

- Analysis Data Model (ADaM) Data Structure for Adverse Event Analysis – May 10, 2012
- Does the ADaM data set have to be called ADAE?
- SDTM.AE + flags for incidence counts
- For analysis within a **mapped dictionary hierarchy**
- Data Structure – ADAE class/model can be used for:
  - ADAE
  - ADCM
  - ADMH

ADAE is Not

- **Not** ADSL: Not subject-level
- **Not** BDS: No PARAM or AVAL/AVALC
- **Not** ADTTE:
  - Time to Event AE data goes into the BDS structure ADTTE
- **Not** a vertical structure
  - Flags are added horizontally
- **Not** technically an “occurrence” structure; but, it could be in the future as ADaM team develops general occurrence model

AE Table
Example

Table AE

Incidence of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment

Safety Population

System Organ Class Preferred Term	Drug A (N = xxx)	Drug B (N= xxx)
Any Adverse Event	xxx (xx)	xxx (xx)
SOC Term 1	xxx (xx)	xxx (xx)
PT Term 1	xxx (xx)	xxx (xx)
PT Term 2	xxx (xx)	xxx (xx)
...		
SOC Term 2	xxx (xx)	xxx (xx)
PT Term 1	xxx (xx)	xxx (xx)
PT Term 2	xxx (xx)	xxx (xx)
...		

ADaM ADAE to Support AE Table

Example Data

USUBJID	AETERM	AEDECOD	AEBODSYS	AOCCFL	AOCCSFL	AOCCPFL
01-001	BACK PAIN	Back Pain	Musculoskeletal and connective tissue disorder	**Y**	**Y**	**Y**
01-001	HEADACHE	Headache	Nervous system disorder		**Y**	**Y**
01-001	HEADACHE	Headache	Nervous system disorder			
01-001	ANXIETY	Anxiety	Nervous system disorder			**Y**

Explore AOCCzzFL

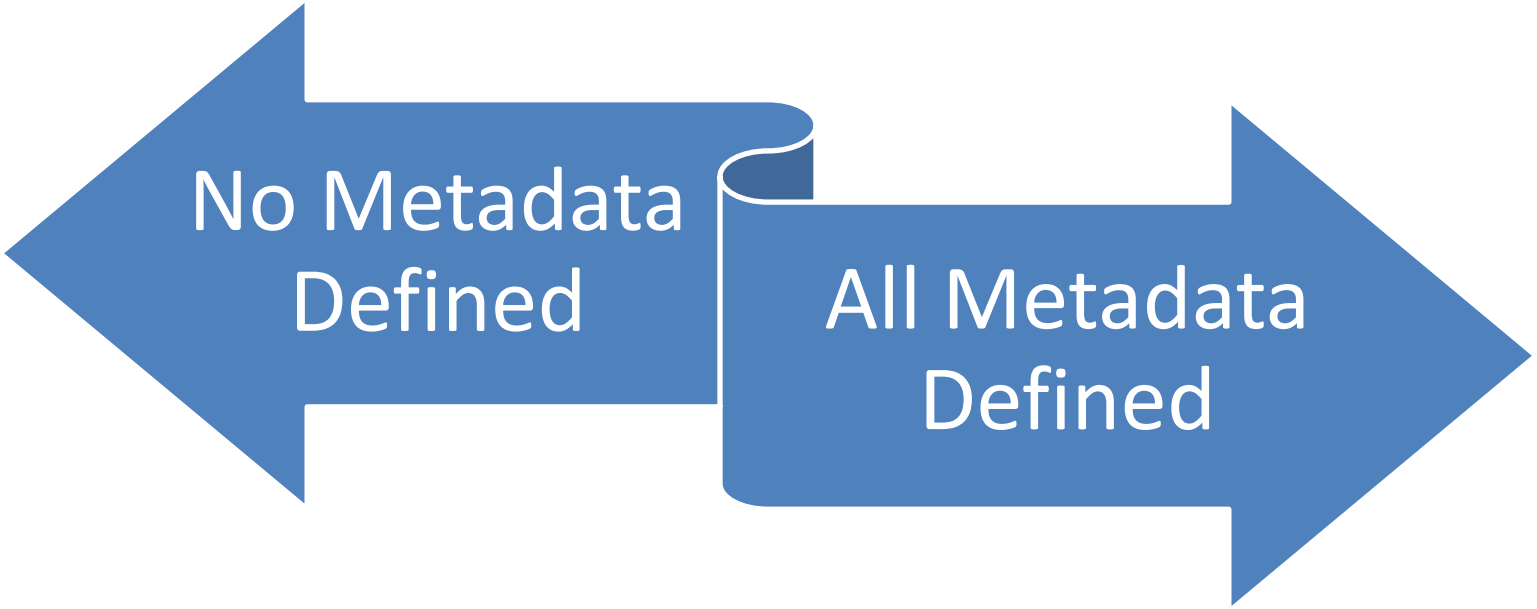
ADAE
Occurrence Flag Variables

ADAE – Adverse Event Analysis Dataset				
Variable Name	**Variable Label**	**Type**	**Code List / Controlled Terms**	**Core**
AOCCFL	1st Occurrence of Any AE Flag	Char	Y	Perm
AOCCSFL	1st Occurrence of SOC Flag	Char	Y	Perm
AOCCPFL	1st Occurrence of Preferred Term Flag	Char	Y	Perm
AOCCIFL	1st Max Sev./Int. Occurrence Flag	Char	Y	Perm
AOCCSIFL	1st Max Sev./Int. Occur Within SOC Flag	Char	Y	Perm
AOCCPIFL	1st Max Sev./Int. Occur Within PT Flag	Char	Y	Perm
AOCCzzFL	1st Occurrence of ….	Char	Y	Perm

AOCCzzFL

1st Occurrence of…

- When to create AOCCzzFL?
- Create additional flag variables as needed for analysis. Derivation for these flags need **to be described in the metadata**



AOCCzzFL – ADAE Description

1st Occurrence of…

- The Occurrence Flags (AOCCzzFL) are permissible. The main purpose is to facilitate traceability between records in the dataset and unique counts in the summary displays

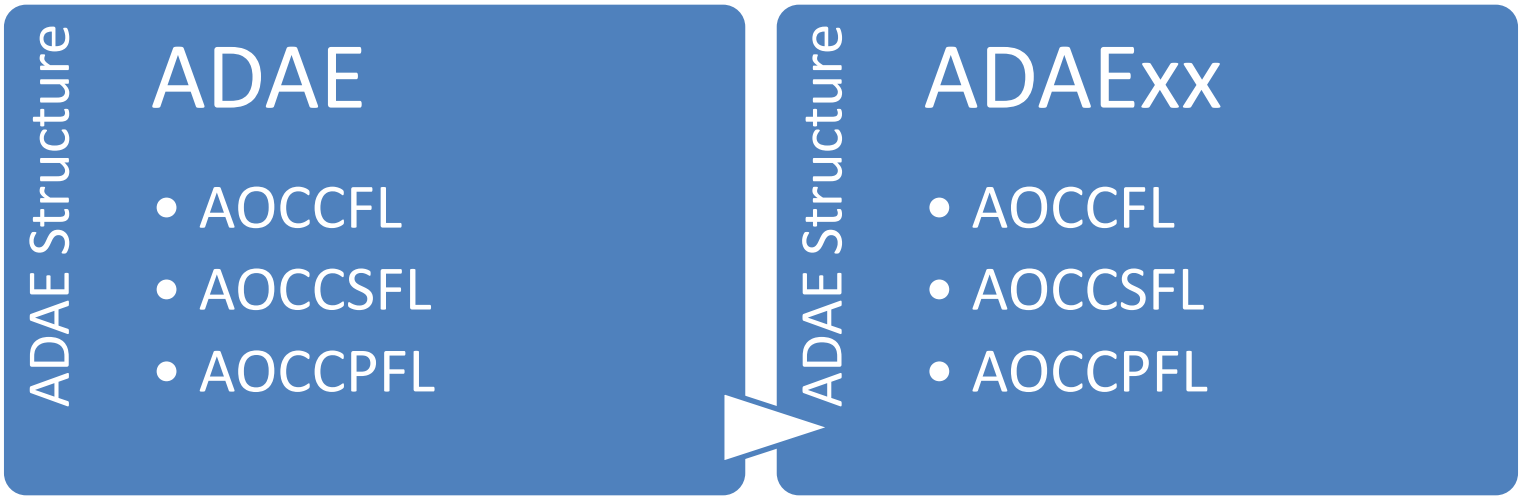
- If additional analysis is built off of ADAE, the flags provide a link between the summary records and the source of the records in ADAE

- If the producer of the ADAE dataset has standard programs in place to summarize unique counts of events then they may chose not to create these flags

Create > One ADAE Structure

ADAExx

- If the producer of the ADAE dataset has **standard programs** in place to summarize unique counts of events then **they may chose not to create these flags**



Re-use Metadata
ADAE & ADAER

Table Level

Dataset	Label	Structure	Class
ADAE	AE Analysis Dataset	One record per subject per each AE	ADAE
ADAE**R**	**Related** AE Analysis Dataset	One record per subject per each AE	ADAE

Variable Level

Same Variable Level Metadata for ADAE & ADAER

Data set	Var.	Label	Type	Len	Algorithm
ADAE	AOCCFL	1st Occurrence of Any AE Flag	text	1	Sort by USUBJID ASTDT AESEQ and flag first record
ADAE	AOCCSFL	1st Occurrence of SOC Flag	text	1	Sort by USUBJID AEBODSYS ASTDT AESEQ and flag first record
ADAE	AOCCPFL	1st Occurrence of PT Flag	text	1	Sort by USUBJID AEBODSYS AEDECOD ASTDT AESEQ and flag first record

Re-use Metadata

ADAE & ADAER

ADAE

Back Pain is Not Related

USUBJID	AETERM	AEDECOD	AEBODSYS	AOCCFL	AOCCSFL	AOCCPFL
01-001	BACK PAIN	Back Pain	Musculoskeletal	**Y**	**Y**	**Y**
01-001	HEADACHE	Headache	Nervous system		**Y**	**Y**
01-001	HEADACHE	Headache	Nervous system			
01-001	ANXIETY	Anxiety	Nervous system			**Y**

ADAER

Headache and Anxiety are Related

USUBJID	AETERM	AEDECOD	AEBODSYS	AOCCFL	AOCCSFL	AOCCPFL
01-001	HEADACHE	Headache	Nervous system	**Y**	**Y**	**Y**
01-001	HEADACHE	Headache	Nervous system			
01-001	ANXIETY	Anxiety	Nervous system			**Y**

Create New Occurrence Flags
AOCCzzFL

- TEAEs
  - AOCCFL – Any AE Flag
  - AOCCSFL – SOC Flag
  - AOCCPFL – PT Flag
- Serious AEs
  - AOCCYFL – Any SAE Flag
  - AOCCYSFL – SAE SOC Flag
  - AOCCYPFL – SAE PT Flag
- Related AEs
  - AOCCRFL – Any Rel. AE Flag
  - AOCCRSFL – Rel. SOC Flag
  - AOCCRPFL – Rel. PT Flag
- Sev./Int. AEs
  - AOCCIFL – Any Sev. AE Flag
  - AOCCISFL – Sev. SOC Flag
  - AOCCIPFL – Sev.PT Flag
- Serious & Rel. AEs
  - AOCCXFL – Any SAE Flag
  - AOCCXSFL – SAE SOC Flag
  - AOCCXPFL – SAE PT Flag
- Sponsor Defined AEs
  - AOCCDFL – Any SponDef AE Flag
  - AOCCDSFL – SponDef SOC Flag
  - AOCCDPFL – SponDef PT Flag

Create New Metadata
For Each AOCCzzFL

Dataset	Variable	Label	Type	Code List	Len	Algorithm
ADAE	AOCC*zz*FL	1st Occurrence of *<fill in>*	text	CL.YES	1	*<fill in>*
	AOCCYFL					
	AOCCYSFL					
	AOCCYPFL					
	AOCCXFL					
	AOCCXSFL					
	AOCCXPFL					

Create New Metadata

For Each AOCCzzFL

USUBJID	AE TERM	AE DECOD	AE BODSYS	AREL	AOCCFL	AOCCSFL	AOCCPFL	AOCCRFL	AOCCRSFL	AOCCRPFL
01-001	BACK PAIN	Back Pain	Musculoskeletal		Y	Y	Y			
01-001	HEADACHE	Headache	Nervous system disorder	Y		Y	Y	Y	Y	Y
01-001	HEADACHE	Headache	Nervous system disorder							
01-001	ANXIETY	Anxiety	Nervous system disorder	Y			Y			Y

Exercise Time!

Real World Example

- Analysis required: 2 arm parallel design AE incidence table for TEAEs
- 4 additional AE incidence tables, identical to the first, based on subsets of the Safety population (e.g., subjects with hepatic AEs, etc.)

Challenge
ADAE Structure

- Given mock AE analysis table(s)
- Given a standard for ADAE (metadata)
- Create study specifications for one or more ADAE data set structures – **Occurrence FLAG Variables Only**

Challenge #1

Mocks

Table AE #1

Table AE #1

Incidence of **Related*** Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment

Safety Population

System Organ Class Preferred Term	Drug A (N = xxx) **Related**	Drug B (N= xxx) **Related**
Any Adverse Event	xxx (xx)	xxx (xx)
SOC Term 1	xxx (xx)	xxx (xx)
PT Term 1	xxx (xx)	xxx (xx)
PT Term 2	xxx (xx)	xxx (xx)
…		
SOC Term 2	xxx (xx)	xxx (xx)
PT Term 1	xxx (xx)	xxx (xx)
PT Term 2	xxx (xx)	xxx (xx)
…		

* **Related** TEAEs: Definitely Related, Possibly Related, Likely Related, or missing

Standard ADAE

Variable Level Metadata

Dataset	Variable	Label	Type	Code List	Length	Algorithm
ADAE	USUBJID	Unique Subject ID.	text		12	STUDYID||"-"|| SITEID||"-"||SUBJID
ADAE	AESEQ	Sequence Number	integer		8	AE.AESEQ
ADAE	AETERM	Reported Term for the AE	text		200	AE.AETERM
ADAE	AEREL	Causality	text	CT.AEREL	40	AE.AEREL
ADAE	TRTP	Planned Treatment	text	CL.TRT	40	TRTP = ADSL.TRT01P
ADAE	TRTPN	Planned Treatment (N)	integer	CL.TRTN	8	TRTPN = ADSL.TRT01PN

Standard ADAE

Variable Level Metadata

Dataset	Variable	Label	Type	Code List	Len	Algorithm
ADAE	AOCCFL	1st Occurrence of Any AE Flag	text	CL.YES	1	Subset by TRTEMFL="Y" Sort by USUBJID ASTDT AESEQ and flag first record
ADAE	AOCCSFL	1st Occurrence of SOC Flag	text	CL.YES	1	Subset by TRTEMFL="Y" Sort by USUBJID AEBODSYS ASTDT AESEQ and flag first record
ADAE	AOCCPFL	1st Occurrence of PT Flag	text	CL.YES	1	Subset by TRTEMFL="Y" Sort by USUBJID AEBODSYS AEDECOD ASTDT AESEQ and flag first record

Additional Metadata

Add New AOCCzzFL or ADAExx

Dataset	Variable	Label	Type	Code List	Len	Algorithm
ADAE*xx*	AOCC*zz*FL	1st Occurrence of *<fill in>*	text	CL.YES	1	*<fill in>*

Dataset	Variable	Label	Type	Code List	Len	Algorithm
ADAE*xx*	AOCC*zz*FL	1st Occurrence of *<fill in>*	text	CL.YES	1	*<fill in>*

Solutions

Vote – Audience Participation

- How many new occurrence flags need to be created?
- **Vote A:**
  - More Flags?
  - Less Flags?

- Does your answer differ if:
  - Only a single ADAE structure data set is created?
  - More than one ADAE structure data set is created? (e.g., ADAE & ADAER)
- **Vote B:**
  - Single ADAE structure data set?
  - More than one ADAE structure data set?

Challenge #2

Mocks

Table AE #2

Table AE #2

Incidence of Treatment Emergent Adverse Events by **Outcome**,

System Organ Class, Preferred Term, and Treatment

Safety Population

System Organ Class	Drug A (N = xxx)		Drug B (N= xxx)	
Preferred Term	**Resolved**	**Persistent**	**Resolved**	**Persistent**
Any Adverse Event	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
SOC Term 1	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
PT Term 1	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
PT Term 2	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
PT Term 3	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
…				
SOC Term 2	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
PT Term 1	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
PT Term 2	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
PT Term 3	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
…				

Note: denominator of percentage is the number of subjects in the column

Mocks

Table AE #3

Table AE #3

Incidence of Treatment Emergent Adverse Events by **Outcome**,

System Organ Class, Preferred Term, and Treatment

Hepatic* Safety Population

System Organ Class	Drug A (N = xxx)		Drug B (N= xxx)	
Preferred Term	**Resolved**	**Persistent**	**Resolved**	**Persistent**
Any Adverse Event	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
SOC Term 1	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
PT Term 1	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
PT Term 2	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
PT Term 3	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
…				
SOC Term 2	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
PT Term 1	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
PT Term 2	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
PT Term 3	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
…				

Note: denominator of percentage is the number of subjects in the column

* **Hepatic Safety Population** is a subset of the Safety Population. It is includes subjects with ABNORMAL Hepatic results at baseline.

Standard ADAE

Variable Level Metadata

Dataset	Variable	Label	Type	Code List	Length	Algorithm
ADAE	USUBJID	Unique Subject ID.	text		12	STUDYID||"-"|| SITEID||"-"||SUBJID
ADAE	AESEQ	Sequence Number	integer		8	AE.AESEQ
ADAE	AETERM	Reported Term for the AE	text		200	AE.AETERM
ADAE	AEOUT	Outcome of Adverse Event	text	CT.AEOUT	40	AE.AEOUT
ADAE	TRTP	Planned Treatment	text	CL.TRT	40	TRTP = ADSL.TRT01P
ADAE	TRTPN	Planned Treatment (N)	integer	CL.TRTN	8	TRTPN = ADSL.TRT01PN

Standard ADAE

Variable Level Metadata

Dataset	Variable	Label	Type	Code List	Len	Algorithm
ADAE	SAFFL	Safety Population Flag	text	CL.NY	1	ADSL.SAFFL
ADAE	HEPFL	Hepatic Population Flag	text	CL.NY	1	ADSL.HEPFL
ADAE	AOCCFL	1st Occurrence of Any AE Flag	text	CL.YES	1	Subset by TRTEMFL="Y" Sort by USUBJID ASTDT AESEQ and flag first record
ADAE	AOCCSFL	1st Occurrence of SOC Flag	text	CL.YES	1	Subset by TRTEMFL="Y" Sort by USUBJID AEBODSYS ASTDT AESEQ and flag first record
ADAE	AOCCPFL	1st Occurrence of PT Flag	text	CL.YES	1	Subset by TRTEMFL="Y" Sort by USUBJID AEBODSYS AEDECOD ASTDT AESEQ and flag first record

Additional Metadata

Add New AOCCzzFL or ADAExx

Dataset	Variable	Label	Type	Code List	Len	Algorithm
ADAE*xx*	AOCC*zz*FL	1st Occurrence of *<fill in>*	text	CL.YES	1	*<fill in>*

Dataset	Variable	Label	Type	Code List	Len	Algorithm
ADAE*xx*	AOCC*zz*FL	1st Occurrence of *<fill in>*	text	CL.YES	1	*<fill in>*

Solutions

Vote – Audience Participation

- How many new occurrence flags need to be created?
- **Vote A:**
  - More Flags?
  - Less Flags?

- Does your answer differ if:
  - Only a single ADAE structure data set is created?
  - More than one ADAE structure data set is created? (e.g., ADAE & ADAER)
- **Vote B:**
  - Single ADAE structure data set?
  - More than one ADAE structure data set?

Real World Solution

- Created 5 ADAExxx data sets
- Re-used all of the metadata from the original standard ADAE study spec, except for the data set name: table level, variable level, and controlled terminology
- Took advantage of global metadata libraries

Questions?

The End

Contact Information

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d-Wise
Moving Beyond the Data