Business & Decision Life Sciences

Understanding the potential of Share: a visual business case and technical use case

Peter Van Reusel, CDISC E3C Chair
Agenda

- Introduction
- Specify by Browsing
- Metadata-driven Process
- Call to Action
Agenda

- Introduction
- Specify by Browsing
- Metadata-driven Process
- Call to Action
The Responsibilities of Clinicians & Statisticians

Clinicians
- Provides input to the operational and financial feasibility of clinical research studies
- Participates in defining key components of clinical protocols
- Data review, analysis, and interpretation
- Analyze emerging safety profile of the drug
- Ensure appropriateness of the chosen subject population
- Assesses performance of techniques used for endpoint measures
- Establishing an objective framework for conducting an investigation
- Placing data and theory on an equal scientific footing
- Designing data production through experimentation
- Quantifying the influence of chance
- Estimating systematic and random effects
- Combining theory and data using formal methods

Statisticians

Data Standards Experts

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# Overview of CDISC Models (OCT 2016)

## Content Standards
- **PROTOCOL**: Protocol v1.0 (Jan 2010), PRM Toolset v1.0 (Apr 2012), Protocol Concepts Guide (Aug 2014)
- **ODM**: ODM v1.1 (Apr 2002), ODM v1.2 (Jan 2004), ODM v1.2.1 (Jan 2005), ODM v1.3 (Dec 2006), ODM v1.3.1 (Feb 2012), ODM v1.3.2 (Mar 2013)
- **THERAPEUTIC AREAS**: Alzheimer v1.0 (Sep 2011), Pain (Jun 2012), Tuberculosis (Jun 2012), Parkinson’s Disease (Oct 2012), Virology v1.0 (Nov 2012), Devices (Dec 2012), PKD (Feb 2013), Alzheimer v2.0, Asthma v1.0, Multiple Sclerosis (May 2014), Diabetes (Aug 2014), Cardiovascular v1.0 (Oct 2014), Influenza v1.0 (Nov 2014), QT Studies v1.0 (Dec 2014), Hepatitis C v1.0 (May 2015), Dislipidemia v1.0 (Jun 2015), Schizophrenia v1.0 (Jun 2015), Virology v2.0 (Sep 2015), Traumatic Brain Injury v1.0 (Dec 2015), ADaM Supplement to Diabetes (Dec 2015), COPD v1.0 (Jan 2016), Tuberculosis v2.0 (Feb 2016), Breast Cancer v1.0 (May 2016), Rheumatoid Arthritis (May 2016), CV Imaging v1.0 (May 2016), Solid Organ (Kidney) Transplant (Jun 2016), Major Depressive Disorder (Jul 2016), Diabetic Kidney Disease v1.0 (Jul 2016), Prostate Cancer v1.0 (Q4 2016), Ebola v1.0 (Q4 2016), Malaria v1.0 (Q4 2016), Vaccines (Q1 2017), Nutritional Standards (Q4 2016)
- **SEND**: Send IG v3.0 (May 2011), SDTM v1.5 + Send IG v3.1 (Q1 2016), Send Dart v1.0 (Q1 2016)
- **SHARE**: CDISC Share, Share API Pilot (Q2 2016)

## Technical Standards
- **CDASH**: CDASH v1.0 (Oct 2008), CDASH v1.1 (Jan 2011), CDASH E2B SAE IG (Nov 2013), CDASH v2.0 (Dec 2016)
- **ADaM**: ADaM v2.0 (Aug 2006), ADaM v2.21 + ADaM IG (Dec 2009), ADaM Validation Checks v1.0 (Sep 2010), ADaM Validation Checks v1.1 (Jul 2011), ADaM Validation Checks v1.2 (Jul 2012), Analysis Results Metadata v1.0 (Jan 2015), ADaM ODDS v1.0 (Jul 2015), ADaM Validation Checks v1.3 (Mar 2015), ADaM IG v1.1 (Feb 2016), ADaM IG v1.2 (Q1 2016), ADaM IG v2.0 (Q4 2016)
- **SDTM**: SDTM v1.0 + SDTM IG v3.1 (Jul 2004), SDTM v1.1 + SDTM IG v3.1.1 (Dec 2014), SDTM v1.2 + SDTM IG v3.1.2 (Nov 2008), SDTM IG v3.1.2 + Amendment 1 (Dec 2011), SDTM Medical Devices v1.0 (Dec 2012), SDTM Associated Persons IG v1.0 (Dec 2013), SDTM v1.4 + SDTM IG v3.2 (Dec 2013), SDTM QRS Supplements (Periodic), SDTM Pharmacogenomics IG v1.0 (May 2015), SDTM v1.6 + SDTM IG v3.3 (May 2014 – Sep 2016), SDTM Device IG v2.0 (Dec 2016), SDTM IG v3.4 Batch 1 (Q1 2017)
- **SEND IG**: Send IG v3.0 (May 2011), SDTM v1.5 + Send IG v3.1 (Q1 2016)
- **SHARE API PILOT**: SHARE API Pilot (Q2 2016)

## Semantics
- **BRIDG**: BRIDG v1.0 (June 2007), BRIDG v1.1 (Oct 2007), BRIDG v1.1.1 (Feb 2008), BRIDG v2.0 (June 2008), BRIDG v2.1 (Oct 2008), BRIDG v2.2 (May 2009), BRIDG v3.0 (Oct 2009), BRIDG v3.0.1 (Feb 2010), BRIDG v3.0.2 (Aug 2010), BRIDG v3.0.3 (Dec 2010), BRIDG v3.1 (Feb 2012), BRIDG v3.2 (Sep 2012), BRIDG v4.0 (Nov 2014), BRIDG v2.0 (Mar 2015)
- **ADaM SUPPLEMENT TO DIABETES**: ADaM Supplement to Diabetes (Dec 2015)
- **SHARED CARE**: Shared Care (Oct 2016)
- **CDISC SHARE**: CDISC Share, Share API Pilot (Q2 2016)

##Upcoming
- **PROTOCOL**: PROTOCOL v1.0 (Jan 2010), PRM Toolset v1.0 (Apr 2012), Protocol Concepts Guide (Aug 2014)
- **ODM**: ODM v1.1 (Apr 2002), ODM v1.2 (Jan 2004), ODM v1.2.1 (Jan 2005), ODM v1.3 (Dec 2006), ODM v1.3.1 (Feb 2012), ODM v1.3.2 (Mar 2013)
- **THERAPEUTIC AREAS**: Alzheimer v1.0 (Sep 2011), Pain (Jun 2012), Tuberculosis (Jun 2012), Parkinson’s Disease (Oct 2012), Virology v1.0 (Nov 2012), Devices (Dec 2012), PKD (Feb 2013), Alzheimer v2.0, Asthma v1.0, Multiple Sclerosis (May 2014), Diabetes (Aug 2014), Cardiovascular v1.0 (Oct 2014), Influenza v1.0 (Nov 2014), QT Studies v1.0 (Dec 2014), Hepatitis C v1.0 (May 2015), Dislipidemia v1.0 (Jun 2015), Schizophrenia v1.0 (Jun 2015), Virology v2.0 (Sep 2015), Traumatic Brain Injury v1.0 (Dec 2015), ADaM Supplement to Diabetes (Dec 2015), COPD v1.0 (Jan 2016), Tuberculosis v2.0 (Feb 2016), Breast Cancer v1.0 (May 2016), Rheumatoid Arthritis (May 2016), CV Imaging v1.0 (May 2016), Solid Organ (Kidney) Transplant (Jun 2016), Major Depressive Disorder (Jul 2016), Diabetic Kidney Disease v1.0 (Jul 2016), Prostate Cancer v1.0 (Q4 2016), Ebola v1.0 (Q4 2016), Malaria v1.0 (Q4 2016), Vaccines (Q1 2017), Nutritional Standards (Q4 2016)

## Healthcare Link
- **CDISC SHARE**: CDISC Share, Share API Pilot (Q2 2016)
Agenda

Introduction

Specify by Browsing

Metadata-driven Process

Call to Action
Visualizing Metadata Today

### Table 1 Demographic Data - Per-Protocol

<table>
<thead>
<tr>
<th></th>
<th>Treatment 1</th>
<th>Treatment 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline body mass index (BMI) [kg/m²]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>167</td>
<td>167</td>
</tr>
<tr>
<td>Mean</td>
<td>20.04</td>
<td>20.04</td>
</tr>
<tr>
<td>95% CI</td>
<td>19.76-20.32</td>
<td>19.80-20.80</td>
</tr>
<tr>
<td>Median</td>
<td>19.70</td>
<td>19.70</td>
</tr>
<tr>
<td>25% quartile</td>
<td>18.50</td>
<td>18.50</td>
</tr>
</tbody>
</table>

**Baseline BMI (categorical) [N (%)]**

<table>
<thead>
<tr>
<th>Range</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.50 kg/m²</td>
<td>41 (24.4%)</td>
<td>71 (43.1%)</td>
</tr>
<tr>
<td>18.50-29.99 kg/m²</td>
<td>60 (35.5%)</td>
<td>130 (79.7%)</td>
</tr>
<tr>
<td>≥30.00 kg/m²</td>
<td>66 (39.5%)</td>
<td>33 (20.6%)</td>
</tr>
</tbody>
</table>

---

**Patient Demographics - Part I**

**Sex**

- Male
- Female

**Age**

**BMI**

- Calculated when screen is closed

**Height**

**Weight**

**Weight circumference**

**VO2max**

**VO2res**

**VO2pres**

**VO2max/VO2res**

**Weight**

---

**Measurement Results (CV)**

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>Type</th>
<th>Code</th>
<th>Description</th>
<th>Units</th>
<th>Options</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Pressure</td>
<td>Nom</td>
<td>BPA</td>
<td>Blood Pressure</td>
<td>mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Glucose</td>
<td>Nom</td>
<td>BG</td>
<td>Blood Glucose</td>
<td>mg/dL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Subject Localisation Data Block (SLDB)**

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>Type</th>
<th>Code</th>
<th>Description</th>
<th>Units</th>
<th>Note</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Identifier</td>
<td>text</td>
<td>STU</td>
<td>Study Identifier</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject Identifier</td>
<td>text</td>
<td>SDR</td>
<td>Subject Identifier</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject Sex</td>
<td>Nom</td>
<td>SEX</td>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject Age</td>
<td>Nom</td>
<td>AGE</td>
<td>Age</td>
<td>years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Visualized Metadata**

- Table format
- Graphical representation
- Diagrams

---

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Visualizing Metadata Today

## Analysis Results

Table 1 Demographic Data - Per-Protocol

<table>
<thead>
<tr>
<th></th>
<th>Treatment 1</th>
<th>Treatment 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline body mass index (BMI) [kg/m</strong>2]**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>167</td>
<td>167</td>
</tr>
<tr>
<td>Mean</td>
<td>29.08</td>
<td>29.04</td>
</tr>
<tr>
<td>SD</td>
<td>4.84</td>
<td>4.80</td>
</tr>
<tr>
<td>Min</td>
<td>20.3</td>
<td>16.0</td>
</tr>
<tr>
<td>Median</td>
<td>28.69</td>
<td>28.47</td>
</tr>
<tr>
<td>Max</td>
<td>40.1</td>
<td>41.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Baseline BMI (categorical) [N (%)]</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 kg/m**2</td>
<td>41 (24.6%)</td>
<td>71 (21.1%)</td>
</tr>
<tr>
<td>25-&lt;30 kg/m**2</td>
<td>60 (35.9%)</td>
<td>130 (38.7%)</td>
</tr>
<tr>
<td>&gt;=30 kg/m**2</td>
<td>66 (39.5%)</td>
<td>135 (40.2%)</td>
</tr>
</tbody>
</table>
# Visualizing Metadata Today

## Analysis Dataset

<table>
<thead>
<tr>
<th>STUDYID</th>
<th>USUBJID</th>
<th>SUBJID</th>
<th>BMI</th>
<th>BMIGR1</th>
<th>BMIGR1N</th>
<th>BMIGR2</th>
<th>BMIGR2N</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>9999-0001</td>
<td>9999-0001-00001</td>
<td>000001</td>
<td>27.777777778</td>
<td>&lt;30 kg/m²</td>
<td>1</td>
<td>25-30 kg/m²</td>
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<tr>
<td>3</td>
<td>9999-0001</td>
<td>9999-0001-00002</td>
<td>000002</td>
<td>25.503615702</td>
<td>&lt;30 kg/m²</td>
<td>1</td>
<td>25-30 kg/m²</td>
</tr>
<tr>
<td>4</td>
<td>9999-0001</td>
<td>9999-0001-00003</td>
<td>000003</td>
<td>26.175194521</td>
<td>&lt;30 kg/m²</td>
<td>1</td>
<td>25-30 kg/m²</td>
</tr>
<tr>
<td>5</td>
<td>9999-0001</td>
<td>9999-0001-00004</td>
<td>000004</td>
<td>35.15625</td>
<td>&gt;=30 kg/m²</td>
<td>2</td>
<td>&gt;30 kg/m²</td>
</tr>
<tr>
<td>6</td>
<td>9999-0001</td>
<td>9999-0001-00005</td>
<td>000005</td>
<td>30.968858131</td>
<td>&gt;=30 kg/m²</td>
<td>2</td>
<td>&gt;30 kg/m²</td>
</tr>
<tr>
<td>7</td>
<td>9999-0001</td>
<td>9999-0001-00006</td>
<td>000006</td>
<td>39.697163916</td>
<td>&gt;=30 kg/m²</td>
<td>2</td>
<td>&gt;30 kg/m²</td>
</tr>
<tr>
<td>8</td>
<td>9999-0001</td>
<td>9999-0001-00007</td>
<td>000007</td>
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<td>&lt;30 kg/m²</td>
<td>1</td>
<td>25-30 kg/m²</td>
</tr>
<tr>
<td>9</td>
<td>9999-0001</td>
<td>9999-0001-00008</td>
<td>000008</td>
<td>30.103806228</td>
<td>&gt;=30 kg/m²</td>
<td>2</td>
<td>&gt;30 kg/m²</td>
</tr>
<tr>
<td>10</td>
<td>9999-0001</td>
<td>9999-0001-00009</td>
<td>000009</td>
<td>32.280962683</td>
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<td>2</td>
<td>&gt;30 kg/m²</td>
</tr>
<tr>
<td>11</td>
<td>9999-0001</td>
<td>9999-0001-00010</td>
<td>000010</td>
<td>28.876133787</td>
<td>&lt;30 kg/m²</td>
<td>1</td>
<td>25-30 kg/m²</td>
</tr>
<tr>
<td>12</td>
<td>9999-0001</td>
<td>9999-0001-00011</td>
<td>000011</td>
<td>29.372397383</td>
<td>&lt;30 kg/m²</td>
<td>1</td>
<td>25-30 kg/m²</td>
</tr>
<tr>
<td>13</td>
<td>9999-0001</td>
<td>9999-0001-00012</td>
<td>000012</td>
<td>26.714852608</td>
<td>&lt;30 kg/m²</td>
<td>1</td>
<td>25-30 kg/m²</td>
</tr>
<tr>
<td>14</td>
<td>9999-0001</td>
<td>9999-0001-00013</td>
<td>000013</td>
<td>32.718613869</td>
<td>&gt;=30 kg/m²</td>
<td>2</td>
<td>&gt;30 kg/m²</td>
</tr>
<tr>
<td>15</td>
<td>9999-0001</td>
<td>9999-0001-00014</td>
<td>000014</td>
<td>28.719723183</td>
<td>&lt;30 kg/m²</td>
<td>1</td>
<td>25-30 kg/m²</td>
</tr>
<tr>
<td>16</td>
<td>9999-0001</td>
<td>9999-0001-00015</td>
<td>000015</td>
<td>32.270420377</td>
<td>&gt;=30 kg/m²</td>
<td>2</td>
<td>&gt;30 kg/m²</td>
</tr>
</tbody>
</table>
Visualizing Metadata Today

### ADaM Define.xml

#### Computational Algorithms (ADSL.BMI)

<table>
<thead>
<tr>
<th>Reference Name</th>
<th>Computation Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADSL.BMI</td>
<td>Continuous variable, calculated using ADSL.WEIGHT/(ADSL.HEIGHT*0.01)**2 value at visit 3 if visit 3 data not available, the last data collected before randomisation</td>
</tr>
</tbody>
</table>

#### Computational Algorithms (ADSL.HEIGHT)

<table>
<thead>
<tr>
<th>Reference Name</th>
<th>Computation Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADSL.HEIGHT</td>
<td>equal to VS.VSSTRESN when VS.VSTESTCD=&quot;HEIGHT&quot;</td>
</tr>
</tbody>
</table>

#### Computational Algorithms (ADSL.WEIGHT)

<table>
<thead>
<tr>
<th>Reference Name</th>
<th>Computation Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADSL.WEIGHT</td>
<td>equal to VS.VSSTRESN when VS.VSTESTCD=&quot;WEIGHT&quot; and VS.VISITNUM=30 if visit 3 data not available, the last data collected before randomisation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference Name</th>
<th>Type</th>
<th>Derived</th>
<th>Computation Method</th>
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<tbody>
<tr>
<td>WEIGHT</td>
<td>integer</td>
<td>Derived</td>
<td>ADSL.BMI</td>
</tr>
<tr>
<td>BMI</td>
<td>integer</td>
<td>Derived</td>
<td>ADSL.BMI</td>
</tr>
<tr>
<td>BMGR1</td>
<td>text</td>
<td>Derived</td>
<td>ADSL.BMI</td>
</tr>
<tr>
<td>BMGR1N</td>
<td>integer</td>
<td>Derived</td>
<td>ADSL.BMI</td>
</tr>
<tr>
<td>BMGR2</td>
<td>text</td>
<td>Derived</td>
<td>ADSL.BMI</td>
</tr>
<tr>
<td>BMGR2N</td>
<td>integer</td>
<td>Derived</td>
<td>ADSL.BMI</td>
</tr>
<tr>
<td>BMGR3</td>
<td>text</td>
<td>Derived</td>
<td>ADSL.BMI</td>
</tr>
<tr>
<td>BMGR3N</td>
<td>integer</td>
<td>Derived</td>
<td>ADSL.BMI</td>
</tr>
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</table>

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Visualizing Metadata Today

### SDTM Define.xml and aCRF

<table>
<thead>
<tr>
<th>Source Variable</th>
<th>Value</th>
<th>Label</th>
<th>Type</th>
<th>Controlled Terminology</th>
<th>Origin</th>
<th>Role</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSTESTCD</td>
<td>DIABP</td>
<td>DIASTOLIC BLOOD PRESSURE</td>
<td>text</td>
<td>CRF Page 13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VSTESTCD</td>
<td>HEIGHT</td>
<td>HEIGHT</td>
<td>text</td>
<td>CRF Page 9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VSTESTCD</td>
<td>PULSE</td>
<td>PULSE RATE</td>
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<td>CRF Page 13</td>
<td></td>
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<td>VSTESTCD</td>
<td>SYSBP</td>
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<td>CRF Page 13</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>VSTESTCD</td>
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<td>WAIST CIRCUMFERENCE</td>
<td>text</td>
<td>CRF Page 9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VSTESTCD</td>
<td>WEIGHT</td>
<td>WEIGHT</td>
<td>text</td>
<td>CRF Page 9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Patient Demographics – Part I**

- **Visit Date**: 11-Dec-2007
- **Informed consent was obtained on**: DSTEM / DSDECOD
- **Gender**: SEX
  - 1 = male, 2 = female
- **Date of birth**: BRTHDTC
  - Age: AGE, AGEU
    - (Age is automatically calculated when screen is saved and closed)
- **Height**: cm
- **Weight**: kg
- **Waist circumference**: cm

**VERSAES / VSEORRESU where VSTESTCD = “HEIGHT”, “WEIGHT”, “WAIST”**
Current Metadata Repository

- Current MDRs represent metadata in a tabular format
Current Metadata Repository

Current MDRs represent metadata in a tabular format.

- Confusing
- Not user friendly
- Clunky
- No Benefits
- Boring
DISCLAIMER NOTE

The following is not a software demonstration

Sole purpose is to illustrate
<table>
<thead>
<tr>
<th>CDASH</th>
<th>SDTM</th>
<th>ADaM</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOMAIN</td>
<td>DOMAIN</td>
<td>DOMAIN</td>
</tr>
<tr>
<td>CDASH Variable</td>
<td>SDTM Variable</td>
<td>ADaM Variable</td>
</tr>
<tr>
<td>Value Level Metadata</td>
<td>Value Level Metadata</td>
<td>ADaM Parameters</td>
</tr>
<tr>
<td>Controlled Terminology</td>
<td>Controlled Terminology</td>
<td>Controlled Terminology</td>
</tr>
<tr>
<td>Computational algorithm</td>
<td>Computational algorithm</td>
<td>Computational algorithm</td>
</tr>
</tbody>
</table>

### CDASH
- **Variable:** AE
- **Events:** Adverse
- **Medical History:** MH
- **Vital Signs:** VS
- **Laboratory Test Results:** LB

### SDTM
- **Variable:** EX
- **Exposure:**
- **Concomitant Medication:** CM
- **Vital Signs:** VS
- **Laboratory Test Results:** LB

### ADaM
- **Variable:** AE
- **Events:** Adverse
- **Medical History:** MH
- **Vital Signs:** VS
- **Laboratory Test Results:** LB

**Metadata:**
- **Controlled Terminology**
- **Computational algorithm**

**Tables, Figures, Listings, End Points**
<table>
<thead>
<tr>
<th>Figures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graphical Approaches to the Analysis of Safety Data from Clinical Trials”. Amit, et. al.</td>
</tr>
<tr>
<td>From “Graphical Approaches to the Analysis of Safety Data from Clinical Trials”. Amit, et. al.</td>
</tr>
<tr>
<td>Mean Change from Baseline in QTc by time and treatment.</td>
</tr>
<tr>
<td>Distribution of ASAT by time and treatment</td>
</tr>
<tr>
<td>Distribution of maximum LFT values by treatment.</td>
</tr>
<tr>
<td>Panel of LFT shift from baseline to maximum by treatment</td>
</tr>
<tr>
<td>LFT Patient profiles</td>
</tr>
<tr>
<td>Most Frequent On Therapy Adverse Events</td>
</tr>
<tr>
<td>Cumulative distribution (with SEs) of time to first AE of special interest</td>
</tr>
<tr>
<td>Listing 2.4 Current Cancer History – All Treated Patients Experiencing Critical Events</td>
</tr>
<tr>
<td>Listing 2.5 Prior and Concomitant Medication – All Treated Patients Experiencing Critical Events</td>
</tr>
<tr>
<td>Listing 2.6 Physical Examination at Screening – All Treated Patients Experiencing Critical Events</td>
</tr>
<tr>
<td>Listing 3.1 Reference Chemotherapy and Concomitant Chemotherapies – All Treated Patients Experiencing Critical Events</td>
</tr>
<tr>
<td>Listing 4.1 Adverse Event Listing. All Pre-Treatment Adverse Events – All Treated Patients Experiencing Critical Events</td>
</tr>
<tr>
<td>Listing 4.2 Adverse Event Listing. Treatment Emergent Adverse Events – All Treated Patients Experiencing Critical Events</td>
</tr>
<tr>
<td>Listing 4.3 Adverse Event Listing. Serious Treatment Emergent Adverse Events – All Treated Patients Experiencing Critical Events</td>
</tr>
<tr>
<td>Listing 4.4 Adverse Event Listing. Serious Treatment Emergent Adverse Events Related To Study Drug</td>
</tr>
<tr>
<td>Listing 4.5 Adverse Event Listing. Serious Treatment Emergent Adverse Events Related To Treatment</td>
</tr>
</tbody>
</table>
## Listing 4.5 Adverse Event Listing. Serious Treatment Emergent Adverse Events Related To “Treatment” – All Treated Patients Experiencing Critical Events

<table>
<thead>
<tr>
<th>Site/ Patient</th>
<th>AE Verbatim Term</th>
<th>MedDRA SOC Name</th>
<th>MedDRA Preferred Term</th>
<th>Start Date/Time</th>
<th>Stop Date/Time</th>
<th>Duration (Days/Hours)</th>
<th>Day of onset</th>
<th>Occurrence</th>
<th>Intensity CTC grade</th>
<th>Relationship to Dexamethasone Taken</th>
<th>Action</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>xxxxxxxxx</td>
<td>xx/xxx</td>
<td>XXXXXXXXXXXX</td>
<td>DDMMTTYY/MM</td>
<td>XX</td>
<td>Intermittent</td>
<td>Grade X</td>
<td>Possibly</td>
<td>None</td>
<td>Resolved</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Analysis dataset: ADAO.SAS7BDAT ddmmyyyy hh:mm**

Note: Critical events are defined as: Serious Adverse Events (extracted from the clinical database reconciled with the safety database), Suspected Unexpected Serious Adverse Reactions (extracted from the safety database), wrong study medication used (patients who received a wrong medication kit by mistake in one cycle, resulting in the administration of drug from both treatment groups during the study).

Note: “Treatment” related adverse events are adverse events with a missing relationship to “Treatment” or assessed by the Investigator as definite, probable, possible or unassessable.

Program: <DIRECTORY\PATH>\XXXXXX.sas; Date & Time program was run: ddmmyyyy hh:mm; Date & Time analysis dataset was run: ddmmyyyy hh:mm
<table>
<thead>
<tr>
<th>Dataset</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAE</td>
<td>One record per subject per adverse event, per date</td>
</tr>
<tr>
<td>Domain</td>
<td>Name</td>
</tr>
<tr>
<td>--------</td>
<td>------------</td>
</tr>
<tr>
<td>ADEAE</td>
<td>USUBJID</td>
</tr>
<tr>
<td>ADEAE</td>
<td>SUBJID</td>
</tr>
<tr>
<td>ADEAE</td>
<td>SITEID</td>
</tr>
<tr>
<td>ADEAE</td>
<td>DOSEEAONU</td>
</tr>
<tr>
<td>ADEAE</td>
<td>DOSEAEON</td>
</tr>
<tr>
<td>ADEAE</td>
<td>COUNTRY</td>
</tr>
<tr>
<td>ADEAE</td>
<td>ASTTM</td>
</tr>
<tr>
<td>ADEAE</td>
<td>ASTDT</td>
</tr>
<tr>
<td>ADEAE</td>
<td>AETERM</td>
</tr>
</tbody>
</table>
### SDTM Domain Variables

#### Controlled Terminology

<table>
<thead>
<tr>
<th>Reference</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADEA.AENDT</td>
<td>Equals to <code>%SDTM_DATE_VARIABLE%</code> transformed into <code>%DATE_NUMERIC_FORMAT%</code> when length (%SDTM_DATE_VARIABLE%) &gt; 9</td>
</tr>
<tr>
<td>ADEA.ADURN</td>
<td>Equals to ADEA.AENDT – ADEA.ASTDT + 1.</td>
</tr>
<tr>
<td>ADEA.DOSEAEON</td>
<td>Equals to EX.EXDOSE where the numeric version of EX.EXSTDTC &lt;= ASTDT &lt;= the Numeric version of EX.EXENDTC.</td>
</tr>
<tr>
<td>ADEA.DOSEAEONU</td>
<td>Equals to EX.EXDOSU where the numeric version of EX.EXSTDTC &lt;= ASTDT &lt;= the Numeric version of EX.EXENDTC.</td>
</tr>
<tr>
<td>ADEA.DOSEAEON</td>
<td>Equals to &quot;DAYS&quot;</td>
</tr>
</tbody>
</table>

### ADaM Domain

#### Variables

<table>
<thead>
<tr>
<th>Reference</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADEA.AENDT</td>
<td>Equals to <code>%SDTM_DATE_VARIABLE%</code> transformed into <code>%DATE_NUMERIC_FORMAT%</code> when length (%SDTM_DATE_VARIABLE%) &gt; 9</td>
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<tr>
<td>ADEA.ADURN</td>
<td>Equals to ADEA.AENDT – ADEA.ASTDT + 1.</td>
</tr>
<tr>
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<td>Equals to EX.EXDOSE where the numeric version of EX.EXSTDTC &lt;= ASTDT &lt;= the Numeric version of EX.EXENDTC.</td>
</tr>
<tr>
<td>ADEA.DOSEAEONU</td>
<td>Equals to EX.EXDOSU where the numeric version of EX.EXSTDTC &lt;= ASTDT &lt;= the Numeric version of EX.EXENDTC.</td>
</tr>
<tr>
<td>ADEA.DOSEAEON</td>
<td>Equals to &quot;DAYS&quot;</td>
</tr>
</tbody>
</table>
ADaM Domain | Variables | Computational Algorithm
---|---|---

**Reference**

**Description**

ADA.E.DOSEAEON

Equals to EX.EXDOSE where the numeric version of EX.EXSTDTC <= ASTDT <= the numeric version of EX.EXENDTC.

<table>
<thead>
<tr>
<th>Name</th>
<th>Label</th>
<th>Origin</th>
<th>Role</th>
<th>Core</th>
</tr>
</thead>
<tbody>
<tr>
<td>AESTDTC</td>
<td>Start date/Time of Adverse Event</td>
<td>CRF</td>
<td>Timing</td>
<td>Exp</td>
</tr>
<tr>
<td>EXDOSE</td>
<td>Dose per administration</td>
<td>Derived</td>
<td>Record Qualifier</td>
<td>Exp</td>
</tr>
<tr>
<td>EXSTDTC</td>
<td>Start date/Time of treatment</td>
<td>CRF</td>
<td>Timing</td>
<td>Exp</td>
</tr>
<tr>
<td>EXENDTC</td>
<td>End date/Time of treatment</td>
<td>CRF</td>
<td>Timing</td>
<td>Perm</td>
</tr>
</tbody>
</table>

**Domain**

**Name**

**Question**

AE | AESTDAT | Start Date
AE | AESTIM  | Start Time
EX | EXAMONT | Dose
EX | EXAMONTU | Units
EX | EXENDAT | End Date
EX | EXENTIM | End Time
EX | EXSTDAT | Start Date

**Related metadata:**

SDTM, ADaM, CDASH, Figures, Listings
Agenda

- Introduction
- Specify by Browsing
- Metadata-driven Process
- Call to Action
Specification, Execution

SDTM Datasets → ADaM Metadata Generator → ADaM Datasets → Analysis Results Metadata Generator → TFLs

SDTM Datasets → ADaM Standard Macros

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**Metadata-driven Process**

- **Study Input Selector**
  - Selected TFLs
  - Study-Specific Input
  - Library Metadata

- **Metadata-driven Script Generator**
  - SDTM Datasets
  - ADaM Generator
  - ADaM Datasets
  - TFL Generator
  - TFLs

- **ADaM Standard Macros**
- **TFL Standard Macros**

**Arrows and Colors**:
- *User Interaction*: Blue
- *Metadata*: Red
- *Data*: Green
What is a Concept Map

- Concept maps = diagram which include “bubbles” representing concepts/ideas/things and labeled arrows that represent the relationships between the concepts/ideas/things.

- Advantage = easier to draw and more accessible than more formal modeling diagrams (e.g. UML diagrams)
Concept Map Legend

**Assessor**
The person or organization that reports about an observation.

**Observation**
A test, examination, or other activity that gathers information about a subject.

**Observation Result**
A finding obtained by an observation.

**Terminology**
Verbatim terms or vocabulary from a code list or dictionary.

**Statistical Concept**
Type of statistical analysis required for an endpoint.

**Document**
Document produced within the Clinical Trial.

**Product**
Anything made. Includes drugs and devices.

**Substance Administration**
An activity that administers a product to a subject.

**Other Activity**
An activity not otherwise classified.

**Variable**
The name and/or label of an attribute when represented as a column in normalized dataset.

**Computational Algorithm**
Algorithm used to calculate some analysis variable or parameter.

**Specimen**
A sample taken from a subject or existing specimen for analysis.

**Specimen Collection**
An activity that takes a Sample for later analysis.

**Composite Activity**
An activity with multiple classifications. Often has component sub-activities.

**CDISC Domain**
A Specification for creating normalized datasets compliant with CDISC standards.

**SAS Script**
SAS script that implements a standard, re-usable, computational algorithm.

**Healthcare Encounter**
Administration to or visit with a healthcare facility or healthcare provider.

**Initiative Procedure**
An invasive treatment or Diagnostic procedure.

**Time Point**
A defined point in time.

**Study Context**
Identifiers and relative timing used to describe a concept as it relates to the study.

**TFL Definition**
Type of TFL used to represent some data or analysis results.
The Tabulation and Analysis Concept Map will link perfectly
Only Semantic Interoperability can achieve real benefits from clinical data standards.
Tabulation Implementation Layer

- **STUDYID** stored in Study
- **VISIT** stored in visit
- **VISITNUM** stored in number
- **Temperature test** results in Temperature measurement
  - **Assessor** reports clinical significance result
    - **VSORRES**
    - **SUPPVS**
  - **result** stored in C42559
  - **unit** equal to C
  - **date** stored in VSDTC
  - **name** equal to C25206
  - **code** equal to C25206
- **timepoint** stored in VSTPT
  - **number** stored in VSTPTNUM
- **Subject** participates in
  - **ID** stored in USUBJID
  - **USUBJID** stored in VSTEST
  - **VSTESTCD**
  - **temperature** stored in TEMP
Analysis Implementation Layer

Study
  has
    hypothesis
can be proven by

Primary Efficacy Endpoint
defined in
  Protocol
      as
          Mean change from baseline
depicted by a

TFL
  specified in
    Statistical Analysis Plan
        as
            Table comparing drug and placebo arms on visit 1 separated by age groups

  presented in
    CSR Section

  has
    hypothesis

can be proven by

Analysis set
  defined as
    Efficacy Population
        meaning that
            ADSLEFFFL equals Y

Selection Criteria
  defined as
    Visit 1
        meaning that
            AVISIT equals Visit 1

Statistical Method
  defined as
    ANOVA

Analysis Sub -Groups
  defined as
    18 to 65; over 65
    calculated using
        MT.ADSL.AGEGR1
        taking as input
            MT_advs_chg.sas
        implemented by
            Mt_adsl_agegr.sas
        equals
            DTYPE

Data Handling Rule
  defined as
    Last Observation Carried Forward
        meaning that
            ADSLAGE
            equals
            LOCIF

Temperature
  meaning that
    PARAMCD equals TEMP

Mt.advs_chg.sas
  taken as input
    BASE
    AVAL
### Analysis Results Metadata

**Table 10-1.01** Primary Endpoint Analysis: ADVS-Temperature - Summary at Visit 1 - LOCF (Efficacy Population)

<table>
<thead>
<tr>
<th>Analysis Parameter(s)</th>
<th>Analysis Variable(s)</th>
<th>Analysis Reason</th>
<th>Analysis Purpose</th>
<th>Data References (incl. Selection Criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARAMCD = &quot;TEMP&quot;</td>
<td>CHG (Change from Baseline)</td>
<td>SPECIFIED IN SAP</td>
<td>PRIMARY OUTCOME MEASURE</td>
<td>ADVS [PARAMCD = &quot;TEMP&quot; and AVISIT = &quot;Visit 1&quot; and EFFFL = &quot;Y&quot;]</td>
</tr>
</tbody>
</table>

**Statistical Analysis Plan**

Linear model analysis of CHG for dose response using randomized dose (0mg for placebo; 10mg for low dose; 50mg for high dose) and site group in model. Used PROC GLM in SAS to produce p-value (from Type III SS for treatment dose).

**SAP Section 10.1.2**

#### Programming Statements

```sas
[SAS version 9.2]
proc glm data = ADVS;
  where EFFFL = 'Y' and AVISIT = 'Visit 1' and PARAMCD = "TEMP";
  class AGEGR1;
  model CHG = TRTPN AGEGR1;
run;
```

---

**Table comparing drug and placebo arms on visit 1 separated by age groups**

<table>
<thead>
<tr>
<th>PARAMCD</th>
<th>MT.ADS.CHG</th>
<th>CHG (Change from Baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;TEMP&quot;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mean change from baseline**

**Temperature**
Agenda

- Introduction
- Specify by Browsing
- Metadata-driven Process
- Call to Action
## Gap Analysis 1

**Protocol & SAP**
- Statistical Method
- Clinical Study Protocol
- Statistical Analysis Plan
- Statistical Requirements

**SDTM**
- Version
- SDTM Domain
- SDTM Variable
- Code List
- Value Level Metadata
- Computational Algorithm
- Data Handling Rules

**Analysis Results**
- Display
- Display Layout
- Footnote
- Titles
- Analysis Rule
- Output Specification Rule
- SAS Code

**CDASH**
- Version
- CDASH Dataset
- CDASH Variable
- Completion Guidelines
- Implementation Guidelines
- Data Validation Rule
- Data Collection Module
- CRF Template

**ADaM**
- Version
- ADaM Domain
- ADaM Variable
- Code List
- Computational Algorithm
- Analysis Sub Groups
- SAS Code

### Color Coding

<table>
<thead>
<tr>
<th>Industry Standard</th>
<th>No industry Standard</th>
</tr>
</thead>
</table>

---

> Not everything is standardized (yet)
Current metadata is tabular

We need concept metadata
Gap Analysis 3
Conclusion

Is this something the industry **wants**?

**Effort** is needed on an industry scale

Source: Dave Iberson-Hurst CDISC Standards and the Semantic Web Slides 12th October 2015 PhUSE Annual Conference, Vienna

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Thank you