MethodDefs, ValueLists and WhereClauses:
How to Define Data Traceability in an MDR

DH09
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Agenda

Data Traceability
Standards
Traceability in Clinical Development Systems
Conclusion
Data Traceability
Data Traceability Drivers

Regulatory requirements

• The US Food & Drug Administration states in their Study Data Technical Conformance Guide section 4.1.3.2.1:

“it is very important that the results presented in the accompanying study report be traceable back to the original data collected”

• The Japanese Pharmaceutical and Medical Devices Agency Notification on Practical Operations of Electronic Study Data Submission asks in section 3(1)a(v) to:

“. explain the traceability between the submitted data (such as the procedures in which both datasets were prepared, the relationship between the variables ..., and whether there was any information used during the preparation)”
Define XML and Data Traceability

Data Traceability Drivers

Business Process Efficiency

Collection eCRF

- LBTPT
- LBPTNUM
- codelist
- -10
- 0
- 10
- 20
- 30
- 60
- 120
- = new value

Tabulation

- LBTPT
- LBPTNUM
- LBTEST
- LBTESTCD
- LBORRES
- LBRESU
- LBTEST
- LBTESTCD
- LBORRES
- LBRESU

Analysis

- ATPTN
- PARAM
- PARAMCD
- AVAL
- CHGT1*
- PCHGT1*

Table xx.x.xx

* --T1 = relative to timepoint where ATPTN = 1
Standards
## CDISC Standards

<table>
<thead>
<tr>
<th>Non-clinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organize</td>
<td>Collect</td>
</tr>
<tr>
<td>SEND</td>
<td>CDASH</td>
</tr>
<tr>
<td>Plan</td>
<td>Organize</td>
</tr>
<tr>
<td>PRM</td>
<td>SDTM</td>
</tr>
<tr>
<td>Analyze</td>
<td>ADaM</td>
</tr>
</tbody>
</table>

- Foundational standards defined separately for lifecycle stages
- Additional metadata needs to be defined to bridge the gaps between the lifecycle stages

### Data Exchange

- Define-XML standard is the only CDISC Data Exchange standard designed to describe data traceability
Define-XML Elements for Data Traceability

* elements in blue are additional compared to ODM

```xml
<ODM>
  <Study>
    <GlobalVariables>
      <MetaDataVersion>
        <def:AnnotatedCRF>
          <def:SupplementalDoc>
            <def:ValueListdef>
              <ItemRef>
                <def:WhereClauseRef>
                  <def:WhereClauseDef>
                    <RangeCheck>
                      <CheckValue>
                        <ItemGroupDef>
                          <ItemRef>
                            <ItemDef>
                              <CodeListRef>
                                <def:Origin>
                                  <def:DocumentRef>
                                    <def:PDFPageRef>
                                      <def:ValueListRef>
                                        <CodeList>
                                          <MethodDef>
                                            <def:CommentDef>
                                              <def:Leaf>
```

Document(s) that provide(s) the mapping of data collection fields to the variables or discrete variable values contained within the datasets

The value list element in combination with the where clause element describes the value level metadata

The origin element provides machine-readable connections between variables

This element ties the ValueList to the field/variable
## Derivation Example

<table>
<thead>
<tr>
<th>ItemGroupDef OID=&quot;IG.DM&quot; Domain=&quot;DM&quot; Name=&quot;DM&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;Description&gt;</td>
</tr>
<tr>
<td>&lt;TranslatedText xml:lang=&quot;en&quot;&gt;Demography&lt;/TranslatedText&gt;</td>
</tr>
<tr>
<td>&lt;/Description&gt;</td>
</tr>
<tr>
<td>&lt;ItemRef ItemOID=&quot;IT.DM.BRTHDTC&quot; OrderNumber=&quot;1&quot; Mandatory=&quot;Yes&quot; MethodOID=&quot;MT.BRTHDTC&quot;/&gt;</td>
</tr>
<tr>
<td>...</td>
</tr>
<tr>
<td>&lt;/ItemGroupDef&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ItemDef OID=&quot;IT.DM.BRTHDTC&quot; Name=&quot;BRTHDTC&quot; DataType=&quot;date&quot; Length=&quot;20&quot; SASFieldName=&quot;BRTHDTC&quot;&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;Description&gt;</td>
</tr>
<tr>
<td>&lt;TranslatedText xml:lang=&quot;en&quot;&gt;Date/Time of Birth&lt;/TranslatedText&gt;</td>
</tr>
<tr>
<td>&lt;/Description&gt;</td>
</tr>
<tr>
<td>&lt;def:Origin Type=&quot;Derived&quot;/&gt;</td>
</tr>
<tr>
<td>&lt;/ItemDef&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MethodDef OID=&quot;MT.BRTHDTC&quot; Name=&quot;Algorithm to derive BRTHDTC“ Type=&quot;Computation&quot; &gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;Description&gt;</td>
</tr>
<tr>
<td>&lt;TranslatedText xml:lang=&quot;en&quot;&gt;Derived from BRTHMO and BRTHYY, appending ‘01’ for the day and concatenated into ISO 8601 format.&lt;/TranslatedText&gt;</td>
</tr>
<tr>
<td>&lt;/Description&gt;</td>
</tr>
<tr>
<td>&lt;/MethodDef&gt;</td>
</tr>
</tbody>
</table>
VLM Example

```xml
<ItemGroupDef OID="IG.VS" Domain="VS" Name="VS">
  <Description>
    <TranslatedText xml:lang="en">Vital Signs</TranslatedText>
  </Description>
  <ItemRef ItemOID="IT.VS.VSORRES" OrderNumber="2" Mandatory="Yes"/>
</ItemGroupDef>
<ItemDef OID="IT.VS.VSORRES" Name="VSORRES" DataType="text" Length="30" SASFieldName="VSORRES">
  <Description>
    <TranslatedText xml:lang="en">Result or Finding in Original Units</TranslatedText>
  </Description>
  <def:Origin Type="CRF">
    <def:DocumentRef leafID="LF.blankcrf">
      <def:PDFPageRef PageRefs="11" Type="PhysicalRef"/>
    </def:DocumentRef>
  </def:Origin>
  <def:ValueListRef ValueListOID="VL.VS.VSORRES"/>
</ItemDef>
```
Define-XML and Data Traceability

VLM Example (cont.)

```xml
<def:ValueListDef OID="VL.VS.VSORRES">
  <ItemRef ItemOID="IT.VS.VSORRES.DIABP" OrderNumber="1" Mandatory="Yes">
    <def:WhereClauseRef WhereClauseOID="WC.VS.VSTESTCD.DIABP"/>
  </ItemRef>
  <ItemRef ItemOID="IT.VS.VSORRES.SYSBP" OrderNumber="2" Mandatory="Yes">
    <def:WhereClauseRef WhereClauseOID="WC.VS.VSTESTCD.SYSBP"/>
  </ItemRef>
  ...
</def:ValueListDef>

<def:WhereClauseDef OID="WC.VS.VSTESTCD.DIABP">
  <RangeCheck SoftHard="Soft" def:ItemOID="IT.VS.VSTESTCD" Comparator="EQ">
    <CheckValue>DIABP</CheckValue>
  </RangeCheck>
</def:WhereClauseDef>

<def:WhereClauseDef OID="WC.VS.VSTESTCD.SYSBP">
  <RangeCheck SoftHard="Soft" def:ItemOID="IT.VS.VSTESTCD" Comparator="EQ">
    <CheckValue>SYSBP</CheckValue>
  </RangeCheck>
</def:WhereClauseDef>
...
```
Data Traceability in Clinical Development Systems
Clinical Development Systems

- Many systems contain data for parts of the clinical data lifecycle
- A metadata repository can manage standards across the data lifecycle and is the primary candidate for defining traceability between stages
Traceability in the MDR: <def:Origin>

- Values: CRF, Derived, Assigned, Protocol, eDT, Predecessor
- Should be defined in context
Traceability in the MDR: `<MethodDef>`

- Unique Name, Type and Description are required
Value Level Metadata

• Most often used in Findings domains

• Providing additional definitions for variables like Result and Unit specific to each value of Test

• References should capture:
  • whether target variable is mandatory
  • the constraint for each of the values, including
  • comparator
  • check value
  • failure type
Traceability in the MDR: VLM

• Mandatory is captured on the context between the SDTM variable and domain

• The constraint can be captured on the relationship between the collection and tabulation variable
Comments for Define-XML should be facilitated on any element.
MDR Output

• When all standards and transformational metadata is captured in an MDR it can produce:
  • Define-XML for submission
  • Annotated CRF

For the SDTM-based dataset, the SDTM variable BRTHDTC is derived from the collected date and time components (BRTHDAT or BRTHYR, BRTHMO, BRTHDY, and BRTHTIM) concatenating as necessary into the ISO 8601 format.
Conclusion
Conclusion

- A metadata repository is well suited for control and versioning of data traceability
- The repository should hold all information about data elements, references and transformations
- Define-XML provides a good framework of the information to be captured in the MDR
- Managing context-dependent attributes facilitates reuse of core data elements
Define - XML and Data Traceability

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Any questions?