

Customer Oriented CDISC Implementation

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October 12, 2005

Efficient Strategy in Clinical Development

Cornerstones:

- ✓ CDISC recommendations
- ✓ FDA expectations
- ✓ Sponsor's requirements
- ✓ Accovion's inventory



Cornerstones (I)

✓ CDISC recommendations:



- Study Data Tabulation Model (SDTM)
- Analysis Dataset Model (ADaM)

✓ FDA expectations:



- SDTM and ADaM compliance recommended (less strict for ADaM)
- Documentation (metadata and links, preferably define.xml)
- Supplemental documents (annotated CRF, programs)

Cornerstones (II)

✓ Sponsor's requirements

- In-house vs out-sourcing
- CDISC relevance
- Sponsor provided material:



→ CRFs only

→ CDMS based study data

→ Other source data (e.g. analysis data)

Cornerstones (III)

✓ Accovion's inventory:



- Software
 - CDMS: Clintrial (CT) and Oracle Clinical (OC)
 - Analysis software: SAS 8.2 and 9.1.3

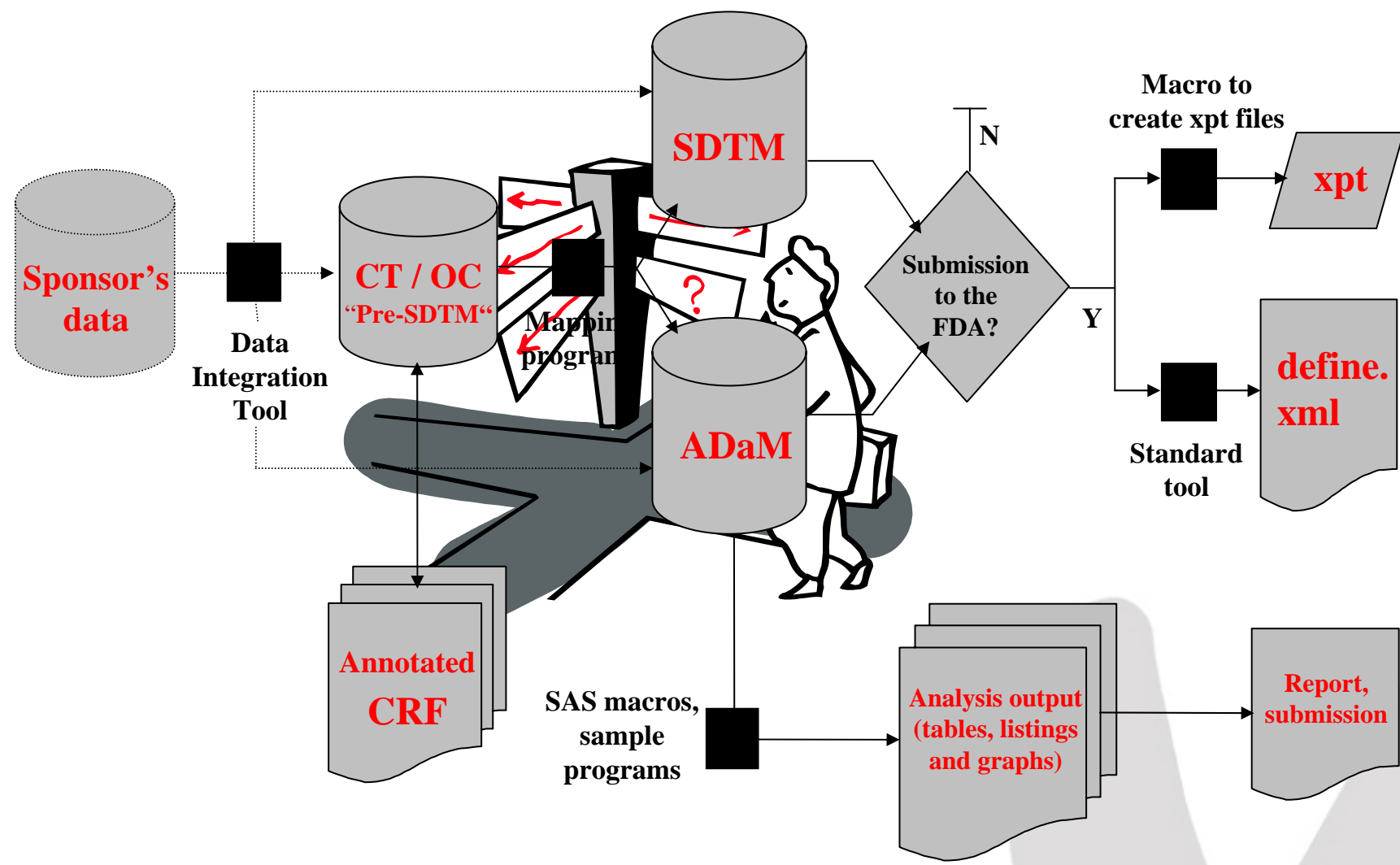


- Core functions
 - Database Programmers (DBP)
 - Statistical Programmers (SP)

Accovion's CDISC relevant tasks

- ✓ Database set-up (DBP)
- ✓ Generation of Full-SDTM and ADaM datasets (SP)
- ✓ Integration of different data structures (SP)
- ✓ Analysis output (SP)

Our workflow



Database set-up

Current situation:

SDTM Implementation Guide (SDTM-IG) recommended by the FDA

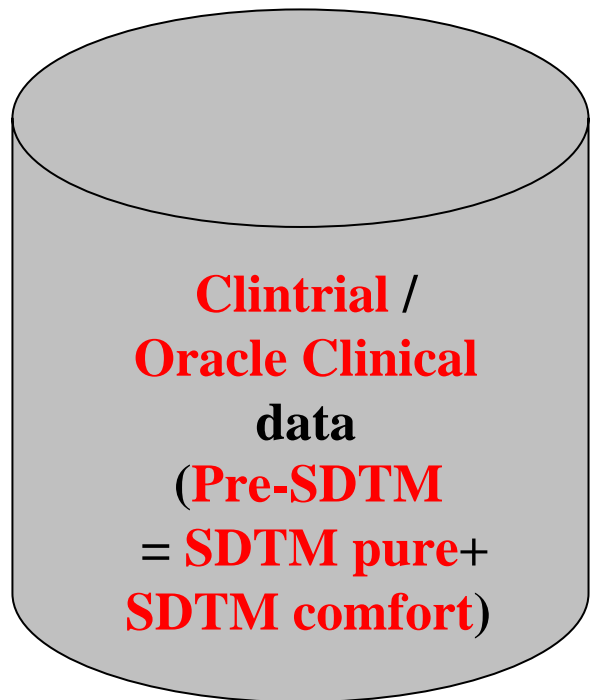
Consequences:

- ✓ Consider SDTM-IG
- ✓ Fill gap, if CDMS is not 100% SDTM compliant
- ✓ Implementation strategies differ between companies

Strategy for Database Set-up

- ✓ Use of metadata libraries based on SDTM
- ✓ Efficient implementation of changes in data structure
- ✓ Flexibility in case of complex derivations
- ✓ Additional variables needed for data analysis

Accovion's strategy



Use global libraries including:

- ✓ SDTM pure: SDTM variables and metadata
- ✓ SDTM comfort: Additional variables for analysis

Copy and adapt on study level

- ✓ CDMS generates a Pre-SDTM: Some variables will be derived in SAS

SDTM comfort: Benefit in relation to SDTM pure

✓ **Date variables:**

Used in analysis and listings

EGDTC (SDTM pure)	EGDT+EGDC (SDTM comfort)
2005-10-12T09:15	12OCT2005 (16721) 12-OCT-2005

✓ **Numeric codes:**

Used for convenient data selection and sorting

DSDECOD (SDTM pure)	DSDECODN (SDTM comfort)
ADVERSE EVENT	1
COMPLETED	2
...	...
NON-COMPLIANCE WITH STUDY DRUG	6
...	...
STUDY TERMINATED BY SPONSOR	13
...	...
OTHER	999

SDTM and ADaM implementation

Topic	SDTM	ADaM
Version	11.1 (SDSV3.1)	General Considerations 1.0, other models 0.x
Reviewer	Medical Reviewer	Statistical Reviewer
Requirements	<ul style="list-style-type: none"> Standardization 	<ul style="list-style-type: none"> Standardization Analysis friendly: "One PROC away"
Characteristics	<ul style="list-style-type: none"> Domain concept No redundancy CRF data and trial design data Textual results 	<ul style="list-style-type: none"> Analysis oriented Common variables in each dataset More derived data Numeric codes

Possible strategies for SDTM and ADaM implementation

✓ CDMS (=SDTM) \Rightarrow ADaM

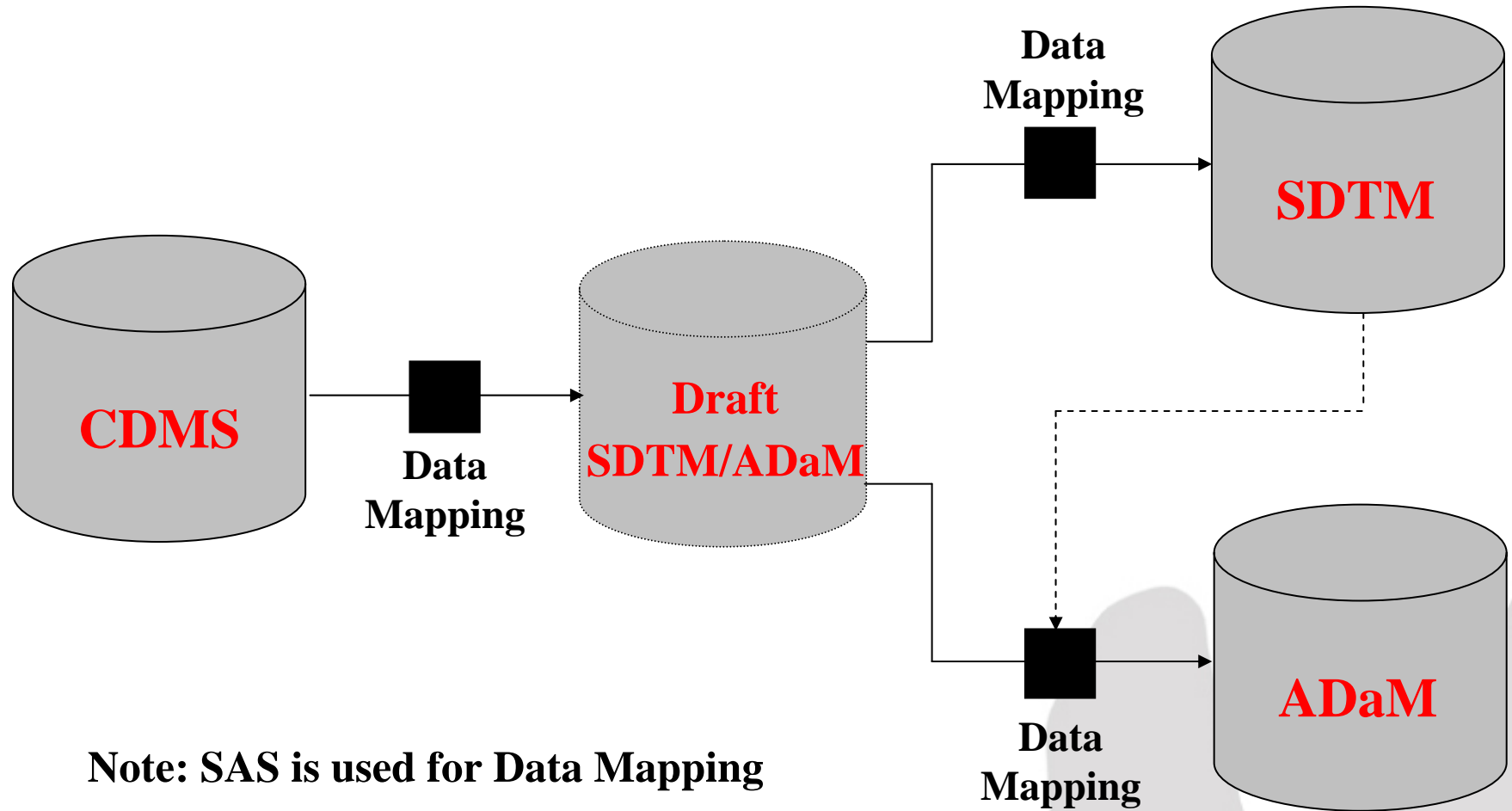
✓ If CDMS not 100% SDTM compliant:

- Independent creation: CDMS \Rightarrow SDTM, CDMS \Rightarrow ADaM
- Consecutive creation: CDMS \Rightarrow SDTM \Rightarrow ADaM
- Other concepts

Selecting a strategy

- ✓ What is available in the CDMS?
- ✓ Dual derivations
- ✓ Inconsistencies
- ✓ Reviewer's needs
- ✓ Potential of standardization

Accovion's strategy



Note: SAS is used for Data Mapping

SAS Post-Processing for Full-SDTM

✓ CDMS \Rightarrow Draft SDTM/ADaM

- Derivation of variables, e.g. treatment start
- Add records, where needed, e.g. baseline records

✓ Draft SDTM/ADaM \Rightarrow SDTM

- Delete comfort variables
- Add datasets, e.g. supplemental qualifier datasets SUPP~ (only if necessary)

ADaM Implementation

CDISC guidance for ADaM:

- ✓ General Considerations V1.0
- ✓ Subject-Level Analysis (ADSL dataset, draft)
- ✓ Other guidance (draft)

ADaM guidelines are not as restrictive as those for SDTM!

ADaM implementation at Accovion

- ✓ Use Draft SDTM/ADaM as input
- ✓ Create ADSL dataset
- ✓ Create other ADaM datasets
 - Add variables, e.g change from baseline
 - Add ADSL information → supports “One PROC away”
 - Derive variables only once
- ✓ Define standards across projects
- ✓ Few study/project specific changes

Tools for SDTM and ADaM Generation

✓ Standardized data mapping using SAS

✓ At Accovion:

SAS program generator

- Dataset mapping table (one per study)
- Variable mapping tables (one per domain)
- Macro creates programs and datasets

Tables to feed program generator

Dataset mapping table: Example study 1234

ADaM domain metadata information				
Studyid	Domain	Description	Structure	Sort order
1234	ADSL	Subject Level Key Information	Special Purpose	USUBJID
1234	ADAE	Adverse Events	Events	USUBJID, AESEQ
1234	ADEF	Efficacy	Findings	USUBJID, EFTESTCD, EFANLTMN

Variable mapping tables: Example domain ADSL

Studyid	ADaM variable metadata information						Source information			Mapping information			
	Domain	Variable	Label	Type	Length	Format	SAS library	Dataset name	Variable name	Task	Transform (SAS code)	Comments	Exec. order
1234	ADSL	SEX	Sex	Char	1		SDTM	DM	SEX	no change			
1234	ADSL	TRTAN	Actual Treatment Group Number	Num			SDTM	EX	EXTRT	macro	%trta(indata, outdata)	...	2

Automation of Documentation

For submission to the FDA:

- ✓ Datasets as xpt files
- ✓ Documentation for SDTM and ADaM in define.xml format

Documentation at Accovion:

- ✓ Standard tool
- ✓ Usage of mapping tables
- ✓ Additional information, e.g. role



Output of Accovion's standard tool

Output 1: Domain level metadata, example study 1234

ADaM Datasets for study 1234						
Dataset	Description	Structure	Purpose	Keys	Location	Documentation
ADSL	<u>Subject Level Key Information</u>	1 record per subject	Analysis	USUBJID	../1234/dds/ adsl.xpt	SAP and/or adsl.sas
ADAE	<u>Adverse Events</u>	1 record per subject per event	Analysis	USUBJID, AESEQ	../1234/dds/ adae.xpt	SAP and/or adae.sas
ADEF	<u>Efficacy</u>	1 record per subject per parameter per analysis time window	Analysis	USUBJID, EFTESTCD, EFANLTMN	../1234/dds/ adef.xpt	SAP and/or adef.sas

Output 2: Variable level metadata, example dataset ADSL

Variable Metadata for Dataset ADSL – 1 record per subject						
Variable	Label	Type	Controlled Terms or Format	Origin	Role	Comment
SEX	Sex	Char		DM.SEX	Result qualifier	No change
TRTAN	Actual Treatment Group Number	Num	0 = 'Placebo' 1 = 'Drug A' 2 = 'Drug B' 3 = 'Drugs A+B'	Derived from EX.EXTRT	Selection, result qualifier	For one subject either one or two treatments in EXTRT are possible

Integrating different data structures (I)

✓ Accovion full service:

- Standardized "Pre-SDTM"
- SDTM
- ADaM

✓ Deviating data structures:

- Legacy studies
- Sponsor's structures

A migration to SDTM and ADaM may be necessary!

Integrating different data structures (II)

✓ Migration to fixed target data:

- Meta-analysis: ADaM only
- Data for submissions: SDTM + ADaM

✓ Study specific source data:

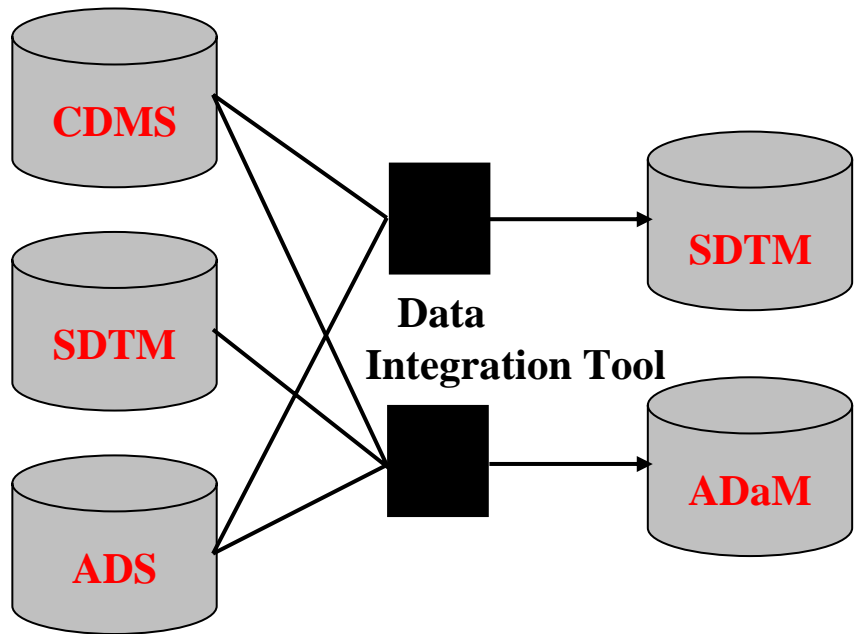
- CDMS structure
- SDTM
- Analysis datasets

Issues for consideration

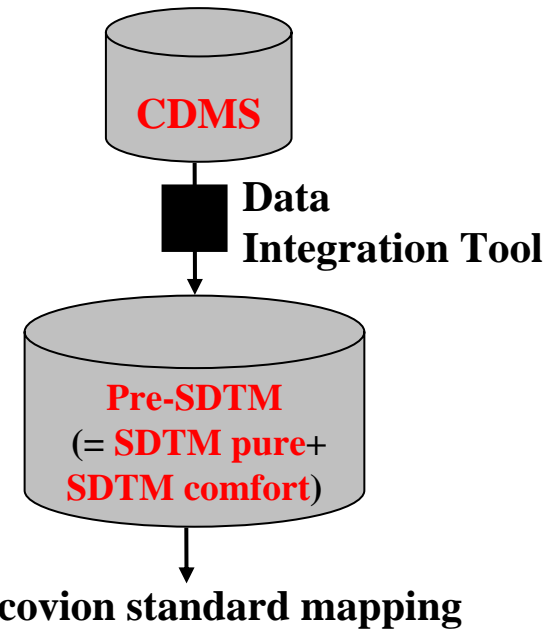
- ✓ Programming effort
- ✓ Validation effort
- ✓ Reusability of programs/potential of standardization
- ✓ Risk of errors
- ✓ Risk of inconsistencies



Accovion's proposals



1. Direct Migration



2. Migration to "Pre-SDTM"

Usage of standard mapping tool for data integration!

Analysis output

- ✓ Programming based on analysis datasets (ADaM)
- ✓ Consider analysis output for ADaM set-up:
 - Review of SAP and TLG shells
 - “Analysis-ready” datasets
- ✓ ADaM standards support usage of standard analysis tools
- ✓ At Accovion a set of 20 standard tables was developed

Relationship ADaM ⇔ analysis output

Example "Change from Baseline in Primary Efficacy Variable – ITT population":

Use efficacy dataset ADEF with selection criteria "WHERE (EFTESTCD='PEF' AND ITT='Y');"

Table 1.1 Change from Baseline in Primary Efficacy Variable - ITT population

Analysis Week	Statistic	Result			Change from Baseline		
		A (N=xx)	B (N=xx)	AB (N=xx)	A (N=xx)	B (N=xx)	AB (N=xx)
Baseline	N with data	xxx	xxx	xxx			
	N missing	xxx	xxx	xxx			
	Mean	xxx.x	xxx.x	xxx.x			
	SD	xxx.xx	xxx.xx	xxx.xx			
	Min	xxx	xxx	xxx			
	Median	xxx.x	xxx.x	xxx.x			
2	Max	xxx	xxx	xxx			
	N with data	xxx	xxx	xxx	xxx	xxx	xxx
	N missing	xxx	xxx	xxx	xxx	xxx	xxx
	Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
	Min	xxx	xxx	xxx	xxx	xxx	xxx
	Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	Max	xxx	xxx	xxx	xxx	xxx	xxx
	p-value ¹				x.xxxx	x.xxxx	
	95% CI				[xx.x;xx.x]	[xx.x;xx.x]	
etc.							

EFANLTMN

EFSTRESN=EFBLRESN

TRTAN

EFSTRESN

EFCHGBL

Note: ¹ p-values from pairwise comparison AB versus A resp. B from t-test; ITT = intention-to-treat; treatment groups as treated.

Documentation of analysis

- ✓ FDA: Recommendation for CDISC analysis metadata structure not yet available
- ✓ Follow ADaM General Considerations:

Analysis-Level Metadata for study 1234				
Analysis Name	Description	Reason	Dataset	Documentation
Table 1.1: ef00001t.lst	Change from Baseline in Primary Efficacy Variable – ITT population	Prespecified in Protocol	<u>../1234/dds/adeft.xpt</u>	<u>SAP, Section X.Y</u> and/or <u>ef00001t.sas</u>
Table 1.2: ef00002t.lst	Proportion of Responders at Endpoint – Per-Protocol population	Prespecified in Protocol	<u>../1234/dds/adeft.xpt</u>	<u>SAP, Section X.Y</u> and/or <u>ef00002t.sas</u>

Summary

- ✓ CDISC impacts the clinical development process
- ✓ CDISC standardization:
 - Efficiency ↑
 - Risk of errors ↓
- ✓ Accovion's modular approach:
 - Benefit from standardization
 - Flexibility:
 - Study specific needs
 - Changes in SDTM and ADaM models
 - Customer specific needs



Thank you!

Thank you for your attention!

Thanks to our colleagues for all the efforts to
develop this strategy!

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