Understanding the potential of Share

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Assero: Dave Iberson-Hurst

11 OCT 2016
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 the key components of clinical protocols
- Data review, analysis, and interpretation
- Analyze emerging safety profile of the drug
- Ensure appropriate size of the chosen subject population
- Assesses performance of data collection and management

Statisticians

- Establishing an objective framework for conducting an investigation
- Placing data and analysis on an equal scientific footing
- Designing data protocols that enhance the study
- Quantifying the influence of chance
- Estimating systematic and random effects
- Combining theory and data using formal methods

Children

- No Data Standards
- No Experts
Updates over time (OCT 2016)

- **Content Standards**
- **Technical Standards**
- **Semantics**
- **Therapeutic Areas**

**2002**
- ODM v1.1
- SDTM v1.0
- SDTM IG v3.1

- Define.xml v1.0

**2003**
- ODM v1.2
- SDTM v1.1
- SDTM IG v3.1.1

**2004**
- ODM v1.2.1

**2005**
- BRIDG v1.0
- BRIDG v1.1
- SDTM v1.2
- SDTM IG v3.1.2

**2006**
- BRIDG v2.0
- BRIDG v1.1.1
- ODM v1.3

**2007**
- BRIDG v2.2
- BRIDG v3.0
- ADaM v2.0

**2008**
- BRIDG v2.1
- ADaM v2.1
- ADaM IG v1.0
- CDASH v1.0

**2009**
- BRIDG v3.0.1
- ADaM Val. Checks v1.0
- Protocol Model v1.0

**2010**
- SDM.XML v1.0
- ODM v1.3.1
- ODM v1.3.1 Am.1

**2011**
- BRIDG v3.1
- Alzheimer v1.0
- SDTM v1.3
- SDTM IG v3.1.1

**2012**
- SDTM v1.3.1 Am.1
- PRM Toolset v1.0
- Virology v1.0
- Pain
- Devices
- Parkinson's Disease
- Tuberculosis
- Alzheimer's Disease
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>N</td>
<td>167</td>
<td>167</td>
</tr>
<tr>
<td>Sex: Male</td>
<td>130</td>
<td>130</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>23.04</td>
<td>23.04</td>
</tr>
<tr>
<td>SD</td>
<td>4.04</td>
<td>4.06</td>
</tr>
<tr>
<td>Max</td>
<td>30.13</td>
<td>25.47</td>
</tr>
<tr>
<td>Median</td>
<td>20.69</td>
<td>23.50</td>
</tr>
</tbody>
</table>

Baseline BMI (categorical) [N | %]

- <25 kg/m²: 41 (24.9%) 71 (43.1%)
- 25-30 kg/m²: 60 (35.9%) 130 (79.7%)
- >30 kg/m²: 66 (40.2%) 33 (20.3%)

![Image of a table showing demographic data for two treatments, with columns for N, Sex, BMI, and categorical BMI distribution.](image-url)
## 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>

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## 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>9999-0001-000001</td>
<td>000001</td>
<td>27.7777777778</td>
<td>&lt;30 kg/m²</td>
<td>1</td>
<td>25-&lt;30 kg/m²</td>
</tr>
<tr>
<td>3</td>
<td>9999-0001</td>
<td>9999-0001-000002</td>
<td>000002</td>
<td>25.503615702</td>
<td>&lt;30 kg/m²</td>
<td>1</td>
<td>25-&lt;30 kg/m²</td>
</tr>
<tr>
<td>4</td>
<td>9999-0001</td>
<td>9999-0001-000003</td>
<td>000003</td>
<td>26.175194521</td>
<td>&lt;30 kg/m²</td>
<td>1</td>
<td>25-&lt;30 kg/m²</td>
</tr>
<tr>
<td>5</td>
<td>9999-0001</td>
<td>9999-0001-000004</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>9999-0001-000005</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>9999-0001-000006</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>9999-0001-000007</td>
<td>000007</td>
<td>25.826446281</td>
<td>&lt;30 kg/m²</td>
<td>1</td>
<td>25-&lt;30 kg/m²</td>
</tr>
<tr>
<td>9</td>
<td>9999-0001</td>
<td>9999-0001-000008</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>9999-0001-000009</td>
<td>000009</td>
<td>32.280962683</td>
<td>&gt;=30 kg/m²</td>
<td>2</td>
<td>&gt;=30 kg/m²</td>
</tr>
<tr>
<td>11</td>
<td>9999-0001</td>
<td>9999-0001-000010</td>
<td>000010</td>
<td>28.876133787</td>
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<td>1</td>
<td>25-&lt;30 kg/m²</td>
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<tr>
<td>12</td>
<td>9999-0001</td>
<td>9999-0001-000011</td>
<td>000011</td>
<td>29.372397383</td>
<td>&lt;30 kg/m²</td>
<td>1</td>
<td>25-&lt;30 kg/m²</td>
</tr>
<tr>
<td>13</td>
<td>9999-0001</td>
<td>9999-0001-000012</td>
<td>000012</td>
<td>26.714852608</td>
<td>&lt;30 kg/m²</td>
<td>1</td>
<td>25-&lt;30 kg/m²</td>
</tr>
<tr>
<td>14</td>
<td>9999-0001</td>
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<td>000013</td>
<td>32.718619869</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>9999-0001-000014</td>
<td>000014</td>
<td>28.719732183</td>
<td>&lt;30 kg/m²</td>
<td>1</td>
<td>25-&lt;30 kg/m²</td>
</tr>
<tr>
<td>16</td>
<td>9999-0001</td>
<td>9999-0001-000015</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**

<table>
<thead>
<tr>
<th>Computational Algorithms (ADSL.BMI)</th>
<th>Computation Method</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference Name</strong></td>
<td><strong>Computation Method</strong></td>
</tr>
<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>

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

<table>
<thead>
<tr>
<th>Computational Algorithms (ADSL.WEIGHT)</th>
<th>Computation Method</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference Name</strong></td>
<td><strong>Computation Method</strong></td>
</tr>
<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><strong>Reference Name</strong></th>
<th><strong>Type</strong></th>
<th><strong>Description</strong></th>
<th><strong>Units</strong></th>
<th><strong>Definition</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>WEIGHT</td>
<td>Baseline Weight (kg)</td>
<td>integer</td>
<td>ADSDL.HEIGHT</td>
<td>Derived</td>
</tr>
<tr>
<td>BMI</td>
<td>Baseline BMI (kg/m**2)</td>
<td>integer</td>
<td>ADSDL.HEIGHT</td>
<td>Derived</td>
</tr>
<tr>
<td>BMIGR1</td>
<td>Category 1 of Baseline BMI</td>
<td>text</td>
<td>BMIGR1L</td>
<td>Derived</td>
</tr>
<tr>
<td>BMIGR1N</td>
<td>Category 1 of Baseline BMI, (N)</td>
<td>integer</td>
<td>BMIGR1N</td>
<td>Derived</td>
</tr>
<tr>
<td>BMIGR2</td>
<td>Category 2 of Baseline BMI</td>
<td>text</td>
<td>BMIGR2L</td>
<td>Derived</td>
</tr>
<tr>
<td>BMIGR2N</td>
<td>Category 2 of Baseline BMI, (N)</td>
<td>integer</td>
<td>BMIGR2N</td>
<td>Derived</td>
</tr>
<tr>
<td>BMIGR3</td>
<td>Category 3 of Baseline BMI</td>
<td>text</td>
<td>BMIGR3L</td>
<td>Derived</td>
</tr>
<tr>
<td>BMIGR3N</td>
<td>Category 3 of Baseline BMI, (N)</td>
<td>integer</td>
<td>BMIGR3N</td>
<td>Derived</td>
</tr>
</tbody>
</table>
Visualizing Metadata Today

- SDTM Define.xml and aCRF

### Value Level Metadata (ValueList.VS.VSTESTCD)

<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 12</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>
<td>text</td>
<td>CRF Page 13</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>VSTESTCD</td>
<td>SYSBP</td>
<td>SYSTOLIC BLOOD PRESSURE</td>
<td>text</td>
<td>CRF Page 13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VSTESTCD</td>
<td>WAIST</td>
<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

- Patient X5 Page 1 (Phone_Vis for Visit 1a) Page 1 of 1

- **DSCAT** = "PROTOCOL MILESTONE"

- **DSSTDTC**

- **SEX**

- **BRTHDTC**

- **AGE**

- **AGEU**

- **VSORRES**

- **VSORRESU**

- **VSSTRESC**

- **VSSTRESN**

**VSORRES / VSORRESU where VSTESTCD = "HEIGHT", "WEIGHT", "WAIST"**
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
### Figures

<table>
<thead>
<tr>
<th>Graphical Approaches to the Analysis of Safety Data from Clinical Trials”. Amit, et. al.</th>
</tr>
</thead>
<tbody>
<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>Listings</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</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 Experiencing Critical Events</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/ Country</th>
<th>Patient ID</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>Day of onset</th>
<th>Occurrence</th>
<th>Intensity to 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>XXXXXXXXXXXXXXXX</td>
<td>XXXXXXXXXXXXXXXX</td>
<td>xxxxxxxxx</td>
<td>DDMmYMM/HH:MM</td>
<td></td>
<td></td>
<td></td>
<td>xx</td>
<td>Intermittent</td>
<td>Grade X</td>
<td>Possibly</td>
</tr>
</tbody>
</table>

**Analysis dataset:** ADAK.SASBDAT 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>\XXXXX.sas; Date & Time program was run: ddmmyyyy hh:mm; Date & Time analysis dataset was run: ddmmyyyy hh:mm
**Dataset** | **Description**
--- | ---
ADAE | One record per subject per adverse event, per date
<table>
<thead>
<tr>
<th>Domain</th>
<th>Name</th>
<th>Label</th>
<th>Computational Algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAE</td>
<td>USUBJID</td>
<td>Unique Subject Identifier</td>
<td></td>
</tr>
<tr>
<td>ADAE</td>
<td>SUBJID</td>
<td>subject identifier for the study</td>
<td></td>
</tr>
<tr>
<td>ADAE</td>
<td>SITEID</td>
<td>Study Site identifier</td>
<td></td>
</tr>
<tr>
<td>ADAE</td>
<td>DOSEAONU</td>
<td>Study Drug Dose at AE Onset Units</td>
<td>ADAE.DOSEAEONU</td>
</tr>
<tr>
<td>ADAE</td>
<td>DOSEAEON</td>
<td>Study Drug Dose at AE Onset</td>
<td>ADAE.DOSEAEON</td>
</tr>
<tr>
<td>ADAE</td>
<td>COUNTRY</td>
<td>Country</td>
<td></td>
</tr>
<tr>
<td>ADAE</td>
<td>ASTTM</td>
<td>Analysis Start Time</td>
<td>ADAE.ASTTM</td>
</tr>
<tr>
<td>ADAE</td>
<td>ASTDT</td>
<td>Analysis Start Time</td>
<td>ADAE.ASTDT</td>
</tr>
<tr>
<td>ADAE</td>
<td>AETERM</td>
<td>Reported Term for the Adverse Events</td>
<td></td>
</tr>
</tbody>
</table>

**Related metadata:**
- **SDTM**
- **CDASH**
- **ADaM**

**Controlled Terminology**
- **ADAE**
- **SDTM**
- **CDASH**

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

ADAE.DOSEAEON

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

### Variables

<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>
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### Domain

<table>
<thead>
<tr>
<th>Name</th>
<th>Question</th>
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<tbody>
<tr>
<td>AE</td>
<td>Start Date</td>
</tr>
<tr>
<td>AE</td>
<td>Start Time</td>
</tr>
<tr>
<td>EX</td>
<td>Dose</td>
</tr>
<tr>
<td>EX</td>
<td>Units</td>
</tr>
<tr>
<td>EX</td>
<td>End Date</td>
</tr>
<tr>
<td>EX</td>
<td>End Time</td>
</tr>
<tr>
<td>EX</td>
<td>Start Date</td>
</tr>
</tbody>
</table>

### Related metadata: SDTM, CDASH
<table>
<thead>
<tr>
<th>CDASH</th>
<th>Domain</th>
<th>Variables</th>
<th>Computational Algorithm</th>
</tr>
</thead>
<tbody>
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<tr>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**ADaM**

**DOMAIN**

**SDTM Variable**

**Value Level Metadata**

**Controlled Terminology**

**Computational algorithm**

**CDASH**

**DOMAIN**

**SDTM Variable**

**Value Level Metadata**

**Controlled Terminology**

**Computational algorithm**

**Related metadata:** SDTM  Domain  Variables  Computational Algorithm  CDASH  Domain  Variables

**DCM’s**

**Domain**

**Variables**

**Computational Algorithm**

**Figures**

**Listings**

**Tables**
Agenda

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

Hypothesis

Protocol → Forms → SDTM → ADaM Generator → ADaM → TFL Generator → TFL End Points → Clinical Study Report

Specification

Execution
Metadata-driven Process:

Pick & select specific Metadata

Metadata Format

Metadata Content

DATA STANDARDS LIBRARY

Pick & select

Retrieve Metadata

STUDY METADATA REPOSITORY

Retrieve Generated Metadata

STUDY SPECIFIC INPUT

Generation

Protocol

Forms

SDTM

ADaM Generator

ADaM

TFL Generator

TFL

End Points

Clinical Study Report

Metadata-driven Process:

Pick & select specific Metadata

Metadata Format

Metadata Content

DATA STANDARDS LIBRARY

Pick & select

Retrieve Metadata

STUDY METADATA REPOSITORY

Retrieve Generated Metadata

STUDY SPECIFIC INPUT

Generation

Protocol

Forms

SDTM

ADaM Generator

ADaM

TFL Generator

TFL

End Points

Clinical Study Report
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 codelist 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.
- **CDISC Domain**: A specification for creating normalized datasets compliant with CDISC standards.
- **SAS Script**: SAS script that implements a standard, re-usable, computational algorithm.
- **TFL Definition**: Type of TFL used to represent some data or analysis results.
- **Specimen**: A sample taken from a subject or existing specimen for analysis.
- **Specimen Collection**: An activity that takes a sample for later analysis.
- **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.
Tabulation concept map

- **STUDYID**: stored in study, has subject ID, stored in USUBJID
- **VISIT**: stored in visit, has number, stored in VISITNUM
- **Assessor**: assesses clinical significance, reports on visit
- **Temperature test**: has code, name, date, stored in VSTESTCD, VTEST, VSDTC, VSTPT
- **Temperature measurement**: has result, unit, number, stored in VSTPTNUM
- **Result**: is stored in VSORRES, VSORRESU
- **Clinical significance result**: is stored in SUPPVS

Assero
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Analysis Concept Map

Study
  has
  Hypothesis
    can be proved by
    Primary Efficacy Endpoint
defined in 
  Protocol
    as
    Mean change from baseline
calculated using
  for parameter
  Temperature
    meaning that
    PARAMCD equals TEMP

TFL
  specified in
  Statistical Analysis Plan
  as
  Table comparing drug and placebo arms on visit 1 separated by age groups
  using
  Analysis Set
    defined as
    Efficacy Population
      meaning that
      ADSL.EFFFL equals YES
  Selection Criteria
    defined as
    Visit 1
  Statistical Method
    defined as
    ANOVA
  Analysis Sub-Groups
    defined as
    18 to 65, over 65
  Data Handling Rule
    defined as
    Last Observation Carried Forward
    meaning that
    DTYPE equals LOCF
Only Semantic Interoperability can achieve real benefits from clinical data standards.
Tabulation Implementation Layer
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

using

Analysis set

defined as

Efficacy Population

meaning that

ADSL.EFFFL

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_adsl_agegr.sas

Data Handling Rule

defined as

Last Observation Carried Forward

meaning that

DTYPE

equals

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

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

Dose Response Analysis for ADVS.TEMP changes from baseline

**PARAMCD** = "TEMP"

**CHG** (Change from Baseline)

Analysis Parameter(s)

Analysis Variable(s)

Analysis Reason

Analysis Purpose

Data References (incl. Selection Criteria)

Statistical Analysis Plan

SAP Section 10.1.2

Programming Statements

[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;
```

Implementation example:

Analysis Results Metadata

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

Temperature Mean change from baseline

**PARAMCD**

**MT.ADV.S.CHG**

**AVISIT**

**ADVS** [PARAMCD = "TEMP" and AVISIT = "Visit 1" and EFFFL = "Y"]

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).

Mt_adsl_agegr.sas
Agenda

1. Introduction
2. Specify by Browsing
3. Metadata-driven Process
4. Call to Action
Gap Analysis 1

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

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

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

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

Clinical Study Report
CSR Section

Clinical Study Report

Color Coding
Industry Standard
No industry Standard

Not everything is standardized (yet)
Current metadata is tabular

We need concept metadata
Conclusion

- Clarity
- Structure
- Complete
- Terminology
- Machine readable
- Reusable

Semantic Technology

Impact Assessment

Automation End-to-End

Traceability

Business Outputs

Exports to Support Today’s Process

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
Thank You