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DRUG INFORMATION ASSOCIATION

Beyond ADaM Basic Structure

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Purpose

- Introduce ADaM special purpose domains
  - ADSL structure from ADaM IG
  - SDTM AE model versus ADaM AE model
- Highlight the advantages of implementing ADaM standards

ADaM Special Purpose Domains

- ADaM Basic structure
  - Not adequate in many analyses situations
- ADSL : Proposal from ADaM IG
- ADAE: in development by ADaM team
- Possibly additional special purpose domains
  - e.g., Exposure Summary

ADSL Features

- One record/subject, regardless of trial design
- One location to describe key subject attributes
- Helps facilitate easy review
- Supports simple merges with other domains
- Designed to contain minimum required, conditionally required and permissible variables

ADSL Required Variables

- Study identifiers
  - Study ID, USUBJID, Site ID
- Demographics
  - AGE, SEX, RACE
- Treatment variables and trial dates
  - TRTxP, TRTSTDT, TRTENDT

ADSL Conditionally Required Variables

- Populations flags
  - FASFL, SAFFL, ITTFL
  - PPROTFL, COMPLFL
- Treatment variables
  - TRTxA, TRTSEQP, TRTSEQA
- Trial Dates
  - RANDDT, TRTxSTDT, TRTxENDT

ADSL Permissible Variables

- Numeric equivalents for
  - Treatment, Population stratification and Demog vars
- Categorical variables for sub group
- Duration of treatment exposure
- Treatment compliance based variables
- Key dates
- Death information
- Other relevant subject facts used in analyses

ADSL: Depression Trial

- Numerical equivalents
  - SEXN, RACEN, AGEGRPN
- Other Permissible variables
  - Completer (Y/N), Consent date, Birth date
  - Screening date, BL height, Weight, BMI
  - End of study date, End of study reason
  - Baseline HAM-D, MADRS total score

ADSL: Oncology Trial

- Numerical equivalents
  - SEXN, RACEN, AGEGRPN
- Other Permissible variables
  - Tumor site, time since diagnosis, stage
  - Histology, Death date, Reason for death
  - Total # of cycles received
  - BL Height, Weight, HR, SBP, DBP, ECOG
  - Use of classes of meds of interest (Y/N)

SDTM AE model

- One record per AE per subject for each unique event
- Changes over time in severity, causality or seriousness are separate events
- Represents data from the CRF module
- Minimal derived variables

Limitations of SDTM AE domain (1/2)

- Does not allow for periods/multiple treatments
- AEs often summarized by actual treatment and are not easily obtained in SDTM
- Need for additional analyses variables to the SDTM structure for AE analyses
- Does not allow for multiple versions of AE dictionary

Limitations of SDTM AE domain (2/2)

- Traceability of original and final coding is lost
- Presents difficulty in integration of multiple studies for NDA
- Does not allow for imputation of start AE dates or missing intensity/relationship

Overview of ADaM AE model (1/2)

- User friendly format for frequently used summaries and analysis of AEs

- Similar structure as SDTM AE dataset but allows
  - Multiple treatment emergent flags
  - Multiple dictionary versions
  - Additional derived variables for analysis e.g., SMQ's
  - Imputation of AE start and end dates

Overview of ADaM AE model (2/2)

- One record per SDTM AE domain record and includes
  - SDTM AE and SUPPAE variables needed for analyses and traceability
  - ADSL variables needed for analyses
  - Other variables needed for analyses e.g., last dose date from EX domain

Examples 1: Analyses of TEAE

Summary of TEAE by SOC and PT

System Organ Class Preferred Term	Treatment A (N=xxx) n (%)	Treatment B (N=xxx) n(%)
Number of Subjects with at least one AE	x (x.x)	x (x.x)
Blood and Lymphatic System Disorders		
At least one event	x (x.x)	x (x.x)
Anemia	x (x.x)	x (x.x)
…….		
Cardiac Disorders		
At least one event	x (x.x)	x (x.x)
Angina Pectoris	x (x.x)	x (x.x)
Coronary artery disease	x (x.x)	x (x.x)
…….		
Other SOCs and PTs		

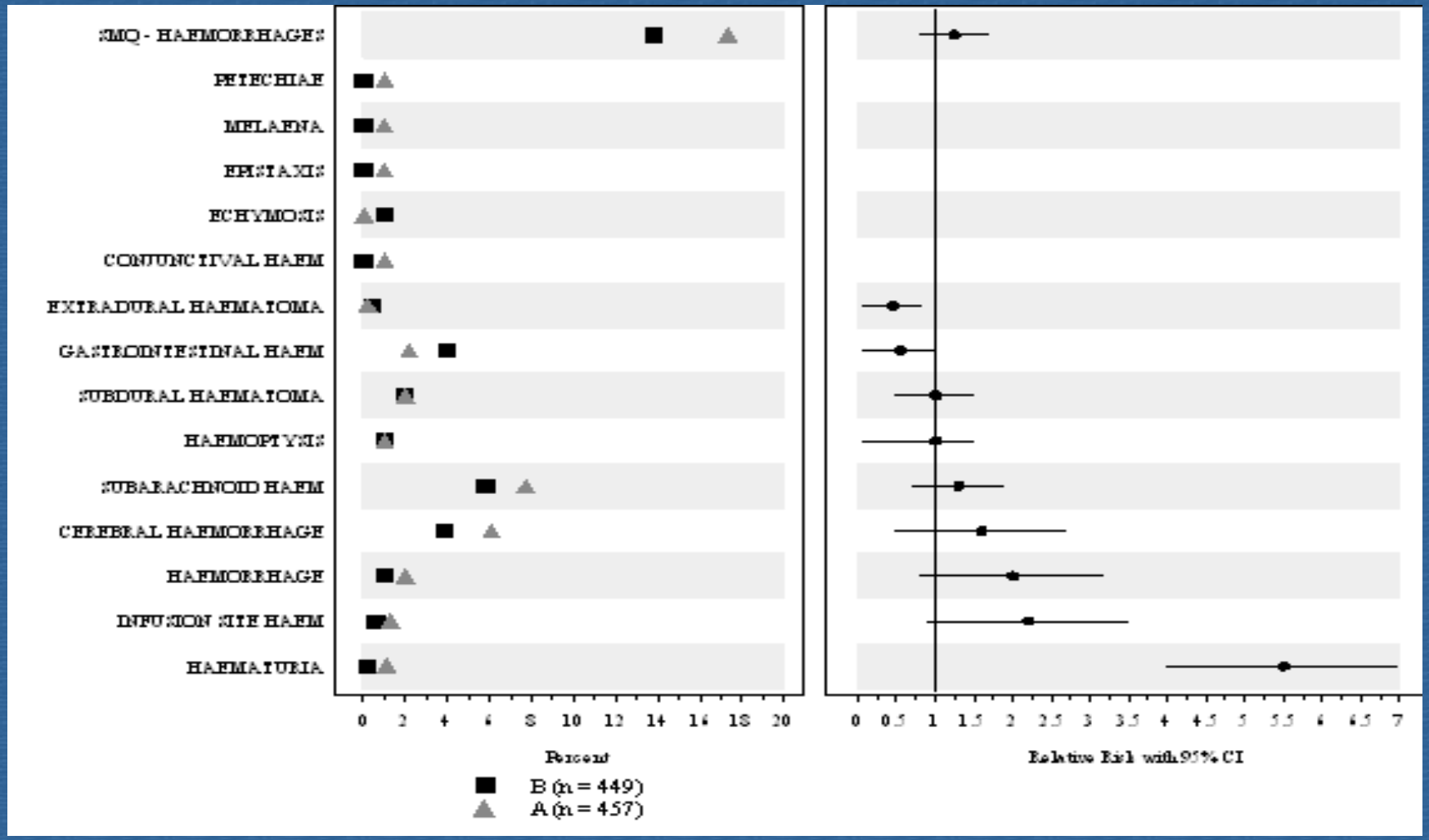
N= Safety Subjects

n= Number of subjects reporting at least 1 AE

AEs are presented by decreasing order of treatment B

SOCs and PTs are coded using MedDRA version x.x

Example 2: SMQ analyses (1/2)



Example 2: SMQ analyses (2/2)

SMQ _Code	SMQ_Name	MedDRA_ version	Term _code	LLT_Name	PT_Code
20000039	Haemorrhage	11,0	10001716	Allergic purpura	10019617
20000039	Haemorrhage	11,0	10001716	Allergic vascular purpura	10019617
20000039	Haemorrhage	11,0	10002214	Anaphylactic vascular purpura	10019617

SUBSMQN	SMQ	version	LLTNCUR	LLTNCUR	NARROWFL
20000039	Haemorrhage	11,0	10001716	Allergic purpura	N
20000039	Haemorrhage	11,0	10001735	Allergic vascular purpura	N
20000039	Haemorrhage	11,0	10002214	Anaphylactic vascular purpura	N

Example 3: Oncology (1/2)

Summary of Cumulative dose quartiles to first onset for PSN by severity grade

Cumulative Dose (mg/m^2)	Number of patients exposed	PSN Grade		
		Number (%) of patients with grade ≥ 1	Number (%) of patients with grade ≥ 2	Number (%) of patients with grade 3
Total number of patients with PSN		x (x.x)	x (x.x)	x (x.x)
1st Quartile (3 cycles)	N	x (x.x)	x (x.x)	x (x.x)
2nd Quartile (6 cycles)	N	x (x.x)	x (x.x)	x (x.x)
3rd Quartile (9 cycles)	N	x (x.x)	x (x.x)	x (x.x)
4th Quartile (12 cycles)	N	x (x.x)	x (x.x)	x (x.x)
Median cumulative Dose to first Onset (mg/m^2)		X	X	X

Example 3: Oncology (2/2)

USUBJID	TRTA	TRTAN	SAFFL	AEDECOD	DOSCUM	DOSCMGRP	AESEV	SEVIN
101-002	A	1	Y	PARESTHESIA	247,06	1	SEVERE	3
101-003	A	2	Y	PARESTHESIA	674,02	3	MODERATE	2
101-005	B	2	Y	PARESTHESIA	0	0	MILD	1
101-006	A	1	Y	PARESTHESIA	900	4	MODERATE	2
101-008	A	1	Y	PARESTHESIA	493,3	2	NONE	0
101-010	A	1	Y	PARESTHESIA	894,29	4		3

Example 4: Analyses of TEAEs in Cross over interaction study (1/3)

Summary of TEAEs by SOC and PT and Treatment Group (Safety Population)

System Organ Class Preferred Term	Treatment A (N=xxx)		Treatment B (N=xxx)		Treatment A+B (N=xxx)	
	n (%)	No. of events	n(%)	No. of events	n (%)	No. of events
Any TEAE	x (x.x)	x	x (x.x)	x	x (x.x)	x
Gastrointestinal Disorder	x (x.x)	x	x (x.x)	x	x (x.x)	x
Nausea	x (x.x)	x	x (x.x)	x	x (x.x)	x
Constipation	x (x.x)	x	x (x.x)	x	x (x.x)	x
Vomitting						
Infections and Infestations	x (x.x)	x	x (x.x)	x	x (x.x)	x
Pharyngitis	x (x.x)	x	x (x.x)	x	x (x.x)	x
Nervous System Disorder	x (x.x)	x	x (x.x)	x	x (x.x)	x
Headache	x (x.x)	x	x (x.x)	x	x (x.x)	x
Dizziness	x (x.x)	x	x (x.x)	x	x (x.x)	x
Syncope	x (x.x)	x	x (x.x)	x	x (x.x)	x

Example 4: Analyses of TEAEs in Cross over interaction study (2/3)

EXAMPLE - Analysis Dataset ADAE										
USUBJID	**TRTA**	**TRTAN**	**SAFFL**	**AEBODYSYS**	**AEDECOD**	**STDTM**	**TRTEM**	**STDY**	**EPOCH**	**APHASE**
101-001	A	1	Y	GASTROINTESTINAL DISORDER	VOMITING	05MAY08:16:10:00	T1	5	FIRST TREATMENT	FIRST TREATMENT
101-001	B	2	Y	INFECTIONS AND INFESTATIONS	PHARYNGITIS	16MAY08:06:42:00	T2	16	SECOND TREATMENT	SECOND TREATMENT
101-001	A+B	3	Y	NERVOUS SYSTEM DISORDER	HEADACHE	01JUN08:15:30:00	T3	32	THIRD TREATMENT	THIRD TREATMENT
101-001	A+B	3	Y	NERVOUS SYSTEM DISORDER	CONSTIPATION	02JUN08:07:15:00	T3	33	THIRD TREATMENT	THIRD TREATMENT
101-001	A+B	3	Y	INFECTIONS AND INFESTATIONS	ORAL HERPES	07JUN08:08:00:00	P	38	FOLLOW-UP	FOLLOW-UP
101-002	B	2	Y	VASCULAR DISORDERS	HYPOTENSION	25MAY08:13:20:00	N	26	SECOND WASHOUT	SECOND WASHOUT
101-002	A+B	3	Y	NERVOUS SYSTEM DISORDER	HEADACHE	27MAY08:22:10:00	T3	28	THIRD TREATMENT	THIRD TREATMENT
101-002	A+B	3	Y	NERVOUS SYSTEM DISORDER	HEADACHE	02JUN08:22:10:00	T3	34	FOLLOW-UP	THIRD TREATMENT

Example 4: Analyses of TEAEs in Cross over interaction study (3/3)

EXAMPLE - Analysis Dataset ADAE

TRT1SDTM	TRT1EDTM	TRT2SDTM	TRT2EDTM	TRT3SDTM	TRT3EDTM
01MAY08:10:05:00	07MAY08:09:10:00	15MAY08:08:15:00	21MAY08:10:30:00	29MAY08:13:50:00	03JUN08:07:20:00
01MAY08:10:05:00	07MAY08:09:10:00	15MAY08:08:15:00	21MAY08:10:30:00	29MAY08:13:50:00	03JUN08:07:20:00
01MAY08:10:05:00	07MAY08:09:10:00	15MAY08:08:15:00	21MAY08:10:30:00	29MAY08:13:50:00	03JUN08:07:20:00
01MAY08:10:05:00	07MAY08:09:10:00	15MAY08:08:15:00	21MAY08:10:30:00	29MAY08:13:50:00	03JUN08:07:20:00
01MAY08:10:05:00	07MAY08:09:10:00	15MAY08:08:15:00	21MAY08:10:30:00	29MAY08:13:50:00	03JUN08:07:20:00
30APR08:12:05:00	06MAY08:08:32:00	14MAY08:11:55:00	20MAY08:08:10:00	26MAY08:15:40:00	01JUN08:09:13:00
30APR08:12:05:0	06MAY08:08:32:00	14MAY08:11:55:00	20MAY08:08:10:00	26MAY08:15:40:00	01JUN08:09:13:00
30APR08:12:05:0	06MAY08:08:32:00	14MAY08:11:55:00	20MAY08:08:10:00	26MAY08:15:40:00	01JUN08:09:13:00

Concluding Remarks

- ADaM basic structure is not for all analysis datasets
- ADSL is the key subject level dataset **required** for all submissions
- ADAE to be used by reviewers over SDTM AE
- Get your companies to implement ADaM standards!