ADaM Structures for Integration

Draft version currently out for public review (through 21-May-2019)

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Agenda

1. Integration, Simple and Complex
2. Structures for Simple Integration
3. Simple Integration Example (ISE)
4. Structures for Complex Integration
   - Model for Integrated ADSL (IADSL)
   - Model for Integrated OCCDS (IOCCDS)
   - Model for Integrated BDS (IBDS)
5. Complex Integration Example (ISS)
6. FAQs & Conclusion

Team Rules

- Use published ADaM standards when possible
- Do not recommend a data flow
- Achieve harmonization of integrated ADaM data
- Consistent variable names, labels, definitions

Section 1: Integration, Simple and Complex

Integration, Simple and Complex

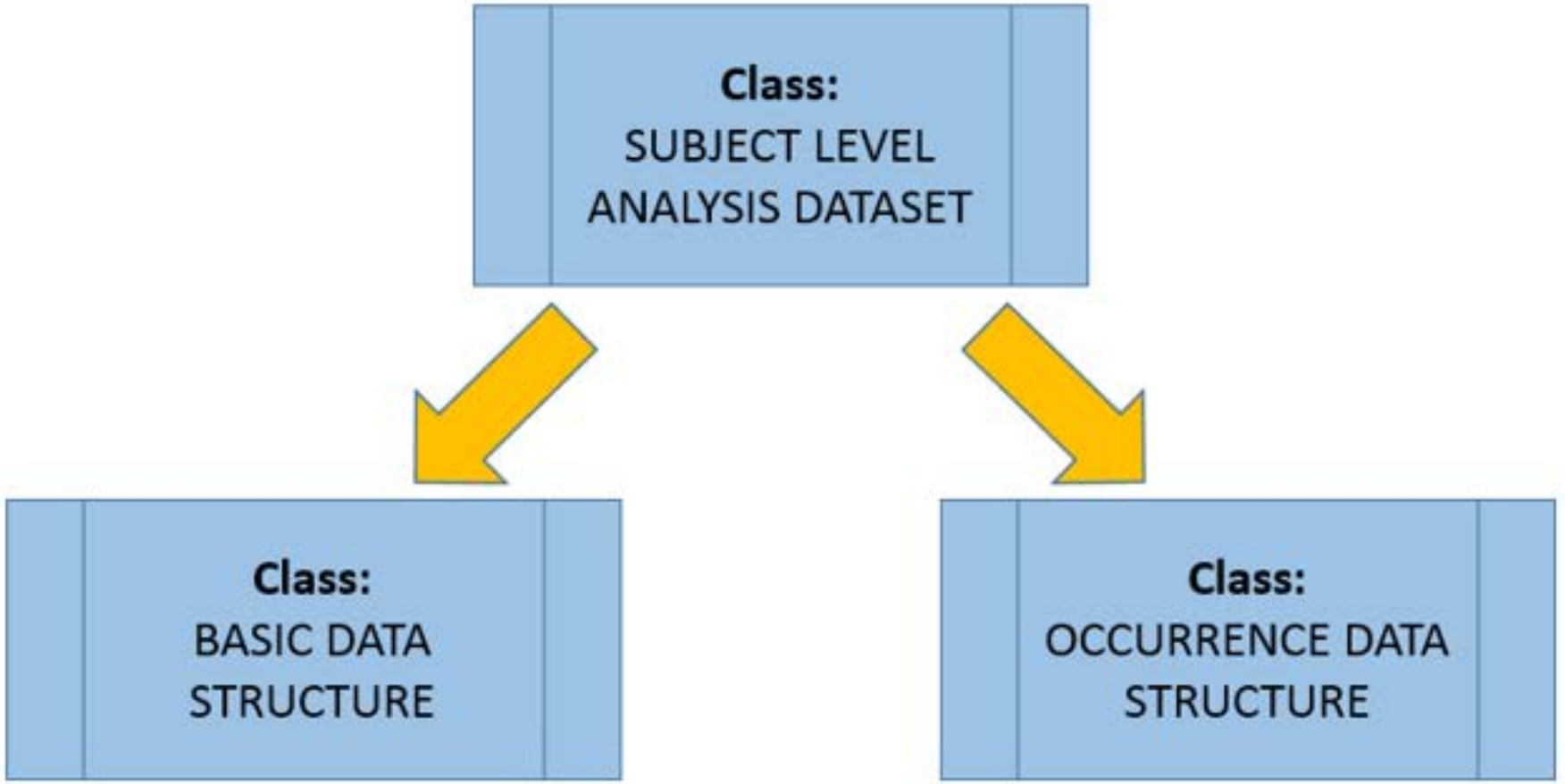
- Pool
  - A term used in integration, typically in Statistical Analysis Plans (SAPs), to define a combination of subjects' clinical trial experience which will be the focus of analysis
  - Pools may include/exclude certain treatment periods
  - Pools may define unique baseline and covariate values
  - For example: A subject participates in both a double-blind (DB) study and an open-label (OL) study. The integration SAP defines both a DB Pool and an active drug Pool. The analysis for each pool will examine a different slice of this subject’s clinical trial experience

Integration, Simple and Complex

	Simple	Complex
Number of studies in which a subject was enrolled	1	> 1
Multiple pools defined in SAP	No	Yes

Section 2: Structures for Simple Integration

Structures for Simple Integration



Structures for Simple Integration

- Subjects enroll in one study, the SAP does not define pools
- Only one set of treatment periods analyzed
- Only one definition for baselines and covariates

- Conclusion: ADSL, BDS, OCCDS classes sufficient

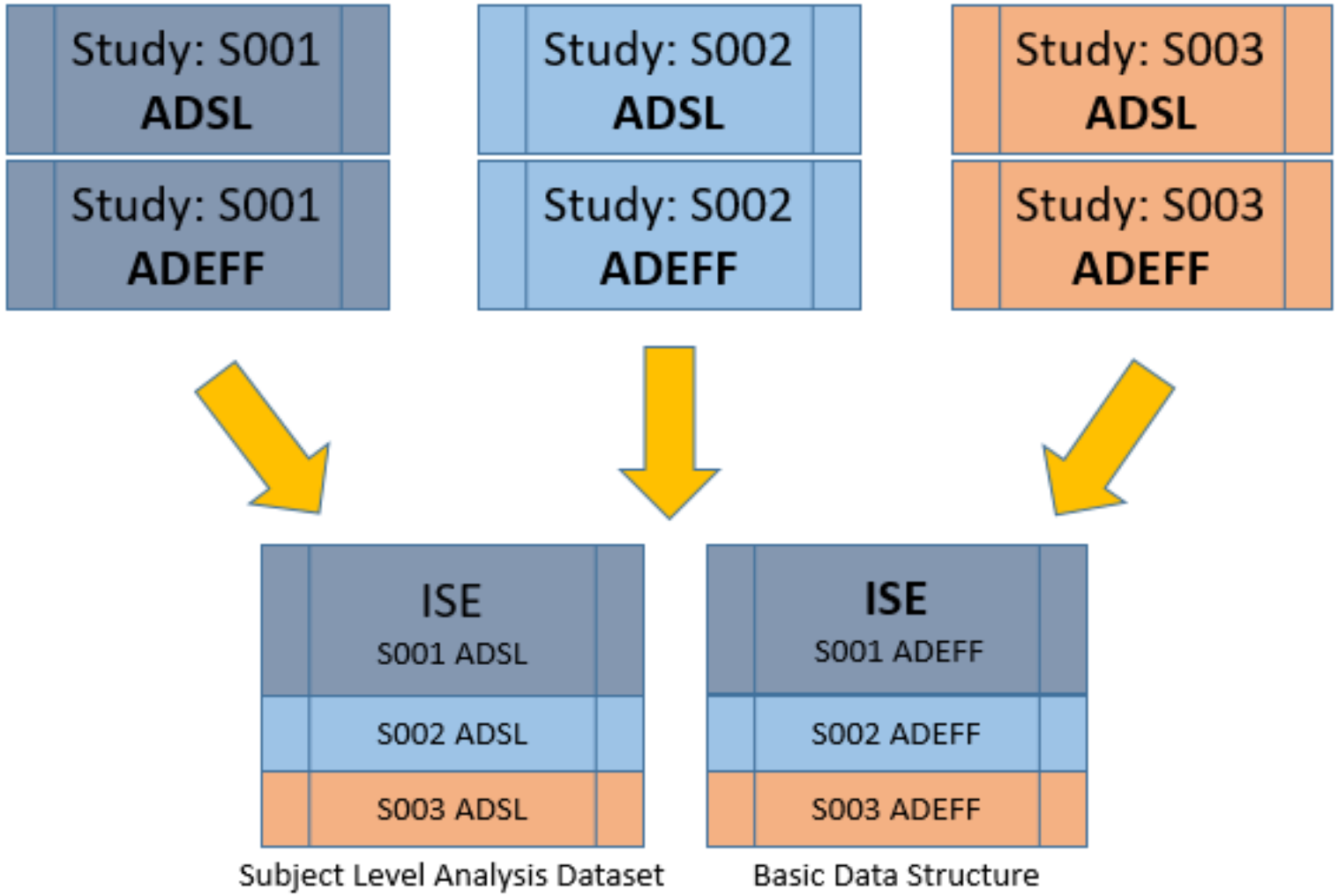
- Differences are minor
  - STUDYID variable has more than one value
  - Population flags that don’t apply for a study may be left missing and explained in the ADRG

Section 3: Simple Integration Example (ISE)

Simple Integration Example (ISE)

- 3 phase III studies
  - Similar study design and statistical analysis
  - No re-enrollment between studies
  - Study-level ADaM datasets used consistent design
- Integration using study-level ADaM as the source
  - Stacking
- Minimal harmonization efforts were needed

Simple Integration Example (ISE)



Section 4: Structures for Complex Integration

Structures for Complex Integration

- Subjects enrolled in multiple studies and phases
- SAP defines Pools

- Pools may include/exclude certain treatment periods
- Pools may define unique baseline and covariate values

Structures for Complex Integration

- Two Studies: DB and OL
- Two Pools: DB and Active Drug
- Subjects may participate in one or both studies

- ADSL Affected?
  - Treatment Variables, e.g. TRTSDT, TRT01P
  - Population Flags, e.g. ITTFL, SAFFL
  - Covariates, e.g. AGE
  - Baselines, e.g. BMIBL

Structures for Complex Integration

- ADSL dataset using ADSL class:

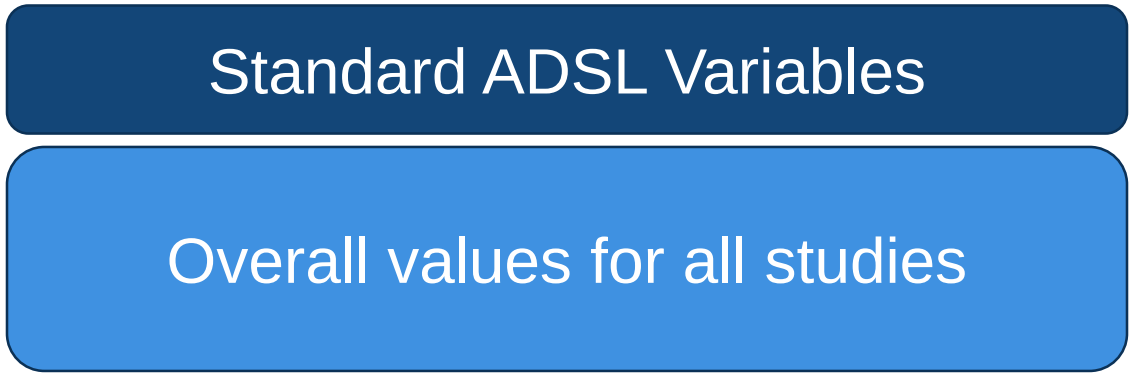
Structures for Complex Integration

- Is this approach doable?
- Challenges
  - Variable naming/labeling
  - Using correct variables for each pool
- Implication for the Integration Standard (ADSL)
  - For impacted variables, create new standard variables names with index
- Feedback – Is there a simpler way?

IADSL Structure

IADSL Structure

- ADSL using IADSL class:



IADSL Structure

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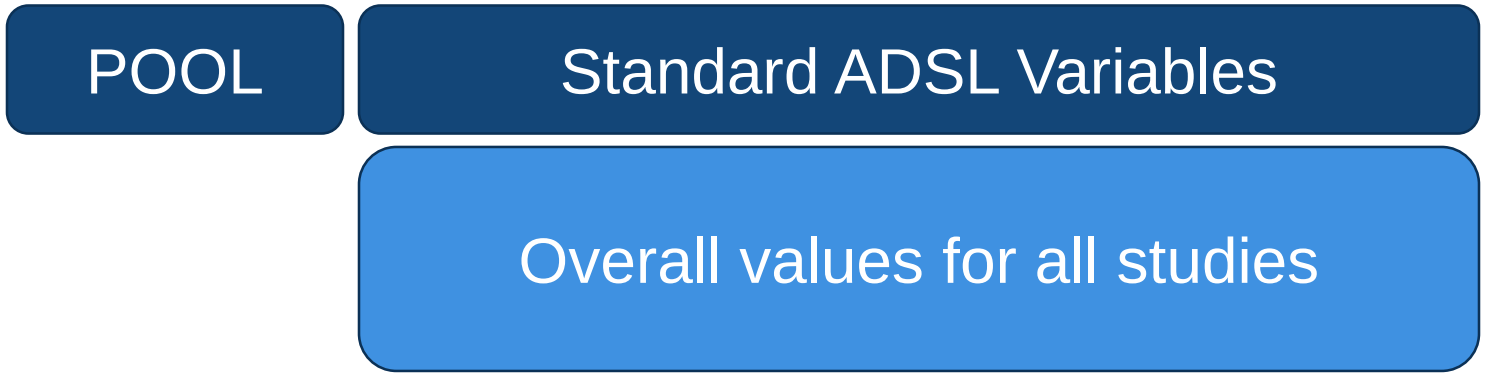


IADSL Structure

- ADSL using IADSL class:

POOL	Standard ADSL Variables
‘OVERALL’	Overall values for all studies
‘DB’	Values supporting DB Pool
‘ACTIVE DRUG’	Values supporting Active Drug Pool

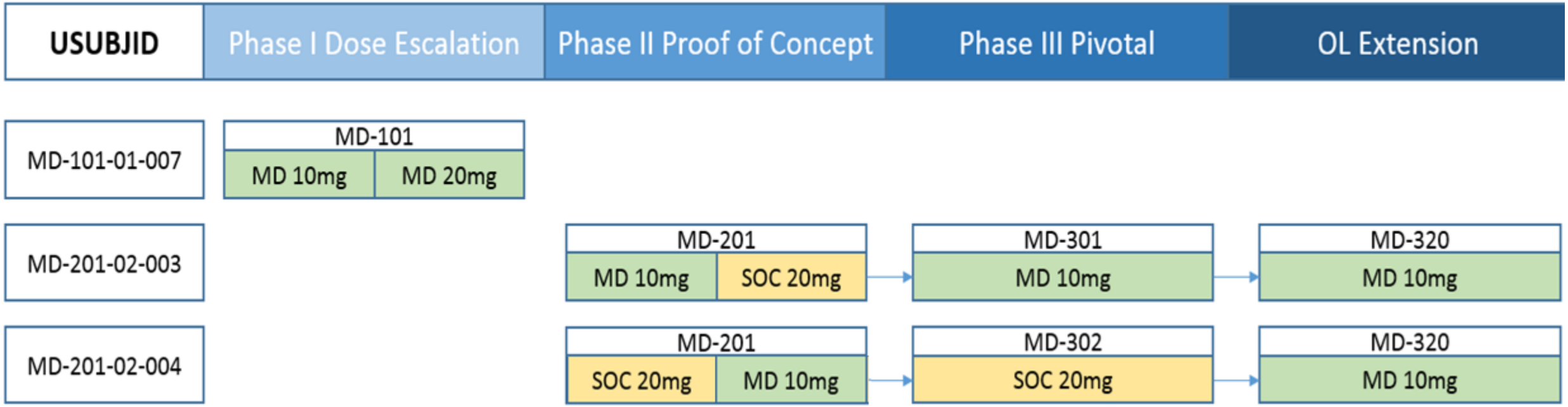
IADSL Structure

- Original one-record-per-subject ADSL preserved in the Overall pool
  - One record for each subject in the Integration
- For other pools, create records only for subjects in pool
  - Examine overall pool record to see why a subject is not in a pool
- Variables only populated when needed
  - If a covariate or baseline variable is not needed for a pool, there is no requirement to populate it

Section 5: ISS Example (IADSL)

ISS Example (IADSL)

- Multiple Studies, Phases



ISS Example (IADSL)

- Multiple Pools, Unique Periods, Baselines, Covariates

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

ISS Example (IADSL)

- ADSL using IADSL class

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

ISS Example (IADSL)

- ADSL using IADSL class

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2	**MD-201-02-003**	**1**	**OVERALL**	**MD-201, MD-301, MD-320**	**MD 10mg**	**2000-08-10**	**2000-09-02**
3	**MD-201-02-003**	**2**	**PIVOTAL**	**MD-301**	**MD 10mg**	**2001-08-21**	**2002-04-11**
4	**MD-201-02-003**	**3**	**COMPARISON**	**MD-201, MD-301**	**MD 10mg**	**2000-08-10**	**2000-09-02**
5	MD-201-02-004	1	OVERALL	MD-201, MD-302, MD-320	SOC 20mg	2000-08-29	2000-09-24
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ISS Example (IADSL)

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IBDS & IOCCDS Structure

IBDS & IOCCDS Structure

- IBDS & IOCCDS:

POOL	Standard BDS/OCCDS Variables	ADSL variables
‘OVERALL’	Overall values for all studies	Values for Overall
‘DB’	Values supporting DB Pool	Values for DB Pool
‘ACTIVE DRUG’	Values supporting Active Drug Pool	Values for Active Drug Pool

IBDS & IOCCDS Structure

- Create a set of records for a pool if needed
  - if there are pools 1, 2, & 3, AE analysis is done only for pools 2, 3, there is no need to create pool 1 records in ADAE.
- Keep relevant records for a pool
  - If there are studies A, B, C, and pool 2 only analyzes study B, it is fine to keep only records from study B for pool 2

IBDS & IOCCDS Structure

- Benefits
  - Timing variables values may change by pool
    - Analysis visit (AVISIT)
    - AE start study day (ASTDY)
  - Baseline record may change by pool
    - Baseline flag, baseline value, change from baseline (ABLFL, BASE, CHG)
  - Slotting of date values may change by pool
    - Treatment emergence, concomitance (TRTEMFL, ONTRTFL)
  - Right covariates merged in from ADSL for each pool
    - for analysis on pool X, subset by POOL=X

Section 5: ISS Example (IBDS)

ISS Example (IBDS)

- ADLB using IBDS class

USUBJID	POOL	STUDYID	LBSEQ	PARAM	AVAL	ADT	ADY	AVISIT	ABLFL	TRTP
MD-201-02-003	**PIVOTAL**	**MD-301**	**1**	**Glucose (mg/dL)**	**96**	**2001-08-21**	**1**	**Baseline**	**Y**	**MD 10mg**
MD-201-02-003	**PIVOTAL**	**MD-301**	**2**	**Glucose (mg/dL)**	**87**	**2001-08-29**	**9**	**Week 1**		**MD 10mg**
MD-201-02-003	COMPARISON	MD-201	1	Glucose (mg/dL)	98	2000-08-10	1	Baseline	Y	MD 10mg
MD-201-02-003	COMPARISON	MD-201	2	Glucose (mg/dL)	78	2000-08-17	8	Days 2-30		MD 10mg
MD-201-02-003	COMPARISON	MD-301	1	Glucose (mg/dL)	96	2001-08-21	377	Days 151-380		MD 10mg
MD-201-02-003	COMPARISON	MD-301	2	Glucose (mg/dL)	87	2001-08-29	385	Days 381-500		MD 10mg

ISS Example (IBDS)

- ADLB using IBDS class

USUBJID	POOL	STUDYID	LBSEQ	PARAM	AVAL	ADT	ADY	AVISIT	ABLFL	TRTP
MD-201-02-003	PIVOTAL	MD-301	1	Glucose (mg/dL)	96	2001-08-21	1	Baseline	Y	MD 10mg
MD-201-02-003	PIVOTAL	MD-301	2	Glucose (mg/dL)	87	2001-08-29	9	Week 1		MD 10mg
MD-201-02-003	**COMPARISON**	**MD-201**	**1**	**Glucose (mg/dL)**	**98**	**2000-08-10**	**1**	**Baseline**	**Y**	**MD 10mg**
MD-201-02-003	**COMPARISON**	**MD-201**	**2**	**Glucose (mg/dL)**	**78**	**2000-08-17**	**8**	**Days 2-30**		**MD 10mg**
MD-201-02-003	**COMPARISON**	**MD-301**	**1**	**Glucose (mg/dL)**	**96**	**2001-08-21**	**377**	**Days 151-380**		**MD 10mg**
MD-201-02-003	**COMPARISON**	**MD-301**	**2**	**Glucose (mg/dL)**	**87**	**2001-08-29**	**385**	**Days 381-500**		**MD 10mg**

Section 6: FAQs and Conclusion

Frequently Asked Questions

- Is the IADSL class required?
  - No
- Is there additional ADSL class support for Integration?
  - No
- Is the dataset name still ADSL?
  - Yes
- What about compliance checks/validation rules?
  - New ADaM compliance checks will be developed for IADSL, IBDS, and IOCCDS classes once document is final

Frequently Asked Questions (2)

- What if USUBJID wasn't correct and unique across studies?
  - Sponsor is expected to have a process to identify the same person across studies, and to consistently assign the same USUBJID value
  - Integration document does not provide a way to handle incorrect USUBJID
- What if I have re-enrollers in different studies or other complicated scenarios?
  - See the Integration document for additional variables, suggestions, and detailed examples
- What about dataset size?
  - Large datasets can be split using variables such as POOL
- Can I implement these new structures now?
  - This is a draft document and possibly subject to change. Has not yet been included in any regulatory agency data standards catalogs

Conclusion

- Draft Version 1.0 ADaM Data Structures for Integration is now out for Public Review
  - Register with CDISC
  - Review the Document
  - **Review period closes May 21**

- We look forward to your review and comments!

ADaM Updates

- ADaM documents in the CDISC development cycle
  - 1 doc recently published

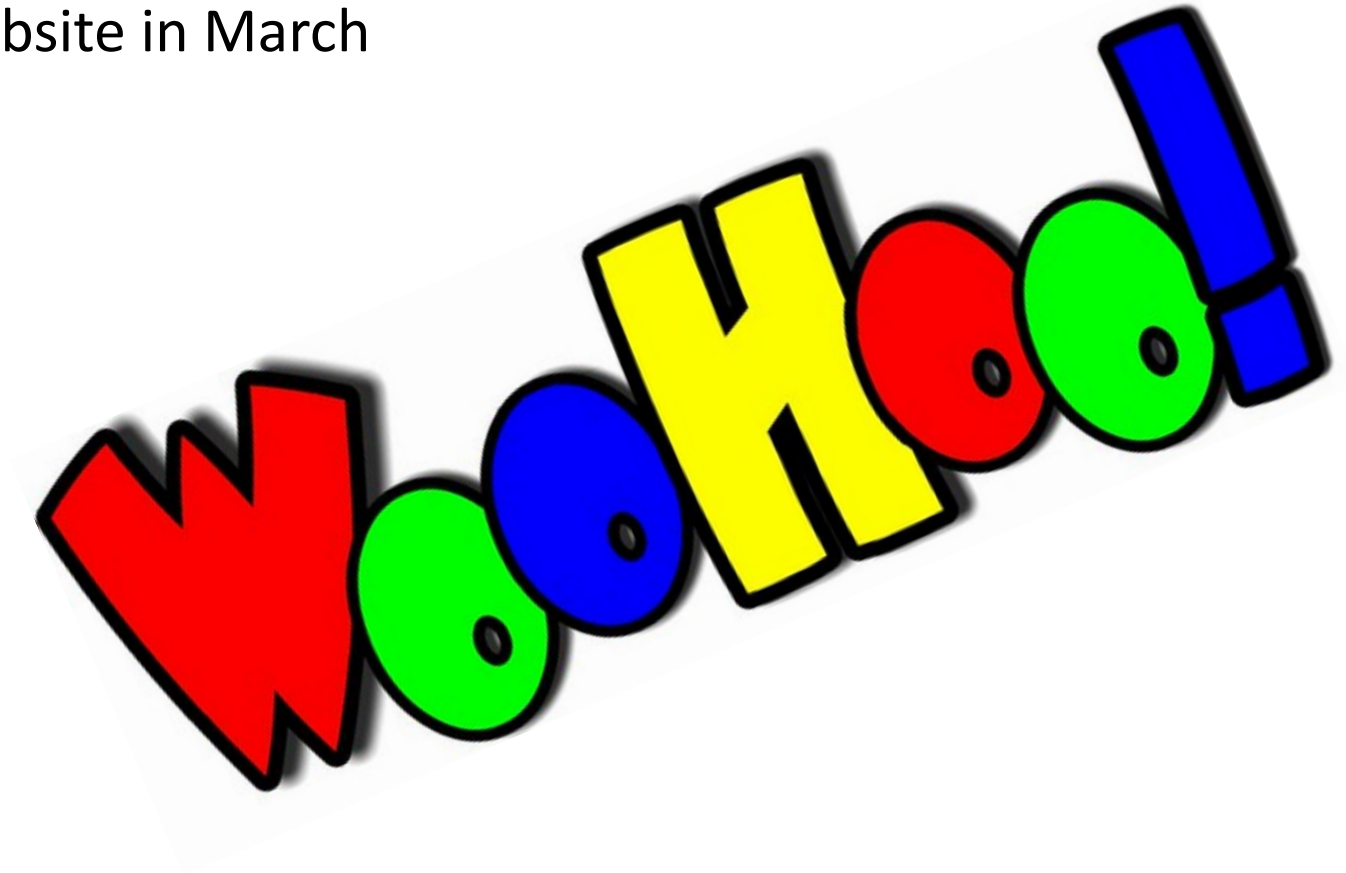
  - 3 docs soon to be finalized
  - 1 doc in public review
  - 2 docs preparing for public review
  - 6+ docs in development

  ———

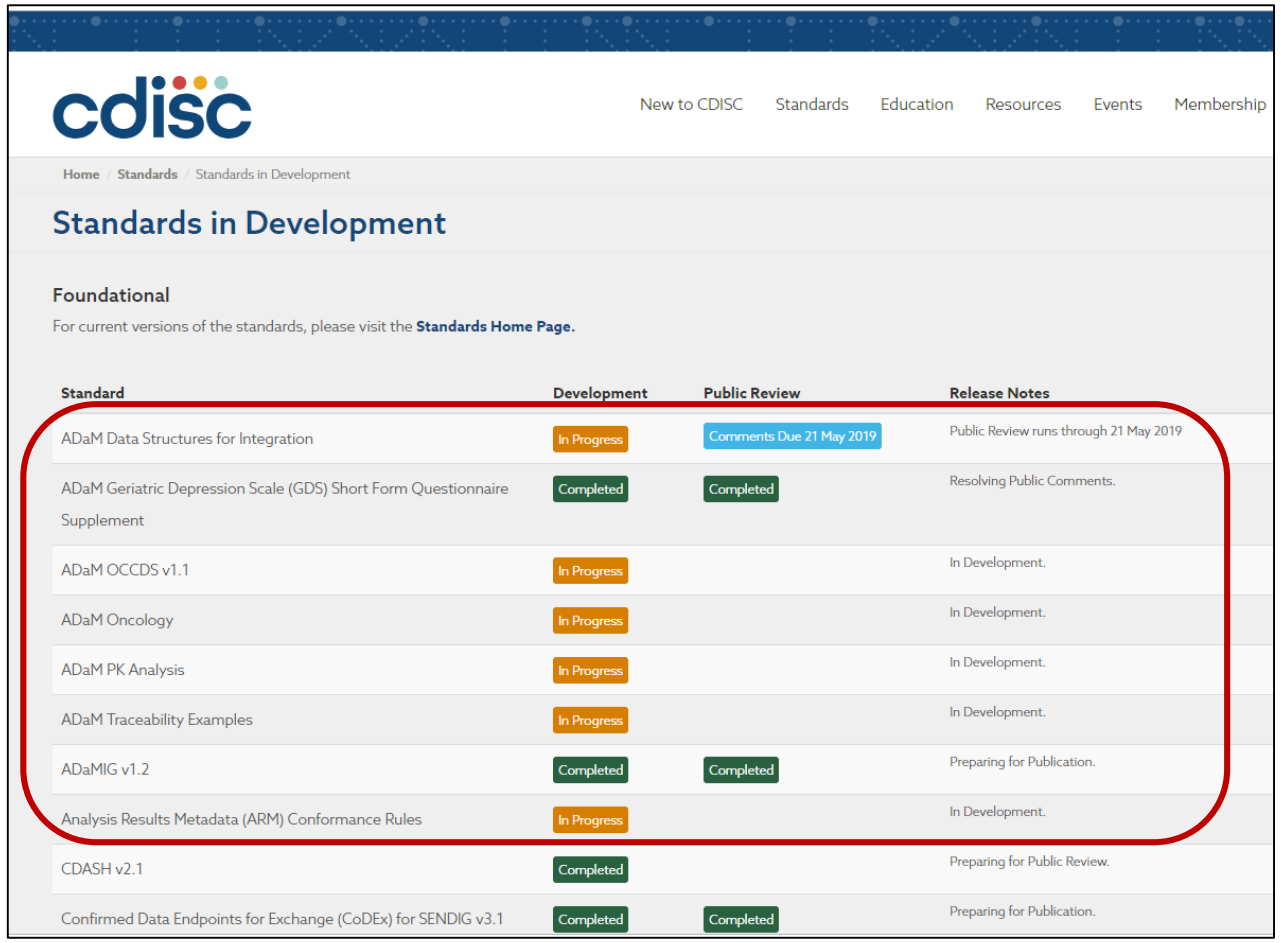
  12+ ADaM docs in various stages of development

Recently Finalized ADaM doc

- ADaM Conformance Rules v2.0
  - Published to CDISC website in March
  - Includes rules for
    - ADaMIG v1.0 and 1.1
    - OCCDS v1.0



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



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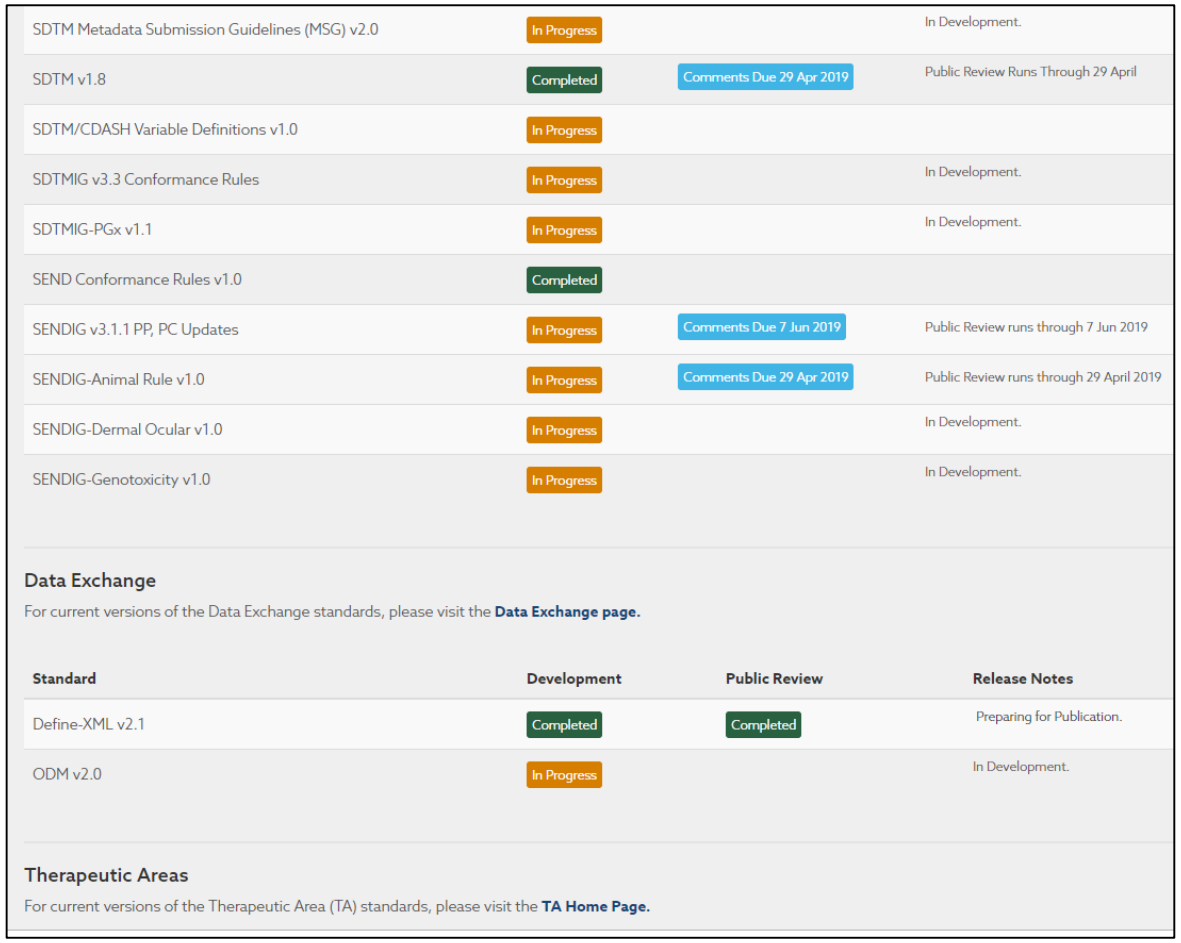
Standards in Development

Foundational

For current versions of the standards, please visit the **Standards Home Page.**

Standard	Development	Public Review	Release Notes
ADaM Data Structures for Integration	In Progress	Comments Due 21 May 2019	Public Review runs through 21 May 2019
ADaM Geriatric Depression Scale (GDS) Short Form Questionnaire Supplement	Completed	Completed	Resolving Public Comments.
ADaM OCCDS v1.1	In Progress		In Development.
ADaM Oncology	In Progress		In Development.
ADaM PK Analysis	In Progress		In Development.
ADaM Traceability Examples	In Progress		In Development.
ADaMIG v1.2	Completed	Completed	Preparing for Publication.
Analysis Results Metadata (ARM) Conformance Rules	In Progress		In Development.
CDASH v2.1	Completed		Preparing for Public Review.
Confirmed Data Endpoints for Exchange (CoDEx) for SENDIG v3.1	Completed	Completed	Preparing for Publication.



SDTM Metadata Submission Guidelines (MSG) v2.0	In Progress		In Development.
SDTM v1.8	Completed	Comments Due 29 Apr 2019	Public Review Runs Through 29 April
SDTM/CDASH Variable Definitions v1.0	In Progress		
SDTMIG v3.3 Conformance Rules	In Progress		In Development.
SDTMIG-PGx v1.1	In Progress		In Development.
SEND Conformance Rules v1.0	Completed		
SENDIG v3.1.1 PP, PC Updates	In Progress	Comments Due 7 Jun 2019	Public Review runs through 7 Jun 2019
SENDIG-Animal Rule v1.0	In Progress	Comments Due 29 Apr 2019	Public Review runs through 29 April 2019
SENDIG-Dermal Ocular v1.0	In Progress		In Development.
SENDIG-Genotoxicity v1.0	In Progress		In Development.

Data Exchange

For current versions of the Data Exchange standards, please visit the **Data Exchange page.**

Standard	Development	Public Review	Release Notes
Define-XML v2.1	Completed	Completed	Preparing for Publication.
ODM v2.0	In Progress		In Development.

Therapeutic Areas

For current versions of the Therapeutic Area (TA) standards, please visit the **TA Home Page.**

Soon to be Finalized ADaM docs

- ADaM v2.1 Considerations *(imminent)*
  - 1-page doc to be attached to ADaM v2.1
  - Describes things to be aware of when using the doc created in 2009:
    - Points to OCCDS (structure not mentioned in ADaM v2.1)
    - Points to Define-XML (more metadata than in Define-XML v1.0)
    - Points to table titled "Other CDISC Documents and their Applicability to ADaMIG Versions”
- ADaMIG v1.2 *(summer?)*
  - Adds stratification variables, bi-directional tox variables
  - Clarifies pre-ADSL, relationships between primary and secondary variables
  - Does not include PARQUAL
- ADaM Geriatric Depression Scale (GDS) Short Form Questionnaire Supplement *(summer?)*

ADaM docs in Public Review

- ADaM Structures for Integration – public comment closes May 21
  - See other presentation for details

ADaM docs Preparing for Public Review

- ADaMIG-MD (Medical Devices) is with CDISC Copy Editing
  - Applies ADSL, BDS, and OCCDS to medical devices
  - Adds SPDEVID
  - Adds structure ADDL (Device-Level Analysis Dataset)
- OCCDS v1.1 is wrapping up CDISC Internal Review
  - Adds more complex examples
    - Multiple input datasets
    - Multiple coding paths
  - Adds SRCDOM and SRCVAR variables (same as in BDS)

ADaM docs in Development

- ADNCA (Non-Compartmental Analysis) doc for PK data
- ADaM Traceability Examples doc
- ADaM Oncology doc
- Additional ADaM Questionnaire Supplements
- More ADaM Conformance Rules for

  Analysis Results Metadata, ADaMIG v1.2, …
- ADaM v3.0
  - Project to combine all (or most?) ADaM documents together

Acknowledgements

- Wayne Zhong – PharmaSUG presentation
- The entire ADaM Integration Subteam

Thank You!