With Standards – Science Will Prevail!

CDISC 360: What’s in It for Me?

Peter Van Reusel
CDISC European Interchange
Session 7 - April 29, 2021
Meet the Speaker

Peter Van Reusel

Title: Chief Standards Officer
Organization: CDISC

Peter Van Reusel provides executive leadership to the development and implementation of clinical standards in line with CDISC’s strategy and operational plans, working closely with the President and CEO, as well as CDISC staff and stakeholders. He has over 20 years’ experience in senior roles in pharma and at CROs, providing standards expertise and carrying out other standards work in various organizational settings. A long-time, CDISC-authorized instructor, Peter has helped significantly in developing CDISC training courses.

He previously served as CDISC’s European Liaison, shepherding relationships with key European regulatory, academic, and biopharma stakeholders. Peter is also an active PhUSE collaborator.
Agenda

1. Common Implementation Challenges Addressed by CDISC 360
2. Four Pillars of CDISC 360 Implementation
3. Summary of Projects
Common Implementation Challenges

What is CDISC 360 trying to address?
Today we are here

CDISC Standards in the Clinical Research Process

PRE-CLINICAL

ORGANIZE

SEND

ORGANIZE

CLINICAL

PLAN

COLLECT

DATA EXCHANGE ODM-XML

DATA EXCHANGE ODM-XML

SDTM

DATA EXCHANGE Define - XML Dataset - XML

SUBMIT PUBLISH REPORT

TAUGS

BRIDG, CONTROLLED TERMINOLOGY AND GLOSSARY
What is not in the standards?

- Lack comprehensive data meaning and relationships
- Do not describe the transformations and derivations
- Have flexibility that allows for inconsistencies, making automation difficult, allowing interpretation & unnecessary variability in using the standards
- Therapeutic published as text instead of machine-readable content with machine executable transformation and derivation algorithms
- Therapeutic Area User Guides provide end-to-end knowledge standardization
  - From data collection to analysis
  - Analog documents, published as text
# Therapeutic Area User Guide Overview

Therapeutic Area (TA) Standards extend the Foundational Standards to represent data that pertains to specific disease areas. TA Standards include disease-specific metadata, examples and guidance on implementing CDISC standards for a variety of uses, including global regulatory submission.

<table>
<thead>
<tr>
<th>Autoimmune</th>
<th>Infectious</th>
<th>Oncology</th>
<th>Other</th>
<th>Rare Diseases</th>
<th>Neurology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis</td>
<td>COVID-19</td>
<td>Breast Cancer</td>
<td>Nutrition</td>
<td>Duchenne Muscular Dystrophy</td>
<td>Alzheimer's</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Ebola</td>
<td>Colorectal Cancer</td>
<td>Traditional Chinese Medicine - Acupuncture</td>
<td>Respiratory</td>
<td>Huntington's Disease</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hepatitis C</td>
<td>Lung Cancer</td>
<td>Rehabilitation</td>
<td>Asthma</td>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td></td>
<td>HIV</td>
<td>Pancreatic Cancer</td>
<td>Pain</td>
<td>COPD</td>
<td>Parkinson's Disease</td>
</tr>
<tr>
<td></td>
<td>Influenza</td>
<td>Prostate Cancer</td>
<td>Vaccines</td>
<td>COVID-19</td>
<td>Traumatic Brain Injury</td>
</tr>
<tr>
<td></td>
<td>Malaria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Virology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>Mental Health</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Kidney Injury</td>
<td>Major Depressive Disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Post Traumatic Stress Disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes - Type 1</td>
<td>Schizophrenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic Kidney Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney Transplant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycystic Kidney Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crohn's Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

→ **44 Therapeutic Area User Guides in 8 years**

[https://www.cdisc.org/standards/therapeutic-areas/disease-area](https://www.cdisc.org/standards/therapeutic-areas/disease-area)
Therapeutic Area Concept Maps

- Provides scope and extent of TA User Guide
- Facilitates communication between scientists and data standards experts

➔ "This is a picture for humans, this knowledge does not exist for machines"
TAUG CRFs and Datasets

Example CRF & Hypoglycemia

➔ Human readable only
3.3 Hypoglycemic Episodes Summary Dataset

The analysis dataset contains one row for each dataset, including the number of subjects, number of events, and event rate. The dataset includes the following variables:
- **Subject ID**
- **Dataset Name**
- **Start Date**
- **End Date**
- **Duration**
- **Number of Subjects**
- **Number of Events**
- **Event Rate**

The dataset is sorted by **Dataset Name** in ascending order. Each row represents a unique dataset.

3.4 Hypoglycemic Episodes Summary Analysis Results

The summary statistics in Table 3.4.1 are presented for all hypoglycemic episodes as well as by ADA classification group. The statistics presented in the current example are the number of subjects experiencing an event, the number of events, and the event rate. To estimate and present the event rate, time is needed. Table 3.4.1 is based on the ADHYSYM dataset.

<table>
<thead>
<tr>
<th>ADA Classification</th>
<th>Treatment</th>
<th>Summary</th>
<th>Safety Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
<td>Drug A</td>
<td>Drug B</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event rate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3.4.1: Summary of Hypoglycemic Episodes by Classification

<table>
<thead>
<tr>
<th>ADA Classification</th>
<th>Treatment</th>
<th>Summary</th>
<th>Safety Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
<td>Drug A</td>
<td>Drug B</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event rate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3.4.2: Summary of Hypoglycemic Episodes by Treatment

<table>
<thead>
<tr>
<th>ADA Classification</th>
<th>Treatment</th>
<th>Summary</th>
<th>Safety Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
<td>Drug A</td>
<td>Drug B</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event rate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3.4.3: Summary of Hypoglycemic Episodes by Safety Analysis Set

<table>
<thead>
<tr>
<th>ADA Classification</th>
<th>Treatment</th>
<th>Summary</th>
<th>Safety Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
<td>Drug A</td>
<td>Drug B</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event rate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 3.4.1: Mean Cumulative Function Plot of Documented and Severe Symptomatic Hypoglycemic Episodes

Documented and Severe Symptomatic Hypoglycemic Episodes - Treatment Emergent - Mean Cumulative Function - Safety Analysis Set
Biomedical Concepts
The CDISC 360 Project: Adding a conceptual layer to standards

• Evolve from normative to informative standards
• Create and store standards as concepts which create meaning
• Electronically publish data standards as linked metadata
• Add computer executable process metadata which enables end to end automation
• Develop concept-based standard definitions, and test and demonstrate end-to-end automation of study specification, data processing, and analysis

→ Test and demonstrate, but not building software
Four Pillars of CDISC 360 Implementation
Four Pillars of CDISC 360 Implementation

Four pillars of 360 implementation emerge from the 360 lessons learned:

1. **Complete** the E2E foundational standards where they are incomplete

2. **Enrich** the foundational standards with the additional metadata needed for full data meaning and relationships by creating a biomedical concept layer

3. **Extend** the CDISC Library model with implementation level metadata

4. **Collaborate** with industry to standup and curate biomedical concepts
Implementing 360: Projects

STANDARDS DEVELOPMENT

1. Complete E2E Foundational Standards
   - Project: eCRF Portal
   - Project: Analysis Results Standard
   - Project: Safety User Guide

2. Enrich Foundational Standards
   - Project: Mining Define.xml's

STANDARDS DELIVERY

3. Extend CDISC Library Model
   - Project: Model concepts
   - Project: Add QRS content

4. Collaborate with Industry
   - Project: Use mining Define.xml project as prototype for collaborative curation process
Implementing 360: Completing E2E Foundational Standards

### STANDARDS DEVELOPMENT

1. Complete E2E Foundational Standards
   - **Project:** eCRF Portal
   - **Project:** Analysis Results Standard
   - **Project:** Safety User Guide

2. Enrich Foundational Standards
   - **Project:** Mining Define.xml’s

### STANDARDS DELIVERY

3. Extend CDISC Library Model
   - **Project:** Model concepts
   - **Project:** Add QRS content

4. Collaborate with Industry
   - **Project:** Use mining Define.xml project as prototype for collaborative curation process
eCRF Portal Project
**eCRF Portal Project**

<table>
<thead>
<tr>
<th>Form AE - Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 AE - Adverse Events</strong></td>
</tr>
<tr>
<td>1.1 Were any adverse events experienced?</td>
</tr>
<tr>
<td>1.2 What is the adverse event term?</td>
</tr>
<tr>
<td>1.3 Start Date (DD-MMM-YYYY)</td>
</tr>
<tr>
<td>1.4 Ongoing (as of [the study-specific time point or period])</td>
</tr>
<tr>
<td>1.5 End Date (DD-MMM-YYYY)</td>
</tr>
<tr>
<td>1.6 Severity</td>
</tr>
</tbody>
</table>

Currently 22 CRFs are available; more to follow.
eCRF Portal – What’s in it for Me?

- Helps complete the end-to-end CDISC vision
- ODM XML file can be used directly in compliant EDC systems
- Comes with underlying CDASH metadata
- CDASH annotation is included

➤ Reduce unnecessary variability in data collection
https://www.cdisc.org/kb/ecrf
Analysis Results Standard Project
Analysis Results Standard

- **Extend** ARM to facilitate automated TFL generation
- **Create** a standardized structure for analysis results to support reuse and dynamic data display generation
- **Tighten** standardization around ADaM datasets for generally accepted analyses
Where Is Our Focus?

- Protocol SAP
  - study design
- CRF: data collection
- SDTM: analysis programming

ADaM: analysis

Static TFLs

Analysis Results Dataset: support

Data Exploration / Visualization
Standardized analysis results support dynamic data display generation.
Analysis Results Standard – What’s in it for Me?

- Add features that support automation of analysis results
- Provide guidance on basic analysis structures towards analysis results generation
- Provide greater traceability between analysis results and analysis data
Why Create a Safety User Guide?

- Currently there is lack of a unified CDISC Safety User Guide that spans from data collection through analysis results.

- Each CDISC Foundational Standard has information on Safety Data that is commonly collected across studies of a wide-variety of indications.

- The TAUGs also often collect disease-specific safety information and examples.

- Will identify the most commonly performed safety analyses.
Scope: From Analysis Results to Collection

Data Collection

Data Aggregation

Analysis

Analysis Results

3.4 Hypoglycemic Episodes Summary Analysis Results

The summary statistics in Table 3.4.1 are presented for all hypoglycemic episodes, as well as by ADA classification group. The statistics presented in the current example are for a single subject, assuming no overall ADA event rate was estimated. To estimate and present the event rate of hypoglycemic episodes, additional tests are needed. Table 3.4.1 is based on the ADIDAS dataset.
Safety User Guide – What’s in it for Me?

• Standardize implementation of the most commonly performed Safety Analyses such as study drug exposure, adverse events, laboratory evaluations, vital signs, and others

• The Safety User Guide will provide:
  • Implementation guidance and examples using the new analysis results standards
  • Analysis datasets
  • Tabulation datasets
  • Data collection metadata
  • eCRFs in the eCRF portal

> Provides common understanding of “how do we do safety”
Mining Biomedical Concepts from Define.xmls
Implementing 360: Standing Up Biomedical Concepts

STANDARDS DEVELOPMENT

1. Complete E2E Foundational Standards
   - Project: eCRF Portal
   - Project: Analysis Results Standard
   - Project: Safety User Guide

2. Enrich Foundational Standards
   - Project: Mining Define.xml’s

STANDARDS DELIVERY

3. Extend CDISC Library Model
   - Project: Model concepts
   - Project: Add QRS content

4. Collaborate with Industry
   - Project: Use mining Define.xml project as prototype for collaborative curation process
Minining Concepts from Define.xmls

- Retrieve metadata from Define.xmls to determine how standards are used in practice
- Curate the metadata (select best practice, standardize VLM) and stand up biomedical concepts
- Biomedical Concept modeling and load in CDISC Library

➤ The first biomedical concepts will be available in the CDISC Library and can be retrieved as an SDTM specification and Define.xml
Select and Identify the Concepts

Mining concepts

Curating concepts
Curate the Concepts

For the selected and identified concepts

- How are standards implemented in real studies?
- Determine the underlying SDTM structure for each concept
- Standardize the SDTM variable data types for each concept
  - e.g., Height STRESN is Float 4.1
- Standardize control terminology for each variable used in each concept
  - e.g., Height UNIT in CM or IN
- What do we consider?
  - Are there differences in how a concept is used across therapeutic areas?
  - Does this align with structure and business rules of the SDTMIG?
  - How do we compromise and reach consensus among different implementations?

Choose the best practice implementation
### Load Concepts into CDISC Library

#### Tabulation Datasets for Study CDISC01 (SDTM-IG 3.1.3)

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Description</th>
<th>Close</th>
<th>Methodology</th>
<th>Purpose</th>
<th>Range</th>
<th>Location</th>
<th>Documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>Trial Arms</td>
<td>FINAL DESIGN</td>
<td>One record per element</td>
<td>Clinical</td>
<td>STUDY</td>
<td>5a.M35</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Trial Elements</td>
<td>FINAL DESIGN</td>
<td>One record per element</td>
<td>Tabulation</td>
<td>STUDY</td>
<td>10.M35</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Trial Inclusion/Exclusion Criteria</td>
<td>FINAL DESIGN</td>
<td>One record per element</td>
<td>Tabulation</td>
<td>STUDY</td>
<td>11.M35</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Trial Baseline</td>
<td>FINAL DESIGN</td>
<td>One record per element</td>
<td>Tabulation</td>
<td>STUDY</td>
<td>15.M35</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Trial Vitals</td>
<td>FINAL DESIGN</td>
<td>One record per element</td>
<td>Tabulation</td>
<td>STUDY</td>
<td>16.M35</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Subject Demographics</td>
<td>SPECIAL PURPOSE</td>
<td>One record per subject</td>
<td>Tabulation</td>
<td>STUDY</td>
<td>20.M35</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Subject Inclusion</td>
<td>SPECIAL PURPOSE</td>
<td>One record per subject</td>
<td>Tabulation</td>
<td>STUDY</td>
<td>21.M35</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Subject Exclusion</td>
<td>SPECIAL PURPOSE</td>
<td>One record per subject</td>
<td>Tabulation</td>
<td>STUDY</td>
<td>22.M35</td>
<td></td>
</tr>
</tbody>
</table>

---

![Diagram](image-url)
Retrieve Concept Metadata from CDISC Library

SDTM Specifications

Define XML
“Mining Define.xmls” – What’s in it for Me?

• Standardizing Value Level Metadata to increase consistency across studies

• Standardizing Data Types and Controlled Terminology per concept

• Linking concepts to SDTM structure to enable automation
  • Ability to Generate Define XML and SDTM Specifications from CDISC Library

This is just the first step of an open path to:

• Link lab concepts to unique LOINC codes
• Link concepts to how they are collected
• How concepts are used in analysis
Summary of Projects
Implementing 360: Projects’ Summary

**STANDARDS DEVELOPMENT**

1. Complete E2E Foundational Standards
   - **Project:** eCRF Portal
   - **Project:** Analysis Results Standard
   - **Project:** Safety User Guide

2. Enrich Foundational Standards
   - **Project:** Mining Define.xml’s

**STANDARDS DELIVERY**

3. Extend CDISC Library Model
   - **Project:** Model concepts
   - **Project:** Add QRS content

4. Collaborate with Industry
   - **Project:** Use mining Define.xml project as prototype for collaborative curation process
Biomedical Concept Layer

Data Collection

Data Aggregation

Analysis

Analysis Results

Data Flow

Presentation Layer
eCRF Portal project

Data Collection

Data Aggregation

Analysis

Analysis Results

Biomedical Concept Layer

Presentation Layer

Data State

Data Flow
"Analysis Results Standard" Project

Data Collection → Data Aggregation → Analysis → Analysis Results

Presentation Layer

Biomedical Concept Layer

Data State

Data Flow
"Safety User Guide" Project

Data Collection

Data Aggregation

Analysis

Analysis Results

Data State

Data Flow
We are on Our Way to

- Complete standards end-to-end (from analysis to collection)
- Content for standards implementation (e.g., value level metadata)
- Digitize therapeutic area user guides
- Extend the CDISC Library model to include biomedical concepts
- Set up a collaborative curation and governance process
Thank You!

Peter Van Reusel
pvanreusel@cdisc.org