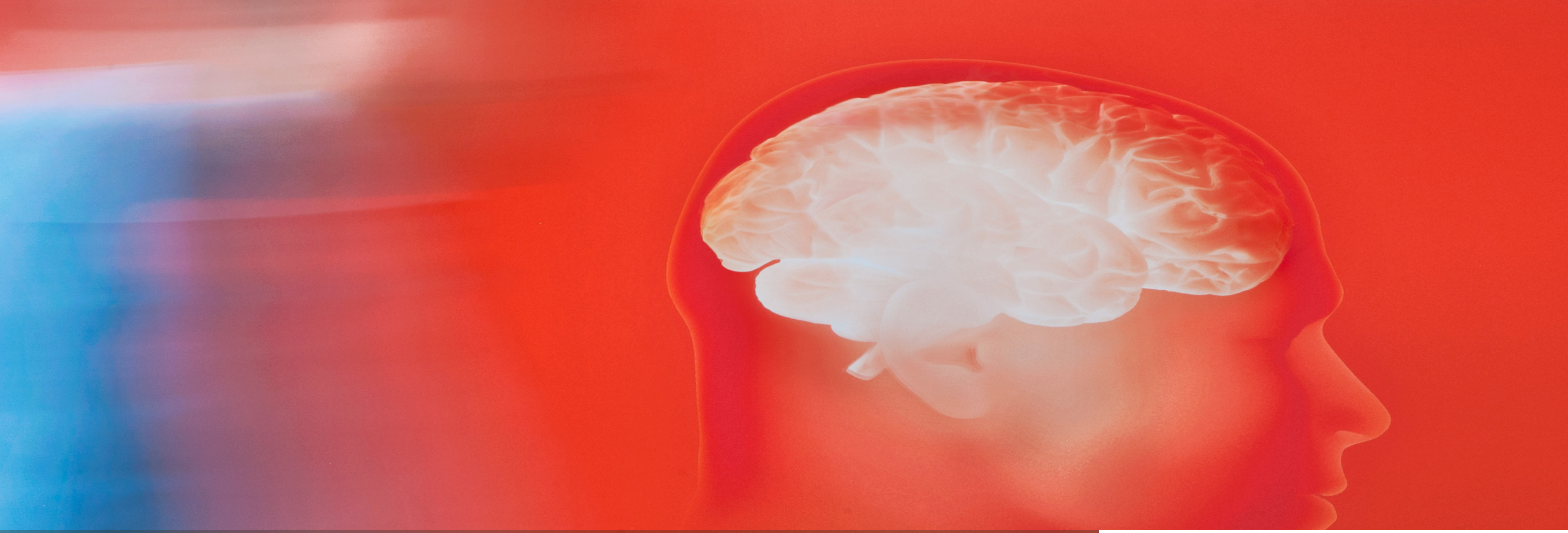


ADAM @ LUNDBECK

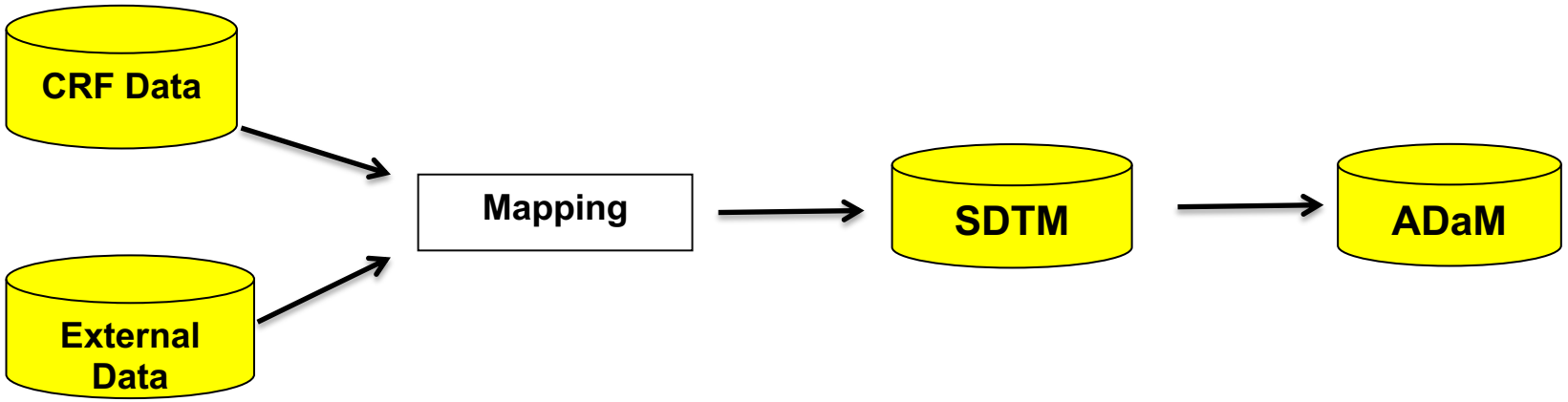
Karin Fleischer Steffensen, June 2019

Agenda

- Introduction
- ADaM @ Lundbeck
  - ADaM Specification & Metadata
  - Lundbeck decisions
  - From ADaM to Clinical Report
  - Validation
- Final comments
  - Advice regarding ADaM
  - Summary & conclusion

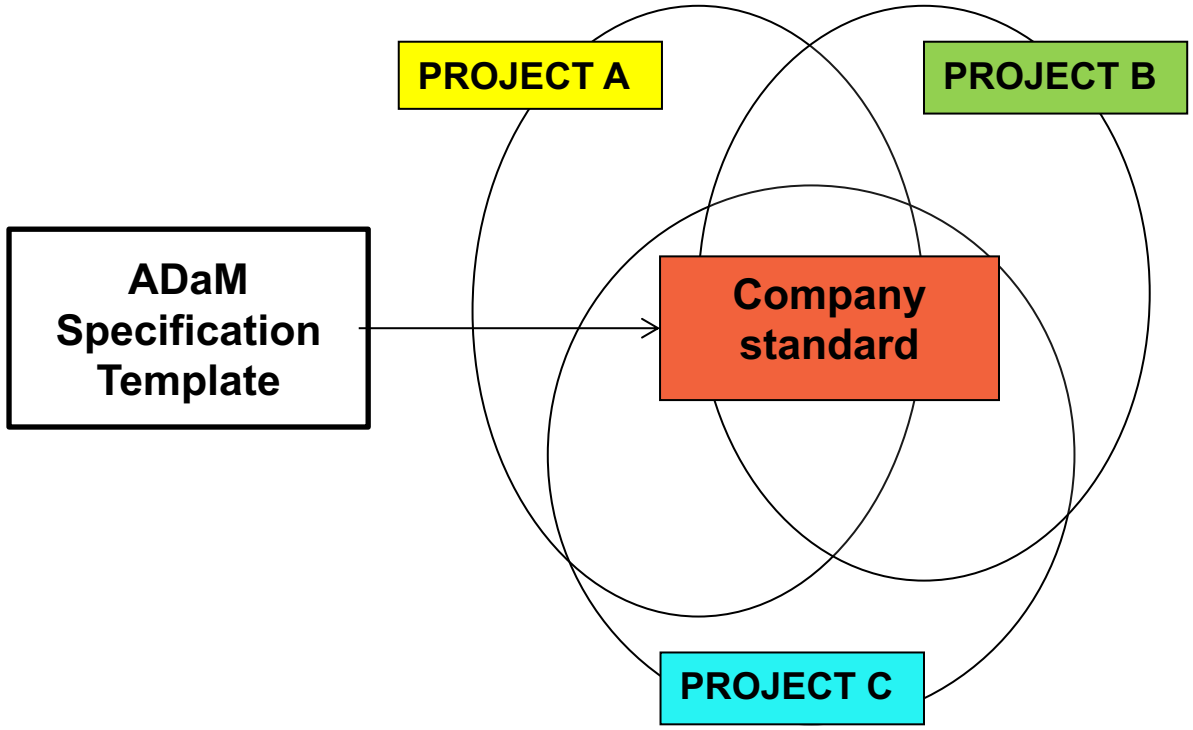
Introduction

- Implementation of ADaM in 2017 – old standard replaced
- Build an operational ADaM standard **and** submission ready
- Data flow: A linear strategy



ADaM @ Lundbeck

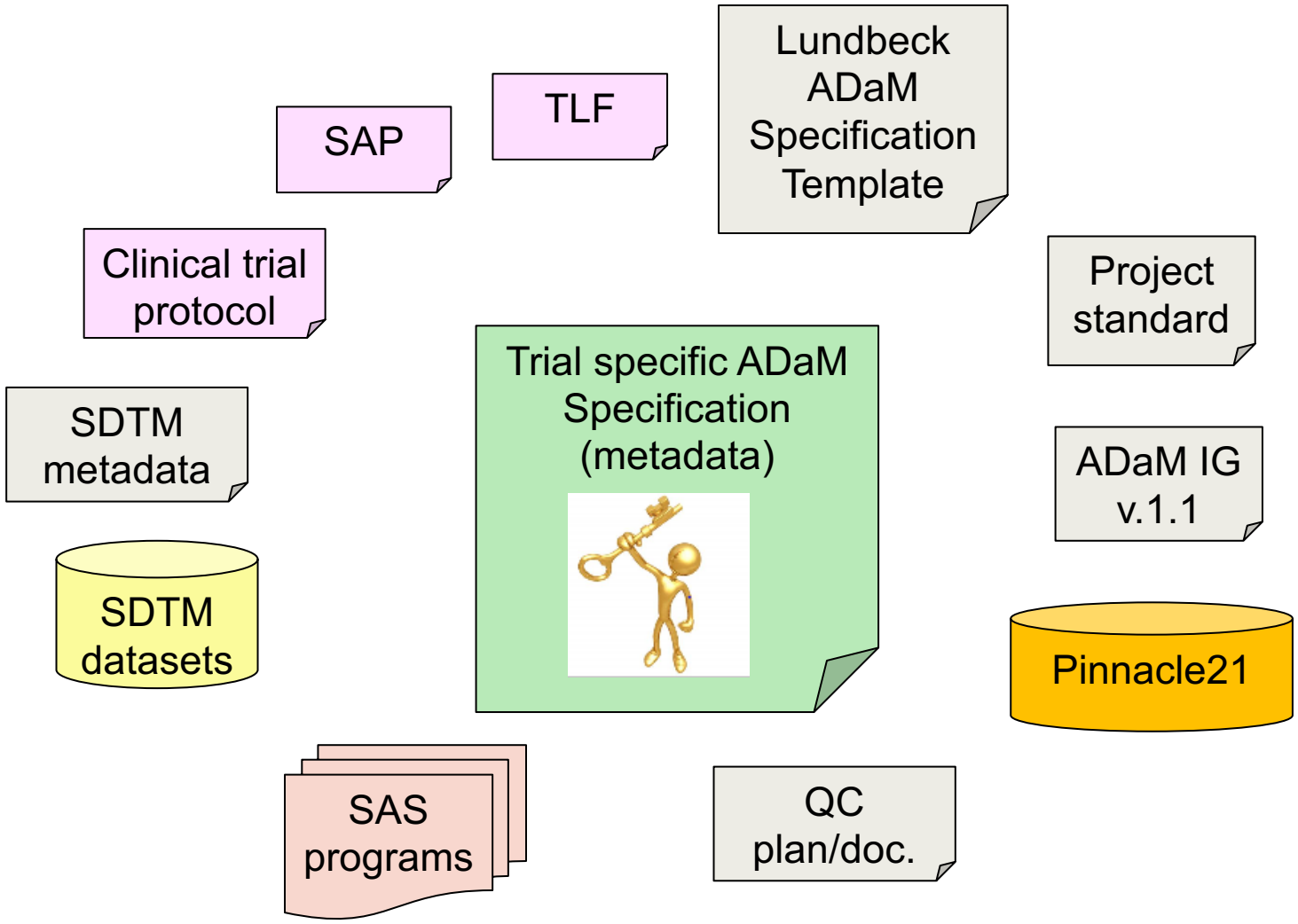
- Standardised across the therapeutic areas



ADaM @ Lundbeck

- Create ADaM datasets with specific analysis results in mind
  - Create what is needed to produce desired results
- BDS and vertical data structure are suited perfectly for standardisation. The data structure is the same but with different content
- ADaM supports standardised reporting of clinical data for regulatory documents (CTR, ISS/ISE, IB, DSUR, PSUR etc.)
- Standard governance
  - Template always the starting point
  - Maintained by Standards group
  - ADaM Specification is adapted to project/study with assistance from ADaM SME

ADaM Specification relationship



ADaM Specification

- ADaM Specification in Excel
- Initiated by the project programmer with input from statistician (endpoint/efficacy)
- Core document for the programmer, statistician and validator
- Reviewed by statistician
- Apply to the fundamental principles of ADaM

ADaM Specification

- ADaM Specification
  - Lundbeck ADaM Specification Template
  - Project specific decisions
  - Study specific decisions

- Data handling issues
  - Statisticians involved early regarding decisions of e.g.
    - Windowing
    - Periods/phases
    - Subgroup analysis
    - Analysis flags

- Submission: ADRG & Define.XML

Metadata

- Analysis dataset metadata:

Dataset	Description	Class	Structure	Key Variables	Documentation
ADSL	Subject Level Analysis Dataset	ADSL	One record per subject enrolled (NOT included screening failures)	USUBJID	SAP
ADDS	Subject Disposition Analysis Dataset	BDS	One record per subject per parameter	USUBJID, APHASE, PARCAT1N	SAP
ADSV	Subjects Visit Analysis Dataset	BDS	One record per subject per visit	USUBJID, VISITNUM, VISIT, SVSTDTC	SAP
ADAE	Adverse Event Analysis Dataset	Occurrence	One record per subject per adverse event per intensity	USUBJID, ASTDT, ASTDTM, AENDT, AENDTM, AEDECOD	SAP. Dictionary used is MedDRA v.xx

- Analysis variable metadata:

Input to define.xml

Dataset	Variable	Label	Sortorder	Type	Length/ Display Format	Controlled Terms or Format	Source/Derivation	Comment	Origin	Core
ADSL	USUBJID	Unique Subject Identifier	2	Text	50		DM.USUBJID	Screening failures are not included	Predecessor	Req
ADSL	SUBJID	Subject Identifier for the Study	3	Text	50		DM.SUBJID		Predecessor	Req
ADSL	RANDNO	Randomisation Number	4	Text	10		RANDNO= SUPPDM.QVAL, where SUPPDM.QNAM = 'RANDNO'		Derived	Cond
ADSL	SITEID	Study Site Identifier	5	Text	50		DM.SITEID		Predecessor	Req
ADSL	REGION1	Geographic Region 1	6	Text	20	Europe, USA/Canada, Rest of the World	If COUNTRY in ('USA' 'CAN') then REGION1 = 'USA/Canada'. If COUNTRY = 'MEX' then REGION1 = 'Rest of the World'. Else REGION1 = 'Europe'.	Description of geographical region	Derived	Perm
ADSL	REGION1N	Geographic Region 1 (N)	7	Integer	8	region1n	Derived from REGION1 using codelist **region1n**	Numeric representation of REGION1	Derived	Perm

Metadata

- Parameter value-level metadata:

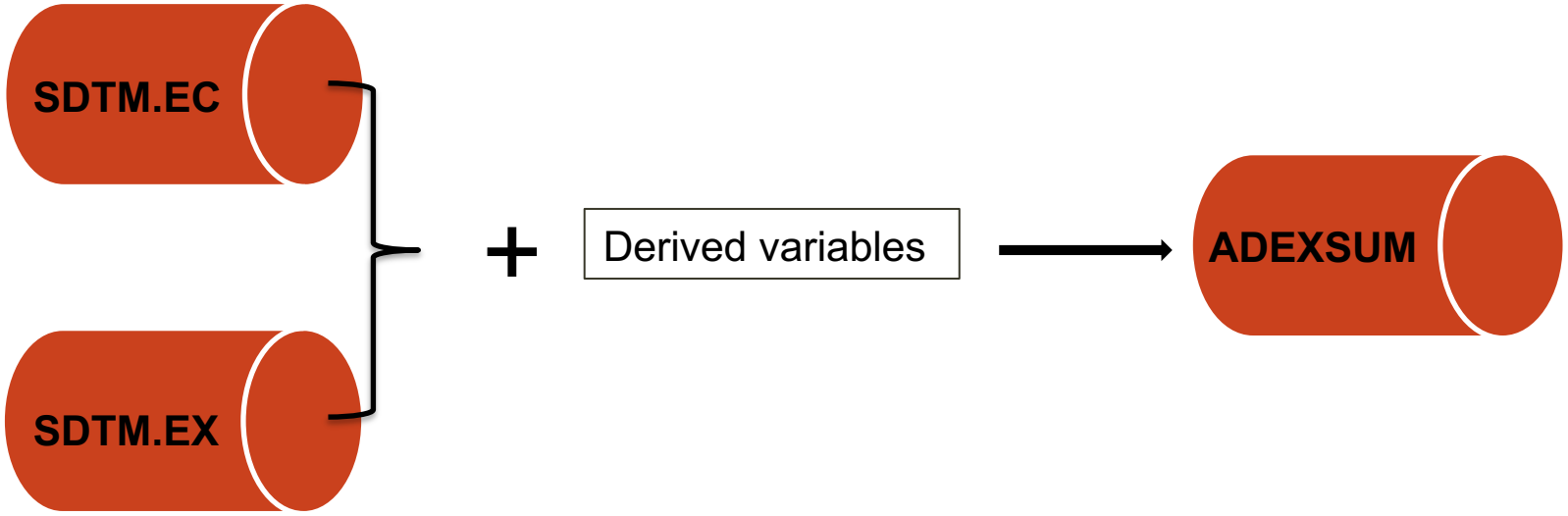
Dataset	Variable	Where	Type	Length/Display Format	Controlled Terms or Form	Source/Derivation
ADVS	AVAL	PARAMCD='OBP'	Float	8		Orthostatic blood pressure is a derived parameter creating a new record with PARAM='Orthostatic Blood Pressure (mmHg), **N** minutes after' AVAL = AVAL (where PARAMCD="SYSST**N**") - AVAL (where PARAMCD="SYSSU**N**"). Add further details if needed
ADVS	AVAL	PARAMCD='OPR'	Float	8		Orthostatic pulse rate is a derived parameter creating a new record with PARAM='Orthostatic Pulse Rate (beats/min), **N** minutes after' AVAL=AVAL (where PARAMCD="PULST**N**") - AVAL (where PARAMCD="PULSU**N**"). Add further details if needed
ADVS	AVAL	PARAMCD not in ('OBP', 'OPR')	Float	8		VS.VSSTRESN
ADEFF	AVALC	<Where PARAMCD = 'XXX'>	Text	3	Y,N	<Add derivation>
ADEFF	AVALC	<Where PARAMCD = 'XXX'>	Text	3	Y,N	<Add derivation>

Input to define.xml

- Analysis results metadata (ARM) …

Lundbeck decisions: Exposure

- ADEXSUM
  - BDS structure used for analysis
  - Contains SDTM.EC, SDTM.EX + derived variables



Lundbeck decisions: Reason for discontinuation

- Reason for discontinuation according to ADaMIG v.1.1:

DCTREAS	Reason for Discontinuation of Treatment	Char		Perm

- LUNDBECK - primary and secondary reason
  - Primary reason
    - **P**DCTREAS (Primary Reason for Disc. of Treatment)
    - Present in ADSL
  - Secondary reason:
    - ADDS (Disposition), where PARAMCD = “SECREAS” and PARCAT1 = “Withdrawal from treatment”

PARCAT1	PARAMCD	PARAM	PARAMN	AVALC
Withdrawal from treatment	PRIMREAS	Primary reason	1	Adverse event
Withdrawal from treatment	SECREAS	Secondary reason	2	Lack of efficacy

Lundbeck decisions: Analysis Range variables

- Relationship between A1LO/A1LOC, A1HI/A1HIC and A1IND
- Issue: ***Gender specific ranges within a parameter***

- First solution:

	USUBJID	PARAMCD	AVAL	A1LO	A1LOC	A1HI	A1HIC	A1IND
1	Subject no. 1	HGBB	13.2	11.5	PCS Low: AVAL <= 11.5	18.5	PCS High: AVAL >= 18.5	Not PCS
2	Subject no. 2	HGBB	12.6	9.5	PCS Low: AVAL <= 9.5	16.5	PCS High: AVAL >= 16.5	Not PCS

- But 1-2-1 mapping is not fulfilled:

AyLOC	Analysis Range y Lower Limit (C)	Char		Perm	Character analysis range y lower limit. AyLOC can be a character string mapping to AyLO, but if so there must be a one-to-one map between AyLO and AyLOC within a given PARAM. AyLOC should not be used to categorize the values of AyLO. Within a given parameter, if there exists a row on which both AyLOC and AyLO are populated, then there must be a one-to-one mapping between AyLOC and AyLO on all rows on which both variables are populated. (In other words, there is no requirement that records with a null value in either AyLO or AyLOC be included when determining whether the one-to-one mapping requirement is satisfied.) On a given record, it is permissible for AyLO, AyLOC, or both to be null.

Lundbeck decisions: Analysis Range variables

- Second solution:

USUBJID	PARAM	A1LO	A1HI	A1LOC	A1HIC	A1IND	A2LO	A2HI	A2LOC	A2HIC	A2IND	A3LO	A3HI	A3LOC	A3HIC	A3IIND
Subject no. 1	HGBB	.	.				.	.				11.5	18.5	PCS Low: AVAL <= 11.5	PCS High: AVAL >= 18.5	Not PCS
Subject no. 2	HGBB	.	.				9.5	16.5	PCS Low: AVAL <= 9.5	PCS High: AVAL >= 16.5	Not PCS	.	.			

- Final solution:

	USUBJID	PARAMCD	AVAL	A1LO	PCSLOW	A1HI	PCSHIGH	A1IND
1	Subject no. 1	HGBB	13.2	11.5	PCS Low: AVAL <= 11.5	18.5	PCS High: AVAL >= 18.5	Not PCS
2	Subject no. 2	HGBB	12.6	9.5	PCS Low: AVAL <= 9.5	16.5	PCS High: AVAL >= 16.5	Not PCS

  - PCSLOW/PCSHIGH only used for storing the information of what is required for a PCS criteria to be fulfilled for each parameter, but are not used in any output or analysis

- A1LO, A1HI and A1IND are compliant and fulfil the requirements in ADaMIG v1.1

AyIND	Analysis Range y Indicator	Char		Perm	Indicates relationship of AVAL to the analysis range variables AyLO and/or AyHI, or the relationship of AVALC to the analysis range variables AyLOC and/or AyHIC.

ADaM data used in Clinical Report

Analysis variables from ADSL used directly in 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%)

ADaM data used in Clinical Report

Analysis variables from ADAM.ADAE used directly in AE output

ASEV

AREL

ASER

Treatment: TRT 1

Subject No.	Age(y)/ Sex/ Race#	Onset Date	End Date	Adverse Event Description	SOC/ Preferred Term	Intensity	Relation	Serious
101	68/M/W	26JUL12	30JUL12	CARDIOGEN SHOCK	CARDIAC DISORDERS/ Cardiogenic shock	Severe	Not related	Yes
			21AUG12	HEARTFAIL URE	CARDIAC DISORDERS/ Cardiac failure	Severe	Not related	No
		24JUL12	26JUL12	ENDOCARDITIS	INFECTIONS AND INFESTATIONS/ Endocarditis	Severe	Not related	Yes

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

Validation

- Validate ADaM datasets against SDTM
- Double programming
- Pinnacle21:
  - Validation Rules Repository (SDTM, ADaM, SEND etc.)
  - No replacement of validation, but a CDISC compliance check!
  - FDA uses Pinnacle21 on your data!

Advice regarding ADaM

- Specify in “words” how the variable is derived
  - ~~PARAMCD=cats(LBTESTCD,substr(LBSPEC,1,1),'F’);~~
  - “PARAMCD is derived as a concatenation of LB.LBTESTCD with the first letter of LB.LBSPEC…”
- Always let analysis need drive the ADaM dataset structure
- Keep variables and rows that are
  - Needed for analysis
  - Helpful for traceability
- Don’t try to put too much into each ADaM dataset
- No need to include all SDTM data in ADaM datasets

Summary & Conclusion

- ADaM Specification:
  - A common ADaM Specification Template for trial reporting across all therapeutic areas
  - Core document with many purposes
  - Submission ready

- Advice
  - Let analysis results drive the definition of ADaM
  - Do not try to force data into a structure where it is too cumbersome to use or makes little sense
  - Follow ADaM fundamental principles and the naming conventions

Questions?