Clinical study oversight: different approaches to using data standards
Common concerns when outsourcing

? Is my CRO collecting the right data?
? Will my data be fit for a regulatory submission?
? My CRO delivers “CDISC”, so I guess that’s good enough?
? Will I be able to compare data between different trials?
? Am I giving the right information to the CRO?
? How do I check the CRO deliverables?
? I am keeping my study data on my server, I guess that’s ok?

➤ You may need Standards
AGENDA

Introduction
Outsourcing and Oversight models
Conclusions
Questions
OUTSOURCING AND OVERSIGHT MODELS

I Feel Lucky

Using a Standards Library

Using an Integrated Standards Library
Outsourcing Model I: Let the CRO decide
What will you get back?

**CRO A**

<table>
<thead>
<tr>
<th>STUDYID</th>
<th>DOMAIN</th>
<th>USUBJID</th>
<th>SUBJID</th>
<th>RFSTDTC</th>
<th>SITEID</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC</td>
<td>DM</td>
<td>ABC-CANI-001</td>
<td>001</td>
<td>2017-04-09</td>
<td>CANI</td>
</tr>
</tbody>
</table>

*RFSTDTC = date of informed consent*

**CRO B**

<table>
<thead>
<tr>
<th>STUDYID</th>
<th>DOMAIN</th>
<th>USUBJID</th>
<th>SUBJID</th>
<th>RFSTDTC</th>
<th>SITEID</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEF</td>
<td>DM</td>
<td>DEFCAN-001</td>
<td>001</td>
<td>2017-04-12</td>
<td>CANI</td>
</tr>
</tbody>
</table>

*RFSTDTC = date of first visit*

**CRO C**

<table>
<thead>
<tr>
<th>STUDYID</th>
<th>DOMAIN</th>
<th>USUBJID</th>
<th>SUBJID</th>
<th>RFSTDTC</th>
<th>SITEID</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHI</td>
<td>DM</td>
<td>GHI-CANI-01001</td>
<td>01001</td>
<td>2017-04-15</td>
<td>CANI</td>
</tr>
</tbody>
</table>

*RFSTDTC = date of first dosing*
When it gets more complex
When it gets more complex

Innovion

CRO A

CRO B

CRO C
Oversight and Quality Control

Clinical team → Protocol Synopsis → Validate → EDC

Study Repository → SDTM

Raw data

SPONSOR

CRO
**Outsourcing Model I: Let the CRO decide**

**ADVANTAGES of this model**
- Minimal investment from sponsor company
- Quick initiation of study set-up activities after final protocol

**DISADVANTAGES of this model**
- Minimal control by sponsor
- Quality Control is re-active
- Across trial variation unavoidable → Data will be difficult to pool or re-use
- No consistency of submission package → Costly conversion required
When does this model work?

- Select 1 CRO and remain with this CRO throughout development program
- Define some conventions, such as formats of USUBJID, reference dates,…
- Sell your assets before planning a submission
Outsourcing Model II: With Standards Library

Clinical team
Sponsor Standards Library

Study Set-up Package

EDC
Raw data
SDTM

SPONSOR
CRO
# Example Standards Library

<table>
<thead>
<tr>
<th>ADVERSE EVENTS</th>
<th>SDTM</th>
<th>CDASH</th>
<th>CRF questions</th>
<th>eDC build instructions</th>
<th>Controlled terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDYID</strong></td>
<td>STUDYID</td>
<td>[Free text]</td>
<td>[Preprinted]</td>
<td>[Preprinted]</td>
<td>[Preprinted]</td>
</tr>
<tr>
<td><strong>SITEID</strong></td>
<td>SITEID</td>
<td>[Free text]</td>
<td>[Preprinted]</td>
<td>[Preprinted]</td>
<td>[Preprinted]</td>
</tr>
<tr>
<td><strong>SUBJID</strong></td>
<td>SUBJID</td>
<td>[Free text]</td>
<td>[Preprinted]</td>
<td>[Preprinted]</td>
<td>[Preprinted]</td>
</tr>
<tr>
<td><strong>Adverse Events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Not Submitted)</td>
<td>AEVENTS</td>
<td>Were any adverse events experienced?</td>
<td>[RadioButton (Yes; No)]</td>
<td>NY</td>
<td></td>
</tr>
<tr>
<td><strong>AESPID</strong></td>
<td>AESPID</td>
<td>AE number</td>
<td>[Numeric field]</td>
<td>[Preprinted]</td>
<td>[Preprinted]</td>
</tr>
<tr>
<td><strong>AETERM</strong></td>
<td>AETERM</td>
<td>What is the adverse event term?</td>
<td>[Free text]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AESTDAT</strong></td>
<td>AESTTIM</td>
<td>Start Date</td>
<td>[Date (DD-MMM-YYYY)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AESTDAT</strong></td>
<td>AESTTIM</td>
<td>Start Time</td>
<td>[24 hr clock]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AEENDAT</strong></td>
<td>AEENTIM</td>
<td>End Date</td>
<td>[Date (DD-MMM-YYYY)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AEENDAT</strong></td>
<td>AEENTIM</td>
<td>End Time</td>
<td>[24 hr clock]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AEONGO</strong></td>
<td>AEREL</td>
<td>Is the adverse event still ongoing?</td>
<td></td>
<td>NY</td>
<td></td>
</tr>
<tr>
<td><strong>AESEV</strong></td>
<td>AESEV</td>
<td>Severity</td>
<td>[RadioButton (Mild; Moderate; Severe)]</td>
<td>AESEV</td>
<td></td>
</tr>
<tr>
<td><strong>AESER</strong></td>
<td>AESER</td>
<td>Is the adverse event serious?</td>
<td>[RadioButton (Yes; No)]</td>
<td>NY</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AEREL</td>
<td>Relationship to Study Treatment</td>
<td></td>
<td>REL</td>
<td>ACN</td>
</tr>
<tr>
<td></td>
<td>AEREL</td>
<td>Action taken with Study Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Provide Expectations

- **Set-up package**
  - Protocol
  - CRO guides for using Standards Library & standards governance
  - Sponsor Standards Library
    - Standard Data Collection Modules
    - CDISC SDTM Library
    - Data Standards Conventions
Oversight and Quality Control

Clinical team

Sponsor Standards Library

Study Repository

Study Set-up Package

Compare

Validate

EDC

Raw data

SDTM

Innovion

SPONSOR

CRO
Enables Additional Quality

- **Review of Annotated CRF**
  - Compare against sponsor Data Collection library
  - Enhances consistent data collection across CROs and Trials
  - Review SDTM mapping

- **Electronic Comparison of datasets and define.xml**
  - Check if data standards conventions were followed
  - Check consistency with Data Standards Library
Outsourcing Model II: With Standards Library

**ADVANTAGES of this model**
- Moderate investment by sponsor company
- Can work with multiple CROs and get same results
- Consistent data collection and representation in CDISC SDTM

**DISADVANTAGES of this model**
- Quality Control is still re-active
- Review steps are needed to verify CRO’s use of the library
- Increased communication with the CRO
- Need to maintain the library by an expert
When does this model work?

- Working with One or Multiple CROs
- Small to midsize companies with a growing portfolio, but limited budget
- Access to standards SME
Outsourcing Model III: Extended Standards Functionality
### Example Extended Standards Library

<table>
<thead>
<tr>
<th>AE</th>
<th>ADVERSE EVENTS</th>
<th>DCM ID: AE_GL_001</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dataset</strong></td>
<td><strong>Description</strong></td>
<td><strong>Class</strong></td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Events</td>
<td>EVENTS</td>
</tr>
</tbody>
</table>

#### AE Event Dataset

<table>
<thead>
<tr>
<th>AE</th>
<th>Variable</th>
<th>Label</th>
<th>Data Type</th>
<th>Length</th>
<th>Significant Digits</th>
<th>Format</th>
<th>Mandatory</th>
<th>Codelist</th>
<th>Origin</th>
<th>Pages</th>
<th>Method</th>
<th>Predecessor</th>
<th>Role</th>
<th>Comment</th>
<th>Core</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>STUDYID</td>
<td>Study Identifier</td>
<td>text</td>
<td>12</td>
<td>Yes</td>
<td>Fixed</td>
<td>Yes</td>
<td>Protocol</td>
<td>Identifier</td>
<td>Req</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td>DOMAIN</td>
<td>Domain Abbreviation</td>
<td>text</td>
<td>2</td>
<td>Yes</td>
<td>AE.DOMAIN</td>
<td>Assigned</td>
<td>USUBJID</td>
<td>Identifier</td>
<td>Req</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td>USUBJID</td>
<td>Unique Subject Identifier</td>
<td>text</td>
<td>18</td>
<td>Yes</td>
<td>Derived</td>
<td>USUBJID</td>
<td>Identifier</td>
<td>Req</td>
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<td>Integer</td>
<td>8</td>
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<td>Derived</td>
<td>SEQ</td>
<td>Identifier</td>
<td>Req</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AE</td>
<td>AEGRPID</td>
<td>Group ID</td>
<td>text</td>
<td>20</td>
<td>No</td>
<td>Derived</td>
<td>AEGRPID</td>
<td>Identifier</td>
<td>Perm</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td>ASID</td>
<td>Reference ID</td>
<td>text</td>
<td>20</td>
<td>No</td>
<td>Derived</td>
<td>CRF</td>
<td>Identifier</td>
<td>Perm</td>
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</tr>
<tr>
<td>AE</td>
<td>ATTERM</td>
<td>Reported Term for the Adverse Event</td>
<td>text</td>
<td>200</td>
<td>Yes</td>
<td>CRF</td>
<td>Topic</td>
<td>Req</td>
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<tr>
<td>AE</td>
<td>AEMODIFY</td>
<td>Modified Reported Term</td>
<td>text</td>
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<td>No</td>
<td>Assigned</td>
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<td>Perm</td>
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<td></td>
</tr>
<tr>
<td>AE</td>
<td>AEELT</td>
<td>Lowest Level Term</td>
<td>text</td>
<td>255</td>
<td>No</td>
<td>Derived</td>
<td>MedDRA</td>
<td>Identifiers</td>
<td>Exp</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Data Type

- **NCI Codelist Code**: C66767
- **Data Type**: text
- **Order**: 8
- **Term**:
  - DOSE INCREASED
  - DOSE NOT CHANGED
  - DOSE REDUCED
- **NCI Term Code**:
  - C49503
  - C49504
  - C49505
- **Decoded Value**:
  - Drug Increased
  - Drug Not Changed
  - Drug Reduced

#### Extensibility

- **Perm**: Yes
- **Exp**: Yes

#### Reference Data

- **Perm**: Yes
- **Exp**: Yes
Provide Specifications

- **Study Build Package**
  - Protocol
  - Electronic Study Specification
    - Define.xml
    - EDC Build File
    - SDTM annotated CRF
Oversight and Quality Control

Clinical team

SDTM, ADaM, TAUGs

Library

Study

MDR

Study Repository

upload

compare

validate

Study Build Package

Automated Study Build

EDC

Raw data

SDTM

SPONSOR

CRO
Quality Control Activities and Timelines

**Clinical CRO**

- **CRO training**
  - study specifications, trial design and metadata selection

- **QC**
  - SDTM annotated CRF and DTAs

- **SDTM and define.xml with Test Data**

- **Pre-final SDTM and define.xml package**

- **Final Transfer**

**Sponsor**

- **CRO selection**
  - Sponsor study specifications, trial design and metadata selection

- **Final Protocol or outline**

- **Start eDC build**

- **FPI**

- **DB lock**

**Relative day**

-95  -45  -40  -30  -25  -10  -5  -30  -25  1
Enables Highest Level Of Control & Quality

- **EDC system is automatically generated**
  - Ensures consistent data collection

- **Provides electronic SDTM specifications for the CRO**
  - Enables electronic check between specifications and CRO datasets
  - Ensures consistency with Data Standards Library

- **Ensures consistency**
  - Between Trials
  - Between CROs
  - Fit for use in analysis poolings and re-usability of trial data
## 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>Baseline body mass index (BMI) [kg/m²]</td>
<td>25.0</td>
<td>26.0</td>
</tr>
<tr>
<td>Weight</td>
<td>61.0</td>
<td>62.0</td>
</tr>
<tr>
<td>Height</td>
<td>170 cm</td>
<td>170 cm</td>
</tr>
</tbody>
</table>

### Vital Signs

<table>
<thead>
<tr>
<th>Subject</th>
<th>Protocol</th>
<th>Planned Timepoint</th>
<th>Study ID</th>
<th>SubjID</th>
<th>SysBP</th>
<th>DystBP</th>
<th>SystBP</th>
<th>Temp</th>
<th>Pulse</th>
<th>Height</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>30 minutes pre-dose</td>
<td>9999-0001</td>
<td>000011</td>
<td>150 mmHg</td>
<td>100 mmHg</td>
<td>130 mmHg</td>
<td>36°C</td>
<td>62 BEATS/MIN</td>
<td>62 KG/CM²</td>
</tr>
</tbody>
</table>

### Interpretation

- Temperature: Normal
- Pulse Rate: Normal
- Systolic Blood Pressure: Normal
- Diastolic Blood Pressure: Normal
- Weight: Normal
- BMI: Clinically Significant

### Analysis Results

- Study ID: 9999-0001
- Subject ID: 000011
- Protocol: 1
- Planned Timepoint: 30 minutes pre-dose
- VSDAT: 2017-06-14T08:55
- VSTIM: 8:55 AM
- VSTPT: 9999-0001-000011
- VSBLFL: Y
- SDTM Data
- CDASH EDC Extract
- CRF
- SDTM Data
- ADaM Data
- CDISC Data Models
Outsourcing Model III: *Extended Standards Functionality*

**ADVANTAGES of this model**
- Full control
- Pro-active Quality Control
- High level of automation possible
- Many automatic quality checks
- Submission ready deliverables

**DISADVANTAGES of this model**
- Higher investment by sponsor company
- Continuous maintenance and governance of standards mandatory
When does this model work?

- Midsize to large companies
- Training is provided
- Intuitive Interfaces for end-users
Conclusion

- Higher level of standardization will lead to better quality
  - Choose the approach that fits your company
    - Expectations
    - Budget
    - Staff
    - Partners
Questions....
INNOVION

Thank you for your attention