Agenda

1. CDISC 360 Intro
2. Project Approach
3. Project Status
4. Concepts Development - status
5. Art of the Possible
1. CDISC 360 Intro
Today we are here

CDISC Standards in the Clinical Research Process

PRE-CLINICAL

ORGANIZE

ORGANIZE

SEND

PLAN

COLLECT

ANALYZE

SUBMIT PUBLISH REPORT

DATA EXCHANGE

DATA EXCHANGE

DATA EXCHANGE

DATA EXCHANGE

ODM-XML

ODM-XML

Define - XML

SDM-XML

Dataset - XML

PRM

CDASH

SDTM

ADaM

TAUGS

BRIDG, CONTROLLED TERMINOLOGY AND GLOSSARY

cdisc
Defined structures

- CDISC Foundational models provide much needed structure
  - Normative Content
  - 2 dimensional (tables, columns)
  - Standard to represent data

- The information itself is not defined
  - We do not need new structures
  - We need to define
    - Entities
    - Semantics (meaning)
    - Relationships between information
    - Rules in the data lifecycle
Why do we need to evolve?

- Data structures are known, but data meaning lacks full definition
- Standards are incomplete
  - protocol content, data collection instruments, analysis/endpoint definition
- Current clinical data standards are implemented inconsistently
  - Across studies and organizations
- Limited process automation in data processing
  - Study build, study conduct, and study reporting
  - Much manual programming needed in these processes
  - Some automation, but lack of fully-scaled automation
- Too much time needed for study specification
- High level of standards expertise needed
How do we evolve?
The CDISC 360 Project: Adding a conceptual layer to standards

- Create and store standards as concepts which create meaning between data
- Electronically publish data standards as linked metadata
- Add computer executable process metadata which enables end to end automation
- CDISC 360 will 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**
Biomedical Concept

Hemoglobin A1C to Hemoglobin Ratio Measurement (C111207) mayHave Specimen Type (C70713)
Hemoglobin A1C to Hemoglobin Ratio Measurement (C111207) mayHave Reference Range (C71474)
Hemoglobin A1C to Hemoglobin Ratio Measurement (C111207) defaultCode % (C25613)
Hemoglobin A1C to Hemoglobin Ratio Measurement (C111207) mustHave Collection Date/Time (C82515)
Hemoglobin A1C to Hemoglobin Ratio Measurement (C111207) mustHave Laboratory Test Code (C83322)
Hemoglobin A1C to Hemoglobin Ratio Measurement (C111207) mayHave Logical Observation Identifiers Names and Codes (LOINC) (C82502)
Laboratory Test Name (C67154) usesCode Hemoglobin A1C/Hemoglobin (C111207)
Laboratory Test Code (C65047) usesCode HBA1C/HGB (C111207)
Hemoglobin A1C to Hemoglobin Ratio Measurement (C111207) mustHave Baseline Flag (C82526)
Hemoglobin A1C to Hemoglobin Ratio Measurement (C111207) mayHave Specimen Condition (C83024)
Hemoglobin A1C to Hemoglobin Ratio Measurement (C111207) mustHave Laboratory Test Name (C117142)
Unit of Measure (C25709) usesNCicodeList Unit (C71620)
Hemoglobin A1C to Hemoglobin Ratio Measurement (C111207) mustHave Unit of Measure (C25709)
if LB.LBSTREN ne to "" and LB.LBTESTCD = "HBA1CHGB"" and LB.LBDTC is uses Laboratory Test Code (C83322)
Planned Time Points (C2826271) specify Time Points
Laboratory Test Result (C36292) mayBeUsedIn Reference Range Comparison (C122757)
Reference Range Indicator (C78736) usesCode ABNORMAL (C78802); HIGH (C78800); LOW (C78801); NORMAL (C78727)
Hemoglobin A1C to Hemoglobin Ratio Measurement (C111207) mustHave Laboratory Test Result (C36292)
Specimen Type (C78734) usesCode BLOOD (C12434)
Hemoglobin A1C to Hemoglobin Ratio Measurement (C111207) belongsTo LB
Specimen Condition (C83024) usesNCicodeList Specimen Condition (C78733)
if LB.LBSTREN ne to "" and LB.LBTESTCD = "HBA1CHGB"" and LB.LBDTC is uses Collection Date/Time (C82515)
if LB.LBSTREN ne to "" and LB.LBTESTCD = "HBA1CHGB"" and LB.LBDTC is uses Reference Range (C71474)
if LB.LBSTREN ne to "" and LB.LBTESTCD = "HBA1CHGB"" and LB.LBDTC is uses Laboratory Test Code (C83322)
if LB.LBSTREN ne to "" and LB.LBTESTCD = "HBA1CHGB"" and LB.LBDTC is usesCode % (C25613); mmol/mol (C11253); fraction of 1 (C105484)
Biomedical Concept

Attributes are linked to the element

<table>
<thead>
<tr>
<th>Class</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable Name</td>
<td>LBORRES</td>
</tr>
<tr>
<td>Variable Label</td>
<td>Result or Finding in Original Units</td>
</tr>
<tr>
<td>Type</td>
<td>Char</td>
</tr>
<tr>
<td>Core</td>
<td>Exp</td>
</tr>
<tr>
<td>Role</td>
<td>Result Qualifier</td>
</tr>
<tr>
<td>CDISC Notes</td>
<td>Result of the measurement or finding as originally received or collected.</td>
</tr>
<tr>
<td>Core</td>
<td>Exp</td>
</tr>
</tbody>
</table>

Sourced from SDTM 1.4 SDTMIG 3.2

Laboratory Test Result (C36292)

CDASH.LB–Local Processing.LBORRES
CDASH.LB–Local Processing.LBORRESU
SDTM.LB.LBORRES
SDTM.LB.LBORGUE
SDTM.LB.LBST
SDTM.LB.LBSTRESN
BRIDG.PerformedObservationResult.value
Biomedical Concept

Linking controlled terminology to the variable

- Laboratory Test Code (CB3222)
- Laboratory Test Name (C83142)
- Specimen Type (C70713)
- Specimen Condition (C80324)
- Unit of Measure (C25709)
- Quantitation Range (C125010)
- Reference Range (C71474)
- Reference Range Comparison (C122757)
- Normal Range Comparison Result (C122756)
- Subject Reference Start Date Time (C83395)

If LB.LBSTRESN ne to "",and LB.LBTESTCD = "HBA1CHGB" and LB.LBDTC is the closest prior date to DM.RFSTDTC then LBBLPL = Y, ELSE LBBLPL = NULL
Biomedical Concept

Standardize value level metadata

Hemoglobin A1C to Hemoglobin Ratio Measurement (C111207)

Collection Date/Time (C82515)

Planned Time Points (C826271)

Logical Observation Identifiers Names and Codes (LOINC) (C82502)

Baseline Flag (C82526)

Subject Reference Start Date Time (C83395)

Reference Range (C122757)

Laboratory Test Result (C36292)

if LB.LBTESTCN == "HBA1CCHGB" and LB.LBTESTCD == "HBA1CCHGB" and LB.LBDTC is the closest prior date to DM.RFSTDTC then LB.BFPL=1 ELSE LB.BFPL=null
Analysis Concept

Mean change from baseline in glycosylated hemoglobin

- Parameter Code
- Parameter
- Derivation Type
- Analysis Value
- Change from Baseline
- Baseline Value
- Analysis Baseline Record Flag
- Analysis Visit
- Planned Treatment
- Intent-To-Treat Population Flag

- HBA1CHGB
- HBA1C/Hemoglobin (%)
- "LOCF” when AVAL is imputed using last observation carried forward (post-baseline only)
- LB.LBTESTCD = "HBA1CHGB"
- AVAL-BASE
- AVAL where ABLFL = "Y"
- Set to "Y" when AVISIT = "Baseline"
- Laboratory Collection date/time
- Laboratory Visit Date

- Laboratory Test Code
- Laboratory Test Name
- Laboratory Unit
- Standardized Laboratory Test Result

Key:
- Derivation
- Terminology
- Variable
- Variable Connector
- Analysis Concept

For all colors, dotted line indicates customizable
Analysis Result

Statistical method
- Test of hypothesis comparing treatments
  - Uses
    - Mean change from baseline in glycosylated hemoglobin
  - Results in
    - Display (TFL)
      - Has Identifier
        - Is Table 4.2.1/Figure 4.2.1
    - Analysis results
      - Has
        - Identification
          - Name
          - Result
            - Has Identifier
              - Is Treatment difference results (LSMean, confidence interval, p-value)
        - Has Metadata
          - Includes Selection criteria
            - Is WHERE ITTFL = "Y" and PARAMCD = "HBA1C" and CHG ne .
              - And ANLO1FL = "Y" and DTYPE = " "
          - Analysis purpose
            - Is Primary outcome measure
              - Is Change in HbA1c from baseline
          - Analysis reason
            - Is Specified in SAP
          - Documentation
            - Includes See SAP Section XX for details. Program: t-hba1c-repmeas.sas
              - LS means and 95% CIs are based on repeated measures model adjusting for planned treatment, baseline HbA1c value, avisit, avisit*baseline and avisit*treatment interaction.
          - Programming statements
            - Based on
              - PROC MIXED DATA = ADHBA1C;
                - WHERE ITTFL = "Y" and PARAMCD = "HBA1C" and CHG ne .
                  - And ANLO1FL = "Y" and DTYPE = " "CLASS TRTP AVISIT;
                - MODEL CHG = TRTP BASE AVISIT BASE*AVISIT AVISIT*TRTP /
                  - DDFM=KR;LSMEANS TRTP / CL DIFF; REPEATED usubjid /
                    - subject = USUBJID TYPE=UN;RUN ;
            - Programming language
              - SAS
                - Has version
                  - Is 9.2
The Biomedical Concept and Analysis Concept are ONE MODEL
The Power of a Conceptual Model for Data Standards

- Linking controlled terminology to the variable – standardize value level metadata
- Machine readable definition of validation rules
- Linking derivations and algorithms to variable(s)
  - Include process metadata (ETL instructions)
- Possibility to standardize Analysis outputs and Collection instruments
  - Combining layout, variables, process information together
- Link Analysis Concepts to Biomedical Concepts
  - Choose an analysis and automatically obtain all related end-to-end metadata

→ All of the above: enables automation, increase confidence in results, true analysis traceability
Use Case 1: Define
Selecting standards concepts and linked metadata needed for a study

Data Standards
- Biomedical Concepts
- Analysis Concepts
- Foundational Standards

Endpoints
- TFL

Stages:
1. Data Collection Modules
2. Collection Metadata
3. Retrieve Collection Standards
4. Tabulation Metadata
5. Retrieve Tabulation Standards
6. Analysis Metadata
7. Retrieve Analysis Standards
8. Standards Metadata Selection

Protocol Outline (Hypothesis)
Standards Selection
Use Case 2: Build
Adding study design, concept configuration & generate artifacts

1. Create Operational Database
2. Operational Database
3. Create Tabulation Datasets
4. Tabulation Datasets
5. Create ADaM Datasets
6. Analysis Datasets
7. Create Analysis Results structures & shells
8. Endpoints
9. TFL
10. Clinical Study Reports

- CDASH
- SDTM
- ADaM
- Define
- XML
- Generate Study artifacts
- Configured study metadata
- Study Build and configuration
- Standards Metadata Selection
Study Build

SDM / XML

Study Build tool

Configured study metadata

Create artifacts (use case 2)

Standards Selection

Study Design
- Study parameters (TS)
- Eligibility criteria
- Schedule of activities (SOA)
- Study workflow

Study Configuration

Study workflow

Schedule of Activities (SoA)

Study Design

Study Parameters (TS)
Use Case 3: **Execute**

Automatic population of data into artifacts

**Operational Database** → **EDC Extract Database** → **Tabulation Datasets** → **ADaM Creation** → **Analysis Datasets** → **Analysis Results Creation** → **Endpoints**

**EDC**

**CDASH**

**eDT**

**Operational Database**

**EDC Extract Database**

**SDTM**

**Tabulation Datasets**

**ADaM**

**Analysis Datasets**

**Analysis Results Creation**

**Clinical Study Reports**

**TFL**

**Configured study metadata**

**eHR**

**ePRO**

**Process Study Data**

**CDISC**
Expected Outcome

• Learn
  • What works and what doesn’t

• Assessment
  • Technology Gap Analysis
  • Standards Gap Analysis

• Building a base for the future
  • Inform and involve stakeholders
  • Effort calculation and Cost / Benefit Analysis
  • Scale up to deliver the standards metadata needed
  • Partnerships with vendors to ensure tools are made available
2. Project Approach
CDISC 360 Advisory Committee

**CDISC 360 Leadership Team**

- David Bobbitt
  CDISC Chief Executive Officer
- Peter Van Reusel
  CDISC Chief Standards Officer
- Sam Hume
  CDISC Vice President Data Sciences
- Barry Cohen
  CDISC 360 Project Manager

**CDISC 360 Board Representation**

- Chris Decker - dWise
- Dave Evans - Accenture
- Dave Hardison - Deloitte
- Pandu Kulkarni - Lilly
- Steve Rosenberg - Oracle
- Ulo Palm - * Transcelerate

**CDISC 360 Committee Members**

- Praveen Garg - Astra Zeneca
- Patrick Genyn - Johnson & Johnson
- Brooke Hinkson - Merck
- Ulo Palm - Allergan
- Mike Hamidi - CDISC
Collaboration Tools

- CDISC 360 Wiki
  - Collaborative content

- Jira
  - Issues management

- CMAP Cloud
  - Concept map development

- Slack
  - Instant messaging

- Cloud Collaboration Platform
  - Use case demo environment
Reason for this scope: the Diabetes TAUG provides standardized artifacts from analysis outputs to data collection. This allows the project team to focus on innovation and not on establishing a new data standard.
Project Standards Scope
FDA Use Case

- 2 safety endpoints:
  - MACE: Major Adverse Cardiac Event
  - AKI: Acute Kidney Injury
- Turn specifications into standard concepts
- Verify analysis outputs and endpoint data vs. specifications
- Explore traceability: analysis outputs to specifications

→ **Reason for this scope:** Document FDA standard safety analysis requirements that may be expressed in the analysis concept maps; ensure the enhanced standards meet reviewers’ needs
CDISC 360 Workstreams

Enhance Standards

Publish Standards

Study Library

Define
Build
Execute
CDISC 360 Workstreams

**Workstream 1 - ENHANCE STANDARDS**
Create concepts in knowledge graphs

**Workstream 2 - PUBLISH STANDARDS**
Biomedical Concepts
Analysis Concepts
Foundational Standards

Load into library

API
Extend API's

Study Library

**Workstream 4 - DEFINE**
Identify and select standards specification (Use Case 1)

**Workstream 5 - BUILD**
Configure study specification and create artifacts (Use Case 2)

**Workstream 6 - EXECUTE**
Automatically process and transform data (Use Case 3)
3. Project Status
# Project Timeline

<table>
<thead>
<tr>
<th>#</th>
<th>Stage</th>
<th>Start</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Initiation, scoping, and internal staffing</td>
<td>Oct 2018</td>
<td>Nov 2019</td>
</tr>
<tr>
<td>2</td>
<td>Planning, recruiting CDISC member participants</td>
<td>Dec 2019</td>
<td>Feb 2019</td>
</tr>
<tr>
<td>3</td>
<td>Align with Transcelerate Digital Data Flow Initiative</td>
<td>Oct 2018</td>
<td>Jan 2019</td>
</tr>
<tr>
<td>3</td>
<td>Onboarding CDISC member participants</td>
<td>Mar 2019</td>
<td>Apr 2019</td>
</tr>
<tr>
<td>5</td>
<td>Kickoff, workstreams briefing</td>
<td>Apr 2019</td>
<td>Apr 2019</td>
</tr>
<tr>
<td>6</td>
<td>Execution of agile sprints</td>
<td>Apr 2019</td>
<td>Oct 2019</td>
</tr>
<tr>
<td>8</td>
<td>Execution of agile sprints</td>
<td>Nov 2019</td>
<td>Mar 2020</td>
</tr>
<tr>
<td>9</td>
<td>Project evaluation – Stage 2 (CDISC EU Interchange)</td>
<td>Mar 2020</td>
<td>Mar 2020</td>
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<tr>
<td>10</td>
<td>Execution of agile sprints</td>
<td>Apr 2020</td>
<td>Nov 2020</td>
</tr>
</tbody>
</table>
Participation Summary

29 Organizations

67 Resources specified

Organization Types:

- Pharma-Biotech Sponsor: 18
- CRO: 4
- Technology Provider: 6
- Regulatory: 1
360 Sprint Cycles for 2019

- **Sprint 1**: 8 April Kick Off
- **Sprint 2**: 11 April WS Briefing
- **Sprint 3**: 30 May
- **Sprint 4**: 27 June
- **Sprint 5**: 8 August
- **Sprint 6**: 29 August
- **Sprint 7**: 26 September
- **Sprint 8**: 24 October
- **Sprint 9**: 21 November
- **Sprint 10**: 12 December

**Today**: 9 January
4. Concepts Development - status
Organizing a Global Team
What is HbA1c?

Glycosylated Hemoglobin

Image source: https://www.ekfdiagnostics.com/res/HbA1c-Hemoglobin-banner
HbA1c, What's In a Name?

HBA1C  OR  HBA1C / HEMOGLOBIN
Finding Balance Between Linking Phrases and Elements

Specimen Collection
- has CDASH collection date
- has CDASH collection time
- has SDTM collection date/time

Specimen Collection
- has date/time
  - is represented in CDASH by LBDAT
  - is represented in SDTM by LBTIM
  - is represented in ADaM by LBDTC
  - is combined to produce --DT
  - is converted to --TM

Hemoglobin A1C to Hemoglobin Ratio Measurement
- has CDASH specimen collection date
- has CDASH specimen collection time
- has SDTM collection date/time

LBDAT
LBTIM
LBDTC
Binding Variables and Attributes to Concepts

Hemoglobin A1C to Hemoglobin Ratio Measurement (C111207) mustHave Collection date/time (C82515)

<table>
<thead>
<tr>
<th>Class</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable Name</td>
<td>LBDTTC</td>
</tr>
<tr>
<td>Variable Label</td>
<td>Date/Time of Specimen Collection</td>
</tr>
<tr>
<td>Type</td>
<td>Char</td>
</tr>
<tr>
<td>Core</td>
<td>Exp</td>
</tr>
<tr>
<td>Controlled Terms</td>
<td>ISO 8601</td>
</tr>
<tr>
<td>Role</td>
<td>Timing</td>
</tr>
<tr>
<td>Core</td>
<td>Exp</td>
</tr>
</tbody>
</table>

Sourced from SDTM 1.4 SDTMIG 3.2

SDTM.LB.LBDTC
CDASLP.Local Processing.LBDAT
CDASLP.Local Processing.LBTIM
Configuration Options for Controlled Terminology

- SITTING (C62122), SUPINE (C62167); STANDING (C62166);
- DECUBITUS (C77532); FOWLERS (C62173);
- LATERAL DECUBITUS (C100758); LEFT LATERAL DECUBITUS (C62172);
- PRONE (C62165); REVERSE TREDELENBURG (C62169);
- RIGHT LATERAL DECUBITUS (C62171); SEMI-FOWLERS (C62174);
- SEMI-RECUMBENT (C111310); SLING (C92604);
- TREDELENBURG (C62168); UNCONSTRAINED (C90480)
Biomedical Concept Specific Maps vs. Reference Maps

- **Vital Signs Test Code (C83466)**
  - usesNCICodeList
  - Blood Pressure (C0005623)
  - mustHave

- **Vital Signs Test Name (C49672)**
  - usesNCICodeList
  - Laboratory Test Result (C36292)
  - mustHave

- **Unit of Measure (C25709)**
  - usesNCICodeList
  - mmHg (C49670)
  - cmHg (C142129)
  - defaultCode

- **Planned Time Points (C2826271)**
  - mayHave
  - Collection date/time (C82515)

- **Position (C27148)**
  - defaultCode
  - SITTING (C62123)
  - SITTING (C62122), SUPINE (C62167), STANDING (C62166)

- **Procedure Location (C117525)**
  - usesNCICodeList
  - Anatomical Location (C74456)
  - LATERALITY (C39071)
  - usesCodes

- **Procedure Laterality (C117526)**
  - usesNCICodeList
  - LEFT (C25229)
  - RIGHT (C25228)

- **SITTING (C62122), SUPINE (C62167), STANDING (C62166)**
  - DECUBITUS (C77532)
  - FOWLERS (C52173)
  - LATERAL DECUBITUS (C100798)
  - LEFT LATERAL DECUBITUS (C62172)
  - PRONE (C62165)
  - REVERSE TRENDELENBURG (C62169)
  - RIGHT LATERAL DECUBITUS (C62171)
  - SEMI-FOLLERS (C62174)
  - SEMI-RECUMBENT (C111310)
  - SLING (C92604)
  - TRENDELENBURG (C62168)
  - UNCONstrained (C30480)

- **Systolic Blood Pressure (C1306620)**
  - Diastolic Blood Pressure (C1305849)
  - usesCodes
  - SYSBP (C1306620)
  - DIABP (C1305849)
Next Steps for Concept Development

• Complete end-to-end metadata mapping
  • Collection
  • Analysis
  • Additional concepts (e.g., demographics, study drug exposure, etc.)

• Decide on the amount of study specific metadata that should be represented in the map

• Incorporate FDA safety end-point use-cases
5. Art of the Possible
CDISC 360 – Art of the Possible

• What will follow is a User Experience presentation

• Purpose:
  • Illustrate how the CDISC 360 concept model will enable automation
  • For illustration only: CDISC 360 will not deliver software to the industry

• Scope of the User Experience:
  • Use the CDISC Library to create a simple study specification
  • Use concepts to generate an eCRF and Define-XML

  These automations reflect what CDISC 360 achieved to date

• After this User Experience, we will show how the back end works today
Thank You!

Peter Van Reusel
Sam Hume