Interpreting ADaM Standards with OpenCDISC

Madhura Paranjape, Cytel
Trupti Bal, Cytel

Session CD04 - PhUSE 2012
Disclaimer

This presentation is based on first-hand experience of the presenters, their opinions and learnings.

However this is not to be construed as an official statement endorsed by Cytel
Agenda

- Introduction
- ADaM datasets workflow
- About OpenCDISC Validator
- Examples
  - Handling TRTP
  - ADaM for ISS
  - AVAL vs. AVALC
  - Additional cases
- Conclusion
- Discussion/Questions
Introduction

Analysis Dataset Model (ADaM)

- CDISC defined and FDA accepted standard
- Introduced in recent past
- Evolving
Ensuring compliance may seem like a tightrope walk due to

a) Evolving standard – as yet unfamiliar

b) Stringent timelines
Introduction

• Validation of datasets plays an important role

✓ Ensure study specific needs are addressed
✓ Datasets are ADaM compliant
OpenCDISC Validator is freely available and easy to use.
The tool for ensuring clinical data compliance with CDISC standards

ADaM compliance check:
• 130 rules based on ADaM Validation Checks

• Gives a detailed report with issues categorized by
  a) Severity: Error, Warning and Notice
  b) Type: Consistency, Format, Limit, Metadata, Presence, System and Terminology

• Extra pair of eyes for ensuring compliance with ADaM
ADaM datasets workflow for examples

SDTM datasets

ADaM Program development

ADaM specs

ADaM datasets

ADaM independent validation

Final ADaM datasets

OpenCDISC Validator
Handling TRTP

AVAL vs. AVALC

Interpreting OpenCDISC messages and Understanding ADaM

ADaM for ISS

Additional Cases
Steps to go through

1. Background
2. Problem
3. Reason
4. Lessons/Solutions
Case 1
Handling TRTP
Handling TRTP

- Study Design: Randomized, parallel
- Phase: III
- Dataset: ADEG
- OpenCDISC version: 1.2.1

TRTP:
- Record level Identifier
- Represents planned Treatment for a record
## Handling TRTP

### ECG Assessment

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>Visit 1</th>
<th>Visit 5</th>
<th>Visit 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRT A</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>TRT B</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

### SDTM EG Dataset

<table>
<thead>
<tr>
<th>USUBJID</th>
<th>EGTESTCD</th>
<th>EGSTRESN</th>
<th>EGSTRESU</th>
<th>VISIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC1201</td>
<td>HR</td>
<td>70</td>
<td>BEATS/MIN</td>
<td>Screening</td>
</tr>
<tr>
<td>ABC1201</td>
<td>HR</td>
<td>70</td>
<td>BEATS/MIN</td>
<td>Visit 1</td>
</tr>
<tr>
<td>ABC1201</td>
<td>HR</td>
<td>72</td>
<td>BEATS/MIN</td>
<td>Visit 5</td>
</tr>
<tr>
<td>ABC1201</td>
<td>HR</td>
<td>71</td>
<td>BEATS/MIN</td>
<td>Visit 9</td>
</tr>
</tbody>
</table>
Handling TRTP

**SDTM EG Dataset**

<table>
<thead>
<tr>
<th>USUBJID</th>
<th>EGTESTCD</th>
<th>EGSTRESN</th>
<th>EGSTRESU</th>
<th>VISIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC1201</td>
<td>HR</td>
<td>70</td>
<td>BEATS/MIN</td>
<td>Screening</td>
</tr>
<tr>
<td>ABC1201</td>
<td>HR</td>
<td>70</td>
<td>BEATS/MIN</td>
<td>Visit 1</td>
</tr>
<tr>
<td>ABC1201</td>
<td>HR</td>
<td>72</td>
<td>BEATS/MIN</td>
<td>Visit 5</td>
</tr>
<tr>
<td>ABC1201</td>
<td>HR</td>
<td>71</td>
<td>BEATS/MIN</td>
<td>Visit 9</td>
</tr>
</tbody>
</table>

**ADEG Dataset**

<table>
<thead>
<tr>
<th>USUBJID (Unique Subject Identifier)</th>
<th>TRTP (Planned Treatment)</th>
<th>PARAMCD (Parameter Code)</th>
<th>AVAL (Analysis Value)</th>
<th>AVISIT (Analysis Visit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC1201</td>
<td>TRT A</td>
<td>HR</td>
<td>70</td>
<td>Screening</td>
</tr>
<tr>
<td>ABC1201</td>
<td>TRT A</td>
<td>HR</td>
<td>70</td>
<td>Visit 1</td>
</tr>
<tr>
<td>ABC1201</td>
<td>TRT A</td>
<td>HR</td>
<td>72</td>
<td>Visit 5</td>
</tr>
<tr>
<td>ABC1201</td>
<td>TRT A</td>
<td>HR</td>
<td>71</td>
<td>Visit 9</td>
</tr>
</tbody>
</table>
Handling TRTP

AD1008: Null Value in variable marked as Required
Handling TRTP

ADEG Dataset

<table>
<thead>
<tr>
<th>USUBJID</th>
<th>TRTP</th>
<th>PARAMCD</th>
<th>AVAL</th>
<th>VISIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC1201</td>
<td>HR</td>
<td>70</td>
<td></td>
<td>Screening</td>
</tr>
<tr>
<td>ABC1201</td>
<td>TRTA</td>
<td>HR</td>
<td>70</td>
<td>Visit 1</td>
</tr>
<tr>
<td>ABC1201</td>
<td>TRTA</td>
<td>HR</td>
<td>72</td>
<td>Visit 5</td>
</tr>
<tr>
<td>ABC1201</td>
<td>TRTA</td>
<td>HR</td>
<td>71</td>
<td>Visit 9</td>
</tr>
</tbody>
</table>

Details of Error:

<table>
<thead>
<tr>
<th>Record</th>
<th>Variables</th>
<th>Values</th>
<th>Rule ID</th>
<th>Message</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>210</td>
<td>TRTP</td>
<td>null</td>
<td>AD1008</td>
<td>Null value in variable marked as Required</td>
<td>Presence</td>
</tr>
</tbody>
</table>
Handling TRTP

- The visit is screening
- No planned treatment at screening
- No valid value for TRTP
- Need to keep it blank
Handling TRTP

Solution

Override error because OpenCDISC Validator used SDTM definition
Handling TRTP

- Required variables can be null
  - SDTM (x) ADaM (✓)

- Required variables in ADaM

<table>
<thead>
<tr>
<th>Can be Null</th>
<th>Can not be Null</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRTP</td>
<td>STUDYID</td>
</tr>
<tr>
<td>USUBJID</td>
<td></td>
</tr>
<tr>
<td>ARM</td>
<td></td>
</tr>
<tr>
<td>PARAM</td>
<td></td>
</tr>
</tbody>
</table>

- Current version of OpenCDISC Validator allows null values in TRTP
Case 2

ADaM for ISS
ADaM for ISS

- Study Design:
  Integrated Safety Summary (ISS) of 3 studies
- Dataset: ADLB
- OpenCDISC version: 1.3
ADaM for ISS

Study Schedule for 3 Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Visits</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
<th>V5</th>
<th>V6</th>
</tr>
</thead>
<tbody>
<tr>
<td>111</td>
<td>SCREENING</td>
<td>Day 1</td>
<td>Week 2</td>
<td>Week 4</td>
<td>Month 2</td>
<td>Month 4</td>
<td>Month 6</td>
</tr>
<tr>
<td>112</td>
<td>DAY 10</td>
<td>Day 1</td>
<td>Month 1</td>
<td>Month 6</td>
<td>Month 12</td>
<td>Follow up</td>
<td></td>
</tr>
<tr>
<td>113</td>
<td>MONTH 1</td>
<td>Day 1</td>
<td>Month 1</td>
<td>Month 2</td>
<td>Month 3</td>
<td>Month 4</td>
<td>Month 5</td>
</tr>
</tbody>
</table>

PhUSE 2012 - CD04
ADaM for ISS

SDTM to ADaM mapping

<table>
<thead>
<tr>
<th>SDTM</th>
<th>ADaM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 111, VISIT Week 2</td>
<td>AVISITN 2</td>
</tr>
<tr>
<td>Study 112, VISIT Day 10</td>
<td>AVISITN 2</td>
</tr>
<tr>
<td>Study 113, VISIT Month 1</td>
<td>AVISITN 2</td>
</tr>
</tbody>
</table>

ADLB snapshot

<table>
<thead>
<tr>
<th>STUDYID</th>
<th>PARAMCD</th>
<th>AVISIT</th>
<th>AVISITN</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC111</td>
<td>ALT</td>
<td>VISIT 1 (DAY 1)</td>
<td>1</td>
</tr>
<tr>
<td>ABC111</td>
<td>ALT</td>
<td>VISIT 2 (WEEK 2)</td>
<td>2</td>
</tr>
<tr>
<td>ABC112</td>
<td>ALT</td>
<td>VISIT 1 (DAY 1)</td>
<td>1</td>
</tr>
<tr>
<td>ABC112</td>
<td>ALT</td>
<td>VISIT 2 (DAY 10)</td>
<td>2</td>
</tr>
<tr>
<td>ABC113</td>
<td>ALT</td>
<td>VISIT 1 (DAY 1)</td>
<td>1</td>
</tr>
<tr>
<td>ABC113</td>
<td>ALT</td>
<td>VISIT 1 (MONTH 1)</td>
<td>2</td>
</tr>
</tbody>
</table>
ADaM for ISS

Background

Problem

Reason

Lessons/Solutions

AD0110: Inconsistent value for AVISIT
Different Visit names for same AVISITN
ADaM consistency principle:

AVISIT and AVISITN should have consistent values for a given PARAMCD
ADaM for ISS

- Different visit schedule for 3 studies
- Analysis was study specific
- Analysis visits were not defined in ISS SAP
Need to have Consistency within visits

Solution 1:
- Study Specific Analysis
  - Drop AVISIT and AVISITN
  - Add SDTM Visits

Solution 2:
- Integrated Analysis
  - Remap to AVISIT and AVISITN
ADaM for ISS

- ADaM IG does not strictly cover ISS/ISE
- How much ADaM compliant datasets should be in such cases?
Case 3

AVAL vs. AVALC
AVAL vs. AVALC

- Design: Placebo Controlled Study
- Phase: III
- Dataset: ADLB
- OpenCDISC version: v1.2.1

- AVAL: Analysis Value (Numeric)
- AVALC: Analysis Value (Character)
- AVAL and AVALC one to one relation
SDTM LB Dataset

<table>
<thead>
<tr>
<th>USUBJID</th>
<th>LBTESTCD</th>
<th>VISIT</th>
<th>LBSTRESC</th>
<th>LBSTRESN</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC01023</td>
<td>GGT</td>
<td>SCREENING</td>
<td>&gt;4</td>
<td>.</td>
</tr>
<tr>
<td>ABC01023</td>
<td>GGT</td>
<td>VISIT 1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>ABC01023</td>
<td>GGT</td>
<td>VISIT 3</td>
<td>&gt;1</td>
<td>.</td>
</tr>
</tbody>
</table>

Snapshot of Statistical analysis Plan

For laboratory assessments if majority of results are indefinite, imputation of these values will be considered. Thus if the result has indefinite value, the upper limit, lower limit or median values need to be used in the summary. (for example, 0.1 can be used if the result is <0.1, >0.1, +0.1, or 0.1+)
AVAL vs. AVALC

SDTM LB Dataset

<table>
<thead>
<tr>
<th>LBSTRESC</th>
<th>AVAL</th>
<th>AVALC</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;4</td>
<td>4</td>
<td>&gt;4</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>&gt;1</td>
<td>1</td>
<td>&gt;1</td>
</tr>
</tbody>
</table>

ADLB Dataset

<table>
<thead>
<tr>
<th>USUBJID</th>
<th>PARAMCD</th>
<th>VISIT</th>
<th>AVALC</th>
<th>AVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC01023</td>
<td>GGT</td>
<td>SCREENING</td>
<td>&gt;4</td>
<td>4</td>
</tr>
<tr>
<td>ABC01023</td>
<td>GGT</td>
<td>VISIT 1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>ABC01023</td>
<td>GGT</td>
<td>VISIT 3</td>
<td>&gt;1</td>
<td>1</td>
</tr>
</tbody>
</table>
**AD0149: Inconsistent value for AVALC**
ADLB Dataset

<table>
<thead>
<tr>
<th>USUBJID</th>
<th>PARAMCD</th>
<th>VISIT</th>
<th>AVALC</th>
<th>AVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC01023</td>
<td>GGT</td>
<td>SCREENING</td>
<td>&gt;4</td>
<td>4</td>
</tr>
<tr>
<td>ABC01023</td>
<td>GGT</td>
<td>VISIT 1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>ABC01023</td>
<td>GGT</td>
<td>VISIT 3</td>
<td>&gt;1</td>
<td>1</td>
</tr>
</tbody>
</table>

Details of Error:

<table>
<thead>
<tr>
<th>Record</th>
<th>Variables</th>
<th>Values</th>
<th>Rule ID</th>
<th>Message</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVALC,</td>
<td>3019 PARAMCD,</td>
<td>&gt;4, GGT, 4</td>
<td>AD0149</td>
<td>Inconsistent value for AVALC</td>
<td>Consistency</td>
</tr>
<tr>
<td></td>
<td>AVAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**AVAL vs. AVALC**

- AVAL values derived as per SAP
- Integer portion of indefinite value is used
- Hence AVALC = AVAL not possible
Solution:

- Dropped AVALC
- Added LBSTRESC and LBSEQ

Lessons:

- Add LBSTRESC and LBSEQ for consistency
- Create different dataset with character and numeric results
Recap

Handling TRTP

Core Attributes of SDTM & ADaM are not ‘interchangeable’

Null values allowed in ADaM “Required” variables

ADaM for ISS

AVISIT AND AVISITN have to be consistent with each other

Need to determine how compliant ISS/ISE needs to be with ADaM

AVAL vs. AVALC

AVAL and AVALC need to have one to one relation

Addition of SDTM variables for consistency and traceability
Additional Cases: 1

**Background**

Study design: Open label
Dataset: ADAQ

**Problem**

Warning: Configuration Unavailable

**Reason**

Structure recently released
Structure: SDTM + Added variables

**Lessons/Solutions**

Non-BDS, Non-ADSL structure cannot be reviewed
Additional Cases: 2

**Study design:** Open label
**Dataset:** ADMH

**AD1005:** Neither AVAL or AVALC present in dataset

**Addition of Central Variable ASTDT to Non-BDS dataset**

**Need to determine structure of dataset beforehand**
**Addition of central variables leads to BDS**
Additional Cases: 3

Study design: Any
Dataset: Any BDS where time is imputed

AD0040: Variable ending in *TMF not in TIMEF codelist (described as D= Day, M= Month, Y= Year)

ASTMF flagged as ‘Y’. Value should be either H= Hours, M= Minutes, S= Seconds)

Correct Check, Incorrect Description!!!
Recap

- Non-BDS cannot be reviewed by OpenCDISC Validator yet
- Addition of Central Variables should be considered for BDS type datasets only
- Need to consult ADaM/Study specific guidelines before acting on a OpenCDISC Message
Conclusion

- ADaM is more flexible than SDTM to address analysis needs.
- Boon: Datasets can be suited to analysis.
- Bane: Interpretation may change as per context/analysis.
- OpenCDISC Validator is a valuable tool offering quick review.
- OpenCDISC is evolving with ADaM.
- Independent validation cannot be substituted.

"Walk the tightrope with OpenCDISC"
Questions?

Thank you!

madhura.paranjape@cytel.com
trupti.bal@cytel.com