Author Name(s) Biography

Wayne Zhong: has worked with SAS to produce submission deliveries for 8 years, has volunteered at the CDISC ADaM team for 4 years, is a member of the ADaM Integration and Compliance sub-teams, and is leading the ADaM Traceability Examples sub-team.

Kim Minkalis: has worked with SAS to produce submission deliveries for more than 10 years, has been on the CDISC ADaM team for 9 years, and is a member of the ADaM Integration, Traceability, Metadata, OCCDS, ADQRS sub-teams

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ADaM Structures for Integration: A Preview

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Contents

Team Rules

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

Section 1: Integration, Simple and Complex

Integration, Simple and Complex

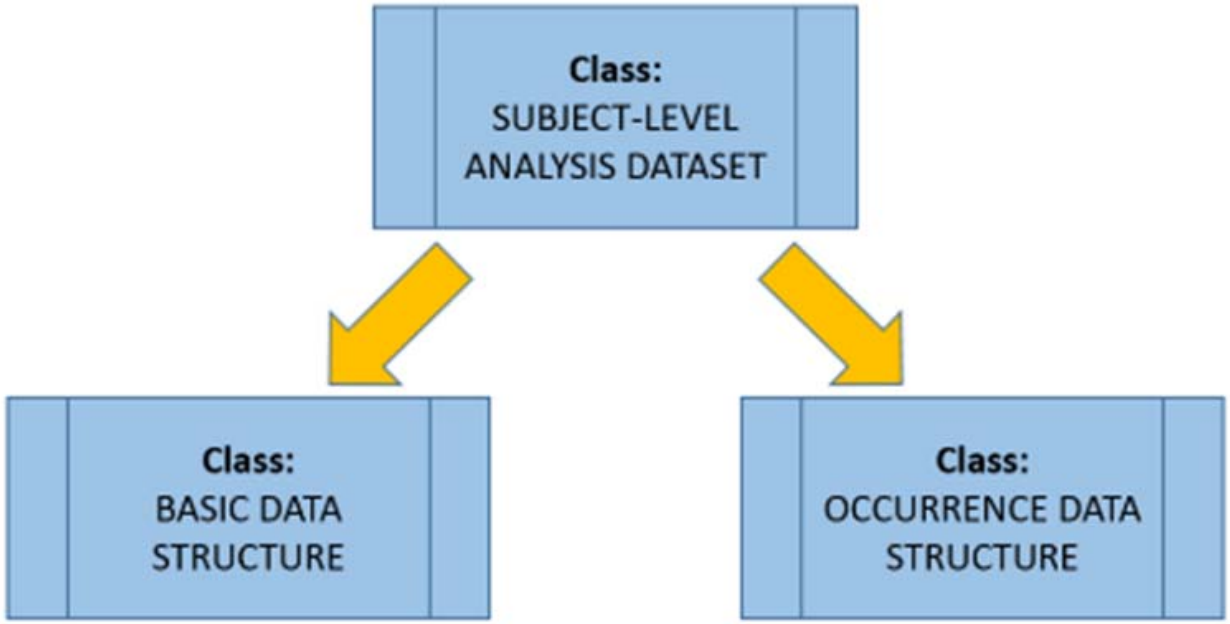
- Pool
  - A term used in integration, typically in Statistical Analysis Plans (SAPs), to define a combination of subjects' clinical trial experience which will be the focus of analysis
  - Pools may include/exclude certain treatment periods
  - Pools may define unique baseline and covariate values
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

Integration, Simple and Complex

- Simple
  - Subjects enrolled in one study
- Complex
  - Subjects enrolled in multiple studies and phases
- Simple
  - SAP does not define Pools
- Complex
  - SAP does define Pools

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

Section 3: Simple Integration Example (ISE)

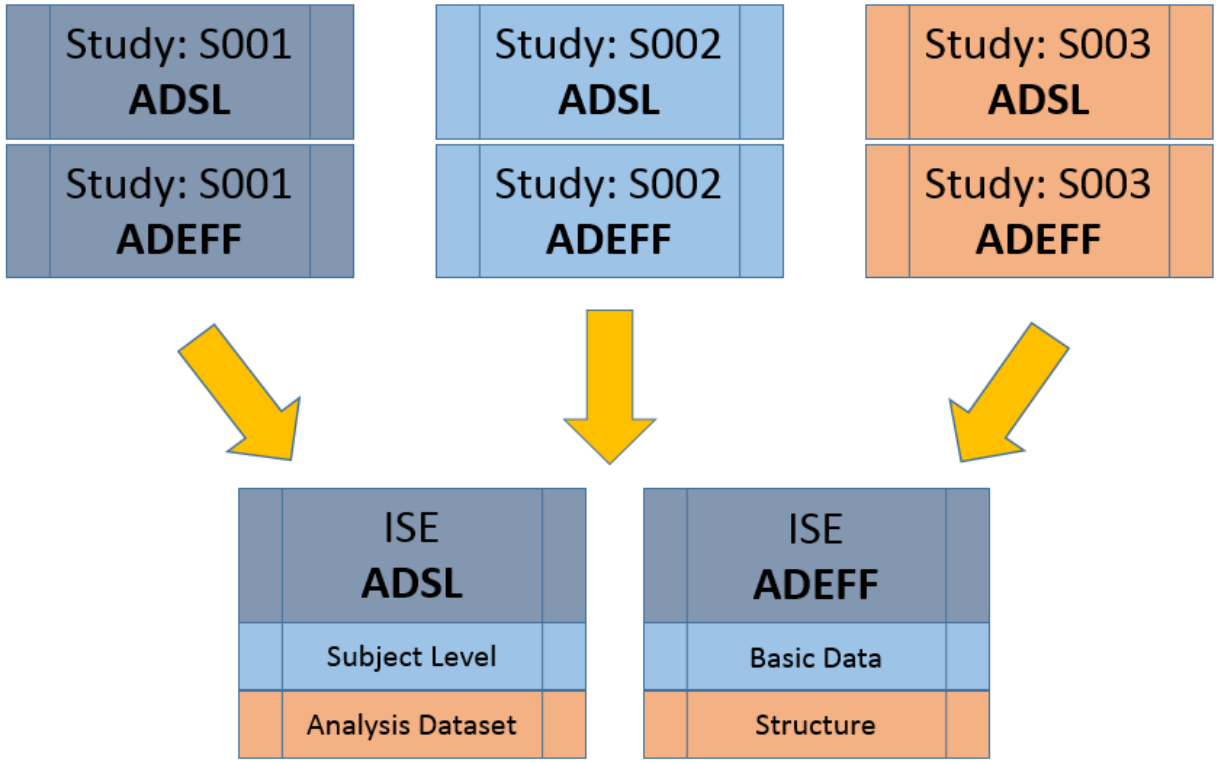
Simple Integration Example (ISE)

- 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 does define 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 OL
- Subjects may participate in one or both studies

- 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:

Standard ADSL Variables	DB Pool Variables	OL Pool Variables
Overall values for all studies	Values supporting DB Pool	Values supporting OL Pool

Structures for Complex Integration

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

Section 5: IADSL Structure

IADSL Structure

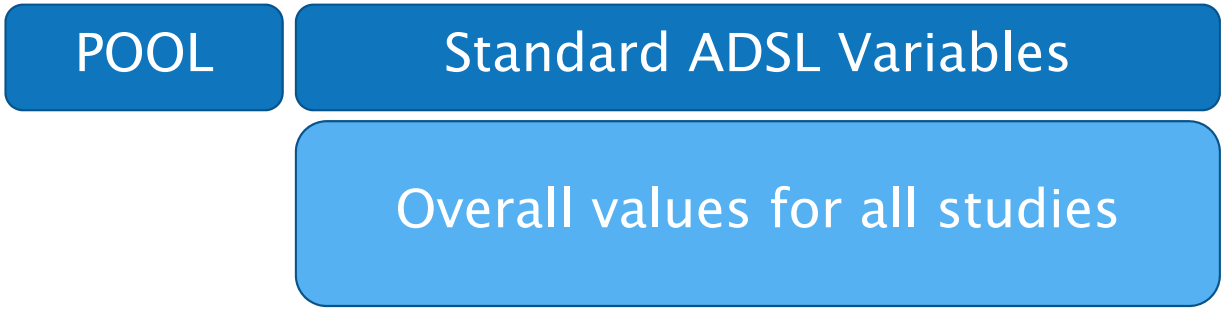
- ADSL using IADSL class:

Standard ADSL Variables

Overall values for all studies

IADSL Structure

- ADSL using IADSL class:



IADSL Structure

- ADSL using IADSL class:

POOL	Standard ADSL Variables
'Overall'	Overall values for all studies
'DB'	Values supporting DB Pool
'OL'	Values supporting OL Pool

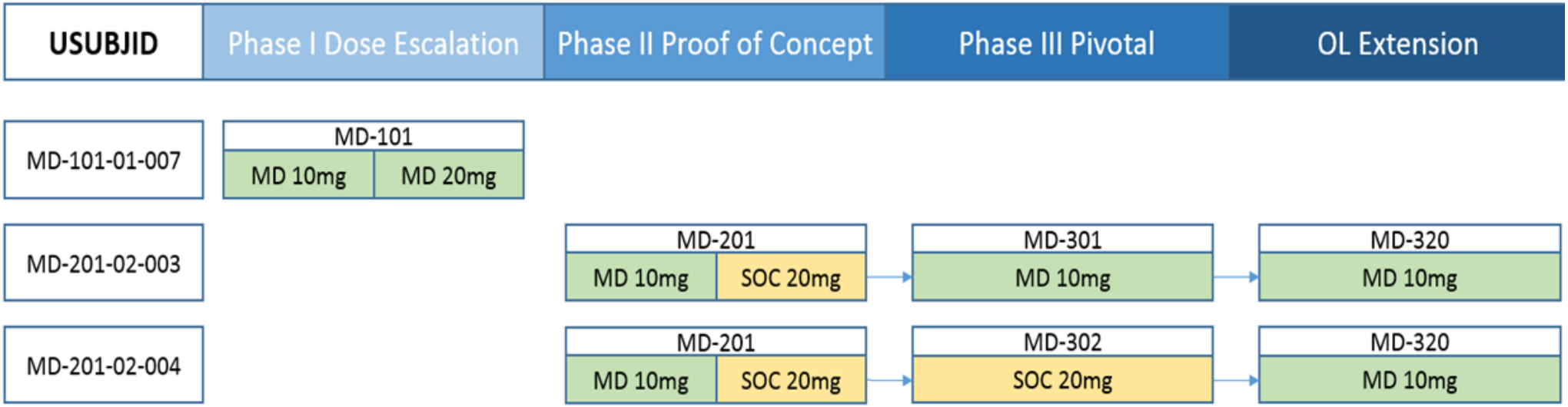
IADSL Structure

- Original one-record-per-subject ADSL preserved in the Overall pool
  - One record for each subject in the Integration
- For other pools, 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 6: 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	POOL	POOLN	STUDIES	TRT01P	TR01SDT	TR01EDT	AP01SDT
1	**MD-101-01-007**	**Overall**	**1**	**MD-101**	**MD 10mg**	**2000-02-01**	**2000-02-07**	**2000-02-01**
2	MD-201-02-003	Overall	1	MD-201, MD-301, MD-320	MD 10mg	2000-08-10	2000-09-02	2000-08-10
3	MD-201-02-003	Pivotal	2	MD-301	MD 10mg	2001-08-21	2002-04-11	2001-08-21
4	MD-201-02-003	Comparison	3	MD-201, MD-301	MD 10mg	2000-08-10	2000-09-02	2000-08-10
5	MD-201-02-004	Overall	1	MD-201, MD-302, MD-320	SOC 20mg	2000-08-29	2000-09-24	2000-08-29
6	MD-201-02-004	Pivotal	2	MD-302	SOC 20mg	2001-09-06	2002-04-27	2001-09-06
7	MD-201-02-004	Comparison	3	MD-201, MD-302	SOC 20mg	2000-08-29	2000-09-24	2000-08-29

ISS Example (IADSL)

- ADSL using IADSL class

ROW	USUBJID	POOL	POOLN	STUDIES	TRT01P	TR01SDT	TR01EDT	AP01SDT
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2	**MD-201-02-003**	**Overall**	**1**	**MD-201, MD-301, MD-320**	**MD 10mg**	**2000-08-10**	**2000-09-02**	**2000-08-10**
3	**MD-201-02-003**	**Pivotal**	**2**	**MD-301**	**MD 10mg**	**2001-08-21**	**2002-04-11**	**2001-08-21**
4	**MD-201-02-003**	**Comparison**	**3**	**MD-201, MD-301**	**MD 10mg**	**2000-08-10**	**2000-09-02**	**2000-08-10**
5	MD-201-02-004	Overall	1	MD-201, MD-302, MD-320	SOC 20mg	2000-08-29	2000-09-24	2000-08-29
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ISS Example (IADSL)

- ADSL using IADSL class

ROW	USUBJID	POOL	POOLN	STUDIES	TRT01P	TR01SDT	TR01EDT	AP01SDT
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6	**MD-201-02-004**	**Pivotal**	**2**	**MD-302**	**SOC 20mg**	**2001-09-06**	**2002-04-27**	**2001-09-06**
7	**MD-201-02-004**	**Comparison**	**3**	**MD-201, MD-302**	**SOC 20mg**	**2000-08-29**	**2000-09-24**	**2000-08-29**

Section 7: 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
'OL'	Values supporting DB Pool	Values for OL Pool

IBDS & IOCCDS Structure

- Create a set of record 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 8: 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**	**96**	**2001-08-21**	**1**	**Baseline**	**Y**	**MD 10mg**
MD-201-02-003	**Pivotal**	**MD-301**	**2**	**Glucose**	**87**	**2001-08-29**	**9**	**Week 1**		**MD 10mg**
MD-201-02-003	Comparison	MD-201	1	Glucose	98	2000-08-10	1	Baseline	Y	MD 10mg
MD-201-02-003	Comparison	MD-201	2	Glucose	78	2000-08-17	8	Days 2-30		MD 10mg
MD-201-02-003	Comparison	MD-301	1	Glucose	96	2001-08-21	377	Days 151-380		MD 10mg
MD-201-02-003	Comparison	MD-301	2	Glucose	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	96	2001-08-21	1	Baseline	Y	MD 10mg
MD-201-02-003	Pivotal	MD-301	2	Glucose	87	2001-08-29	9	Week 1		MD 10mg
MD-201-02-003	**Comparison**	**MD-201**	**1**	**Glucose**	**98**	**2000-08-10**	**1**	**Baseline**	**Y**	**MD 10mg**
MD-201-02-003	**Comparison**	**MD-201**	**2**	**Glucose**	**78**	**2000-08-17**	**8**	**Days 2-30**		**MD 10mg**
MD-201-02-003	**Comparison**	**MD-301**	**1**	**Glucose**	**96**	**2001-08-21**	**377**	**Days 151-380**		**MD 10mg**
MD-201-02-003	**Comparison**	**MD-301**	**2**	**Glucose**	**87**	**2001-08-29**	**385**	**Days 381-500**		**MD 10mg**

Section 9: Last Thoughts and Conclusion

Last Thoughts

- Is the IADSL class required?
  - No
- Is there additional ADSL class support for Integration?
  - No

Last Thoughts

- USUBJID is the single unique identifier for a subject across the entire application
  - 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

Last Thoughts

- ADaM Structures for Integration document provides more
  - New variables
  - Challenges and suggestions
    - What to do if same subject re-enrolls into the same study
  - Detailed examples
    - VLM metadata

Conclusion

- Interested in ADaM Integration?
  - Register with CDISC
  - Review the ADaM Data Structures for Integration public draft when it releases later this year

- Send us feedback

Questions, Comments?

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