CDISC Italian User Network 2019
Milan, Italy | 22 February 2019

ADaM 1.2 e altro da ADaM Team
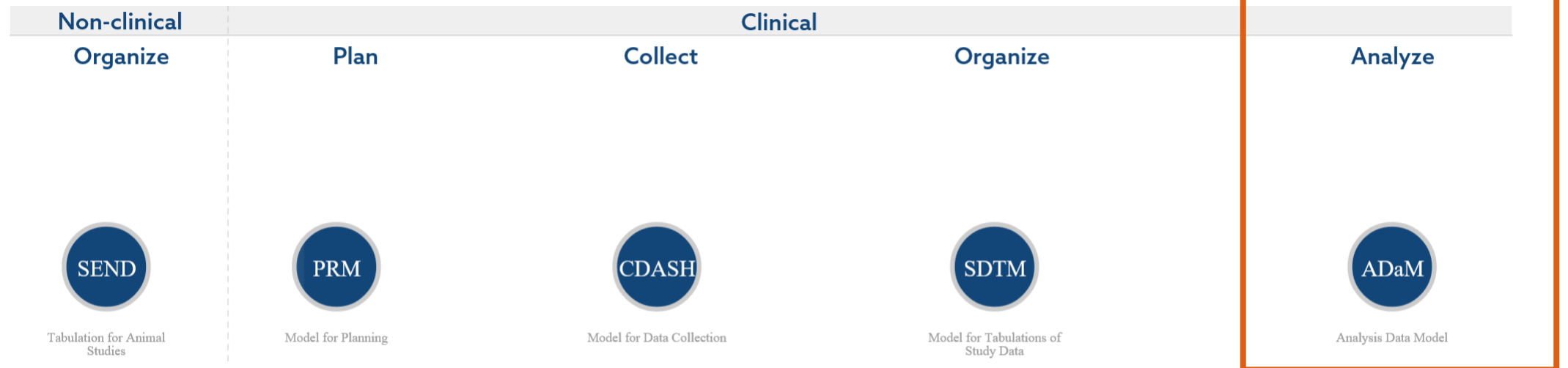Paola Vaghi, Chiesi Farmaceutici

Agenda

- Introduction to ADaM
- ADaM Documents Pipeline
- ADaMIG v1.2 Update
- ADaM Structures for Integration
- ADaM Examples of Traceability
- Overview of the Other ADaM Documents

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Introduction to ADaM - What's ADaM

What is **A**nalysis **Da**ta **M**odel?

- Provides clear, unambiguous communication of the statistical aspects of the trial through the structure and content of the analysis datasets

- Supports efficient generation, replication, and review of analysis results by combining observed and derived data (variables and observations) needed by the statistical analysis

- Allows recipients of analysis datasets to understand data lineage from collection to analysis to results (i.e. traceability)

Non-clinical	Clinical			
Organize	Plan	Collect	Organize	Analyze
SEND	PRM	CDASH	SDTM	ADaM
Tabulation for Animal Studies	Model for Planning	Model for Data Collection	Model for Tabulations of Study Data	Analysis Data Model

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Introduction to ADaM – SDTM vs ADaM

Difference	SDTM	ADaM
Purpose	Store collected data	Facilitate analysis, rapidly answer research questions
Data origin	Source data (including labs) / CDASH	SDTM
Data structure	Defined by content *Sponsor Variables « not allowed »*	Defined by analysis Can include sponsor derived variables
Redundancy	Very little	As needed for easy analysis
Variable type	Primarily Char	Numeric and Char
Datasets	Focused on one domain topic	Contains multiple domain topics
Date/Time Format	ISO 8601 character strings	Formatted as numeric (SAS) dates/times to allow manipulation
Derivations	Very Limited No imputations allowed	Derived Variables, « Imputed » variables, « Imputed » records
Analysis-Ready	No	Yes

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Introduction to ADaM – SDTM vs ADaM

- SDTM is the source
- ADaM can contain additional derived variables
- In SDTM you don't derive variables and you don't impute missing information

AEREL	RELGR1
NOT RELATED	Not Related
NOT RELATED	Not Related
NOT RELATED	Not Related
PROBABLY RELATED	Related
DEFINITIVELY RELATED	Related
	Related
DEFINITIVELY RELATED	Related

From SDTM

Derived in ADaM

- Original value of AEREL copied from SDTM
- New variable RELGR1 created to group into Related / Not Related
- Missing AEREL imputed to « Related » (worst scenario as per SAP)
- Mixed case content makes table production easier

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Introduction to ADaM – ADaM Classes

- ## Subject Level Structure (ADSL)
  - Reserved dataset name 'ADSL'
  - One record per subject, regardless of study design

ADSL Example

Row	STUDYID	USUBJID	SITEID	ARM	TRT01P	TRT02P	TRT03P	TRT04P	TRTSEQP
1	501	501-001	XYZ001	DrugA/DrugB/DrugC/Placebo	Drug A	Drug B	Drug C	Placebo	A-B-C-Placebo
2	501	501-002	XYZ002	DrugB/DrugC/Placebo/DrugA	Drug B	Drug C	Placebo	Drug A	B-C-Placebo-A
3	501	501-003	XYZ004	DrugC/Placebo/DrugA/DrugB	Drug C	Placebo	Drug A	Drug B	C-Placebo-A-B
4	501	501-004	XYZ006	Placebo/DrugA/DrugB/DrugC	Placebo	Drug A	Drug B	Drug C	Placebo-A-B-C

Row	RANDDT	TRTSDT	TRTEDT	TR01SDT	TR01EDT	TR02SDT	TR02EDT	TR03SDT	TR03EDT
1	2009-09-03	2009-09-03	2010-04-02	2009-09-03	2009-10-16	2009-10-29	2009-12-11	2009-12-24	2010-02-05
2	2009-09-02	2009-09-02	2010-04-01	2009-09-02	2009-10-15	2009-10-28	2009-12-10	2009-12-23	2010-02-04
3	2009-09-09	2009-09-09	2010-04-08	2009-09-09	2009-10-22	2009-11-04	2009-12-17	2009-12-30	2010-02-11
4	2009-09-02	2009-09-02	2010-04-01	2009-09-02	2009-10-15	2009-10-28	2009-12-10	2009-12-23	2010-02-04

Row	TR04SDT	TR04EDT	HEIGHTBL	WEIGHTBL	AGE	AGEU	SEXN	SEX	RACE	SAFFL	FASFL
1	2010-02-18	2010-04-02	157	59.0	47	Years	1	M	WHITE	Y	Y
2	2010-02-17	2010-04-01	170	192.8	50	Years	2	F	ASIAN	Y	Y
3	2010-02-24	2010-04-08	178	72.6	69	Years	1	M	WHITE	Y	Y
4	2010-02-17	2010-04-01	180	33.9	57	Years	1	M	WHITE	Y	Y

- Demographics
- Arm/Treatment Variables
- Periods
- Key baseline chars
- Study Population Indicators

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Introduction to ADaM – ADaM Classes

- **Basic Data Structure (BDS)**
  - Designed with the majority of analysis files in mind
  - One or more records per subject per analysis parameter, per analysis time point (if applicable)

BDS Example (ADLB)

	USUBJID	ITTFL	SAFFL	ADT	AVISIT	PARAMCD	PARAM	AVAL	ABLFL	BASE	CHG	PCHG	ATOXGR
1	██████-010-8002	Y	Y	06APR2015	Screening	ALT	Alanine Aminotransferase (U/L)	43		29	.	.	1
2	████-010-8002	Y	Y	20APR2015	Day 1 Baseline	ALT	Alanine Aminotransferase (U/L)	29	Y	29	0	0.0	0
3	████010-8002	Y	Y	13JUL2015	Week 12	ALT	Alanine Aminotransferase (U/L)	29		29	0	0.0	0
4	████-010-8002	Y	Y	05OCT2015	Week 24	ALT	Alanine Aminotransferase (U/L)	39		29	10	34.5	1
5	████-010-8002	Y	Y	06APR2015	Screening	ALB	Albumin (g/L)	47		44	.	.	0
6	████010-8002	Y	Y	20APR2015	Day 1 Baseline	ALB	Albumin (g/L)	44	Y	44	0	0.0	0
7	████-010-8002	Y	Y	13JUL2015	Week 12	ALB	Albumin (g/L)	41		44	-3	-6.8	0
8	████010-8002	Y	Y	05OCT2015	Week 24	ALB	Albumin (g/L)	44		44	0	0.0	0
9	████10-8002	Y	Y	06APR2015	Screening	ALP	Alkaline Phosphatase (U/L)	108		95			0

Subject Identifier   Study Population Indicators   Timing Variables   Analysis Parameter « Topic » of the analysis   Analysis Parameter « Results »

Introduction to ADaM – ADaM Classes

- **Occurrence Data Structure (OCCDS)**
  - Designed specifically for counting occurrences
  - More general version of the old ADAE document

OCCS Example (ADAE)

	USUBJID	SAFFL	AETERM	AEDECOD	AEBODSYS	AESTDTC	ASTDT	AETRTEM	AESER	ASER	A
1	010-8002	Y	SINUS PRESSURE	Paranasal sinus discomfort	Respiratory, thoracic and mediastinal disorders	2015-07-08	08JUL2015	Y	N	N	1
2	010-8007	Y	CARDIAC MURMUR	Cardiac murmur	Investigations	2015-08-12	12AUG2015	Y	N	N	1
3	010-8015	Y	RIGHT HAMMERTOE CORRECTION PAIN	Procedural pain	Injury, poisoning and procedural complications	2015-09-18	18SEP2015	Y	N	N	1

- **Variables coming from SDTM.AE and SDTM.SUPPAE**
- **Additional derived variables can be added**
  - Flags to identify first occurrence within each subject
  - Variables to impute missing information i.e. serioussness AESER (from SDTM) ASER (derived)

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Introduction to ADaM – Fundamental Principles

- Traceability

- Be analysis-ready

- Have metadata

- Be usable with common available tools

Introduction to ADaM – Validation

- CDISC provides a list of checks which may be used to validate ADAM datasets for ADaMIG 1.0

- The following class/datasets are checked
  - ADSL
  - BDS
  - ADAE

- Certain features not checked

CDISC ADaM Validation Checks (1.3)

CDISC ADaM Validation Checks

Version 1.3

Prepared by
CDISC ADaM Compliance Sub-Team

- Issues from an ADAM conformance outputs must be summarized in the Analysis Dataset Reviewer's Guide

- Brief and not technical explanation of the issues must be provided

Introduction to ADaM
Version vs Implementation Guidance (ADaM)

ADaM Document (release date)
Analysis Data Model (ADaM) v2.1 (17-Dec-2009)
Analysis Data Model Implementation Guide (ADaMIG) v1.1* (12-Feb-2016)
ADaM Examples in Commonly Used Statistical Analysis Methods v1.0 (16-Dec-2011)
The ADaM Basic Data Structure for Time-to-Event Analyses v1.0 (08-May-2012)
ADaM Structure for Occurrence Data (OCCDS) v1.0 (12-Feb-2016)
CDISC ADaM Validation Checks v1.3 (16-Mar-2015)
Define-XML v2.0 (24 Apr 2014)
Analysis Results Metadata Specification for Define-XML Version 2 v1.0 (16-Mar-2015)
*Enhancement of ADaM IG v1.0

ADaM v2.1

ADaM Ig V1.1

https://www.cdisc.org/standards/foundational/adam

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Introduction to ADaM – Requirements for Data Submission

- ADaM is one of the required standards for data submission to FDA (U.S.) and PMDA (Japan)
- **FDA** Data Standards Catalog

Data Exchange Standard	Exchange Format	Supported Implementation Guide Version	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins (MM/DD/YYYY)
Analysis Data Model (ADaM)	XPT	**1.0**	Ongoing	03/15/2019 [1] 03/15/2020 [2]	12/17/2016 [1] 12/17/2017 [2]
ADaM	XPT	**1.1**	03/15/2018		03/15/2019 [1] 03/15/2020 [2]

https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm#Catalog

[1] For New Drug Applications, Abbreviated New Drug Applications, and certain Biologic License Applications.
[2] For certain Investigational New Drug Applications.

Pay Attention! Available Validation checks for 1.0 only

- **Pmda** Data Standards Catalog

Use	Data Exchange Standard	Supported Version(s)	Implementation Guide Version	Exchange Format	Date Support Begins (YYYY-MM-DD)	Date Support Ends (YYYY-MM-DD)
Clinical study datasets	ADaM	2.1	**1.0**	XPT	2016-10-01	

http://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0002.html

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ADaM Documents Pipeline

Standard	Development	Internal Review	Public Review Prep.	Public Review	Resolve Public Review Comments	Publication Prep.	Est. Publication Date (Goal)
ADaMIG v1.2						X	? 2019
ADaM Comformance Rules V2.0						X	Q1 2019
QRS-GDSSF ADAM Supplement					X		
ADaM Medical Devices			X				
ADaM Integration			X				
ADaM Model v2.2 (or 3.0)	X						
ADaM OCCDS v1.1	X						
ADaM Traceability Examples	X						
ADaM Education Materials	X						
ADaM PK Analysis	X						
ADaM Oncology	X						
Analysis Results Metadata (ARM) Validation Rules	X						

https://www.cdisc.org/standards/in-development

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ADaMIG v1.2 Update

ADaMIG v1.2

- Implements updates to the ADaM Implementation Guide and release a new version release in 2018
- Status: Public Review Comment Resolution
- Expected to be finalized as soon as possible

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ADaMIG v1.2 Update - History of ADaMIG Versions

- ADaMIG v1.0 released late 2009
- Two structure outlined:
  - ADSL
  - BDS
- BDS TTE v1.0 released mid-2012
- ADAE v1.0 released mid-2012
- ADaMIG v1.1 released early 2016
- Concurrently created is a third analysis data structure
  - OCCDS v1.0
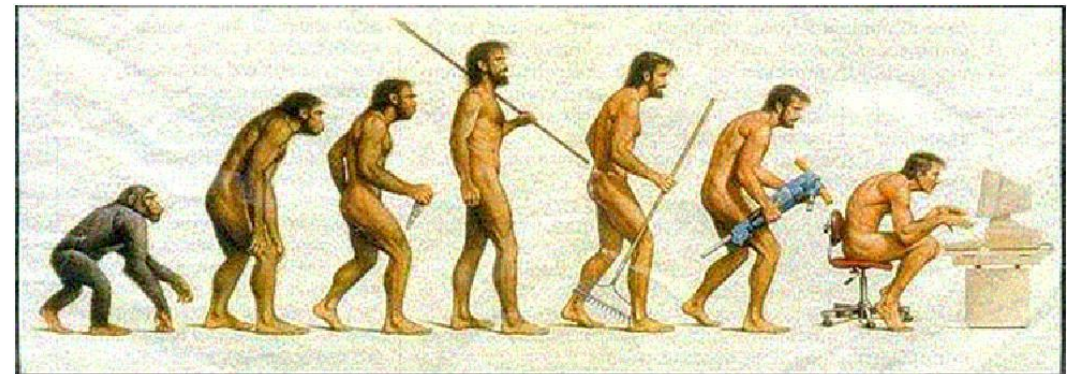
ADaMIG v1.2 Update - Overview

- No substantial change in the ADaMIG structure compared to the previous version
- No fundamental changes in ADaM Classes (ADSL,BDS,OCCDS)
- New useful variables in ADSL and BDS
- Additional description, clarification, refinement of text and examples

ADaMIG v 1.1

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**Analysis Data Model
Implementation Guide**
Version 1.1

**Prepared by the
CDISC Analysis Data Model Team**

Notes to Readers
This Implementation Guide is Version 1.1 and corresponds to Version 2.1 of the CDISC Analysis Data Model.

Revision History

Date	Version	Summary of Changes
2016-02-12	1.1 Final	Released version reflecting all changes and corrections identified during comment period.

ADaMIG v 1.2

ADaMIG - compiled

CDISC

Analysis Data Model Implementation Guide

Version 1.2
DRAFT

Prepared by the
CDISC Analysis Data Model Team

**Notes to Readers**
This Implementation Guide is Version 1.2 and corresponds to Version 2.1 of the CDISC Analysis Data Model.

https://wiki.cdisc.org/

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ADaMIG v1.2 Update - Stratification variables within ADSL

- Stratified randomization is used to ensure balance of treatment assignments across one or more prognostic factors

- For analysis, we may need
  - As randomized – the values used to randomized the subject
  - As Verified – the actual value for the subject
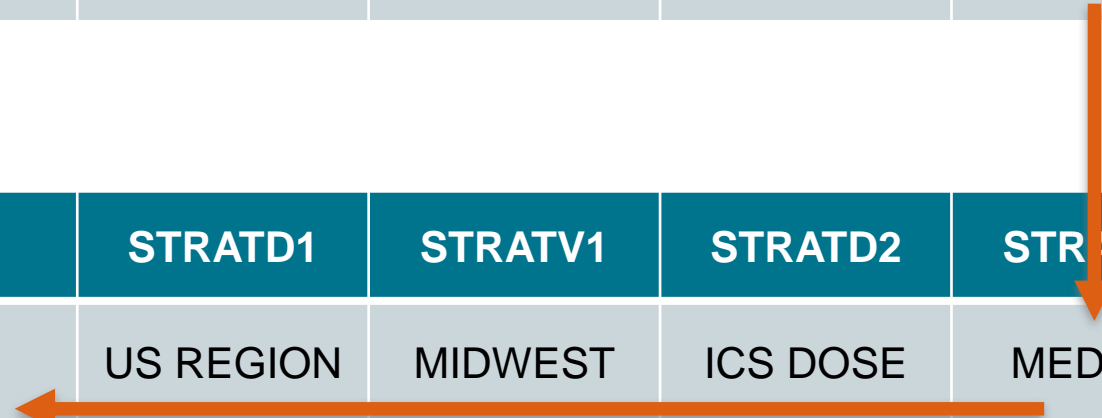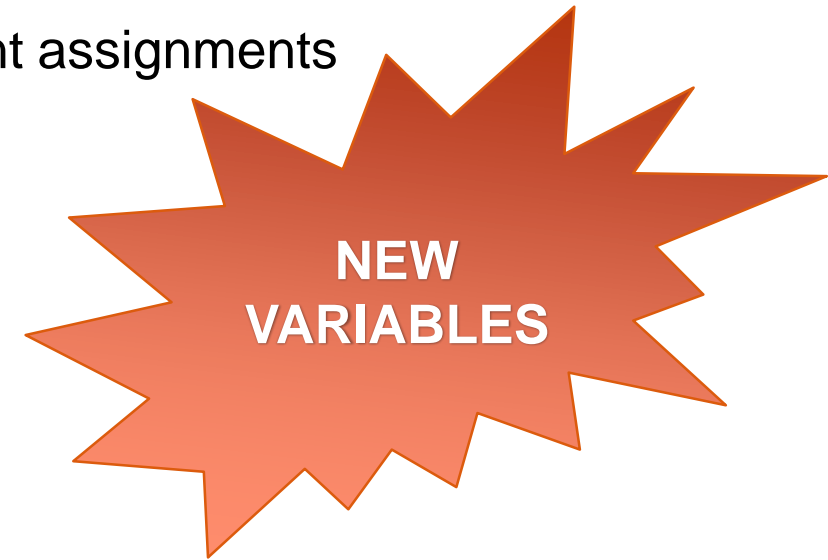
NEW VARIABLES

ADaMIG v1.1	ADaMIG v1.2
Ad-hoc additional variables to be created by the user	New Standardized variables added to collect the strata description, the randomization value and the verified value

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ADaMIG v1.2 Update – Example of Stratification variables within ADSL

- From the protocol: *A balanced block randomization scheme stratified by <u>US Region</u> (based on US Census Bureau Regions: West, Midwest, South, Northeast) and <u>ICS dose before study</u> (low/medium daily dose)*

SUBJID	STRATAR	STRATD1	STRATR1	STRATD2	STRATR2
1	MIDWEST, LOW	US REGION	MIDWEST	ICS DOSE	LOW

SUBJID	STRATAV	STRATD1	STRATV1	STRATD2	STRATV2
1	MIDWEST, MEDIUM	US REGION	MIDWEST	ICS DOSE	MEDIUM

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ADaMIG v1.2 Update - Stratification variables within ADSL

Variable Name	Variable Label	Type	Core	Example
STRATAR	Strata from Randomization	Char	Perm	STRATAR=">=50, Treatment experienced, N"
STRATARN	Strata from Randomization (N)	Num	Perm	STRATARN=3 when STRATAR=">=50, Treatment experienced, N"
STRATAV	Strata from Verification Source	Char	Perm	STRATAV=">=50, Treatment experienced, Y"
STRATAVN	Strata from Verification Source (N)	Num	Perm	STRATAVN=3 when STRATAV=">=50, Treatment experienced, Y"
STRATRw	Strat Factor w Value from Rand	Char	Perm	STRATR3="N"
STRATRwN	Strat Factor w Value from Rand (N)	Num	Perm	STRATR3N=0 when STRATR3="N"
STRATDw	Description of Stratification Factor w	Char	Perm	STRATD3="Hypertension"
STRATVw	Strat Factor w Value from Verif Source	Char	Perm	STRATV3="Y"
STRATVwN	Strat Fact w Val from Verif Source (N)	Num	Perm	STRATV3N=1 when STRATV3="Y"

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ADaMIG v1.2 Update - Bi-directionality varaibles within BDS

- Lab limits often need to be assessed in more than one direction (CTC grades for example)

ADaMIG v1.1	ADaMIG v1.2
Additional row to be created (not an optimal solution for summaries and analyses)	New Standardized variables added to handle bi-directional lab limits

NEW VARIABLES

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ADaMIG v1.2 Update – Example of Bi-directionality

Row	USUBJID	PARAMCD	VISITNUM	AVAL	BASE	ABLFL	ANRLO	ANRHI
1	001-0001	HGB	1	7.4	7.4	Y	11	16.1
2	001-0001	HGB	2	20.5	7.4		11	16.1
3	001-0001	SGOT	1	33	33	Y	5	25
4	001-0001	SGOT	2	55	33		5	25
5	001-0001	SGOT	3	60	33		5	25
6	001-0001	SGOT	4	77	33		5	25
7	001-0001	PLAT	1	250	250	Y	150	450
8	001-0001	PLAT	2	100	250		150	450
9	001-0001	PLAT	3	99	250		150	450
10	001-0001	PLAT	4	75	250		150	450
11	001-0001	PLAT	5	49	250		150	450
12	001-0002	HGB	1	21.1	21.1	Y	11	16.1

Row	ATOXDSCL	ATOXGRL	BTOXGRL	ATOXDSCH	ATOXGRH	BTOXGRH
1	Anemia	Grade 3	Grade 3	Hemoglobin increased	Grade 0	Grade 0
2	Anemia	Grade 0	Grade 3	Hemoglobin increased	Grade 3	Grade 0
3				Aspartate aminotransferase increased	Grade 1	Grade 1
4				Aspartate aminotransferase increased	Grade 1	Grade 1
5				Aspartate aminotransferase increased	Grade 1	Grade 1
6				Aspartate aminotransferase increased	Grade 2	Grade 1
7	Platelet count decreased	Grade 0	Grade 0			
8	Platelet count decreased	Grade 1	Grade 0			
9	Platelet count decreased	Grade 1	Grade 0			
10	Platelet count decreased	Grade 1	Grade 0			
11	Platelet count decreased	Grade 3	Grade 0			
12	Anemia	Grade 0	Grade 0	Hemoglobin increased	Grade 3	Grade 3

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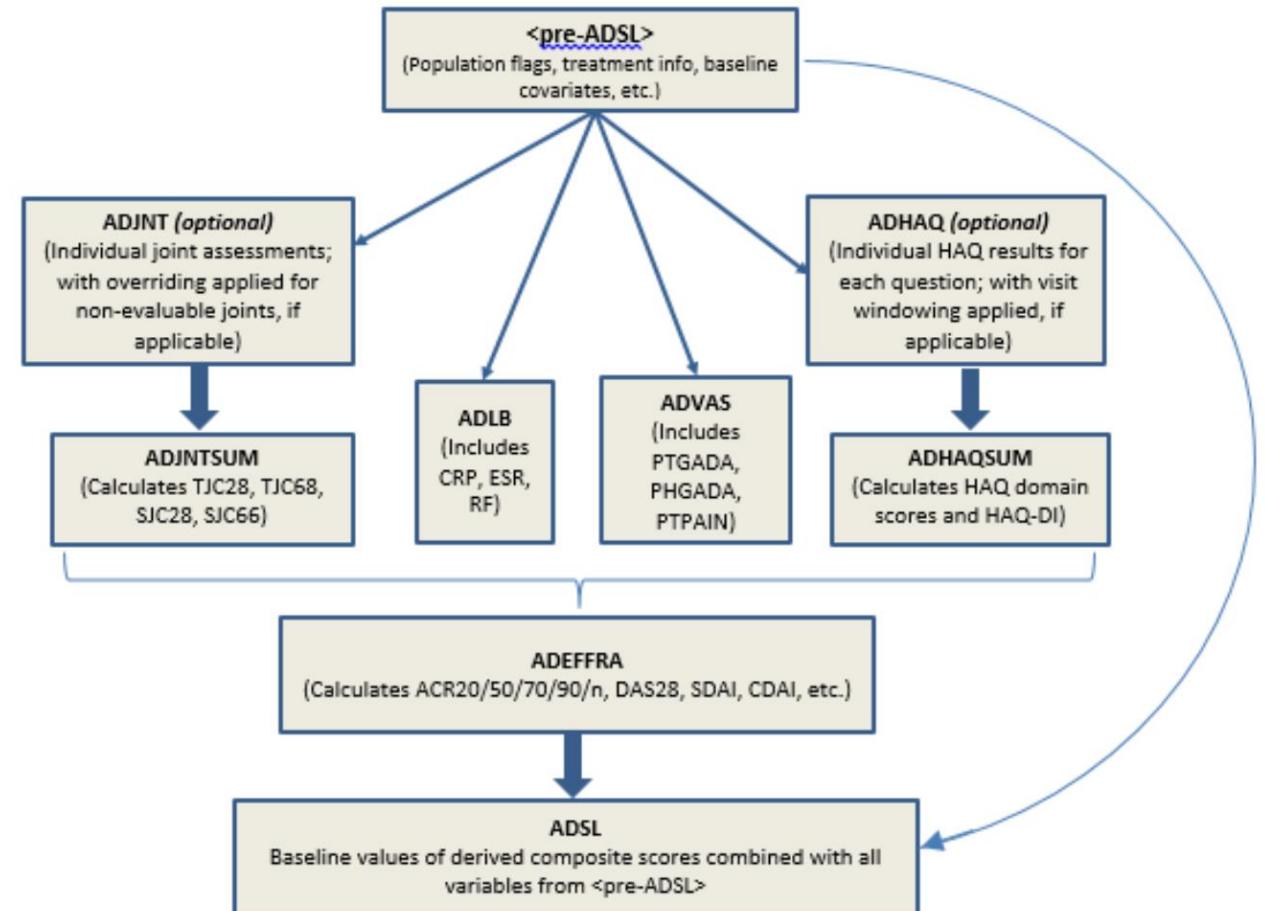# ADaMIG v1.2 Update – Example of Bi-directionality

- Variables with suffixes *GRL and *GRH included to indicate variables that pertain to low/high toxicity grades

- The **Orange** box demonstrates the following:
  - ATOXDSCL is populated whenever AVAL is not null and grading is in the LOW direction, even if ATOXGRL is null
  - ATOXDSCH is populated whenever AVAL is not null and grading is in the HIGH direction, even if ATOXGRH is null

- The **Red** box demonstrates the following:
  - PARAMCD PLAT has toxicity grading only in the low direction, only BTOXGRL, ATOXGRL and other toxicity variables in the low direction are populated
  - None of the high direction toxicity variables for PARAMCD PLAT are ever populated, even if the value is out of range in the high direction (ANRIND=HIGH)

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ADaMIG v1.2 Update - Bi-directionality

Variable Name	Variable Label	Type	Core	Comments
ATOXGRL	Analysis Toxicity Grade Low	Char	Perm	Used to assess when a subject's lab value falls within the low toxicity range.
ATOXGRLN	Analysis Toxicity Grade Low (N)	Num	Perm	Numeric version of ATOXGRL.
ATOXGRH	Analysis Toxicity Grade High	Char	Perm	Used to assess when a subject's lab value falls within the high toxicity range.
ATOXGRHN	Analysis Toxicity Grade High (N)	Num	Perm	Numeric version of ATOXGRH.
BTOXGRL	Baseline Toxicity Grade Low	Char	Perm	Used to establish the shift in toxicity level from baseline level when a subject shifts to lower readings.
BTOXGRLN	Baseline Toxicity Grade Low (N)	Num	Perm	Numeric version of BTOXGRL.
BTOXGRH	Baseline Toxicity Grade High	Char	Perm	Used to establish the shift in toxicity level from baseline level when a subject shifts to higher readings.
BTOXGRHN	Baseline Toxicity Grade High (N)	Num	Perm	Numeric version of BTOXGRH.
ATOXDSCL	Analysis Toxicity Description Low	Char	Perm	Used to describe the low end of the lab test criteria preferred term.
ATOXDSCH	Analysis Toxicity Description High	Char	Perm	Used to describe the high end of the lab test criteria preferred term.

ADaMIG v1.2 Update - Preparatory Partial ADSL Concept: pre-ADSL

- High derived variables to be included in ADSL

- Derivations of these variables may better be performed in another ADaM

- One-possible solution is the creation of a pre-ADSL

- Final ADSL is created and collates variables from any ADaM

- Since pre-ADSL is a subset of ADSL, it is the sponsor's decision whether to include pre-ADSL in a regulatory submission

<pre-ADSL>
(Population flags, treatment info, baseline covariates, etc.)

ADJNT (optional)
(Individual joint assessments; with overriding applied for non-evaluable joints, if applicable)

ADHAQ (optional)
(Individual HAQ results for each question; with visit windowing applied, if applicable)

ADJNTSUM
(Calculates TJC28, TJC68, SJC28, SJC66)

ADLB
(Includes CRP, ESR, RF)

ADVAS
(Includes PTGADA, PHGADA, PTPAIN)

ADHAQSUM
(Calculates HAQ domain scores and HAQ-DI)

ADEFFRA
(Calculates ACR20/50/70/90/n, DAS28, SDAI, CDAI, etc.)

ADSL
Baseline values of derived composite scores combined with all variables from <pre-ADSL>

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ADaMIG v1.2 Update

Deprecation of PARAMTYP

- There was confusion regarding the differences between DTYPE and PARAMTYP

- PARAMTYP may still be used if required by analysis needs

Parameter Qualifier PARQUAL not available for this release

- In the ADaMIG that went through public review the Parameter Qualifier PARQUAL was added as a new variable

- The ADaM leadership team has determined that further development of the concept was needed

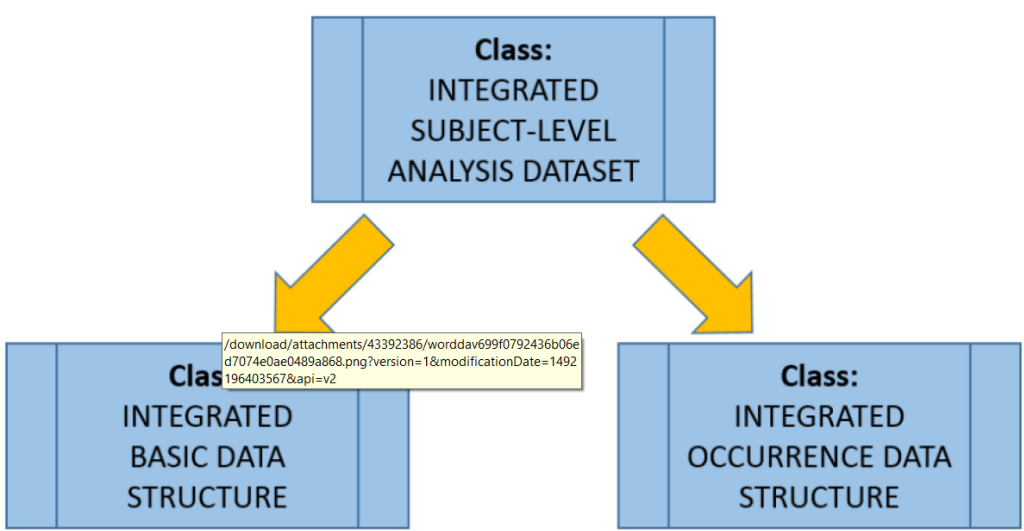| Row	PARAM	AVISIT	AVISITN	VISITNUM	VSSEQ	ABLFL	AVAL	BASE	CHG	PARAMTYP	DTYPE
1	Weight (kg)	Screening	-4	1	1164		99	100	.		
2	Weight (kg)	Run-In	-2	2	1165		101	100	.		
3	Weight (kg)	Baseline	0	3	1166	Y	100	100	0		
4	Weight (kg)	Week 24	24	4	1167		94	100	-6		
5	Weight (kg)	Week 48	48	5	1168		92	100	-8		
6	Weight (kg)	Week 52	52	6	1169		95	100	-5		
7	**Weight (kg)**	**Endpoint**	**9999**				**93.5**	**100**	**-6.5**		**AVERAGE**
8	Log10(Weight (kg))	Screening	-4	1	1164		1.9956	2	.	DERIVED	
9	Log10(Weight (kg))	Run-In	-2	2	1165		2.0043	2	.	DERIVED	
10	Log10(Weight (kg))	Baseline	0	3	1166	Y	2	2	0	DERIVED	
11	Log10(Weight (kg))	Week 24	24	4	1167		1.9731	2	-0.0269	DERIVED	
12	Log10(Weight (kg))	Week 48	48	5	1168		1.9638	2	-0.0362	DERIVED	
13	Log10(Weight (kg))	Week 52	52	6	1169		1.9777	2	-0.0223	DERIVED	
14	**Log10(Weight (kg))**	**Endpoint**	**9999**				**1.9708**	**2**	**-0.0292**	**DERIVED**	**AVERAGE**

ADaM Integration

- Document details structures of ADaM datsets to support integrated analysis, including IADSL, IBDS and IOCCDS
- Status: Preparing for Public Review
- 60days Public Review expected in early 2019
- Webinar 18 April 2019
- Final Document expected in 2019/2020

https://www.pharmasug.org/proceedings/2018/DS/PharmaSUG-2018-DS03.pdf

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ADaM Structures for Integration

- Integration and analysis of data across all studies in a submission is a vital part of applications for regulatory approval (Integrated Summary of Safety – ISS and Integrated Summary of Efficacy –ISE)
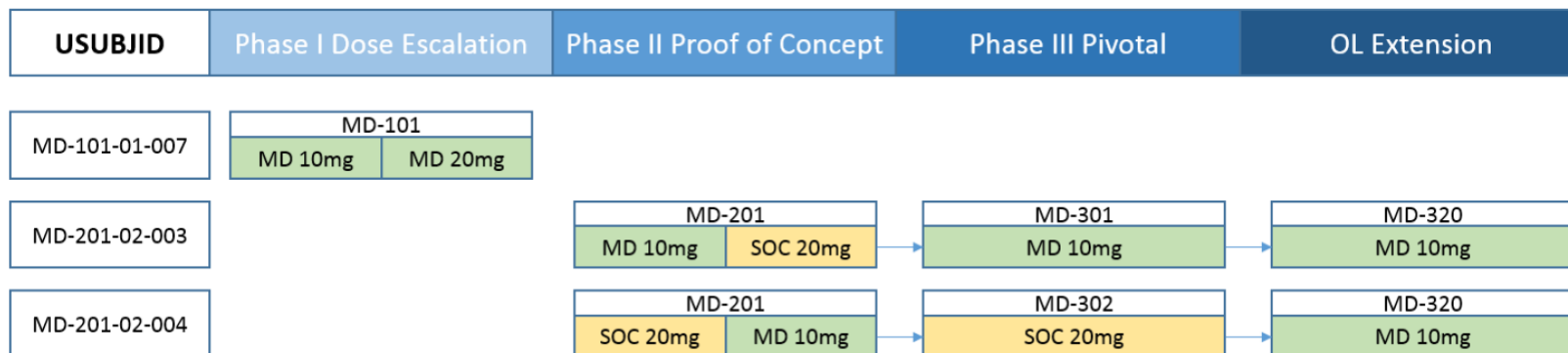
ADaM V1.1	ADaM Integration
The existing ADaM classes (ADSL,BDS,OCCDS) support simple cases of integration analysis	New standars classes (IADSL,IBDS,IOCCDS) are in development to support complex integration analyses

ADaM Structures for Integration - IADSL

ADaM V1.1	ADaM Integration
One-record-per-subject	One-record-per-subject-per-pool
Key: USUBJID	Key: USUBJID, POOL (POOLC and STUDIES added also)
For the same subject the variable must take the same value	For the same subject the variable can take different values in each pool
ADSL merged with BDS and OCCDS	IADSL merged with IBDS and IOCCDS

ADaM Structures for Integration - Example

Study and Treatment Progression for Three Subjects

Pool	Studies	Definition	Purpose
1	101, 201, 301, 302, 320	Overall Pool: Includes all periods.	Support treatment overview of all enrolled subjects, demographics and disposition
2	301, 302	Pivotal Pool: Includes all periods. Re-enrollers counted as distinct subjects for each enrollment.	Support pooled safety and efficacy analysis of pivotal studies
3	201, 301, 302	Comparison Pool: Includes all periods.	Support pooled safety analysis between study drug and comparators

Sample Pool Definitions

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ADaM Structures for Integration - Example

IADSL

ROW	USUBJID	POOL	POOLC	STUDIES	TRT01P	TR01SDT	TR01EDT	AP01SDT
1	MD-101-01-007	1	Overall	MD-101	MD 10mg	2000-02-01	2000-02-07	2000-02-01
2	MD-201-02-003	1	Overall	MD-201, MD-301, MD-320	MD 10mg	2000-08-10	2000-09-02	2000-08-10
3	MD-201-02-003	2	Pivotal	MD-301	MD 10mg	2001-08-21	2002-04-11	2001-08-21
4	MD-201-02-003	3	Comparison	MD-201, MD-301	MD 10mg	2000-08-10	2000-09-02	2000-08-10
5	MD-201-02-004	1	Overall	MD-201, MD-302, MD-320	SOC 20mg	2000-08-29	2000-09-24	2000-08-29
6	MD-201-02-004	2	Pivotal	MD-302	SOC 20mg	2001-09-06	2002-04-27	2001-09-06
7	MD-201-02-004	3	Comparison	MD-201, MD-302	SOC 20mg	2000-08-29	2000-09-24	2000-08-29

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ADaM Structures for Integration - Example

IOCCDS

USUBJID	POOL	STUDYID	AESEQ	AEDECOD	ASTDT	TRTP	TRTEMFL
MD-201-02-003	2	MD-301	1	Epistaxis	2001-09-12	MD 10mg	Y
MD-201-02-003	2	MD-301	2	Hypotension	2002-04-19		
MD-201-02-003	3	MD-201	1	Headache	2000-08-10	MD 10mg	Y
MD-201-02-003	3	MD-201	2	Back pain	2000-09-11	SOC 20mg	Y
MD-201-02-003	3	MD-301	1	Epistaxis	2001-09-12	MD 10mg	Y
MD-201-02-003	3	MD-301	2	Hypotension	2002-04-19	MD 10mg	Y
MD-201-02-004	2	MD-302	1	Hypotension	2001-11-06	SOC 20mg	Y
MD-201-02-004	2	MD-302	2	Diarrhoea	2002-04-05	SOC 20mg	Y
MD-201-02-004	3	MD-201	1	Back pain	2000-09-20	SOC 20mg	Y
MD-201-02-004	3	MD-201	2	Epistaxis	2000-11-05		
MD-201-02-004	3	MD-302	1	Hypotension	2001-11-06	SOC 20mg	Y
MD-201-02-004	3	MD-302	2	Diarrhoea	2002-04-05	SOC 20mg	Y

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ADaM Structures for Integration - Example

IBDS

USUBJID	POOL	STUDYID	LBSEQ	PARAM	AVAL	ADT	ADY	AVISIT	ABLFL	TRTP
MD-201-02-003	2	MD-301	1	Glucose	96	2001-08-21	1	Baseline	Y	MD 10mg
MD-201-02-003	2	MD-301	2	Glucose	87	2001-08-29	9	Week 1		MD 10mg
MD-201-02-003	3	MD-201	1	Glucose	98	2000-08-10	1	Baseline	Y	MD 10mg
MD-201-02-003	3	MD-201	2	Glucose	78	2000-08-17	8	Days 2-30		MD 10mg
MD-201-02-003	3	MD-301	1	Glucose	96	2001-08-21	377	Days 151-380		MD 10mg
MD-201-02-003	3	MD-301	2	Glucose	87	2001-08-29	385	Days 381-500		MD 10mg
MD-201-02-004	2	MD-302	1	Glucose	71	2001-09-06	1	Baseline	Y	SOC 20mg
MD-201-02-004	2	MD-302	2	Glucose	75	2001-09-13	8	Week 1		SOC 20mg

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ADaM Examples of Traceability

- New document with in-depth ADaM examples with an emphasis on providing clear traceability in data and metadata. Examples range from simple to complex data flow scenarios
- Status: Preparing for ADaM full-team review
- 60days Public Review expected in 2019
- Final Document expected in 2020

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ADaM Example of Traceability - When creating rows

- Analysis value derived from multiple rows from a preceding SDTM dataset
- DTYPE indicates the derived variable

ADEG

USUBJID	EGSEQ	EGREFID	PARAM	AVISIT	EGDTC	BASE	AVAL	CHG	DTYPE	ABLFL	TRTA
XYZ-1001	4	1st MEASURE	QTcF Interval (msec)	VISIT 2	2016-03-08T09:45:11	393.3	384	-9.3			Placebo
XYZ-1001	5	2nd MEASURE	QTcF Interval (msec)	VISIT 2	2016-03-08T09:48:07	393.3	393	-0.3			Placebo
XYZ-1001	6	3rd MEASURE	QTcF Interval (msec)	VISIT 2	2016-03-08T09:51:04	393.3	388	-5.3			Placebo
XYZ-1001			QTcF Interval (msec)	VISIT 2		393.3	388.3	-5.0	AVERAGE		Placebo

Value Level Metadata for ADEG

Variable	Where	Type	Length/Display Format	Controlled Terms/ Formats	Source/Derivation/Comment
AVAL	DTYPE='AVERAGE'	Float	5.1		DERIVED: Average of the triplicate values collected at each visit for the parameter.
AVAL	DTYPE Not Equal 'AVERAGE'	Integer	3		Predecessor: EG.EGSTRESN

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ADaM Example of Traceability
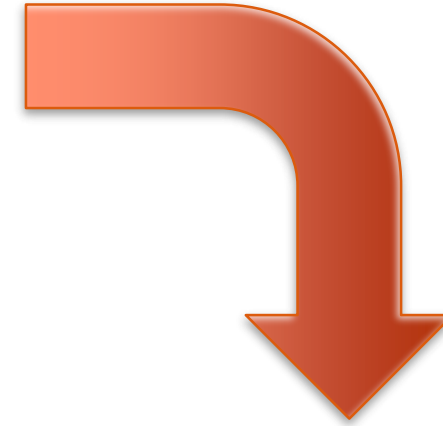## When multiple Analysis Variables are needed on the same row

- Statistical modelling requires multiple dependent/independent variables on the same row

- Step 1: to create a BDS datasets making use of the traceability of BDS standards to explain origin, derivations, imputations and other complexities
  - PARAM and PARAMCD are choosen with the intention of using them as variable name and label in a wide format dataset

- Step 2: the BDS dataset is fully transposed to a wide format in ADaM-Other Class dataset

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ADaM Example of Traceability
When multiple Analysis Variables are needed on the same row

ADQS

Row	USUBJID	TRTP	VISIT	PARAMCD	PARAM	AVAL
1	XYZ-001	DRUG A	BASELINE	S01	Score 1	40
2	XYZ-001	DRUG A	MONTH 1	S01	Score 1	55
3	XYZ-001	DRUG A	BASELINE	S02	Score 2	30
4	XYZ-001	DRUG A	MONTH 1	S02	Score 2	40
5	XYZ-001	DRUG A	BASELINE	S03	Score 3	45
6	XYZ-001	DRUG A	MONTH 1	S03	Score 3	40

ADQST

USUBJID	TRTP	VISIT	S01	S02	S03	S04	S05	S06	UPPER	LOWER
Unique Subject Identifier	Planned Treatment	Visit Name	Score 1	Score 2	Score 3	Score 4	Score 5	Score 6	Upper Body Score	Lower Body Score
XYZ-001	DRUG A	MONTH 1	15	10	-5	10	-5	0	20	5
XYZ-002	DRUG B	MONTH 1	0	5	20	15	5	5	25	25
XYZ-003	DRUG A	MONTH 1	30	10	15	20	25	30	55	75
XYZ-004	DRUG B	MONTH 1	-5	0	-10	0	5	5	-15	10
XYZ-005	DRUG A	MONTH 1	10	0	5	-10	-5	0	15	-15
XYZ-006	DRUG B	MONTH 1	10	5	0	0	5	5	15	10

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Overview of the Other ADaM Documents

ADaM PK Analysis

- Develop a specific BDS for the analysis of non-compartmental analysis (NCA)
- ADNCA : one record per subject per parameter (analyte) per analysis visit (dose event) and per analysis timepoint (sample)
- Difference between AVISIT in ADNCA and day in SDTM
- Exclusion Flags
  - PKEFL for subject-level exclusion
  - PKREFL for record-level exclusion
- https://www.lexjansen.com/phuse-us/2018/ds/DS07.pdf

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Overview of the Other ADaM Documents

ADaM Comformance Rules v2.0

- Revised ADaMIG v1.0 checks
- Develop checks specific to OCCDS v1.0 and ADaMIG v1.1

ADaM Medical Devices

- Documents describes how to apply the current ADaM standard structures and use new medical-device-specific ADaM structures for analysis of medical device data

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Overview of the Other ADaM Documents

ADaM Oncology

- Include Oncology structures, variables, and examples in existing ADaM documents and TAUGs
- Create new ADaM docs for Oncology-specific needs

Analysis Results Metadata (ARM) Validation Rules

- Developing ARM validation rules to be used for define.xml compliance checks

ADaM OCCDS v1.1

- Updates to OCCDS v1.0 including more complex examples

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Conclusions

- New guidelines will be availables in the next 2 years with the aim to improve the implementation of ADaM Standards

- No fundamental changes are expected from ADaMIG 1.2

- ADaM Versions supported in the regulatory agencies should be implemented to be compliant with submission requirements

- However a periodic overlook on what's the new/ what's the future and a review on the new proposals is recommended

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Questions

My special thanks to Annamaria Muraro who first introduced me to ADaM in the 1° CDISC Italian Meeting ten years ago

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