Top Five Challenges in Complying with CDISC Standards

By Mikkel Traun & Trine Danø Klingberg
Novo Nordisk A/S
Top 5 Challenges and Requirements

1. Collection of Race & Ethnicity Data
2. Pharmacokinetic Parameters (PP) Domain
3. Standardized Units
4. Event Adjudication Results
5. Associated Person (AP) Domain
Collection of Race & Ethnicity Data
Background

• Between 2008-2013, 20% of new drugs demonstrated some differences in exposure and/or response across racial/ethnic groups

• Critical for identifying population-specific signals

• More consistent demographic subgroup data collection
  • Inside and outside USA

Collection of Race and Ethnicity Data in Clinical Trials

Guidance for Industry and Food and Drug Administration Staff

Document issued on October 26, 2016

For questions about this document, contact the FDA Office of Minority Health at 240-402-5084 or omh@fda.hhs.gov.
Challenges

- The development of the standard is done backwards
  - FDA guidance -> 2 new code lists included in SDTM CT -> SDTMIG pending (Race & Ethnicity details have not changed in the draft version)

- FDA Guidance for Collection of Race & Ethnicity and SDTM code lists
  ‘Race as collected’ and ‘Ethnicity as collected’ are not aligned
  - Which concept to follow?
  - What about other authorities?
Missing Alignment Between FDA Guidance and CDISC CT

FDA guidance on collection of detailed Ethnicity

Ethnicity Data Standard
Are you Hispanic, Latino/a, or of Spanish origin? (One or more categories may be selected)

- a. No, not of Hispanic, Latino/a, or Spanish origin
- b. Yes, Mexican, Mexican American, Chicano/a
- c. Yes, Puerto Rican
- d. Yes, Cuban
- e. Yes, Another Hispanic, Latino/a or Spanish origin

Synonyms?

These categories roll up to the Hispanic or Latino category of the OMB standard

How do we map to CDISC CT?

<table>
<thead>
<tr>
<th>Code list Name</th>
<th>CDISC Submission Value</th>
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<tbody>
<tr>
<td>Ethnicity As Collected</td>
<td>ETHNICC</td>
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<tr>
<td>Ethnicity As Collected</td>
<td>ASHIKENAZI JEW</td>
</tr>
<tr>
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</tr>
<tr>
<td>Ethnicity As Collected</td>
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<td>CUBAN AMERICAN</td>
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<tr>
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<td>LATIN AMERICAN</td>
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</tr>
<tr>
<td>Ethnicity As Collected</td>
<td>NOT HISPANIC OR LATINO</td>
</tr>
<tr>
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<td>PUERTO RICAN</td>
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<tr>
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<td>SEPHARDIC JEW</td>
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<td>SOUTH AMERICAN</td>
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<td>Ethnicity As Collected</td>
<td>SPANISH</td>
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Pharmacokinetic Parameters (PP) Domain
SDTM.PP Challenges

Pharmacokinetic Parameters as a derived dataset instead of source data

The SDTM standard

SDTM is created by Data Management

Internal Processes

SDTM.PP created based on ADaM.ADPP

Dataflow

Redundant data ADaM.ADPP and SDTM.PP

Datasets

CDISC Standards in the Clinical Research Process

Plan  Collect  Organize  Analyze

Different requirements

Regulatory Authorities

From cdisc.org/standards
PP Challenges – The Organisation and Process

Data Management – SDTM

SDTM.PC

SDTM.PP

Biostatistics – ADaM

ADPC

ADPP
Standardized Units in SDTM
What is the ‘Standardized’ Unit in SDTM?

- The international conventional units used in the Clinical Trial Report?
- The SI units?
- The US conventional units?
### ‘Standardized’ Units in SDTM

<table>
<thead>
<tr>
<th>TEST</th>
<th>ORRESU</th>
<th>STRESU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td>inch</td>
<td>cm</td>
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<tr>
<td>Systolic</td>
<td>mmHg</td>
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<td>Xx/zz</td>
<td>mg/dL</td>
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<tr>
<td>Lab2</td>
<td>Zz/xx</td>
<td>mmol/L</td>
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SDTM

<table>
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<th>AVAL</th>
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<tr>
<td>Height (cm)</td>
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<tr>
<td>Systolic (mmHg)</td>
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</tr>
<tr>
<td>Lab1 (mg/dL)</td>
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<tr>
<td>Lab2 (mmol/L)</td>
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ADaM

We would like to present results in international conventional units.

**Report**

Table XYZ – Summary of xyz

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<th></th>
<th>X</th>
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<tr>
<td>Systolic (mmHg)</td>
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<td>xx</td>
<td>xx</td>
</tr>
<tr>
<td>Lab1 (mg/dL)</td>
<td>xx.x xx.x xx.x</td>
<td></td>
<td></td>
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<tr>
<td>Lab2 (mmol/L)</td>
<td>xx.x xx.x xx.x</td>
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</table>

We would like to present results in international conventional units.
**'Standardized' Units in SDTM**

**STRESU Unit should match UNIT in PARAM**

**Unit in PARAM and AVAL must match output**

**SDTM**

<table>
<thead>
<tr>
<th>TEST</th>
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<tr>
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<td>xx</td>
</tr>
<tr>
<td>Lab1 (mg/dL)</td>
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</tr>
<tr>
<td>Lab2 (mmol/L)</td>
<td>xx.x</td>
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</table>

**Report**

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**PMDA request SI Units**

**FDA request US conventional Units**
Our Solution for ‘Standardized’ Units in SDTM

SDTM LB

<table>
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<tr>
<th>TEST</th>
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<tbody>
<tr>
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<td>mg/dL</td>
</tr>
<tr>
<td>Lab2</td>
<td>Zz/xx</td>
<td>mmol/L</td>
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PMDA request SI Units

SDTM ‘ZL’

<table>
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<tr>
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<tr>
<td>Lab2</td>
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FDA request US conventional Units

SDTM ‘XL’

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<td>mg/dL</td>
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<tr>
<td>Lab2</td>
<td>Zz/xx</td>
<td>mg/dL</td>
</tr>
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Our Solution for ‘Standardized’ Units in SDTM

- Duplicate data in additional sponsor defined domains
  - LB holds data in reported standardized units
  - XL/ZL in regulatory required standardized units

- This support simple traceability from SDTM, ADaM to CTR
  - But give redundant data in domains
  - Preferable compared to having SI unit in –STRESU and values in –STRESN and then have the conventional units and values in supplemental qualifiers

- Currently accepted by FDA and PMDA
  - But must be confirmed for each submission (not a general acceptance)
Event Adjudication Results
Event Adjudication - Requirements

- Event Adjudication – what is it?
- FDA Technical Conformance Guide
  - Clearly identify investigator reported data from adjudication data
- Different types of event data
  - Different diseases with different details
- No existing standards or best practices
  - SDTMIG does not offer explicit guidance
Considerations

- Novo Nordisk has implemented a sponsor defined stand-alone domain based on the SDTM Findings About domain.

- Flexible structure that can accommodate various types of adjudication data.

- Only the final agreed assessments from the two independent adjudicators are submitted in our SDTM data set.
Example of Sample Reported Data

One record per adjudication outcome per result, per date and subject as required by FDA

<table>
<thead>
<tr>
<th>--LNKID</th>
<th>--REFID</th>
<th>--TESTCD</th>
<th>--TEST</th>
<th>--OBJ</th>
<th>--ORRES</th>
<th>--EVAL</th>
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<tbody>
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<td>SOURADEV</td>
<td>Source of adjudicated event</td>
<td>ACS</td>
<td>INVESTIGATOR REPORTED</td>
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<td>Adjudication outcome</td>
<td>ACS</td>
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<tr>
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<td>MICLASS</td>
<td>Classification of Myocardial Infarct</td>
<td>ACS</td>
<td>ST ELEVATION MYOCARDIAL INFARCTION</td>
<td>ADJUDICATION COMMITTEE</td>
<td>PRIMARY ADJUDICATION</td>
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<tr>
<td>14</td>
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<td>ACS</td>
<td>TYPE 1 MYOCARDIAL INFARCTION</td>
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<tr>
<td>14</td>
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<td>CONFEVT</td>
<td>Confirmation of event</td>
<td>ACS</td>
<td>FULL DOCUMENTATION AVAILABLE</td>
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<td>PRIMARY ADJUDICATION</td>
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Associated Person (AP) Domain
AP Domain Challenges

CDISC AP IG
Lack of use case in IG related to pregnancy

Data
Differentiate between mothers, foetus and infant data in source

Annotation
One CRF to 7 SDTM domain mapping and relationship among them

System
APID and SUPPQUAL implementation

Pregnancy Trial
These are initial learning from latest experiences from implementation
Example on Complexity

APDD = Associated Persons Death Details
APQS = Associated Persons Questionnaires
APRP = Associated Persons Reproductive System Findings
APCE = Associated Persons Clinical Events
APFACE = Associated Persons Findings About Clinical Events
APDM = Associated Persons Demographics
APVS = Associated Persons Vital Signs

CEREFID
FAREFID
VSREFID
QSREFID
RPREFID
APID
APID
APID
APID
APID
APID
APID

N OT SUBMITTED
BRTHDTC
RPDTC

RPORRES when RPTESTCD=GWUSCAN
RPORRES when RPTESTCD=LIVEBRT
DDORRES when DDTESTCD=TMINFDH

RELREC: APDD, AE
RELREC: APCE, APAE

VPORSRES when VSTESTCD=UMBCOPH

RELREC: APDD, APAE
RELREC: APCE, APAE

PERINDTH in SGAPDD

DTHDTC
DDDTC

FAORRES when FATESTCD=CONGANOM
Summary and Recommendations
Summary

- CDISC standards are open for interpretation
- Regulatory guidance’s are not always aligned with CDISC standards

Recommendations

- Using CDISC data standards should not be an implementation issue for pharmaceutical companies requiring individual case-by-case agreements at pre-NDA or e-data consultancy meetings
- CDISC standards should be specific and less open for interpretation
- Regulatory agencies should increase engagement in data standards development to ensure standards fulfil review needs
  - Limit data standard requirements in technical conformance guides
Thank you for your attention 😊
Presenters

**Mikkel Traun**  
Principal System Developer  
CDW & Systems Support  
Novo Nordisk A/S  
mt@novonordisk.com

**Trine Danø Klingberg**  
Principal Standards Specialist  
Clinical Data Standards  
Novo Nordisk A/S  
trdk@novonordisk.com