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ADaM Datasets - Standard and Submission Ready

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Agenda

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- ✓ Introduction
 - ✓ ADaM at Ferring
 - ✓ Why and how to update
- ✓ Problems and solutions
 - ✓ Straight forward
 - ✓ Less obvious
 - ✓ OpenCDISC ADaM Validator
- ✓ Summary & Conclusion

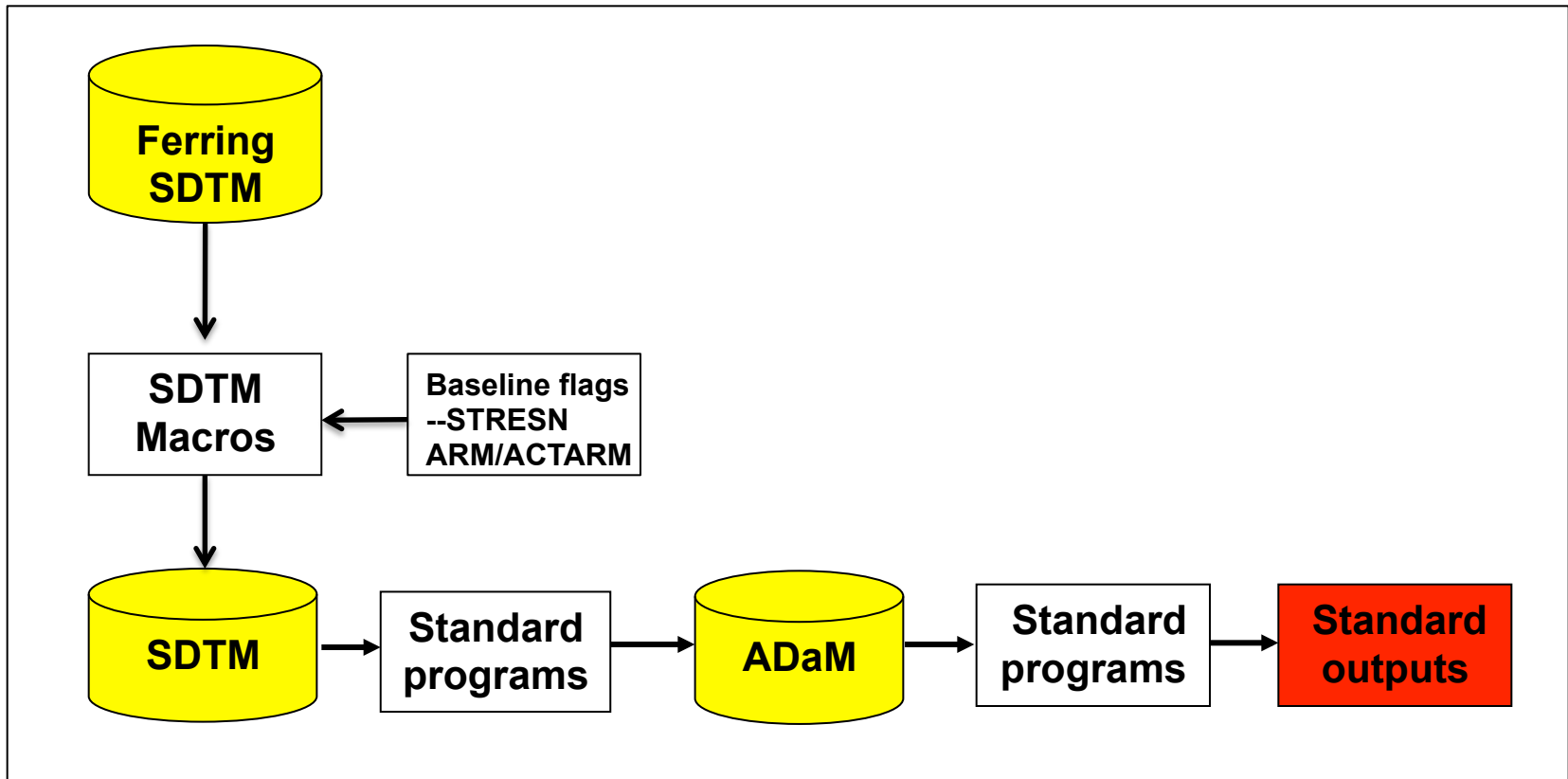
Introduction

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- ✓ Implementation of ADaM in 2009
- ✓ Primary reason for ADaM update due to new procedures at Ferring and changes in SDTM standards
- ✓ Prioritize to build standardized operational ADaM datasets
- ✓ BDS and vertical data structure are suited perfectly for standardization
- ✓ When creating ADaM datasets, we have the final output in mind => start at the end

Introduction

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Ferring Data Flow

ADaM derived from SDTM and not internal raw data

Problems and solutions

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Analysis variables ASEV, ASER, AREL used directly in AE output

Treatment: TRT 1									
	Subject No.	Age(y)/Sex/Race#	Onset Date	End Date	Adverse Event Description	SOC/Preferred Term	Intensity	Relation	Serious
ASEV	101	68/M/W	26JUL12	20JUL12	CARDIOGENIC SHOCK	CARDIAC DISORDERS/ Cardiogenic shock	Severe	Not related	Yes
AREL				21AUG12	HEART FAILURE	CARDIAC DISORDERS/ Cardiac failure	Severe	Not related	No
ASER			24JUL12	26JUL12	ENDOCARDITIS	INFECTIONS AND INFESTATIONS/ Endocarditis	Severe	Not related	Yes

ASEV, ASER, AREL are an analysis version of the SDTM variables not only for imputation, but also where letter case can be altered

Problems and solutions

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ASEX, ARACE, AETHNIC always present in ADSL for use directly in (standard) output:

ASEX →

AETHNIC →

ARACE →

Demographics		TRT 1	
Age (years), N (%)			
Female		20	(48%)
Male		22	(52%)
Total		42	(100%)
Ethnicity, N (%)			
Hispanic or latino		2	(5%)
Not hispanic or latino		0	(95%)
Total		42	(100%)
Race, N (%)			
American indian/alaska native			
Asian			
Black or african american		1	(2%)
White		41	(98%)
Total		42	(100%)

Reason for discontinuation

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Reason for discontinuation? Needed in output. Create new variables:

DS.DSDECOD ➡ REAS

- ADVERSE EVENT ➡ **Adverse Event**
- WITHDRAWAL BY SUBJECT ➡ **Withdrew consent**
- PROTOCOL VIOLATION ➡ **Protocol violation**
- CANCELLATION OF CYCLE ➡ **Cancellation of cycle**
- Etc..

DS.DSTERM ➡ REASSPE

- < 3 FOLLICLES >= 10 MM ➡ **Poor Response**
- > 25 FOLLICLES WITH A DIAMETER OF ➡ **Excessive Response**
- Early ovulation ➡ **Other**
- Etc..

Reason for discontinuation

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REAS →

REASSPE →

Subject Disposition	TRT1		TRT2		Total	
	N	(%)	N	(%)	N	(%)
Screened subjects					xx	(100%)
ITT Analysis Set	xx	(xxx%)	xx	(xxx%)	xx	(xxx%)
Full Analysis Set	xx	(xxx%)	xx	(xxx%)	xx	(xxx%)
PP Analysis set	xx	(xxx%)	xx	(xxx%)	xx	(xxx%)
Safety Analysis set	xx	(xxx%)	xx	(xxx%)	xx	(xxx%)
Completed study	xx	(xx%)	xx	(xx%)	xx	(xx%)
Discontinued	xx	(xx%)	xx	(xx%)	xx	(xx%)
Reason for discontinuation:						
{ Withdrew consent	xx	(xx%)	xx	(xx%)	xx	(xx%)
{ Adverse Event	xx	(xx%)	xx	(xx%)	xx	(xx%)
{ Protocol violation	xx	(xx%)	xx	(xx%)	xx	(xx%)
{ Cancellation of cycle	xx	(xx%)	xx	(xx%)	xx	(xx%)
{ Poor response	xx	(xx%)	xx	(xx%)	xx	(xx%)
{ Excessive response	xx	(xx%)	xx	(xx%)	xx	(xx%)
{ Other	xx	(xx%)	xx	(xx%)	xx	(xx%)
Other	xx	(xx%)	xx	(xx%)	xx	(xx%)

The content of REAS and REASPE are NOT standardized but the variable names are. They are placed in ADSL

Analysis reference range

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Analysis reference range variables:

Standard output with SHIFT1 based on BNRIND and ANRIND:

SUBJID	PARAMCD	AVAL	ANRLO	ANRHI	BNRIND	ANRIND	SHIFT1
XXX1	ALP	28	35	105	Normal	Low	Normal -> Low

SHIFT1 is used directly in display:



Test / shift	TRT 1		
	N	n	(%)
Alanine Aminotransferase (IU/L)			
Normal -> High	45	1	(2%)
Normal -> Low	45		
Low -> High	45		
Low -> Normal	45	1	(2%)
High -> Low	44		
High -> Normal	44	1	(3%)

Analysis evaluation

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Analysis evaluation, e.g. if an assessment is clinical significant or not.
For standard output we need variables for that:

Is it a criteria?

Is it a flag?

Is it a categorization?

Or something entirely different?



Test /criteria	TRT 1		
	N	n	(%)
Alanine Aminotransferase (IU/L)			
Abnormal CS	55		
Abnormal NCS	55	3	(5%)
Alkaline Phosphatase (IU/L)			
Abnormal CS	56		
Abnormal NCS	56	1	(2%)
Aspartate Aminotransferase (IU/L)			
Abnormal CS	62	1	(2%)
Abnormal NCS	62	4	(6%)

According to paper¹ from PharmaSUG 2012 it is recommended to
use AVALCATy

¹ “Common Misunderstandings about ADaM Implementation” by Nate Freimark, Susan Kenny, Jack Shostak and John Troxell

Analysis evaluation

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Recommendation with AVALCATy:

SUBJID	SEX	PARAMCD	AVAL	BASE	AVALCAT1
XXX1	F	PLAT	9.5	12.1	Significant
XXX2	M	PLAT	9.5	15.9	Not significant (?)
XXX3	M	PLAT	14.7	13.8	'Normal' or ' (?)
...					

But what if AVAL = 9.5 => AVALCAT1 = 'Significant'
=> AVALCAT1 = 'Not significant'

CDISC ADaM Validation Checks Version 1.2:

Check Number	ADaMIG 1.0 Section Number	Text from ADaMIG	ADaM Structure Group	Functional Group	ADaM Variable Group	Machine-Testable Failure Criteria
221	S.3.2.4	AVALCATy must have the same value for all records within a paramter for a given value of AVAL	BDS	Value Consistency	Analysis Parameter Variables	Within a given value of PARAMCD there is more than one value of AVALCATy for a given value of AVAL and y

Analysis evaluation

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Ferring solution:

SUBJID	SEX	PARAMCD	AVAL	BASE	BEVL	AEVL	SHIFT1
XXX1	F	PLAT	9.5	12.1	Abnormal NCS	Abnormal CS	Abnormal NCS -> Abnormal CS
XXX2	M	PLAT	9.5	15.9	Normal	Abnormal NCS	Normal -> Abnormal NCS
XXX3	M	PLAT	14.7	13.8	Abnormal NCS	Normal	Abnormal NCS -> Normal

SHIFT1



	TRT1		
	N	n	(%)
Normal -> Abnormal NCS	0	0	
Normal -> Abnormal CS	0	0	
Abnormal NCS -> Abnormal CS	4	0	(0%)
Abnormal CS -> Abnormal NCS	0	0	
Abnormal NCS -> Normal	4	1	(25%)
Abnormal CS -> Normal	4	1	(25%)

Relative time variables

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- ✓ Variables whose names end in DY are relative day variables
- ✓ No day 0 in SDTM and ADaM (rule # 8 ADaMIG section 3)
- ✓ E.g. occurrence on same day as treatment => e.g. day 0
- ✓ Uses Analysis Relative Time (to an anchor time)

ARELTM = ADT - ADSL.TRTSDT

- ✓ ADSL.TRTSDT is the anchor time
- ✓ ADT is the date associated with AVAL/AVALC

Relative time variables

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Ferring solution:

Analysis Relative Start Time (rule # 9 ADaMIG section 3):

$$\text{ARELSTM} = \text{ASTDT} - \text{ADSL.TRTSDT}$$

Analysis Relative End Time (rule # 10 ADaMIG section 3):

$$\text{ARELETM} = \text{AENDT} - \text{ADSL.TRTSDT}$$

E.g. used in cases with prevalence and incidence

9/10 : Names of timing start/end variables end with an S/E followed by the two characters indicating the type of timing

OpenCDISC ADaM Validator



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- ✓ Free download from www.opencdisc.org
(New version 1.4.1 released 12. September 2013)
- ✓ Validation Rules Repository (pooled knowledge of CDISC to create a central listing of validation rules from each standard (SDTM, ADaM, define.xml, SEND))
- ✓ Creates log with errors, warnings and details
(Label mismatch (e.g. TRTSDT) corrected in V. 1.4.1)
- ✓ No replacement of validation, but a check for CDISC compliance

OpenCDISC ADaM Validator

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Log with errors:

1	Variables	Values	Rule ID	Message	Category	Severity
2	VARIABLE	TRTP	AD1001	Required variable is not present within dataset	Presence	Error
3	PARAM, PARAMN	Unexplained infertility, 1	AD0146	Inconsistent value for PARAM based on PARAMN	Consistency	Error
4	PARAM, PARAMN	Tubal infertility, 2	AD0146	Inconsistent value for PARAM based on PARAMN	Consistency	Error

TRTP(required in BDS): Planned treatment for a given period (on record-level)

- No analysis based on TRTP (based on planned ARM or actual)
- Can be complicated to add (not always a one-to-one mapping between TRTA and TRTP)

OpenCDISC ADaM Validator

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In ADaMIG:

PARAMCD: One-to-one mapping with PARAM

PARAMN : One-to-one mapping with PARAM

PARCATy : A categorization of PARAM

PARCATy - PARAMN => One-to-one mapping!

PARCAT1	PARCAT1N	PARAMCD	PARAM	PARAMN	
Infertility history	1	DUR	Duration of infertility (months)	1	←
Infertility history	1	PREASON	Primary reason for infertility	2	←
Reason for infertility	2	UNXINF	Unexplained infertility	1	←
Reason for infertility	2	TUBALINF	Tubal infertility	2	←
Reason for infertility	2	MIMF	Mild male factor	3	
Reason for infertility	2	MOMF	Moderate male factor	4	
Reason for infertility	2	SEMF	Severe male factor	5	

Summary & Conclusion

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- ✓ Important to have a common analysis dataset standard for trial reporting across all therapeutic areas which can easily be upgraded to be submission ready
- ✓ ADaM Model/ADaMIG are created for submission for a single trial, so lack of definitions and missing examples when trying to implement standards from them
- ✓ Follow ADaM fundamental principles ➡ True ADaM (with additional variables added – acc. to ADaMIG and naming conventions)
- ✓ Standardized AND submission ready ADaM datasets!

Questions?

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