White Paper

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Summary

The CDISC Foundational Standards define research data and metadata structures but writing these standards as documents has yielded more text than metadata. Gaps in standards metadata limit automation opportunities. The inherent flexibility provided by the standards supports a broad range of implementations, yet that flexibility allows for inconsistencies that make scaling automation difficult. The lack of a conceptual foundation for the standards further contributes to these inconsistencies. The relationships that would be expressed by these concepts remain largely implicit in the current versions of the standards.

CDISC 360 seeks to implement standards as linked metadata with a conceptual foundation providing the additional semantics needed to support metadata-driven automation across the end-to-end clinical research data lifecycle. This will enable software developers to develop new tools (proprietary and open source) that consume this novel metadata to ease standards' implementations, while increasing data processing efficiencies.

The aim of the CDISC 360 is to demonstrate the feasibility of standards-based, metadata-driven automation as a start toward realizing the full benefits expected of the CDISC standards: substantially improved efficiency, consistency, and re-usability across the clinical research data lifecycle. These benefits drive the return on investment in the CDISC standards implementations expected by CDISC stakeholders.

This White Paper describes the output of the CDISC 360 Proof of Concept as well as the technical prototypes developed using CDISC standards as linked metadata. The CDISC 360 standards content provides the additional semantics needed to support metadata-driven automation across the end-to-end clinical research data lifecycle.

Proof of Concept extensions to the CDISC standards have been developed by enabling metadata to support automation of end-to-end, clinical-study-data-artifact creation. A minimal amount of background-processing software was developed to demonstrate and confirm the viability of the standards-metadata extensions to drive such automation.

The Proof of Concept centered on three use cases:

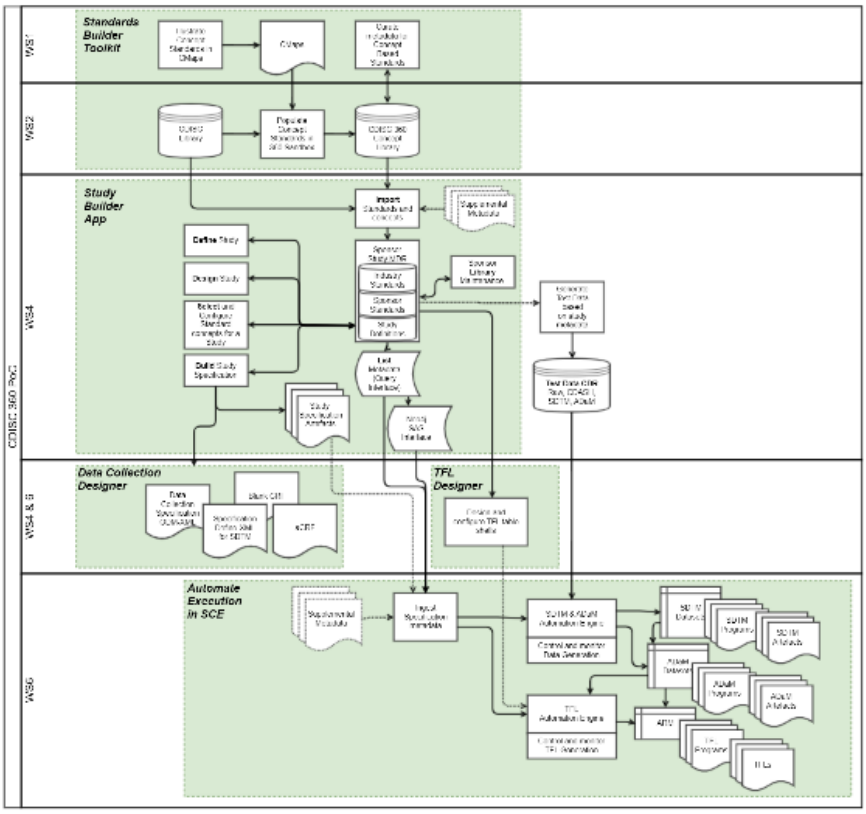
- **Use Case #1:** Create end-to-start, standards-based specification. The intent of this use case was to produce a machine-readable, standards-based specification from concept-based standard analysis output definitions in CDISC Library.
- **Use Case #2:** Generate start-to-end, study-specific metadata. To accomplish this, the project used the standards-based specification from the first use case to generate machine-readable, study-specific metadata artifacts.
- **Use Case #3:** Transform data start-to-end. To do so, the project used the machine-readable study-specific metadata from the second use case to process the study data. This demonstrated the ability to execute data transformations given the study-specific metadata.

CDISC invited employees from our membership community to participate in the project. Project teams were organized into the following seven workstreams:

- **Workstream #1:** Create concepts in knowledge graphs.
- **Workstream #2**: Transform concepts in machine-readable form
- **Workstream #3:** Add transformation semantics
- **Workstream #4:** Identify and select standards specification (Use Case 1)
- **Workstream #5:** Configure study specification and create artifacts (Use Case 2)
- **Workstream #6:** Automatically process and transform data (Use Case 3)
- **Workstream #7:** Document FDA analysis requirements in knowledge graphs. Verify analysis requirements, data and metadata traceability

The seven workstream teams started their work concurrently, requiring them to mock up their own set of inputs from previous workstreams. As the project progressed, they would share their outputs with each of the teams to ensure that they were aligned. In the end, while the Proof of Concept was not able to run automatically, it was able to prove the three use cases individually and showed that the alignment between the teams did indeed prove that an end-to-start specification could be generated by selecting the relevant biomedical concepts; that the specification could be used to generate study specific, machine-readable metadata artifacts; and drive the data transformations needed to implement end-to-end standards automation.

Diagram 1 illustrates the workflow within and across the CDISC 360 teams. A component model that shows the various functional elements the teams focused on in delivering the project follows the workflow diagram. Together, these diagrams provide the context needed to interpret how the project achieved a successful Proof of Concept.



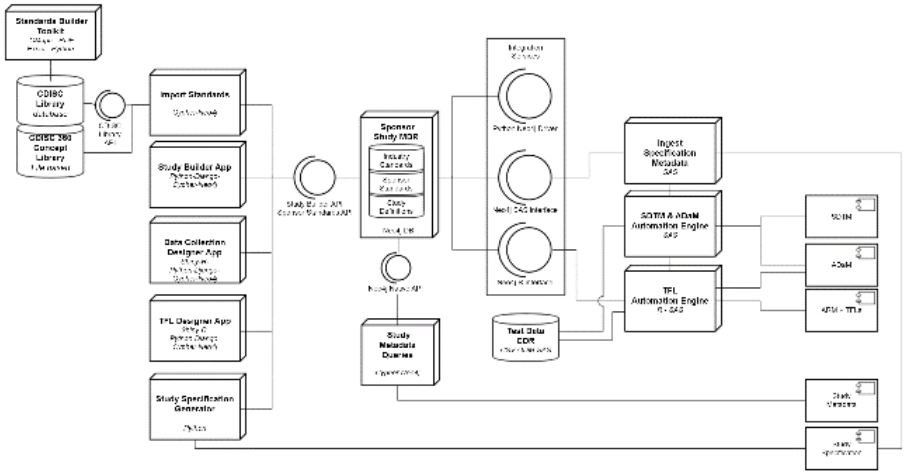


Diagram 1: Project Team Workflow and Component Model

CDISC 360 Test Data Clinical Data Repository

Illustrating the application of concept-based standards that support end-to-end automation can only be achieved using realistic test data. Since it was not possible to use data from real trials, the project generated artificial, subject-level test data for an imaginary study within diabetes. Generated test data do not hold any reference to real trials, protocols, subjects, patients or other personal data for any individuals.

The generated test data focused on CDASH, SDTM and ADaM datasets. Data domains for Trial Design datasets (TS, TA, TE and TV) as well as a few core datasets (DM, DS, SV, VS, LB and AE) were used. The test data included the corresponding CDASH data (DM, VS, LB and AE domain) and a set of ADaM datasets covering ADSL, ADVS, ADAE, and ADLB.

Technologies

Test data was generated via metadata-driven, SAS programs external to the project; files were transferred into the CDISC 360 Git repository. The data was then imported into the SAS DevTest Lab SAS computing environment in Azure.

Test datasets were represented as:

- SAS Transport files including Define.xml
- csv files
- Native SAS Dataset files (.sas7bdat)
- Other supporting files as PDF and Text

CDISC 360 Proof of Concept Trial Design and Scope

Test data was created based on a mock Phase III study that compared human insulin with Metformin for subjects with Type 2 diabetes. This approach enabled the team to simulate real drugs in the domains EX and TS – with codes for PCLASS and UNII. A mock protocol document was created based on the Common Protocol Template to document the generated test data in more detail. This document is located with the SDTM dataset so a link can be made from the Define.xml.

The trial design comprises a simple, two-arm, parallel group design with two weeks of screening, 26 weeks of treatment and four weeks follow-up – a total of 32 weeks with regularly scheduled visits during the trial. This is typical for Phase III diabetes trials with efficacy and safety endpoints described in the Diabetes Therapeutic Area User Guides as well as MACE.

SDTM Trial Design datasets were created (TA, TE, TV, TS) and study was added to the CDISC 360 Study Library in Neo4j.

Data for 100 subjects are generated. At the moment all subjects pass screening and completes the trial (i.e., no screening failures, withdrawals or lost to follow-up); this can be added later, if applicable.

Biomedical Concept Definition

The CDISC 360 Workstream 1 team defined Biomedical Concepts as high-level building blocks of clinical research information that encapsulate lower-level implementation details, such as variables and terminologies. A Biomedical Concept is a unit of knowledge created by a unique combination of characteristics that specifies an observation concept in a clinical study, but it does not specify how to capture the data or how to group observations together. Biomedical Concepts exist independently of any given standards implementation, such as SDTMIG v3.2 or CDASHIG v2.0.

The Workstream 1 team was charged with finding a way to represent Biomedical Concepts as linked metadata within the confines of CDISC standards.

An early decision was to represent Biomedical Concepts as concept maps using CMapTools developed by the Institute for Human-Machine Cognition. Multiple styles and formats for producing these maps were experimented with before ultimately deciding on using the ISO 11179 standard for representation of metadata; a logical choice since ISO 11179 is also the basis on which CDISC Library is built. To accommodate all concept attributes required for representing Biomedical Concepts in a manner useful for downstream workstreams, components outside of ISO 11179 were added.

In the course of the Proof of Concept project, the team made a decision to produce higher-level, template maps with a focus on reusability across related concepts (e.g., a high-level, vital signs map that could be instantiated for specific vital signs measurement). Instantiation of these concept maps involved the creation of metadata files to bind the concepts to the specific, required Controlled Terminology in CDISC Library. The maps produced for CDISC 360 are designed to be human and machine-readable.

Finally, files were produced to illustrate the mapping of collected concepts from CDASH to SDTM.

Following this approach, we produced concept maps and associated metadata files for the following:

- Vital signs
    - Systolic blood pressure
    - Diastolic blood pressure
    - Temperature
- Adverse events
- Insulin administration
- Labs
    - HbA1C
    - Hemoglobin
    - Total cholesterol
    - LDL cholesterol
- Subject demographics
- Disposition events and milestones
- Trial arms
- Trial elements
- Trial summary parameters
- Trial visits

The final maps and files were handed off to the CDISC 360 Workstream 2 team for further processing.

Sub-components

- Biomedical Concept definition
- Concept maps
- Metadata files
    - Binding files
    - CDASH-SDTM mapping files

Technologies

- Concept maps were constructed using CMapTools from IHMC.
- Metadata files were created using Microsoft Excel.

Scope of Functionalities

Concept maps are visual representations of concepts expressed as linked metadata, including:

- Data elements and their relationships
- Controlled Terminology and associated codelists
- Derivations, where applicable

Most concept maps produced for CDISC 360 represent SDTM-observation concepts (e.g., HbA1c, systolic blood pressure, insulin administration, etc). Some are template maps designed to be re-used for any of a number of related concepts (e.g., labs or vital signs measurements). A small number of analysis concept maps were produced, but more robust testing of these maps is required.

Binding files are tabular representations of the information contained in the concept maps intended as content for CDISC Library. They show the bindings of variable values to the appropriate Controlled Terminology.

Project Status

The Workstream 1 team developed concepts as described above for the listed concepts. Work has begun on analysis concept maps; further testing and development is required.

Sources/Reference documents

CmapTools: https://cmap.ihmc.us/cmaptools/

Illustrations

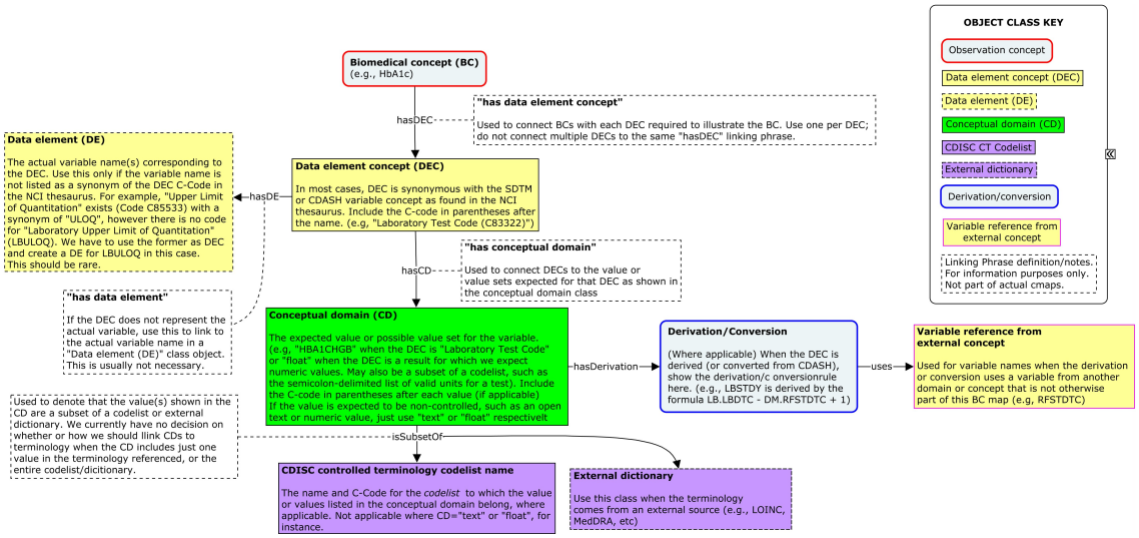


Diagram 2: Key for the Development of Concept Maps in Workstream 1.

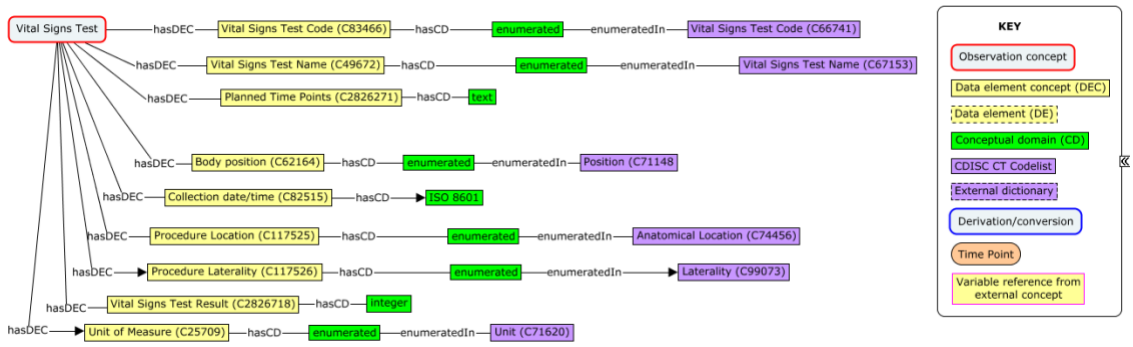


Diagram 3: Example of an Abbreviated Template Concept Map (Not All Variables Shown) for Vital Signs Measurements

Limitations and Assumptions

ISO 11179 was not a perfect fit for our needs in representing Biomedical Concepts and required augmentation. Implications for interfacing with CDISC Library are still being explored and workarounds may be required.

Suggested Next Steps

Going forward, we intend to expand concept-based development to additional concepts with a focus on the most commonly collected concepts across a survey of study sponsors. Working with the newly formed CDISC Analysis Results Metadata standards team, we aim to further refine the process of using concept maps in standards development in a new use case for representing the dataflow into analysis outputs like tables, listings and figures. Work has begun on analysis concept maps; further testing and development is required.

Standards Builder Toolkit

Workstream 2 used the Standards Builder Toolkit, which is a set of Python tools used to transform the Biomedical Concepts and mappings developed by Workstream 1 into a virtual Metadata Repository Sandbox. The Sandbox can serve as a source for creating Define-XML and ODM exports for the study design, build and execute teams.

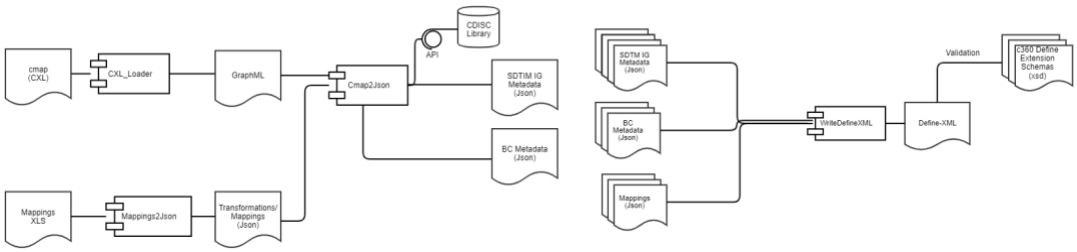


Diagram 4: Standard Builder Toolkit Schematic

Sub-components

Name	Type	Description
CXL_Loader	Python tool	Converts CMAP CXL export to GraphML
Cmap2JSON	Python tool	Uses GraphML to drive CDISC Library queries, generate Biomedical Concept Metadata and SDTM Clib Metadata output by domain. Domain specific output files are used by WriteDefineXML to create a Define-XML for all available Biomedical Concepts.
Mappings2JSON	Python tool	Uses Mappings Spreadsheet to drive CDISC Library queries Domain specific output files are used by Write DefneXML to create Define-XML for all available Biomedical Concepts. JSON output is used by Cmap2JSON.

Name	Type	Description
WriteDefineXML	Python tool	Generates Define-XML for a preconfigured list of domains. For each domain, the Biomedical Concept JSON file and mappings files generated.
C360WriteODMXML	Python tool	Generates ODM forms for Biomedical Concepts.
c360-define-schemas	XSD files	Schema extensions for Define-XML.
c360-odm-schemas	XSD files	Schema extensions for ODM.
define2-1-forC360	XSL file	Adaptation of 'standard' Define-XML stylesheet updated to support schema extensions.
C360 ODM stylesheet	XSL file	Updated version of legacy ODM to CRF stylesheet.
Biomedical Concept Metadata	JSON Files	For each domain in the C360 and Mace+ scope, xx_bcConcept.json file.
Define-XML File Archive	Wiki page	See the Define-XML folder in the C360WS2Tools GitHub repository referenced below.
ODM File Archive	Wiki page	See the ODM-XML folder in the C360WS2Tools GitHub repository referenced below.
CMAP File Archive	CXL Files	See the data/CMAP- XML folder in the C360WS2Tools GitHub repository referenced below.
JSON File Archive	JSON Files	See the data/bcJsonFiles folder in the C360WS2Tools GitHub Repository referenced below.

Table 1: Standards Builder Toolkit Sub-components

Github: https://github.com/scassells/C360WS2Tools

Biomedical Concepts SDTM Bindings Metadata

Standard and Version Metadata

Index	Content	Comments
Parent	string:$domain-sdtmig	
prodVers	string:sdtmig-$vers	
$domain_bcConcepts	List	

Domain Level Biomedical Concepts

$domain_bcConcepts	Content	Comments
Ordinal	int	
bcID	string	"BC"$domain{bcName}

$domain_bcConcepts	Content	Comments
bcName	string	Remove spaces in bcTopicVar
bcTopicVar	string	Label of Observational Concept in Cmap
bcCond	string	Specified in short comment from Observational Concept in Cmap
_links	sdtm-topic:{"href":URL,,"title":string,"type":string}	
bcVarList	List	List of Biomedical Concept SDTM variable bindings

Biomedical Concept SDTM Variable Bindings

index	Content	Comments
DEC	string: SDTM Variable Name	Specified in short comment in first DEC node in the cmap.
CLibRef	"self":{"href":URL,"title":string,"type":string}	
cdType	"integer" "text" "ISO 8601"	
cdVal	subsetSpecification:{"subset":sting} valueSpecification:{"value":string}	The subset string is label of a CD node in the CMAP with semicolon(";") separator, linefeeds removed. The value string is the label of a CD node in the CMAP with a single value. It may or may not include a C-Code.
"origin"	MappingType: "Predecessor", "Assignment", "Computation" Content dependent on MappingType	

CDISC Library References for Variable and Codelist

ClibRef	Content	Comments
self	"href": URL, "title":string,"type":string	get Endpoint
codelist	"href": URL, "title":string,"type":string	get Endpont

Biomedical Concept Mapping Information

Predecessor Origin	Content	Comments
MappingType	Predecessor	from mappings spreadsheet
Description	sting	from mappings spreadsheet
SourceVar	string	String is formatted as CDASH-$domain:$sourceVarName

Mapping Method Metadata

Method Origin	Content	Comments
MappingType	Computation	from mappings spreadsheet
Description	String	
InputVariables	List{"Standard":$standardName."Domain":$domain,"VarName":string,"Value":string}	from mappings spreadsheet
Preferred	"Yes"	from mappings spreadsheet

CMAP CXL Archive

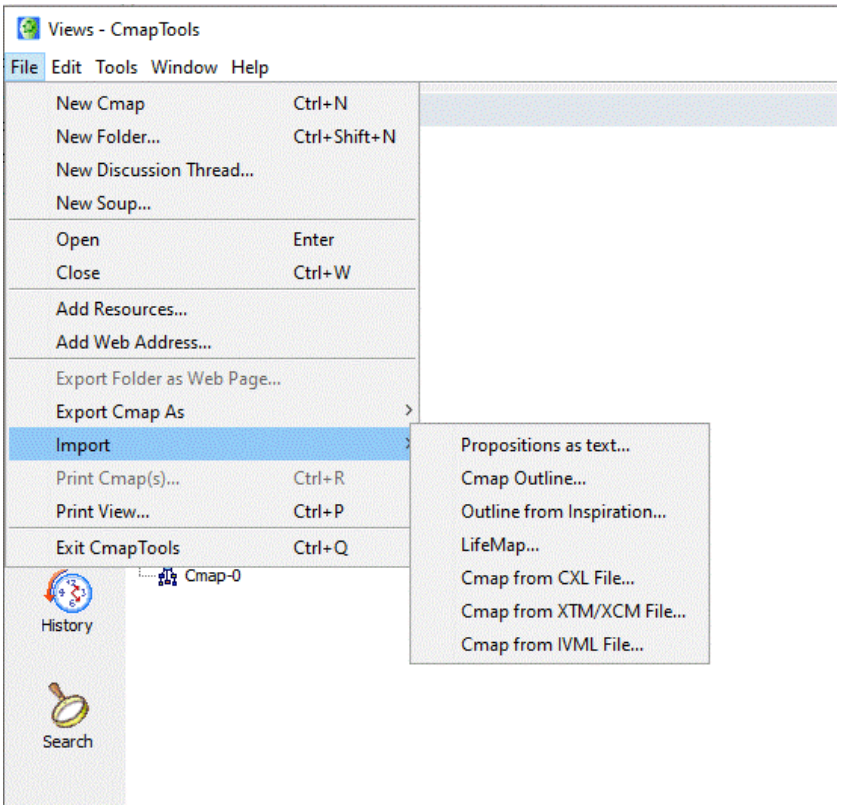


Diagram 5: CXL exports can be imported into the Cmaps tool as shown in the screenshot.

MACE+ Analysis Concept ADaM Bindings Metadata

Index	Content	Comments
Parent	string:$domain-sdtmig	
prodVers	string:admig-$vers	
$domain_bcConcepts	List	

$domain_bcConcepts	Content	Comments
Ordinal	int	
acID	string	"BC"$domain{bcName}
acName	string	remove spaces in bcTopicVar
acTopicVar	string	Label of Observational Concept in Cmap
acCond	string	Specified in short comment from Observational Concept in Cmap
_links	AVAL, PAaram	
acVarList	List	

Index	Content	Comments
DEC	string: ADaMVariable Name	Specified in short comment in first DEC node in the cmap
CLibRef	"self":{"href":URL,"title":string,"type":string}	
cdType	"integer" "text" "ISO 8601"	
cdVal	subsetSpecification:{"subset":sting} valueSpecification:{"value":string}	The subset string is label of a CD node in the CMAP with semicolon(";") separator, line feeds removed. The value string is the label of a CD node in the CMAP with a single value. It may or may not include a C-Code.
"origin"	MappingType: "Predecessor", "Assignment", "Computation" content dependent on MappingType	

ClibRef	Content	Comments
self	"href": URL, "title":string,"type":string	get Endpoint
codelist	"href": URL, "title":string,"type":string	get Endpont

Predecessor Origin	Content	Comments
MappingType	Predecessor	from mappings spreadsheet
Description	sting	from mappings spreadsheet
SourceVar	string	String is formatted as CDASH-$domain:$sourceVarName

Method Origin	Content	Comments
MappingType	Computation	from mappings spreadsheet
Description	String	
InputVariables	List{"Standard":$standardName."Domain":$domain,"VarName":string,"Value":string}	from mappings spreadsheet
Preferred	"Yes"	from mappings spreadsheet

CDISC 360 Concept Library Proof of Concept Component

The CDISC 360 Concept Library Proof of Concept Component is intended to serve as the sandbox library holding the new concept-based library. The files were generated to represent the concept-based standards but were not imported directly.

Additional information needed for the Proof of Concept standards was represented in supplemental metadata loaded into the Sponsor Study MDR.

Sub-components

XML files

Represent Biomedical Concept.

Supplemental Metadata

Generated and imported manually into Sponsor Study MDR.

Technologies

XML and CSV files.

Scope of Functionalities

For the CDISC 360 Proof of Concept, additional metadata was generated for Biomedical Concepts not currently available in the CDISC Library.

Component	Implementation
Identifiers	Biomedical Concept ID, Name and DEC bindings
bcCond	Define-XML WhereClause
bcVarList	Define-XML ItemGroup
DEC	SDTM Variable names – bound to domain definition in SDTMIG Version identified in Biomedical Concept parent and prodVers
ClibRef	URIs for CDISC Library variable and codelist endpoints.
cdVal	Concept Domain - subsets
origin	CDASH-SDTM mappings and derivations

Deployment of Component

Standards Builder Toolkit.

Project Status

Only the minimum needed for the 360 Proof of Concept have been made.

Sources/Reference Documents

WS4 Supplemental Metadata

Study Designer App 360 Proof of Concept Component

SDTM Trial Design datasets were created (TA, TE, TV, TS) and the study was added to the CDISC 360 Study Library in Neo4j.

Workstream 4's Proof of Concept component described here is a prototype for a CDISC 360 Study Designer App. The Study Designer App starts with a Protocol Outline and delivers a complete Study Specification, including structured protocol elements. This was accomplished via an API-based connection to a Sponsor Study Metadata Repository and can be done via a file-based solution.

The first step was to create basic definitions for the study, covering identifiers, study title and the selected data standard versions. Note: We envision that you can decide at any time to up or down version any data standards.

The linked graph model supported identifying any consistency issues – a benefit of applying a linked graph data model.

Next, we created the specification of the study design, including the planned interventions. Then followed the selection, configuration and scheduling of the Biomedical Concepts in the form of objectives, endpoints, activities and assessments.

Finally, the Build Process for generating various study-specification artifacts was created with the ability to browse and export the study metadata in various representations from the List menu.

The key focus was the use of the new 360 concept-based standards to drive the study specification, which is tool and system agnostic. We illustrated this using the new standards to

create a study specification via a simple, web-based Study Designer App connected to a Neo4j based Study MDR.

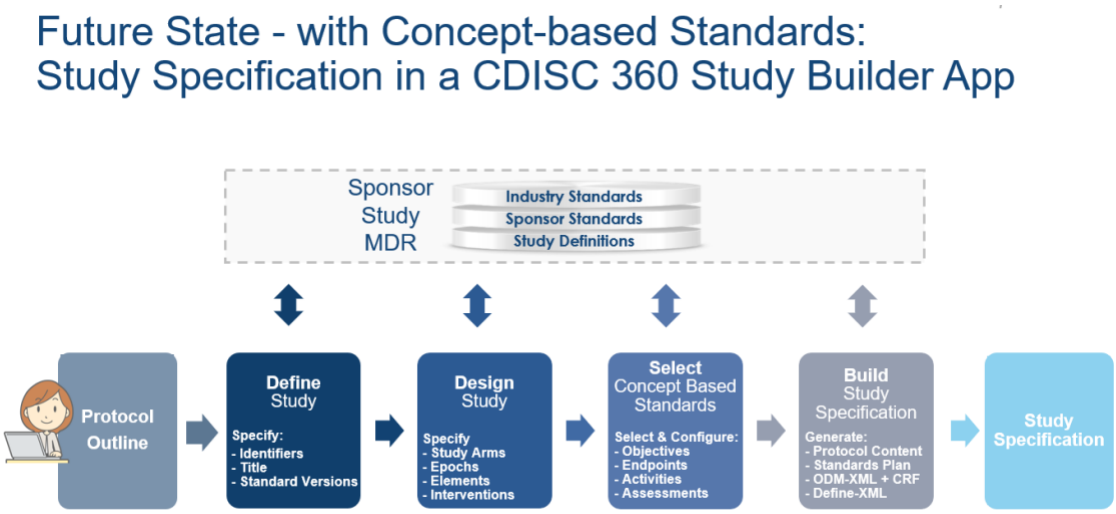


Diagram 6: Future State with Concept-based Standards: Study Specification in a CDISC 360 Study Designer App

Sub-components

- Front-end application based on a Python-Django framework.
- Back-end application based on a Python-Django-API framework managing the connection to the Neo4j database.
- Various Python packages are also used in the Proof of Concept.

Technologies

- Both front-end and back-end parts run as a Python-Django application on an Azure app service.
- The connection to the Neo4j database is fully handled by the Python drivers available at: https://neo4j.com/docs/api/python-driver/
- The network data visualization intended to follow the user in the study build process and data exploration is handled with vis.js network package available at: https://visjs.org/
- The necessary data manipulation between the cypher-query results and the front-end application are handled with Pandas and Numpy.
- The editable tables in the design page are powered by the GIJGO grid package: https://gijgo.com/grid/
- The main CSS framework used across the application is Bootstrap https://getbootstrap.com/; however, only key components necessary for project scope are fully responsive.

Scope of Functionalities

The Study Designer App illustrates the Study Define, Design, Select and Configure Biomedical Concepts and then builds a Study Configuration via an MDR solution. We prototyped one way, but there are many ways of applying the CDISC 360 concept-based standards as long as the solution is tool and system agnostic. A file-based solution design would also work.

Key Features in the Study Designer App

Library

Import definitions from external libraries.

Manage sponsor defined selections and definitions.

Define Identifiers and a general set of trial summary parameters for the study

Design Study design parameters as well as defining study arms, elements, epochs and visits

Select Search and select concept-based standards and define schedule of activities and assessments

Build Generate study specification artefacts that support automation of study setup and execution

List

Extract study metadata in tabular format for down stream usage.

From within the App with export to multiple format as well as direct from SAS.

Goal for Workstream 4: Create a linked graph model for a Sponsor Study MDR.

We did not create a 360 Sandbox Library, and since all teams had to start in parallel, the file-based, Biomedical Concept representation was not available to us at the start. Therefore, we created supplemental metadata as simple csv files, which we used to load the enhanced metadata currently not available in the CDISC Library. We aligned content and structure on an ongoing basis. The process flow for the Study Designer App is illustrated in the lower half of Diagram 7.

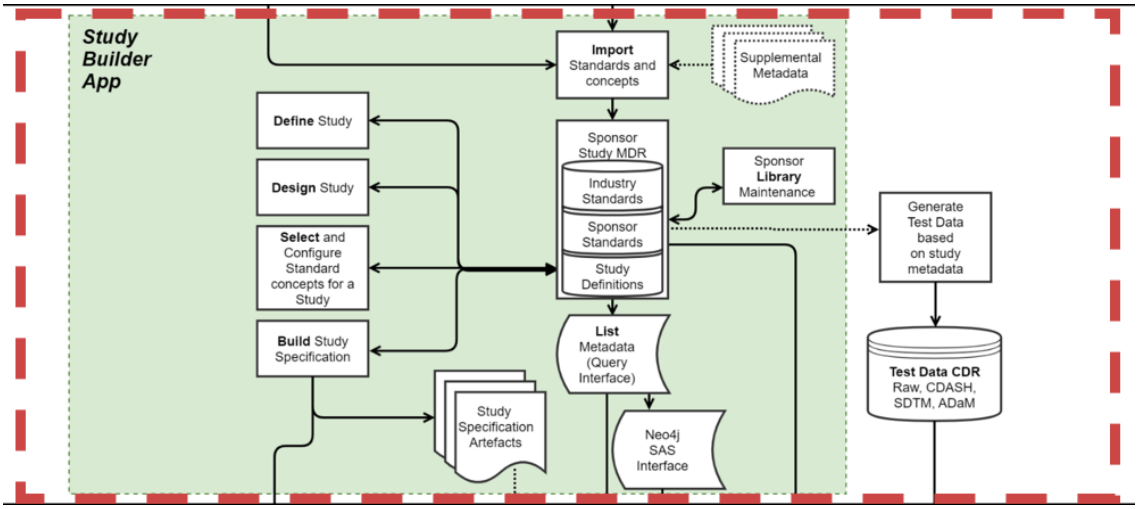


Diagram 7: Study Designer App Process Flowchart

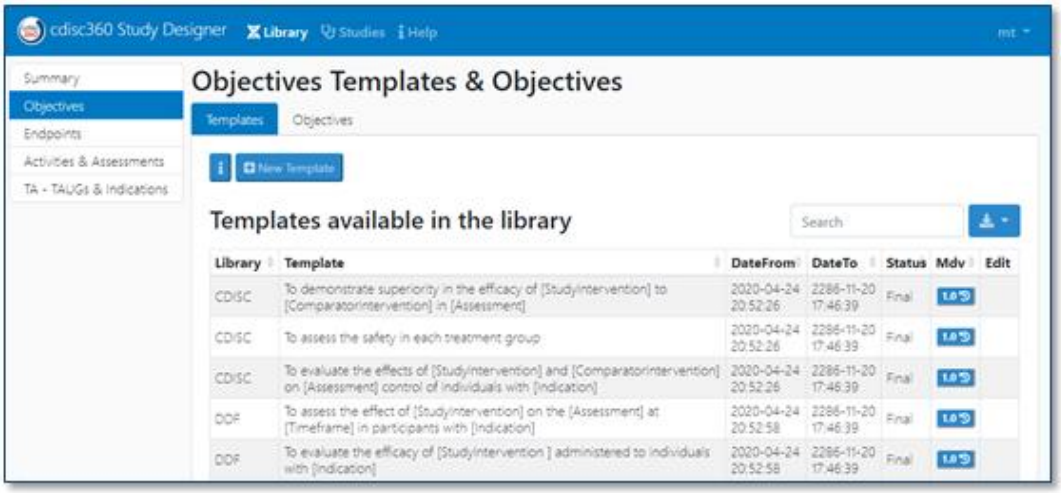
Component Deployment

A release pipeline from the Azure Git repository published the application on the Azure App service.

Examples

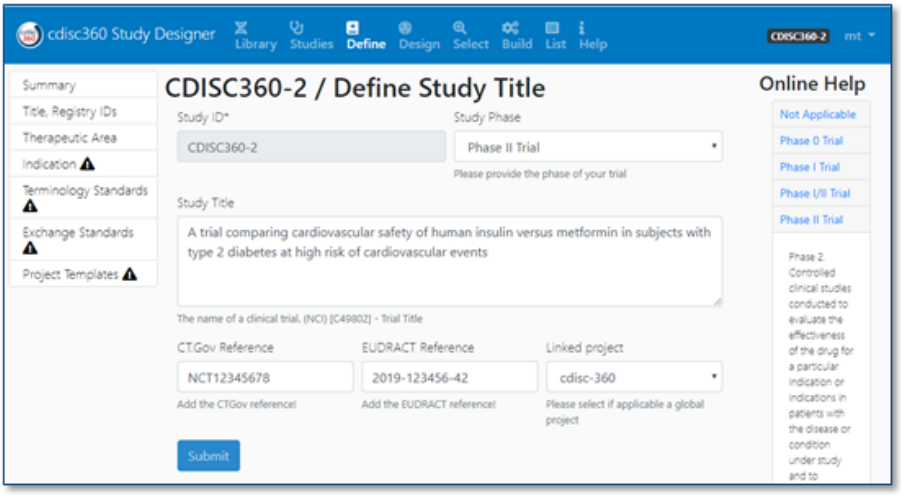
On the **Library** menu, the user:

- Creates additional templates for Objectives and Endpoints.
- Creates instantiations of imported or sponsor defined templates.
- Includes references to dependent parameters from instances of Objective and Endpoints.



On the **Define** menu, the user:

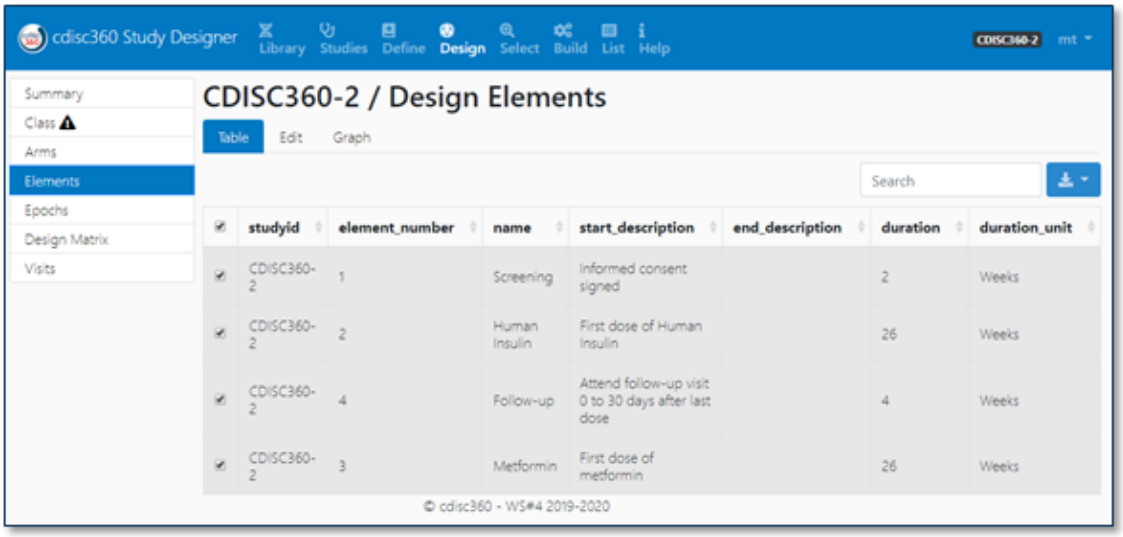
- Enters the basic description (e.g., the study phase, title, registry identifiers) of the trial.
- Enters study therapeutic area and CDISC TAUGs used.
- Enters version of CDISC Controlled Terminology.
- Enters version of Data Exchange Standards.

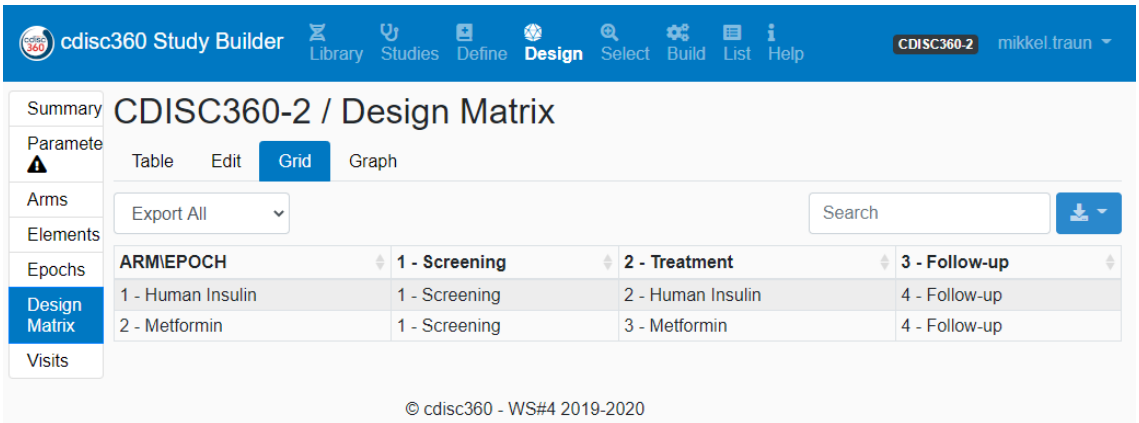


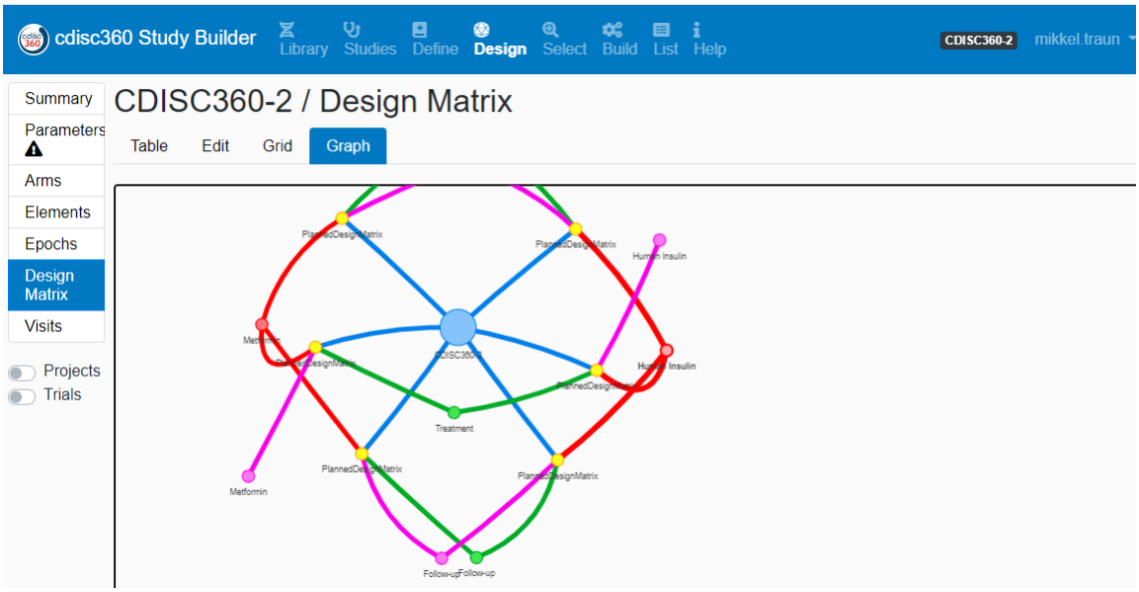
On the **Design** Menu, the user:

- Makes a basic selection of trial-design-related summary parameters (e.g., Intervention Type, Intervention Model etc.).
- Defines the Trial Arms, Epochs, Elements and the Design matrix.
- Defines the Visit Schedule.

- Define the Planned Interventions.

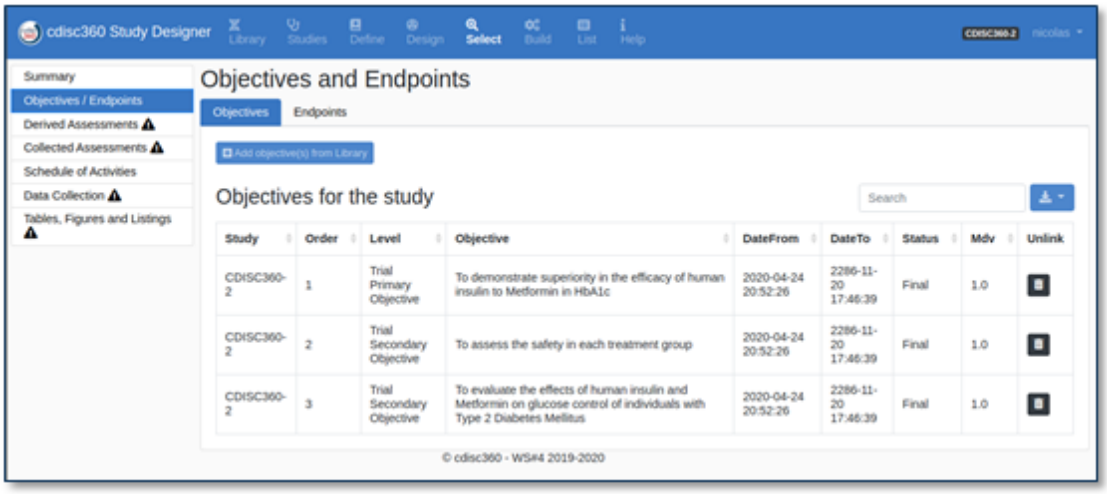


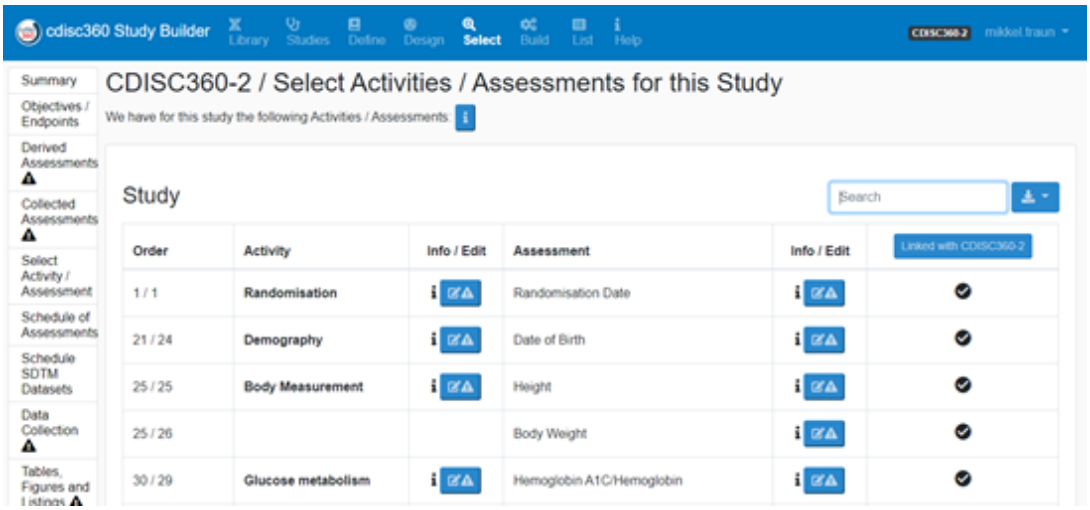


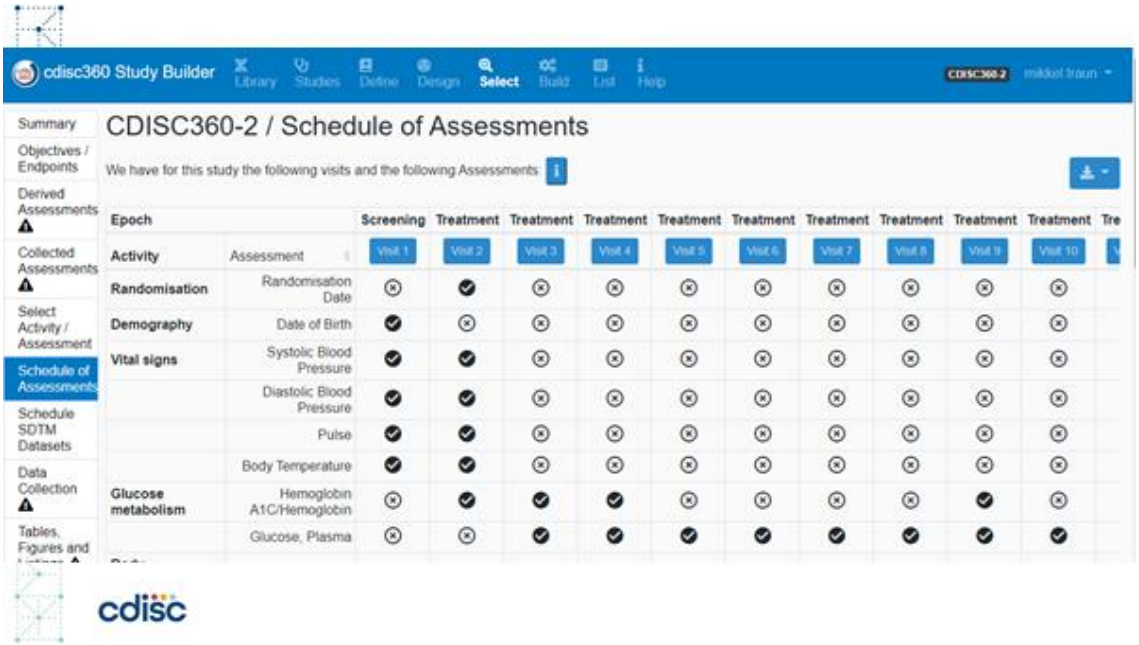


On the **Select** menu, the user:

- Selects the concept-based standards from the libraries to be used in the study. Standards can be based on templates instantiated in the local library.
- Selects Objectives and Endpoints.
- Selects Activities and Assessments.
- Selects Schedule of Activities and Assessments.

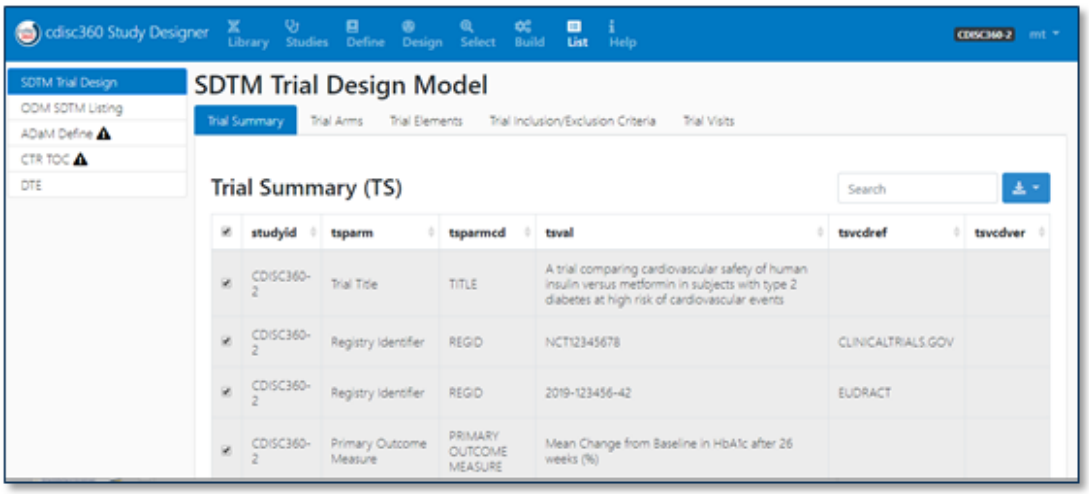


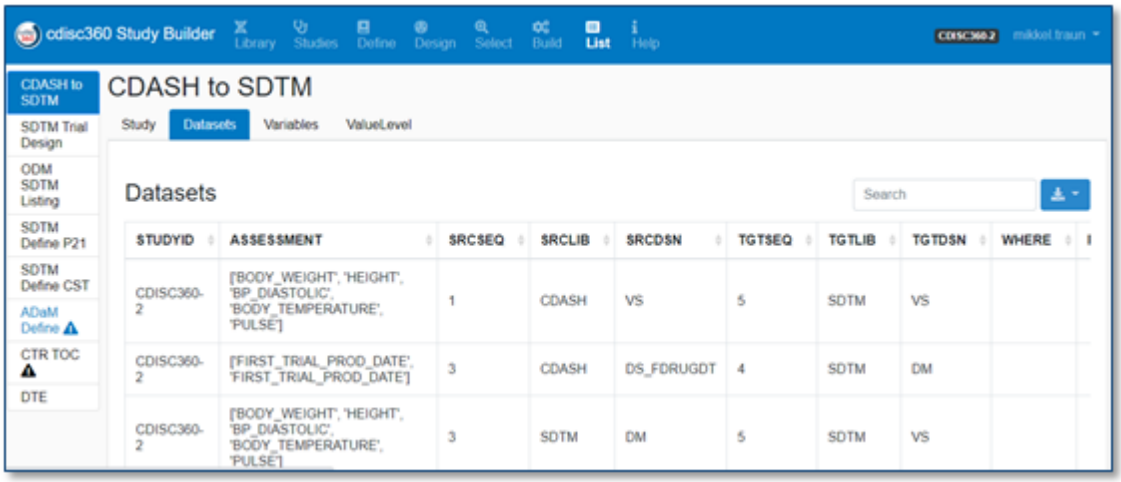




On the **List** Menu the user can:

- Browse all study metadata in tabular form.
- Export metadata into various file formats.
- Create a SAS-based interface to the Study Metadata Library enabling extract of study metadata into SAS datasets, including CDASH2SDTM and SDTM2ADaM Bindings).





Interface View of Trial Summary and Datasets

Technologies

Test data was generated by metadata-driven, SAS programs external to the project; files were transferred into the Git repository. The data was then imported into the SAS DevTest Lab SAS computing environment in Azure.

Test datasets were represented as:

- SAS Transport files, including Define.xml
- csv files
- Native SAS Dataset files (.sas7bdat)
- Other supporting files as PDF and Text

Description of CDASH Generation

In the 360 Proof of Concept, we reverse-engineered the generated SDTM data to create CDASH data. While not optimal, this was the simplest and most pragmatic approach considering the expedited timeframe and lack of a robust test data sample.

Description of SDTM Generation

DM Data

All subjects had a random date for screening from 01-JAN-2019 and 60 days forward; all other dates were offset from generated data of screening according to the planed trial time (currently hardcoded in the program and not driven by metadata).

Subjects were randomly allocated to each trial arm and sex; age was random from 18 to 64 years. Other qualifiers can be added later, if applicable.

DS Data

All subjects had the following disposition events and protocol milestones as completers, according to their planned trial time offset from the generated screening visit:

DSCAT	DSTERM / DSDECOD
PROTOCOL MILESTONE	INFORMED CONSENT OBTAINED
PROTOCOL MILESTONE	FIRST DATE ON TRIAL PRODUCT
PROTOCOL MILESTONE	RANDOMIZED
PROTOCOL MILESTONE	LAST DATE ON TRIAL PRODUCT
PROTOCOL MILESTONE	COMPLETED TREATMENT
DISPOSITION EVENT	COMPLETED

SV Data

All subjects attended all planned visits at the planned visit time according to their reference start date in the trial.

VS Data

All subjects had all the planned Vital Signs assessments at the planned visits at the planned time. Data for Vital Signs are generated in the CDASH Denormalized/Horizontal implementation option and a SDTM.VS dataset is provided with a suggested mapping.

SDTM.VS is defined with the following VSCAT, VSTESTCD, VSTEST:

VSCAT	VSTESTCD	VSTEST
VITAL SIGNS	SYSBP	Systolic Blood Pressure
VITAL SIGNS	DIABP	Diastolic Blood Pressure
VITAL SIGNS	PULSE	Pulse Rate
VITAL SIGNS	TEMP	Temperature
BODY MEASUREMENT	HEIGHT	Height
BODY MEASUREMENT	WEIGHT	Weight

AE Data

20 typical AE terms within MACE+ have been created, and each is assigned to one subject (005, 010, 015, etc.). Some result in hospitalization or are fatal; details in the generated data can be changed to be more meaningful, complete or to support scenarios in TLFs. The AE terms within MACE+ were flagged in the ADaM dataset ADAE.

Additionally, 1 to 20 non-MACE AEs of common terms were randomly assigned to each subject from a list of typical AE terms within diabetes. This approach provided approximately 1500+ AE records, the actual number and values change for each regeneration of test data.

LB Data

Currently the lab data holds the following tests:

lbtestcd	lbtest
ALB	Albumin

lbtestcd	lbtest
ALT	Alanine Aminotransferase
CHOL	Cholesterol
CREAT	Creatinine
HBA1CHGB	Hemoglobin A1C/Hemoglobin
HCT	Hematocrit
HDL	HDL Cholesterol
HGB	Hemoglobin
LDL	LDL Cholesterol
PLAT	Platelets

Description of ADaM Generation

The following ADaM datasets were generated based on the SDTM test data, which were intended to be used within the CDISC 360 project.

- **ADSL**: Subject Level Analysis
- **ADLB**: Lab Analysis
- **ADVS**: Vital Signs Analysis
- **ADAE**: Adverse Events Analysis dataset
- **ADTTE**: Data for the Time to Event Analyses

The following information describes how the Analysis datasets are generated:

ADSL: Subject Level Analysis

ADSL contains one record per subject (USUBJID, the unique identifier); variables, such as subject-level population flags; planned and actual treatment variables, demographic information, subgrouping variables, stratification factors, and important dates.

The input SDTM test datasets (i.e., SDTM.DM and SDTM.DS) have been used to generate ADSL.

The main population flags derived in ADSL are FASFL and SAFFL. TRT01A and TRT01P are the treatment variables, which merged with other BDS and OCCDS datasets.

Additionally, by using disposition SDTM dataset, the following variables are derived:

- EOTSTT: End of Treatment Status
- EOSTT: End of Study Status

Moreover, the key dates and duration variables are derived and available in ADSL.

- **TRTSDT**: Date of First Exposure to Treatment
- **TRTEDT**: Date of Last Exposure to Treatment
- **EOTDT**: End of treatment date

- **EOSDT**: End of study date
- **TRTDURD**: Total Treatment Duration (Days)
- **TRTDURY**: Total Treatment Duration (Years)
- **INTRDURD**: In Trial Observation Time (Days)
- **INTRDURY**: In Trial Observation Time (Years)

Along with the above variables, there are demographic variables (e.g., AGE, SEX, RACE, ETHNIC, COUNTRY and AGEGR1).

AGEGR1 has been created by stratifying AGE variable into the following three groups:

1) 15<= to <30 years

2) 30<= to <45 years

3) >=45 years

ADLB: Lab Analysis (BDS)

The ADLB dataset is based on the SDTM.LB and contains data for laboratory assessments for BIOCHEMISTRY, GLUCOSE METABOLISM, HAEMATOLOGY and LIPIDS.

ADLB is a BDS dataset that contains one or more records per subject, per analysis parameter, per analysis timepoint. Per the Basic Data Structure definition, analysis timepoint represents Analysis Visit (AVISIT).

For all the parameters, the data collected at week 0 is considered baseline value; ABLFL has been derived by this baseline value.

In addition, other variables like CHG (Change from Baseline), PCHG (Percentage Change from Baseline), BASE (Baseline Value), R2BASE (Ratio to Baseline) and ADY (Analysis Relative Day) are derived for analysis purpose.

As stated in the protocol, the secondary endpoint is “Proportion of Subject with HBa1C < 7% (Count). Timeframe: after 26 weeks.” As a result, we derived the CRIT1 (Analysis Criterion 1) variable, which indicates whether HBa1C value is <7 % or not and the corresponding flag variable (i.e., CRIT1FL (Criterion 1 Evaluation Result Flag)), which have the values Y or N.

Along with the above-mentioned analysis variables, the core variables are merged with ADLB from ADSL dataset.

ADVS: Vital Signs Analysis (BDS)

The ADVS dataset is based on the SDTM.VS and contains data of assessments for Body Measurement (Height and Weight) and Vital Signs (Diastolic Blood Pressure, Pulse Rate, Systolic Blood Pressure and Temperature).

ADVS is a BDS dataset that contains one or more records per subject, per analysis parameter, per analysis timepoint. Per the Basic Data Structure definition, analysis timepoint represents Analysis Visit (AVISIT).

For all parameters, the data collected at week 0 is considered baseline value; ABLFL has been derived by this baseline value.

In addition, other variables like CHG (Change from Baseline), PCHG (Percentage Change from Baseline), BASE (Baseline Value), R2BASE (Ratio to Baseline) and ADY (Analysis Relative Day) are derived for analysis purpose.

Along with the above-mentioned analysis variables, the core variables are merged with ADVS from ADSL dataset.

ADAE: Adverse Events Analysis Dataset

The ADAE dataset contains all collected and reported events in SDTM.AE, meeting the definition of an adverse event (AE). All events from the first trial-related activity, after the subject has signed the informed consent until the end of the post-treatment, follow-up period, are included.

The treatment emergent duration is defined as the duration for which the subject is on treatment, including an ascertain window of 7 days (i.e., TRTEMFL = "Y" when TRTSDT <= ASTDT <= TRTEDT+7)

As stated in the CDISC 360 protocol, the primary objective is “Time to first occurrence of MACE+, a composite endpoint consisting of: CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina.”

The external data have been used here. For example, AE_MACE_1, which includes the list of AETERMS, satisfies MACE criteria and derives the flag variable MACEPFL (MACE Plus Flag). This variable was used in ADTTE dataset for performing time-to-event analysis.

Some of the core AE variables listed in the following table are available in ADAE.

Column	Label
AETERM	Reported Term for the Adverse Event
AEDECOD	Dictionary-Derived Term
AEBODSYS	Body System or Organ Class
AEBDSYCD	Body System or Organ Class Code
AELLT	Lowest Level Term
AELLTCD	Lowest Level Term Code
AEPTCD	Preferred Term Code
AEHLT	High Level Term
AEHLTCD	High Level Term Code
AEHLGT	High Level Group Term
AEHLGTCD	High Level Group Term Code
AESOC	Primary System Organ Class
AESOCCD	Primary System Organ Class Code
AESEV	Severity/Intensity
AEREL	Relationship to trial product
AESER	Serious Event
AEOUT	Outcome of Adverse Event
AESHOSP	Requires or Prolongs Hospitalization

Along with the above-mentioned analysis variables, the core variables are merged with ADAE from ADSL dataset.

ADTTE: Data for the Time-to-Event Analyses

The ADTTE dataset is based on the ADAM.ADAE and contains data for the following parameters:

- Time to first occurrence of MACE+(days)
- Time from randomization to death (days)

The structure of ADTTE is a BDS dataset that contains one record per subject, per analysis parameter as well as the parameters mentioned above.

As stated above, to create ADTTE, ADAE is the input dataset by filtering MACEPFL = "Y" for the PARAMCD = “MACE+” and AEOUT = “FATAL” for the PARAMCD = DEATH”.

CNSR variable is created based on the event occurrence and the values are 0 (when the event occurs) and 1 (completed the study without having the event). The corresponding AVAL variable (timing variable in days) is derived.

EVNTDESC is the censor description variable derived for both parameters.

The following table provides additional details on analysis variables and the possible values.

Parameter	PARAMCD	EVNTDESC	CNSR
Time to first occurrence of MACE+(days)	MACE+	FIRST MACE+	0
Time to first occurrence of MACE+(days)	MACE+	COMPLETED STUDY	1
Time from randomization to death (days)	DEATH	DEATH	0
Time from randomization to death (days)	DEATH	COMPLETED STUDY	1

Along with the above-mentioned analysis variables, the core variables are merged with ADTTE from ADSL dataset.

Project Status

Selected parts of the application are fully functioning and connected live to the Neo4j database.

Some menu items, tagged with ⚠ have been added to illustrate the intended scope.

Sources/Reference documents

- WS4 - Study Designer App
- Git repository StudyDesignerApp

Limitations and Assumptions

A mock dataset for 100 subjects based on a Phase V sample protocol, only represents subjects who passed the initial screening and completed the trial (i.e., no screening failures, withdrawals or lost to follow-up).

Suggested Next Steps

Use a Phase III sample dataset to enable a larger scope that includes screening failures, withdrawals or lost to follow-up.

Study Builder and Sponsor Standards API CDISC 360 Proof of Concept Component

API Interface for the Sponsor MDR

Workstream 4's API Interface manages sponsor-defined extensions to CDISC standards as well as Study Definitions.

The goal of this component is to conduct all interactions with the Sponsor MDR via a standardized API, enabling the use of multiple tools from different vendors. The API service layer manages access control, versioning and audit trail.

Technologies

- Python-Django API framework using Cypher statements
- API is documented by Open API (Swagger)

Scope of Functionalities

For the CDISC 360 Proof of Concept, only a few API endpoints were defined and tested to validate how this could be done and what it requires in the technical application design.

We started with a limited scope design as we learned how best to work with the API framework and iterated it to a full scope pilot implementation.

Suggested Next Steps

A pilot implementation of the API-driven design should demonstrate a redesigned full scope implementation and be available as part of the CDISC Open Source Alliance (COSA) scheduled for deployment in late 2021.

Sponsor Study MDR 360 Proof of Concept Component

Linked graph database that holds connected metadata for:

- CDISC Standards
- Sponsor-defined Extensions
- Study-specific Metadata for the Study Definition

Technologies

Neo4j database. A number of Neo4j Cypher scripts create graph model constraint definitions and load test metadata data into the Neo4j database (see: https://neo4j.com/product/).

Scope of Functionalities

The scope and purpose of the Sponsor Study MDR is to support the clinical study process from planning, study design, study specification, and study set up to drive downstream automation. Such a solution is deeply related to the data domain of clinical studies. A domain-driven design is applicable for this IT solution and fits well with an API-based architecture, where the API endpoints are closely related to the data domain.

This section describes the data model for the Sponsor Study MDR component at different levels of abstraction, each with a dedicated focus. The initial purpose of the data model description is to support the design and implementation process during the system development process of a Sponsor Study MDR system. Equally important, the data model description needs to support the usage and maintenance of a Sponsor Study MDR after go live. The data model description is an important outcome of the CDISC 360 Proof of Concept and a crucial part of the coming development of a CDISC 360-based Study MDR solution.

The first step is to define the boundaries of the data domain that the system should cover by identifying its high-level data domains and subject areas. This step is important for the scoping and identifying dependencies needed for the system components as well as for project planning in the development phase and the maintenance phase.

The next step is to design the logical data model needed to solve the tasks and deliverables for the system and identify the data entities, attributes and their relationships.

Final steps: 1) Design how these data elements are to be exchanged via the system interfaces (APIs) between the different system components and the domain data model. 2) Determine how the data model is to be implemented in the actual data storage, the physical data model.

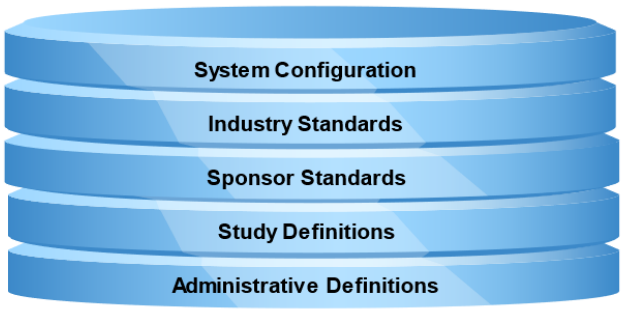
The following table provides an overview of the different types of data models, their definition and purpose.

Data Model Type	Definition	Purpose
Conceptual Data Model	A high-level description of informational needs underlying the design of a database.	Define the scope for the data domain and subject areas the data model should cover.
Logical Data Model	A high-level description of informational needs underlying the design of a database.	Define the scope for the data domain and subject areas the data model should cover.
Domain Data Model	A domain model is a representation of the data, independent of the way the data is stored in the database.	Define the way data can be exchanged between systems (e.g., by an API based interface). Can be in various exchange formats like JSON, XML, CSV, etc.
Physical Data Model	A representation of a data design as implemented in a database management system.	The technical specification for the design of the data base implementation.

Conceptual Data Model – Domain Areas

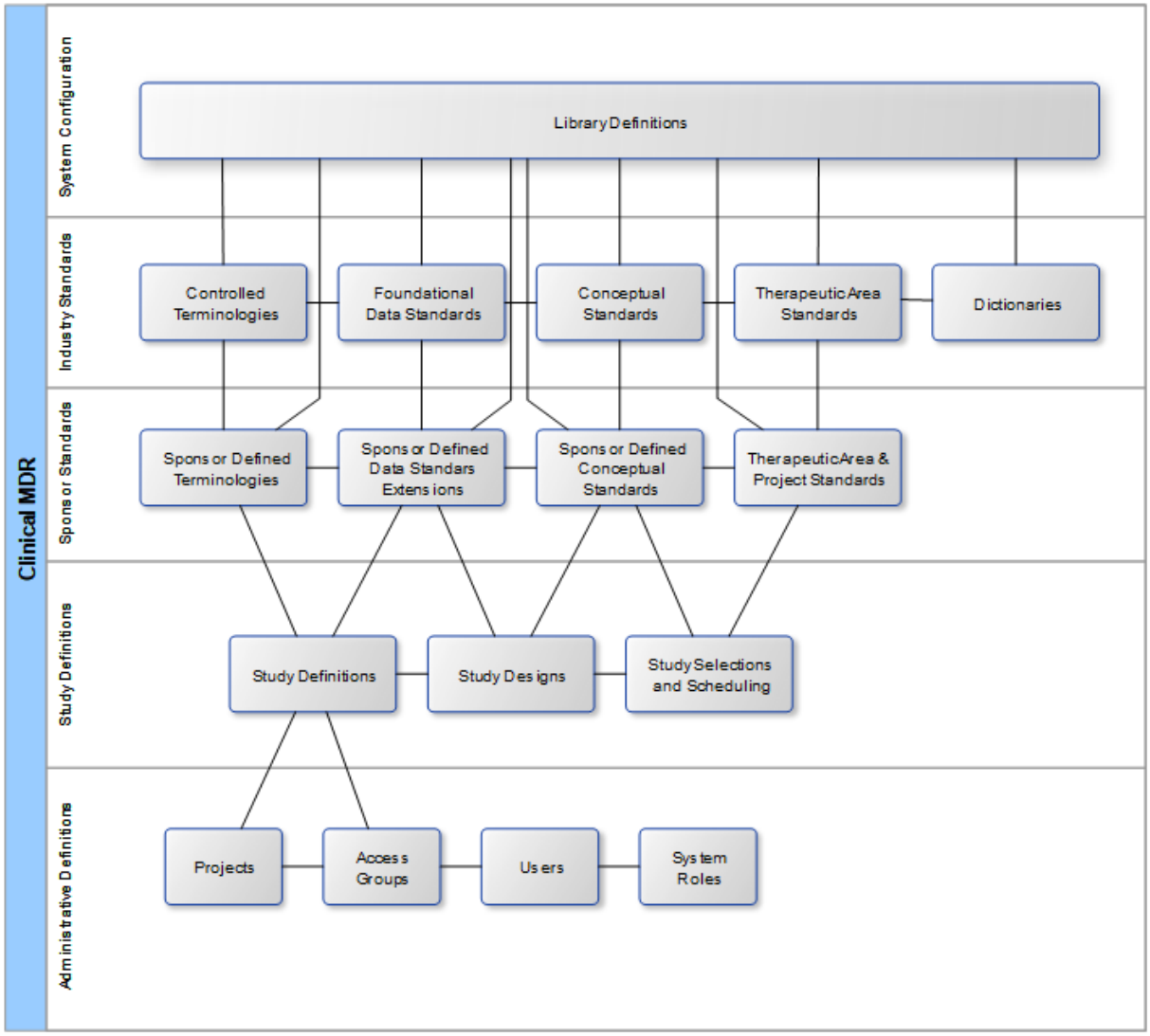
The purpose of the domain areas in the conceptual data model is to define the overall data scope for the Sponsor Study MDR system component. The system includes the following data model domain areas in the following sections:

- System Configuration
- Industry Standards
- Sponsor Standards
- Study Definitions
- Administrative Definitions



Conceptual Data Model – Subject Areas

The purpose of the subject areas in the conceptual data model is to define the main data domains and their relationships in order to define a more detailed scope for identifying dependencies. This insight can be used for planning the implementation order for the different components as well as dependencies when they later are maintained. The conceptual data model diagram is layered by each data domain area and shows each subject area with their main relationships.


Clinical MDR
System Configuration
Library Definitions
Industry Standards
Controlled Terminologies
Foundational Data Standards
Conceptual Standards
Therapeutic Area Standards
Dictionaries
Sponsor Standards
Sponsor Defined Terminologies
Sponsor Defined Data Standars Extensions
Sponsor Defined Conceptual Standards
Therapeutic Area & Project Standards
Study Definitions
Study Definitions
Study Designs
Study Selections and Scheduling
Administrative Definitions
Projects
Access Groups
Users
System Roles

System Configuration

The System Configuration domain area holds the various entities (e.g., connected external and defined internal libraries) that form the system configuration.

- Library Definitions hold system definitions such as external CDISC Library and internal Sponsor Library.

Industry Standards

The Industry Standards domain area holds the imported industry standards, initially only from CDISC Library (i.e., Controlled Terminologies and Foundational Standards). Additional standards (LOINC, SNOMED and MedDRA dictionaries) will be added later.

- **Controlled Terminologies**
  - The Controlled Terminologies subject area in the Industry Standards domain area holds Controlled Terminologies as codelists and terms that are imported into the Clinical MDR. When imported as a reference to the source library, they will be kept as a reference to the external versioning information.
- **Foundational Data Standards**
  - The Foundational Data Standards subject area in the Industry Standards domain area holds the clinical data standards, including models, domains and specifications for data representation. When imported into the Clinical MDR as a reference to the source library, they will be kept as external versioning information.
- **Conceptual Standards**
  - The Conceptual Standards subject area holds the CDISC 360 Biomedical Concepts in the form of Activities, Assessments and Analysis Concepts related to data derivation, analysis and analysis results.
- **Therapeutic Area Standards**
  - The Therapeutic Area Standards subject area holds the definitions from the various CDISC Therapeutic Area User Guides, which will reference the CDISC conceptual standards, applied Foundational Standards as well as usage of Controlled Terminology.
- **Dictionaries**
  - The Dictionaries subject area holds rich and highly specialized, medical terminologies that facilitate sharing and exchange of clinical information (e.g., LOINC, MedDRA, SNOMED, etc.).

Sponsor Standards

The Sponsor Standards domain area holds the sponsor-defined extensions to the industry standards as well as sponsor-defined, supplemental standards.

- **Sponsor Defined Terminologies**
  - The Sponsor Defined Terminologies subject area holds extensions to standard terminologies, initially only for CDISC Controlled Terminologies.
- **Sponsor Defined Data Standards Extensions**
  - The Sponsor Defined Data Standards Extensions subject area holds extensions and configuration to Foundational Standards, initially only for CDISC Foundational Standards so that they can be extended (i.e., adding standard SDTM variables to SDTM dataset domains or creating sponsor-defined SDTM domains).

- **Sponsor Defined Conceptual Standards**
    - The Sponsor Defined Conceptual Standards subject area holds sponsor-defined Biomedical Concepts in the form of Activities, Assessments and Analysis Concepts related to data derivation, analysis and analysis results based on the CDISC 360 model.
- **Therapeutic Area and Project Standards**
    - The Therapeutic Area and Project Standards subject area holds the sponsor-defined definitions of Therapeutic Area as well as a project-specific selection of standards and will reference the new CDISC conceptual standards, applied Foundational Standards as well as usage of Controlled Terminology. They can refer to what is required or optional to apply by the sponsor.

Study Definitions

The Study Definitions domain area holds the study level metadata for study definitions and specifications.

- **Study Definitions**
    - The Study Definitions subject area holds the basic definition for a study in the form of the study identification, study title, phase, type and the selected data standard versions.
- **Study Designs**
    - The Study Designs subject area holds the structural description of the study design in the form of study arms, epochs, elements, visit schedules and planned interventions.
- **Study Selections and Scheduling**
    - The Study Selections and Scheduling subject area holds the selection, configuration and scheduling of biomedical and analysis concepts (e.g., schedule of activities and assessments) for the study.

Administrative Definitions

The Administrative Definitions domain area holds the system administrative definitions.

- **Projects**
    - The Projects subject area holds the project definitions and the relationship to therapeutic area, investigational drugs and indications.
- **Access Groups**
    - The Access Groups subject area holds the defined access groups that can be assigned to users.
- **Users**
    - The Users subject area holds the users of the Study Sponsor MDR system with their relationship to access groups and system roles.
- **System Roles**
    - The System Roles subject area holds the defined system roles that can be assigned to users.

Logical Data Model

The Logical Data Model defines the entities, their relationship and attributes of the data domain independently and how they are implemented or exchanged.

As an example, please see Diagram 8 or the Objectives and Endpoints subject area. The Objectives and Endpoints comprise part of the top levels of the conceptual standards that refer to Activities and Assessments, identical similar to Industry and Sponsor Standards, depending on the relationship to the Library entity.

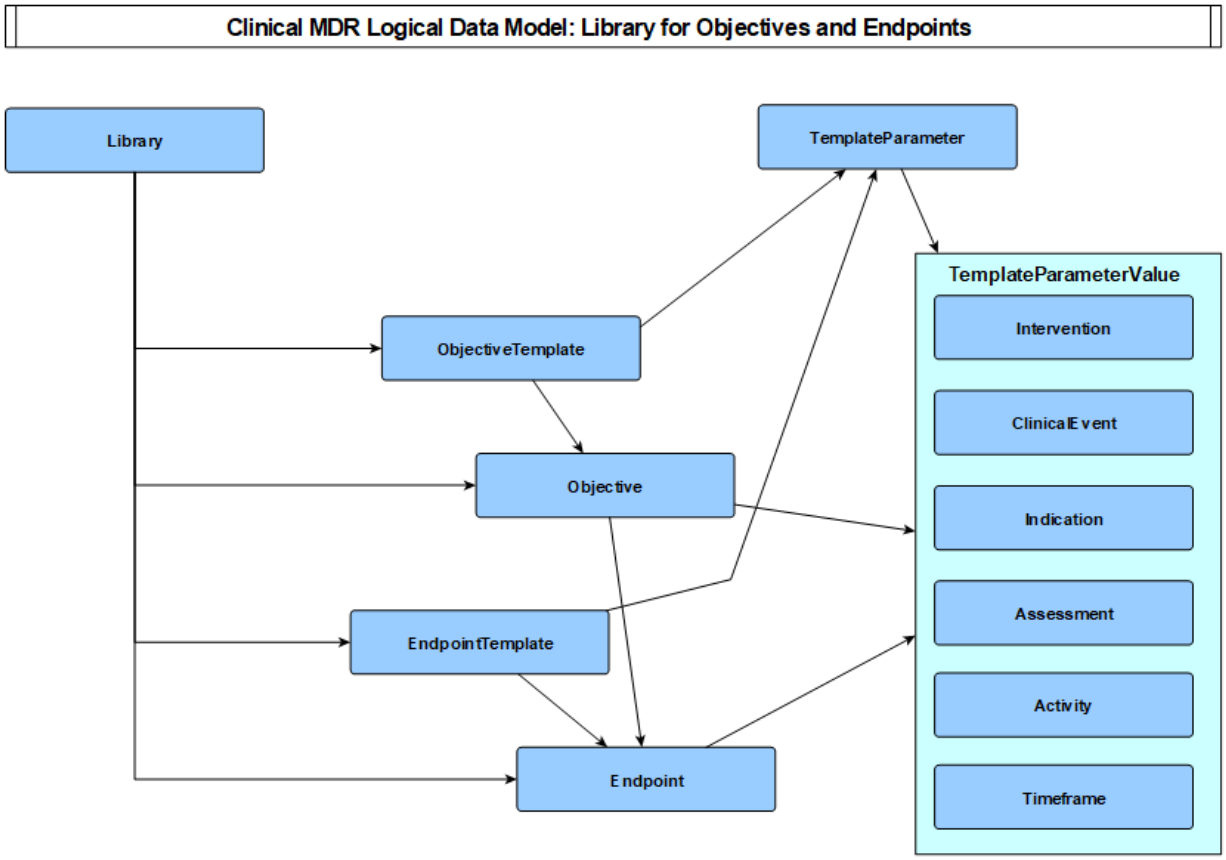


Diagram 8: Objectives and Endpoints Subject Area

Logical Data Model

Entity	Definition	Example
Library	Entity holds the name and definition of the library that are the source and owner for the elements in the library.	The CDISC Library and a sponsor-specific library.
ObjectiveTemplate	A sentence syntax for an objective text, including reference to parameters that can be replaced with standardized values.	To demonstrate superiority in the efficacy of [StudyIntervention] to [ComparatorIntervention] in [Assessment]
Objective	A sentence that represents a specific objective sentence based on a template where the parameters are replaced with specific standardized values.	To demonstrate superiority in the efficacy of human insulin to Metformin in HbA1c
EndpointTemplate	A sentence syntax for an endpoint text, including reference to parameters that can be replaced with standardized values.	Mean Change from Baseline in [Assessment] after [Timeframe] ([Unit])
TemplateParameter	A sentence that represents a specific endpoint sentence based on a template where the parameters are replaced with specific standardized values.	Mean Change from Baseline in HbA1c after 26 weeks (%)
TemplateParameterValue	Hold the specific standardized values, which are categorized by the specific types of template parameters.	Human insulin (StudyIntervention), HbA1c (Assessment)

Domain Data Model

The Domain Data Model represents how the data is returned from the API calls and is made as an Object-Oriented class diagram representing the returned result file from an API call. It can be represented in various exchange file formats (JSON, XML, CSV, etc.); for the Sponsor Study MDR system, JSON is mainly used. For certain API endpoints, other file formats will be supported, which can be used to support exports into other systems.

Diagram 9 is an example of an Objectives Templates data domain, sub-part of the conceptual standards subject area, corresponding to the /objective-templates API endpoint. It is identical for Industry and Sponsor Standards, depending on the relationship to the Library entity.

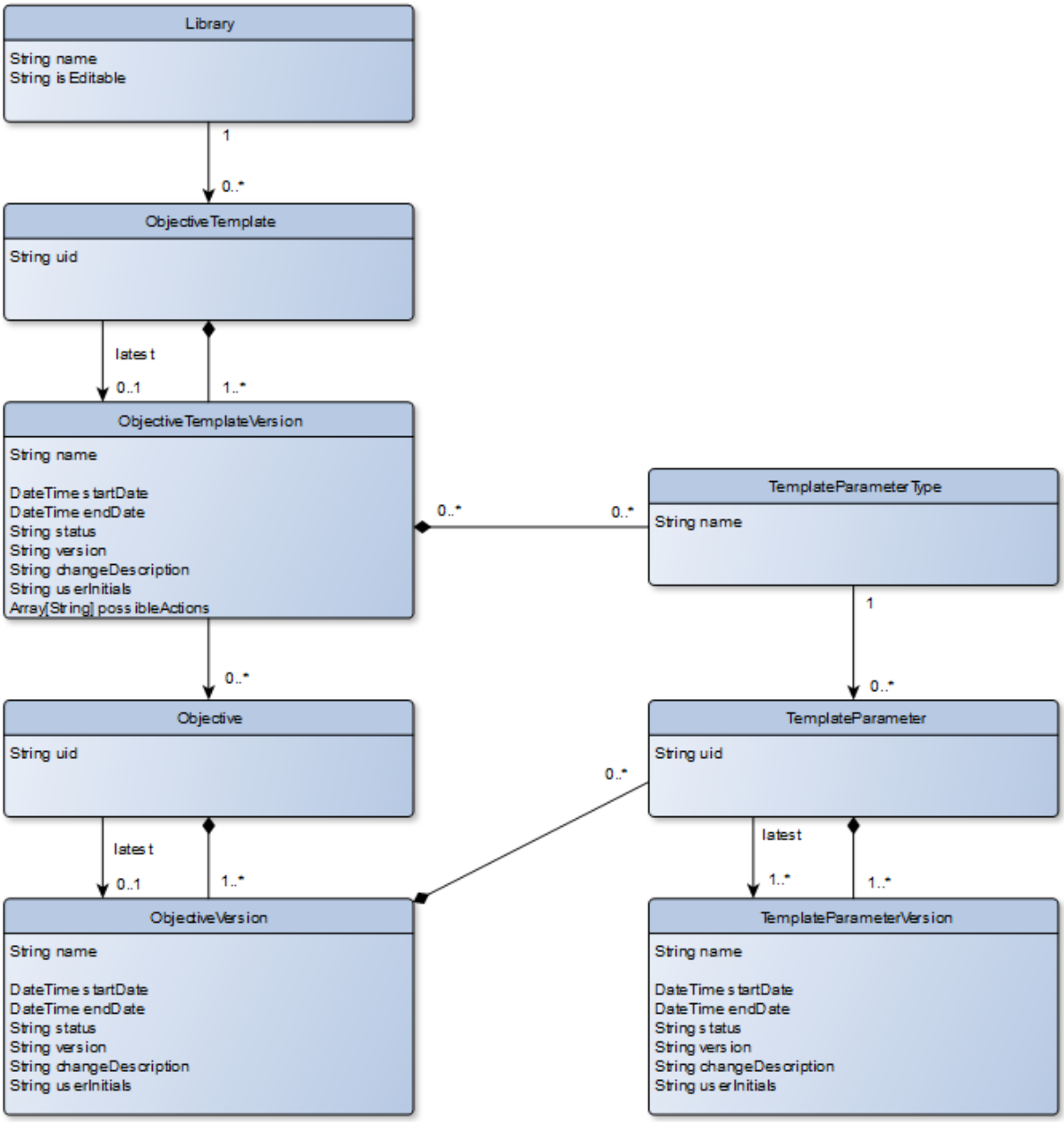


Diagram 9: Objectives Templates Data Domain

Physical Data Model

The Physical Data Model represents the actual data model as it is implemented in the database. For the Sponsor Study MDR system, the database is a Labeled Property Graph database (Neo4j). The Physical Data Model, therefore, describes the nodes and relationships with properties as implemented in Neo4j.

Diagram 9 is an example of the Objectives Templates nodes and relationships, sub-part of the conceptual standards subject area, corresponding to the /objective-templates API endpoint. It is identical for Industry and Sponsor Standards, depending on the relationship to the Library entity.

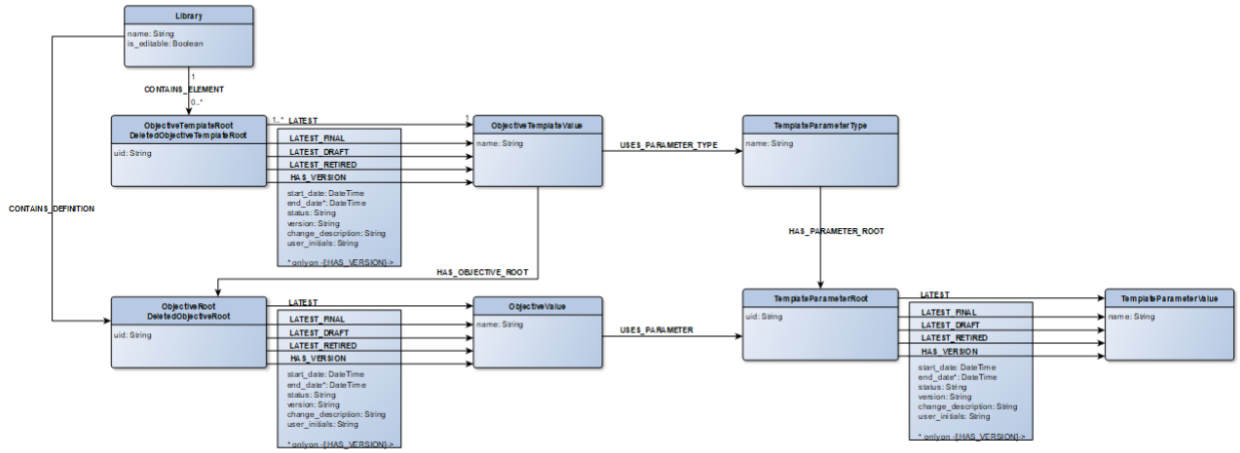


Diagram 10: Objectives Templates Nodes and Relationship

One of the main design elements in the physical Neo4j data model is the support of full versioning and audit trail capabilities. This is achieved by separating nodes that identify data elements from the data element values and capturing all data state attributes as relationship properties between the identifier and value nodes. The identifier nodes will include the 'Root' post fix in their name and the value nodes 'Value' as their name post fix. All the state attributes as action, timestamps, user names, change description etc. will be saved as part of relationship properties.

Deployment of Component

- Neo4j database running on Virtual Machine in Azure DevOps.
- Git repositories linked via pipelines directly to VM, releasing updates directly of test data and scripts.

Project Status

The Neo4j database implemented that supports various parts of the Proof of Concept scope and the database implementation actually cover a bit more than implemented in the Study Designer App.

See also: Import Standards 360 Proof of Concept Component

- Load directly from CDISC Library:
  - Controlled Terminology
  - CDASH
  - SDTM
  - Partial ADaM
- Concept-based standards
  - Load a number of supplemental metadata covering additional metadata needed for concept-based standards, see also: WS4 Supplemental Metadata
- Sponsor-defined standards
  - Load extensions to CDISC standards, included in load of WS4 supplemental Metadata
- Load of Study Definition metadata
  - Used to initialize the study metadata set up for the Study Designer App. Covers a bit more scope than illustrated in the App.

Study Metadata Queries

The Study Metadata Queries extract metadata from the Study Metadata Library for downstream usage. They can be executed from a Neo4j Browser, the Neo4j-SAS Interface, from within the Study Designer App or any other client that connect to a Neo4j graph database.

Technologies

Neo4j Cypher graph query scripts.

Scope of Functionalities

The Study Metadata Queries initially cover the following scope:

- Information for the Study Data Standards Plan
- Information to cover basic study design parameters as well as listing objectives and endpoints for a study matching the table structure of the Common Protocol Template
- Listing metadata for study design (TS, TA, TE, TV) datasets
- Listing metadata for SDTM-Define-XML in SAS CST and Pinnacle 21 format
- Listing metadata for CDASH-SDTM and SDTM-ADaM bindings based on CDISC 360 Proof of Concept model

Examples

Samples of how Study Metadata Queries can be made in Neo4j Cypher:

```
// CPT Objectives and Endpoints
MATCH (s:Study)-->(po:PlannedObjective)-->(ol:ObjectiveLevel),
    (po)-[r1:ROOT_OBJECTIVE]->(ro:RootObjective)-[r2:HAS_VERSION]->(o:Objective),
    (po)-->(pe:PlannedEndpoint)-->(e:Endpoint),
    (pe)-->(ocl:OutcomeLevel)
WHERE r2.status = 'Final' and r2.date_from <= r1.date < r2.date_to
RETURN s.id, po.order, pe.endpoint_order, ol.name, ro.uri, o.name, ocl.name, e.name
ORDER BY s.id, po.order, pe.endpoint_order;


// List SDTM.TA
MATCH (s:Study {id: $studyid})-->(n:PlannedDesignMatrix)<--(a:PlannedArm),
    (n)<--(e:PlannedEpoch), (n)<--(l:PlannedElement)
RETURN toUpper(s.id) as STUDYID,
     'TA' as DOMAIN,
     toUpper(a.arm_code) as ARMCD,
     toUpper(a.name) as ARM,
     e.epoch_number as TAETORD,
     'E' +  n.element_number as ETCD,
     toUpper(l.name) as ELEMENT,
     '' as TABRANCH,
     '' as TATRANS,
     toUpper(e.name) as EPOCH
ORDER BY n.arm_number, n.epoch_number, n.element_number;


// List SDTM Variables for a Study in P21 format
MATCH (s:Study {id: $studyid})-->(ig:SDTMIGVersion)-[r:REQUIRED_DOMAINS]->(d:SDTMDataset)--
>(v:SDTMVariable)
OPTIONAL MATCH (v)-->(rl:RootCTCodeList)<--(l:RootCTCodeListName)
RETURN toInteger(v.ordinal) as order,
     d.name as Dataset,
     v.name as Variable,
     v.label as Label,
     v.xmldatatype as Data_Type,
     toInteger(v.length) as Length,
     '' as Significant_Digits,
     '' as Format,
     '' as Mandatory,
     coalesce(l.name,"") as Codelist,
     '' as origin,
     '' as Pages,
     '' as Method,
     '' as Predecessor,
     v.role as role,
     '' as comment
ORDER BY toInteger(d.ordinal), toInteger(v.ordinal)
UNION
MATCH (s:Study {id: $studyid})-->(pm:PlannedAssessment)-->(a:Assessment)-[r:MAPPED_TO]-
>(d:SDTMDataset)-->(v:SDTMVariable),
    (s)-->(ig:SDTMIGVersion)
OPTIONAL MATCH (v)-->(rl:RootCTCodeList)<--(l:RootCTCodeListName)
```

```
RETURN toInteger(v.ordinal) as order,
    d.name as Dataset,
    v.name as Variable,
    v.label as Label,
    v.xmldatatype as Data_Type,
    toInteger(v.length) as Length,
    '' as Significant_Digits,
    '' as Format,
    '' as Mandatory,
    coalesce(l.name,"") as Codelist,
    '' as origin,
    '' as Pages,
    '' as Method,
    '' as Predecessor,
    v.role as role,
    '' as comment
ORDER BY toInteger(d.ordinal), toInteger(v.ordinal);
```

Sources/Reference Documents

- Git repository Neo4j-StudyLibrary, folder: List-Study-Metadata
- List Study Metadata Task Team
- https://neo4j.com/docs/api/python-driver/current/
- https://neo4j.com/docs/api/python-driver/current/
- https://pypi.org/project/neo4j/

Neo4j SAS Interface 360 Proof of Concept Component

The Neo4j SAS Interface 360 Proof of Concept Component developed by Workstream 4 uses the Neo4j REST API to submit Cypher (CQL) statements to extract SAS datasets.

Neo4j-to-SAS-Interface_20200623.pdf

Technologies

- SAS 9.4M6 with SAS/Base (PROC HTTP and PROC LUA).

Scope of Functionalities

- Creates template for SAS datasets to be developed
- Submits a GET request via the REST API to the Neo4j server
- Converts the response JSON file into SAS dataset

Deployment of Component

Download from repository and configure folder paths and credentials.

Sources/Reference documents

- The ABCs of the HTTP Procedure
- REST Easier with SAS®: Using the LUA Procedure to Simplify REST API Interactions
- SAS PROC Lua documentation
- Driving SAS® with Lua
- Simple JSON Encode/Decode in Pure Lua
- Lua Reference Manual
- The Neo4j HTTP API

SDTM and ADaM Dataset Automation

Workstream 6 developed a prototype for automating the process of generating SDTM and ADaM datasets. The automation execution uses CDISC 360-enriched-mapping specification and study-level, CDASH/SDTM data as input and delivers target SAS program datasets in SAS7BDAT format. Submission-ready define.xml were also generated using the same metadata and target datasets.

Sub-components

- Front-end application, based on a R-Shiny framework
- Back-end application, based on SAS

Technologies

- Both front and back-end applications run under Microsoft Azure DevLab VM, using Windows Server 2019 Datacenter ver.1809.
- Front-end application uses R version 3.6.3 and R-Studio version 1.2.5033.
- Back-end application uses SAS 9.4 (TS1M6).
- Version control application uses Visual Studio Code version 1.46.1.

Scope of Functionalities

During the automation execution process, the user will be able to import metadata with multiple file formats (default is XML obtained from Study Designer App), review/edit metadata, generate target SAS programs, corresponding SAS datasets, and submission-ready define.xml.

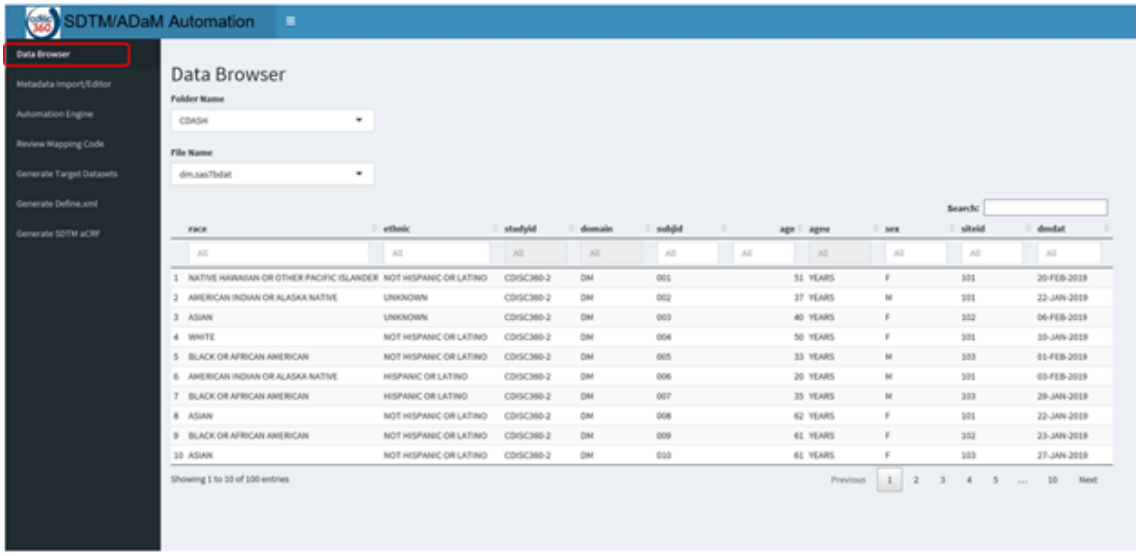
Deployment of Component

SAS datasets, programs, and define.xml are executed using VM Windows platform and stored under the designated study folders.

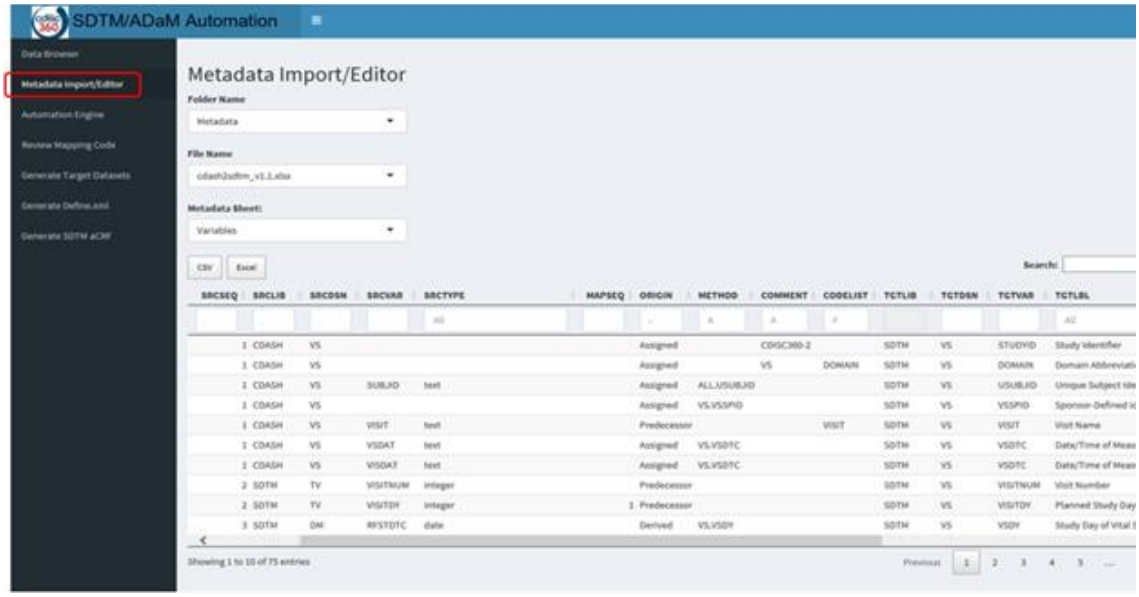
Examples

User Interface

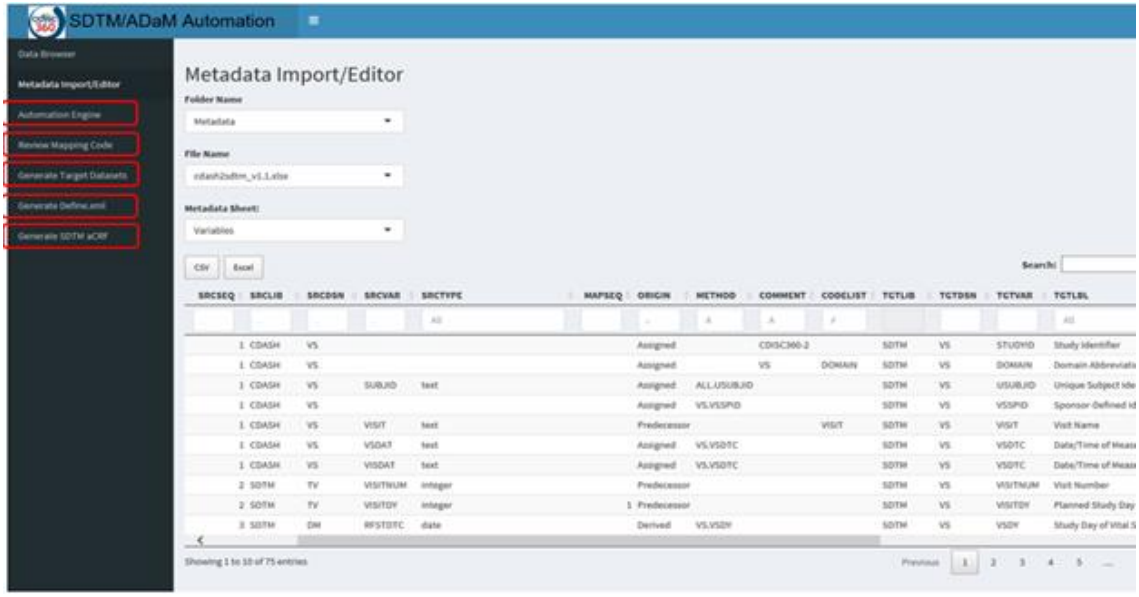
On the **Data Browser** menu, users will be able to review the input study data:



On the **Metadata Import/Editor** menu, users will be able to import study specification metadata, review, and make adjustment as needed.

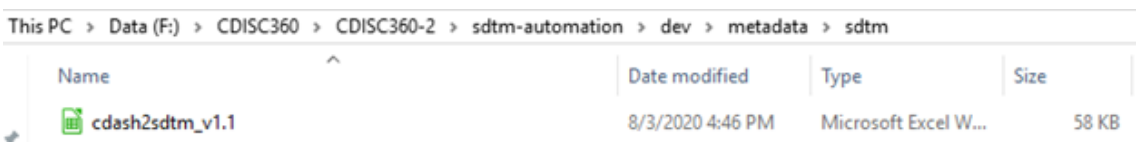


Once the specification metadata are ready to go, users can leverage the Automation Engine to generate target-dataset SAS code, use Review Mapping Code to review the generated SAS codes and go back to make adjustment on metadata using Metadata Import/Editor, generate target SAS datasets using Generate Target Datasets, and generate define.xml using Generate Define.xml.



Specification Metadata

Specification Metadata, including initial version from upstream and updated version by user, are stored under designated study metadata location.



The final mapping specification used for the Proof of Concept can be found at:

CDASH to SDTM: https://www.cdisc.org/sites/default/files/2021-06/cdash2sdtm_v1.1.xlsx

SDTM to ADaM: https://www.cdisc.org/sites/default/files/2021-06/sdtm2adam_v1.1.xlsx

Screenshots of the Specification Metadata:

- Metadata Specification - Dimension 1

Source				Mapping					Target						
Source Sequence	Source Library	Source Dataset	Source Variable	Map Sequence	Origin	Method	Comment	Code List	Target Library	Target Dataset	Target Variable	Target Description	Target Data Type	Target Length	Target Sorting Order
1	CDASH	VS			Assigned		CDISC360-2		SDTM	VS	STUDYID	Study Identifier	text	10	1
1	CDASH	VS			Assigned		VS	DOMAIN	SDTM	VS	DOMAIN	Domain Abbreviation	text	2	2
1	CDASH	VS	SUBJID		Assigned	ALL.USUBJID			SDTM	VS	USUBJID	Unique Subject Identifier	text	14	3
1	CDASH	VS			Assigned	VS.VSSPID			SDTM	VS	VSSPID	Sponsor-Defined Identifier	text	4	5
1	CDASH	VS	VISIT		Convert			VISITNUM	SDTM	VS	VISITNUM	Visit Number	integer	8	16
1	CDASH	VS	VISIT		Predecessor			VISIT	SDTM	VS	VISIT	Visit Name	text	18	17
1	CDASH	VS	VSDAT		Assigned	VS.VSDTC			SDTM	VS	VSDTC	Date/Time of Measurements	date	10	19
1	CDASH	VS	VISDAT		Assigned	VS.VSDTC			SDTM	VS	VSDTC	Date/Time of Measurements	date	10	19
1	CDASH	VS			Derived	VS.VSBLFL			SDTM	VS	VSBLFL	Baseline Flag	text	1	14
2	SDTM	DM	RFSTDTC		Derived	VS.VSDY			SDTM	VS	VSDY	Study Day of Vital Signs	integer	8	20
2			VSDTC		Derived	VS.VSDY			SDTM	VS	VSDY	Study Day of Vital Signs	integer	8	20
3	SDTM	SV	VISITDY	1	Predecessor				SDTM	VS	VISITDY	Planned Study Day of Visit	integer	8	18
3	SDTM	SV	EPOCH	2	Predecessor			EPOCH	SDTM	VS	EPOCH	Epoch	text	9	15
4				3	Assigned	VS.VSTESTCD		VSTESTCD	SDTM	VS	VSTESTCD	Vital Signs Test Short Name	text	6	6
4				4	Derived	VS.VSORRES			SDTM	VS	VSORRES	Result or Finding in Original Units	text	4	9
4				5	Derived	VS.VSORRESU		VSUNIT	SDTM	VS	VSORRESU	Original Units	text	9	10
4				6	Assigned	VS.VSSTRESU		VSUNIT	SDTM	VS	VSSTRESU	Standard Units	text	9	13
4				7	Derived	VS.VSSTRESN			SDTM	VS	VSSTRESN	Numeric Result/Finding in Standard Units	float	8	12
4				8	Derived	VS.VSSTRESC			SDTM	VS	VSSTRESC	Character Result/Finding in Std Format	text	4	11
4				9	Assigned	VS.VSPOS		VSPOS	SDTM	VS	VSPOS	Position	text	7	13
5			VSTESTCD		Convert			VSTEST	SDTM	VS	VSTEST	Vital Signs Test Name	text	24	7
5			VSTESTCD		Convert			VSCAT	SDTM	VS	VSCAT	Category for Vital Signs	text	16	8
5					Derived	VS.VSSEQ			SDTM	VS	VSSEQ	Sequence Number	integer	8	4

- Metadata Specification - Dimension 2

Dataset Level

Source			Mapping					Target		
Source Sequence	Source Library	Source Dataset	Subset Condition	Pre Processing	Join Timing	Join Type	Merge Key	Target Sequence	Target Library	Target Dataset
1	CDASH	VS						5	SDTM	VS
2	SDTM	TV			PRE	TARGET	VISIT	5	SDTM	VS
3	SDTM	DM			PRE	TARGET	USUBJID	5	SDTM	VS
4	SDTM	SE		VS.SE.SE_EPOCH	PRE	TARGET	USUBJID, VSDTC	5	SDTM	VS
5	WORK	VS4				SORT	USUBJID, VISITNUM, VSDTC	5	SDTM	VS
6	WORK	VS5		VS.VS5.VSBASEFL	PRE	TARGET	USUBJID, VSPOS, VSTESTCD, VSDTC	5	SDTM	VS
7	WORK	VS6				SORT	USUBJID, VSTESTCD, VISITNUM, VSDTC	5	SDTM	VS

Variable Level

Source Sequence	Source Library	Source Dataset	Source Variable	Mapping Sequence	Origin	Method	Comment	Code List	Taget Library	Target Dataset	Target Variable	Target Description	Target Type	Target Length	Target Sorting Order
5	WORK	VS4		3	Assigned	VS.VSTESTCD		VSTESTCD	SDTM	VS	VSTESTCD	Vital Signs Test Short Name	text	6	6
5	WORK	VS4		4	Derived	VS.VSORRES			SDTM	VS	VSORRES	Result or Finding in Original Units	text	4	9
5	WORK	VS4		5	Derived	VS.VSORRESU		VSUNIT	SDTM	VS	VSORRESU	Original Units	text	9	10
5	WORK	VS4		6	Assigned	VS.VSSTRESU		VSUNIT	SDTM	VS	VSSTRESU	Standard Units	text	9	13
5	WORK	VS4		7	Derived	VS.VSSTRESN			SDTM	VS	VSSTRESN	Numeric Result/Finding in Standard Units	float	8	12
5	WORK	VS4		8	Derived	VS.VSSTRESC			SDTM	VS	VSSTRESC	Character Result/Finding in Std Format	text	4	11
5	WORK	VS4		9	Assigned	VS.VSPOS		VSPOS	SDTM	VS	VSPOS	Position	text	7	13

Value Level

Source Sequence	Source Library	Source Dataset	Source Variable	Where Clause	Condition	Output	Mapping Sequence	Origin	Method	Comment	Code List	Target Library	Target Dataset	Target Variable	Target Data Type	Target Length
5	WORK	VS4	DIABP_VSORRES	VS.PARAMCD.EQ.DIABP	DIABP_VSPERF = 'Y'	Y	7	Copy				SDTM	VS	VSSTRESN	integer	8
5	WORK	VS4	SYSBP_VSORRES	VS.PARAMCD.EQ.SYSBP	SYSBP_VSPERF = 'Y'	Y	7	Copy				SDTM	VS	VSSTRESN	integer	8
5	WORK	VS4	HR_VSORRES	VS.PARAMCD.EQ.PULSE	HR_VSPERF = 'Y'	Y	7	Copy				SDTM	VS	VSSTRESN	integer	8
5	WORK	VS4	TEMP_VSORRES	VS.PARAMCD.EQ.TEMP	TEMP_VSPERF = 'Y'	Y	7	Copy			10.1	SDTM	VS	VSSTRESN	float	8
5	WORK	VS4	HEIGHT_VSORRES	VS.PARAMCD.EQ.HEIGHT	HEIGHT_VSPERF = 'Y'	Y	7	Derived	VS.VSSTRESN.item1		10.2	SDTM	VS	VSSTRESN	float	8
5	WORK	VS4	WEIGHT_VSORRES	VS.PARAMCD.EQ.WEIGHT	WEIGHT_VSPERF = 'Y'	Y	7	Copy				SDTM	VS	VSSTRESN	integer	8

Mapping Specifications: **Dataset Level**

	Source Sequence	Source Library	Source Dataset	Subset Condition	Pre Processing	Join Timing	Join Type	Merge Key	Target Sequence	Target Library	Target Dataset
1	1	CDASH	VS						5	SDTM	VS
2	2	SDTM	TV			PRE	TARGET	VISIT	5	SDTM	VS
3	3	SDTM	DM			PRE	TARGET	USUBJID	5	SDTM	VS
4	4	SDTM	SE		VS.SE.SE_EPOCH	PRE	TARGET	USUBJID, VSDTC	5	SDTM	VS
5	5	WORK	VS4				SORT	USUBJID, VISITNUM, VSDTC	5	SDTM	VS
6	6	WORK	VS5		VS.VS5.VSBASEFL	PRE	TARGET	USUBJID, VSPOS, VSTESTCD, VSDTC	5	SDTM	VS
7	7	WORK	VS6				SORT	USUBJID, VSTESTCD, VISITNUM, VSDTC	5	SDTM	VS

```
data VS1;
   set CDASH.VS;
   /********
    variable level: Source Sequence = 1
    ********/
run;
```

1

```
proc sort data=VS1;  by SUBJID;
proc sort data=CDAHS.DM OUT=DM2; by USUBJID;

data VS2;
   merge DM2(in=a) VS1(in=b);
   by USUBJID;
   if b;
   /********
    variable level: Source Sequence = 2
    ********/
run;
```

2

... Sequence 3, 4, 5, 6 3 4 5 6

```
proc sort data=VS6;
   by USUBJID VSTESTCD VISITNUM VSDTC;
run;

data SDTM.VS;
   set VS6;
   by USUBJID VSTESTCD VISITNUM VSDTC;

 /********
    variable level: Source Sequence = 5
    ********/

run;
```

7

cdisc

Mapping Specifications: **Variable Level**

Source Sequence	Source Library	Source Dataset	Source Variable	Map Sequence	Origin	Method	Comment	Code List	Target Library	Target Dataset	Target Variable	Target Description	Target Data Type	Target Length	Target Sorting Order
1	CDASH	VS			Assigned		VS	DOMAIN	SDTM	VS	DOMAIN	Domain Abbreviation	text	2	2
1	CDASH	VS	SUBJID		Assigned	ALL.USUBJID			SDTM	VS	USUBJID	Unique Subject Identifier	text	14	3
1	CDASH	VS	VISIT		Convert			VISITNUM	SDTM	VS	VISITNUM	Visit Number	integer	8	16
1	CDASH	VS	VISIT		Predecessor			VISIT	SDTM	VS	VISIT	Visit Name	text	18	17
1	CDASH	VS	VSDAT		Assigned	VS.VSDTC			SDTM	VS	VSDTC	Date/Time of Measurements	date	10	19
1	CDASH	VS			Derived	VS.VSBLFL			SDTM	VS	VSBLFL	Baseline Flag	text	1	14

ID	Description	Function	Parameter
ALL.USUBJID	Concatenation of STUDYID and SUBJID	Concatenate	dot/STUDYID/SUBJID
VS.VSDTC	Convert assessnent date (VISDAT/VSDAT) to ISO8601 date format.	ISODTC	VISDAT/VSDAT
VS.VSBLFL	Baseline flag set to Y when the assessment is collected at the visit marked as baseline in the trial flowchart.	Baseline	"VISIT/VISIT 2 (WEEK 0)"

SAS Code

```
USUBJID = catx('.', STUDYID, SUBJID);
if not missing(VISDAT) then
  VSDTC = put(VISDAT, e8601da.);
else if not missing(VSDAT) then
  VSDTC = put(VSDAT, e8601da.);

if VISIT = "VISIT 2 (WEEK 0)" then VSBLFL = 'Y';
```

```
data VS1;
   set CDASH.VS;

 **** Variable level processing ;
DOMAIN   = 'VS';
USUBJID  = catx('.', STUDYID, SUBJID);
VISITNUM = input(put(VISIT, $VISITNUM.), BEST.);

[origin = Predecessor, do nothing];

if      not missing(VISDAT) then
   VSDTC = put(VISDAT, E8601DA.);
else if not missing(VSDAT)  then
   VSDTC = put(VSDAT, E8601DA.);

if VISIT = "VISIT 2 (WEEK 0)" then VSBLFL = 'Y';
run;
```

Mapping Specifications: **Value Level**

Source Sequence	Source Library	Source Dataset	Source Variable	Where Clause	Condition	Output	Map Sequence	Origin	Method	Comment	Code List	Target Library	Target Dataset	Target Variable	Target Data Type	Target Length	Significant Digits
3	CDASH	VS		VS.VSTESTCD.EQ.DIABP	DIABP_VSPERF = 'Y'	Y	3	Assigned		DIABP		SDTM	VS	VSTESTCD	text	6	
3	CDASH	VS	DIABP_VSORRES	VS.VSTESTCD.EQ.DIABP	DIABP_VSPERF = 'Y'	Y	4	Predecessor				SDTM	VS	VSORRES	text	4	
3	CDASH	VS	DIABP_VSORRESU	VS.VSTESTCD.EQ.DIABP	DIABP_VSPERF = 'Y'	Y	5	Predecessor				SDTM	VS	VSORRESU	text	9	
3	CDASH	VS		VS.VSTESTCD.EQ.DIABP	DIABP_VSPERF = 'Y'	Y	6	Assigned		mmHg		SDTM	VS	VSSTRESU	text	9	
3	WORK		VSORRES	VS.VSTESTCD.EQ.DIABP	DIABP_VSPERF = 'Y'	Y	7	Convert			best.	SDTM	VS	VSSTRESN	float	8	0
3	WORK		VSSTRESN	VS.VSTESTCD.EQ.DIABP	DIABP_VSPERF = 'Y'	Y	8	Convert			4.0	SDTM	VS	VSSTRESC	text	6	
3	CDASH	VS	DIABP_VSPOS	VS.VSTESTCD.EQ.DIABP	DIABP_VSPERF = 'Y'	Y	9	Predecessor				SDTM	VS	VSPOS	text	7	
3	CDASH	VS		VS.VSTESTCD.EQ.HEIGHT	HEIGHT_VSPERF = 'Y'	Y	3	Assigned		HEIGHT		SDTM	VS	VSTESTCD	text	6	
3	CDASH	VS	HEIGHT_VSORRES	VS.VSTESTCD.EQ.HEIGHT	HEIGHT_VSPERF = 'Y'	Y	4	Predecessor				SDTM	VS	VSORRES	text	4	
3	CDASH	VS	HEIGHT_VSORRESU	VS.VSTESTCD.EQ.HEIGHT	HEIGHT_VSPERF = 'Y'	Y	5	Predecessor				SDTM	VS	VSORRESU	text	9	
3	CDASH	VS		VS.VSTESTCD.EQ.HEIGHT	HEIGHT_VSPERF = 'Y'	Y	6	Assigned		m		SDTM	VS	VSSTRESU	text	9	
3	CDASH	VS	HEIGHT_VSORRES	VS.VSTESTCD.EQ.HEIGHT	HEIGHT_VSPERF = 'Y'	Y	7	Derived	VS.VSSTRESN.item1			SDTM	VS	VSSTRESN	float	8	2
3	CDASH	VS	VSSTRESN	VS.VSTESTCD.EQ.HEIGHT	HEIGHT_VSPERF = 'Y'	Y	8	Convert			4.2	SDTM	VS	VSSTRESC	text	6	
3	CDASH	VS		VS.VSTESTCD.EQ.HEIGHT	HEIGHT_VSPERF = 'Y'	Y	9	Assigned		NULL		SDTM	VS	VSPOS	text	7	

```
data VS3;
   set CDASH.VS;

   if DIABP_VSPREF = 'Y' then do;
      VSTESTCD = 'DIABP';
      VSORRES  = DIABP_VSORRES;
      VSORRESU = DIABP_VSORRESU;
      VSSTRESN = 'mmHg';
      VSSTRESN = INPUT(VSORRES, BEST.);
      VSSTRESC = PUT(VSSTRESN, 4.0);
      VSPOS    = DIABP_VSPOS;
      OUTPUT;
   end;
```

```
 *** CONTINUTE ***;

   if HEIGHT_VSPREF = 'Y' then do;
      VSTESTCD = 'HEIGHT';
      VSORRES  = HEIGHT_VSORRES;
      VSORRESU = HEIGHT_VSORRESU;
      VSSTRESN = 'm';
      VSSTRESN = INPUT(VSORRES, BEST.);
      VSSTRESC = PUT(VSSTRESN, 4.0);
      OUTPUT;
   end;
run;
```

Automation Engines

The Automation Engine SAS programs are stored under designated study program location. Ideally, when final and well packaged, they should be stored under a central macro location.

This PC › Data (F:) › CDISC360 › CDISC360-2 › sdtm-automation › dev › program › sdtm

Name	Date modified	Type	Size
vs	10/7/2020 8:50 PM	SAS System Progr...	9 KB
pgm_ini	6/26/2020 2:56 PM	SAS System Progr...	2 KB
lb	10/7/2020 8:50 PM	SAS System Progr...	8 KB
dm	10/7/2020 8:50 PM	SAS System Progr...	7 KB
define_engine	9/8/2020 11:46 PM	SAS System Progr...	14 KB
auto_engine	10/5/2020 6:53 PM	SAS System Progr...	27 KB

SAS Programs

Generated SAS programs are stored under designated study program location.

This PC › Data (F:) › CDISC360 › CDISC360-2 › sdtm-automation › dev › program › sdtm ›

Name	Date modified	Type	Size
dm	10/7/2020 8:50 PM	SAS System Progr...	7 KB
lb	10/7/2020 8:50 PM	SAS System Progr...	8 KB
vs	10/7/2020 8:50 PM	SAS System Progr...	9 KB

SAS Datasets

Automation-execution-generated-target-SAS datasets, along with trail-design-domain datasets provided by workstream (WS4), are stored under the designated study data location.

This PC › Data (F:) › CDISC360 › CDISC360-2 › sdtm-automation › dev › data › sdtm ›

Name	Date modified	Type	Size
vs	10/7/2020 8:52 PM	SAS Data Set	448 KB
formats	10/7/2020 8:50 PM	SAS Catalog	17 KB
tv	10/7/2020 12:24 AM	SAS Data Set	128 KB
dm	10/6/2020 1:39 PM	SAS Data Set	128 KB
se	6/26/2020 2:56 PM	SAS Data Set	192 KB
ae	5/22/2020 2:50 PM	SAS Data Set	896 KB
ds	5/22/2020 2:50 PM	SAS Data Set	256 KB
suppae	5/22/2020 2:50 PM	SAS Data Set	384 KB
sv	5/22/2020 2:50 PM	SAS Data Set	512 KB
ta	5/22/2020 2:50 PM	SAS Data Set	192 KB
te	5/22/2020 2:50 PM	SAS Data Set	192 KB
ts	5/22/2020 2:50 PM	SAS Data Set	288 KB

Live Demo

SDTM/ADaM Automation Engine - Live Demo

Project Status

Back-end Applications

- Automation engine is fully functional based on the latest version of specification metadata structure.
- Define-XML engine was fully functional based on previous version of specification metadata structure.

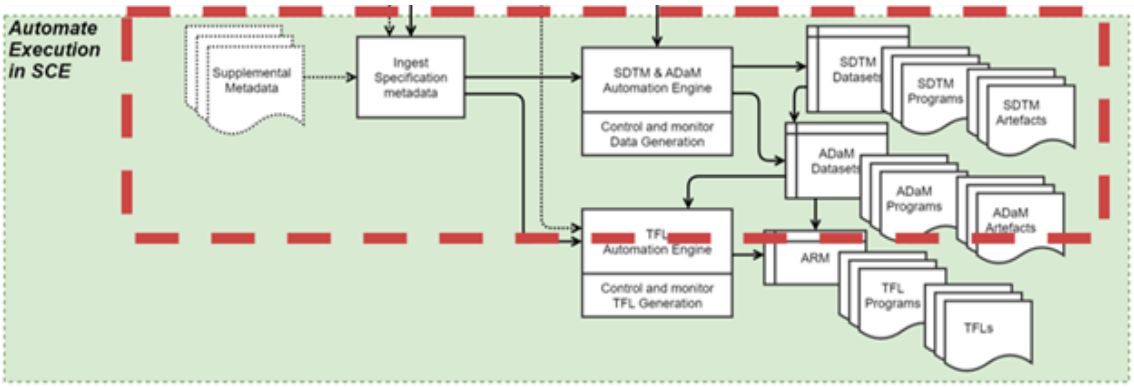
Front-end Application

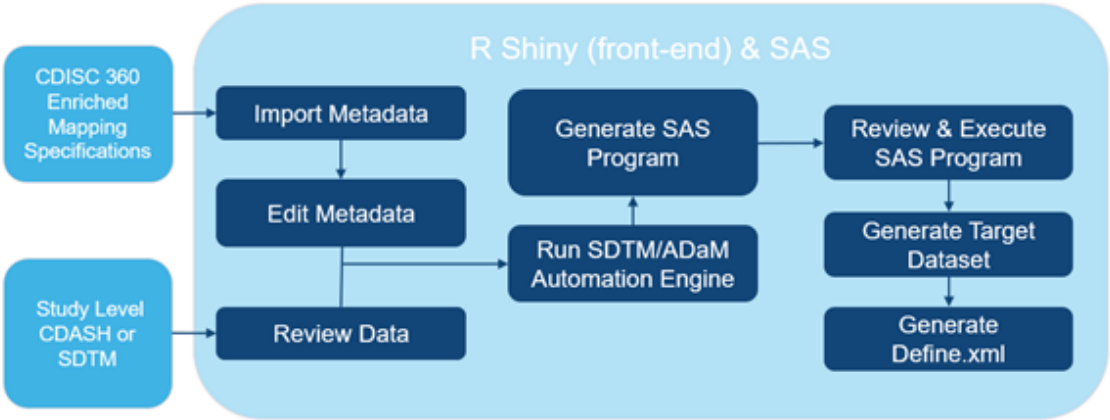
- Infrastructure is built, but functionalities need to be further developed and connected to back-end applications.

Sources/Reference documents

- WS6 - SDTM ADaM Metadata Structure
- WS6-360-Automation-CDASH-to-SDTM-ADaM-Final-v1.0.pptx

Illustrations





Limitations and Assumptions

Assumptions

- Specification metadata is automatically generated based on current data standards and sponsor-study MDR in XML format.
- Specification metadata in structure of Proof of Concept demonstrated layout.
- Corresponding study data are provided via Neo4j SAS interface utility and loaded to the designated study source data area.

Limitations

- Mapping elements may vary from study to study. The Biomedical Concept used for this prototype might be able to provide some target information in a standard, but incomplete way. This will require the user to take lots of time to fill in the missing pieces before automation starts.
- The current specification metadata structure was developed based on a SAS implementation. It will need to be enhanced to automate the execution of applications developed in other languages, such R or SQL.

Suggested Next Steps

- Explore alternative ways to obtain/establish the elements needed, for example, through Biomedical Concept (source), MDR (template containing both info), and IG (target).
- Explore alternative ways to describe relationship between source and target to make it more machine readable and application independent.

TFL Automation 360 Proof of Concept Component

Workstream 6 also developed a prototype for TFL automation. The usage of the automation execution uses CDISC-360 enriched, TFL metadata (ARM++) and study level ADaM data as input and delivers target tables/figures/listings in RTF format.

Sub-components

- Front-end application based on a R-Shiny framework
- Back-end application based on SAS

Technologies

- Both front-end and back-end applications run under Microsoft Azure DevLab VM, using Windows Server 2019 Datacenter ver.1809.
- Front-end application uses R version 3.6.3 and RStudio version 1.2.5033.
- Back-end application uses SAS 9.4 (TS1M6).
- Version control application uses Visual Studio Code version 1.46.1.

Scope of Functionalities

During automation execution process, the user will be able to select TFLs of interest, select TFL layouts from templates, review input data, customize TFL layout and metadata, and generate SAS programs/ outputs and define.xml with ARM.

Deployment of Component

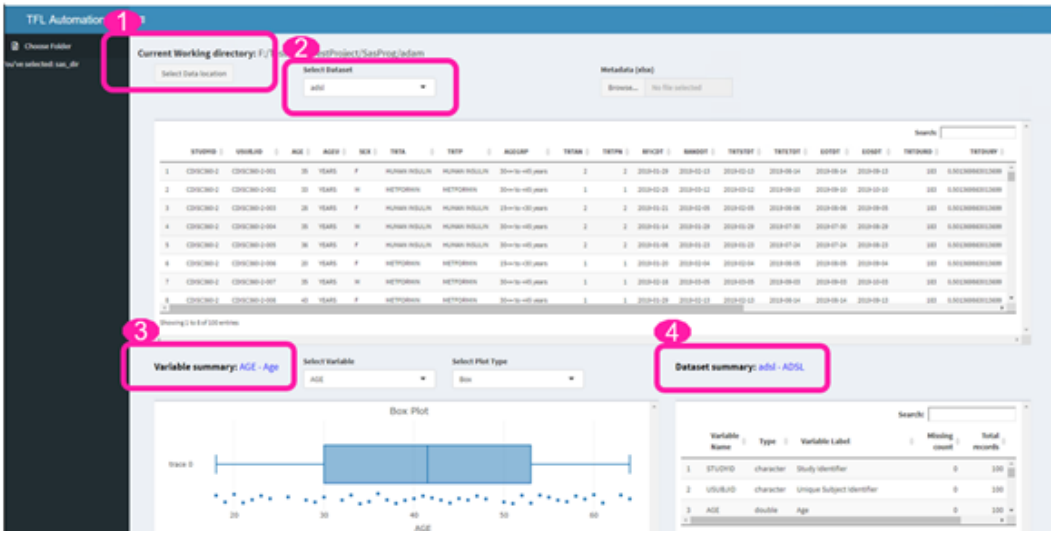
Customized metadata, SAS programs, outputs, and define.xml are executed using VM Windows platform and stored under the designated study folders.

Examples

User Interface

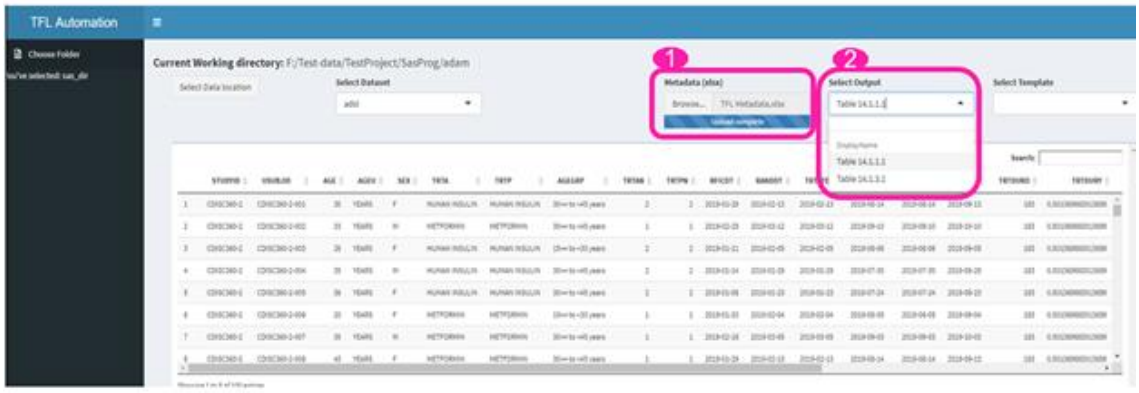
On the **Review Data** menu users will be able to review the input study data.

Review data

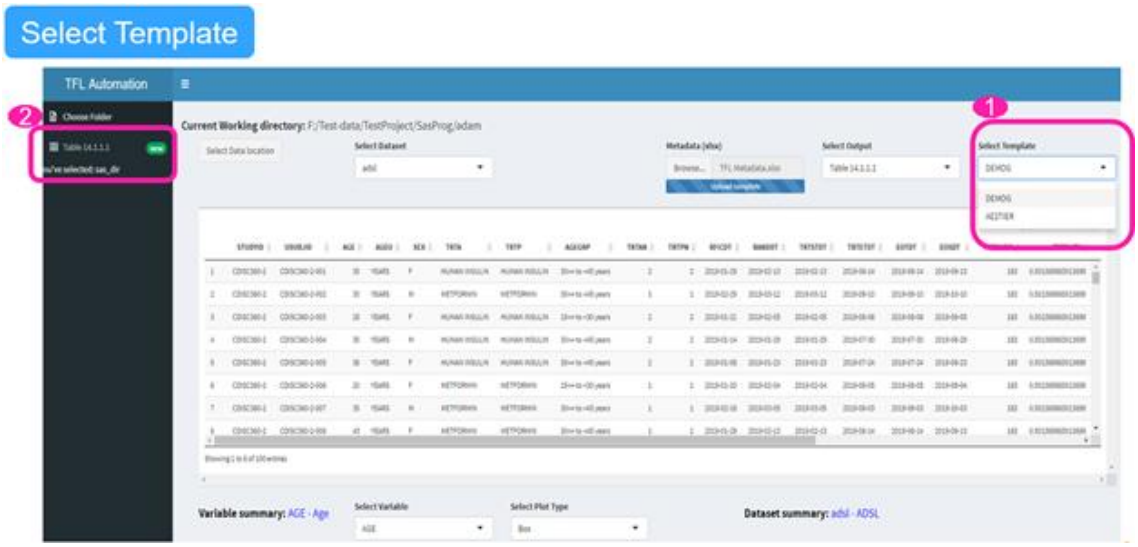


On the **Select Output** menu users will be able to select input metadata, study data, and output wanted to work on.

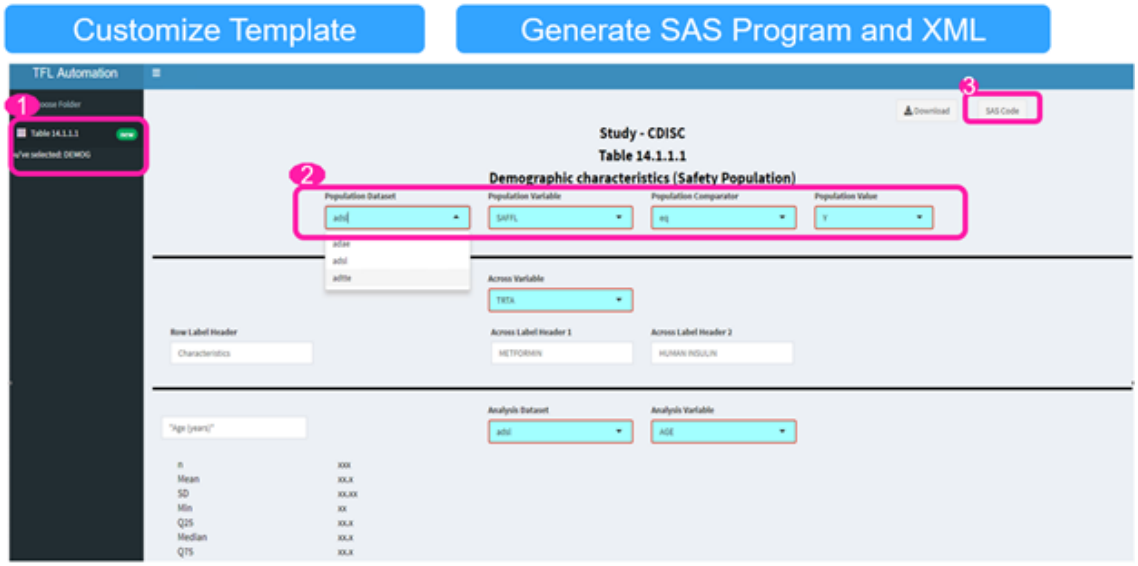
Select Output



On the **Select Template** menu users will be able to select the output template to be applied to the selected output.



Once the selected output displays on the side bar, users will be able to customize the template and generate corresponding SAS program.



SAS program execution and output review will be implemented under Windows platform.

Execute SAS Program

› This PC › Data (F:) › CDISC360 › CDISC360-2 › tfl-automation › dev › program › tables ›

Name	Date modified	Type	Size
tmace_edpt_fas	5/22/2020 2:46 PM	SAS System Progr...	3 KB
tdemog_saf	5/22/2020 2:46 PM	SAS System Progr...	4 KB
tae_soc_pt_saf	5/22/2020 2:46 PM	SAS System Progr...	3 KB

```
/*****************************************************************************************
*                                    Cdisc 360 - TFL programming
* Program Name          :  tdemog_saf
* Author                :  prasanna.murugesan
* Creation Date         :  Tue Apr 28 15:42:31 2020
* Purpose               :  Table 14.1.1.1 Demographic characteristics (Safety Population)
* Data sets used        :
* Modification History  :
*****************************************************************************************/

%include " F:\CDISC360\CDISC360-2\dev\program\macros\source\setup.sas ";

%pop(pop_dsn      =  adsl
    ,pop_out      =  T14111_SAF_DEMOG
    ,pop_var      =  SAFFL
    ,pop_comp     =  eq
    ,pop_value    =  Y
    ,AcrossVar    =  TRT01A
    ,AcrossOrdFmt =  trtord
     );

%stats (s_dsn  =  T14111_SAF_DEMOG
       ,s_sec  =  T14111_01_SAF_DEMOG
       ,s_trtn =  trtord
       ,s_svar =  AGE , s_slbl =  "Age (years)"
```

Review Output

Study - CDISC

Table 14.1.1.1
Demographic characteristics (Safety Population)

Characteristics	METFORMIN N=54	HUMAN INSULIN N=46
Age (years)		
n	54	46
Mean	38.2	44.4
SD	15.13	12.43
Min	18	18
Q25	24.0	35.0
Median	36.0	45.0
Q75	48.0	56.0
Max	64	63
Age Group - n (%)		
15 - <30 years	18 (33.3)	6 (13.0)
30 - <45 years	18 (33.3)	16 (34.8)
>=45 years	18 (33.3)	24 (52.2)
Gender - n (%)		
Male	27 (50.0)	22 (47.8)
Female	27 (50.0)	24 (52.2)

TFL Metadata

The TFL Metadata used in the Proof of Concept was based on CDISC ARM v1.0 for Define-XML v2.0, with some extensions included to support automation. This is referred to as the ARM++ Metadata in the Proof of Concept.

TFL metadata is stored under designated study location.

This PC › Data (F:) › CDISC360 › CDISC360-2 › tfl-automation › dev › script › RProg ›

Name	Date modified	Type	Size
UI_SERVER	5/22/2020 2:46 PM	File folder	
cdisc360-statistical-analysis-plan	5/22/2020 2:46 PM	Adobe Acrobat D...	39 KB
define	5/22/2020 2:46 PM	XML Document	116 KB
define_plus_arm	5/22/2020 2:46 PM	XML Document	123 KB
define2-0-0	5/22/2020 2:46 PM	XSL Stylesheet	184 KB
generate_sas_code_demog	5/22/2020 2:46 PM	R Source File	6 KB
Protocol_cdisc360	5/22/2020 2:46 PM	Adobe Acrobat D...	39 KB
server	5/22/2020 2:46 PM	R Source File	121 KB
TFL Metadata	5/22/2020 2:46 PM	Microsoft Excel W...	23 KB

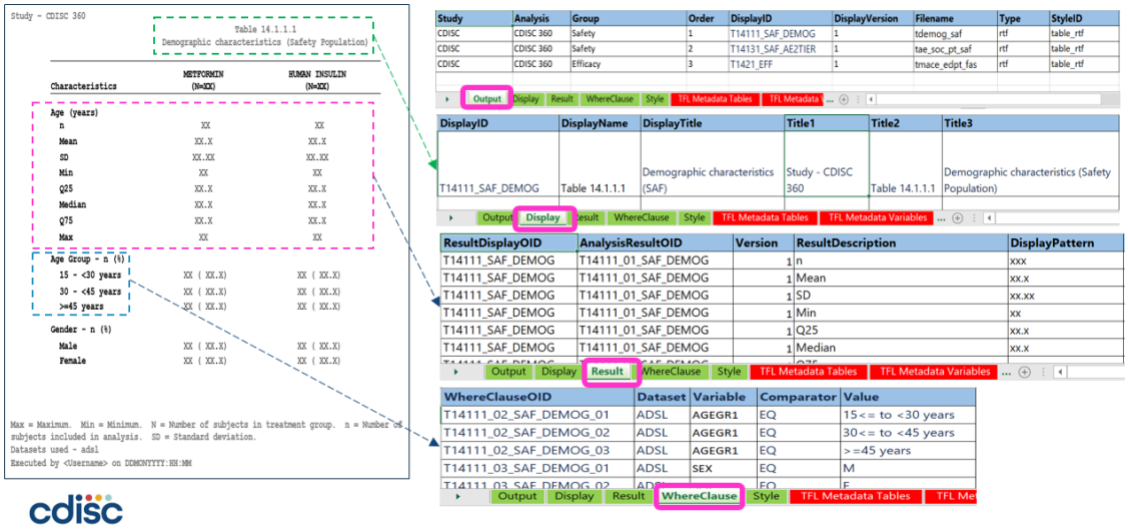
The final mapping specification used for the Proof of Concept can be found at:

ADaM to TFL

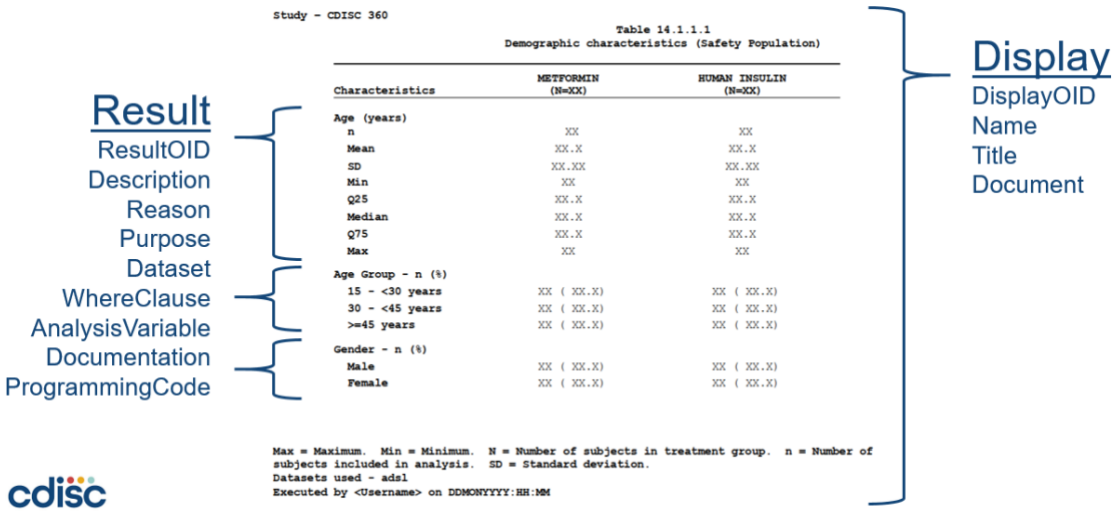
[WS6_TFL_Metadata_Views_Final_v1.0.xlsx]

Screenshots of the ARM++ Metadata

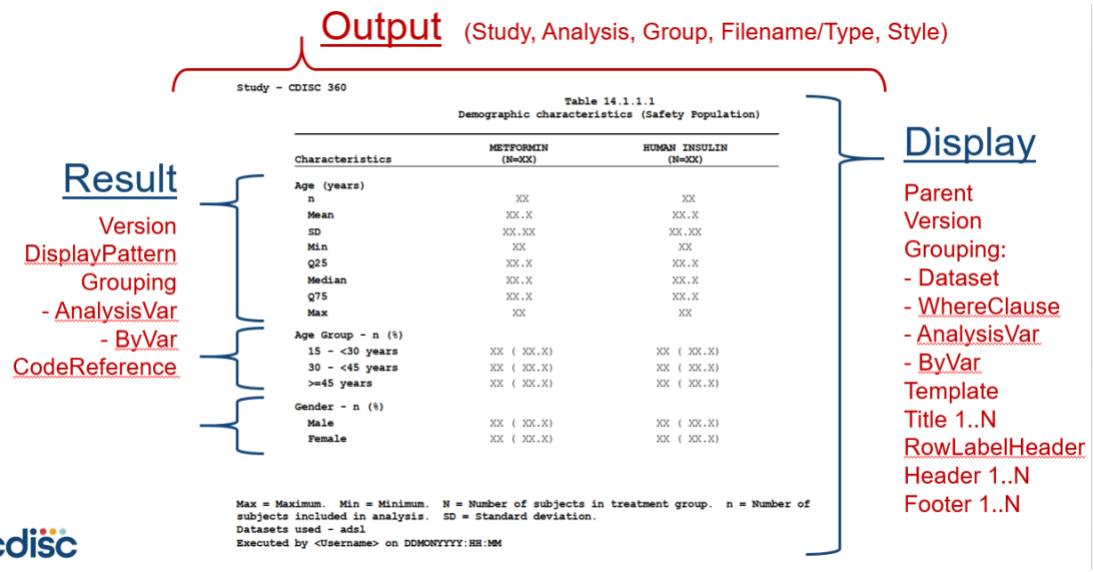
- Sample TFL Metadata (ARM++)



- TFL Metadata from ARM v1.0 for Define-XML v2.0



- TFL Metadata extensions to ARM v1.0 for Define-XML v2.0
- Added to support automation
- New elements added: OUTPUT and STYLE
- ARM v1.0 for Define-XML v2.0 Elements extended: DISPLAY and RESULT
- Extensions based on consideration of many real-world use cases beyond Proof of Concept requirements



Description of TFL Metadata Extensions

- **OUTPUT.** New element (not in ARM v1) that is used to model the file, which contains the TFL (i.e., the Display). An output has a filename, a type (e.g., PDF, RTF, etc.) and contains one or more Display for a specific Analyses within a specific Study.
- **STYLE**. New element (not in ARM v1) that is used to model the stylesheet (e.g., layout, margins, colors, fonts, etc.), which is used for a specific type of output. This allows a single Display to be included in two different outputs with each output styled differently (e.g., same table in a PDF and PowerPoint presentation).

- **PARENT**. New Attribute added to ARM v1 Display and Results elements to support hierarchical modeling of TFL. Used to model (e.g., repeat tables) or where slight variations of a basic table are used in different analyses, etc.
- **VERSION**. New attribute added to ARM v1 Display and Result elements to support different versions of TFL and allow a plot to be extended for final analysis to include more time in follow-up. However, it is the same TFL used in the first interim analysis with slight modification, etc.
- **GROUPING**. New grouping attributes added to ARM v1 Display and Result elements to support grouping of analysis variables. These variables can be considered the 'columns' in a table, where the Display grouping metadata is used to derive 'big N' numerator, and the Result grouping metadata is the 'small-n' denominator. Typically, these variables will use treatment arms, but could also be used to model data (e.g., shift from baseline, etc.).
- **BYVAR**. New attributes added to ARMv1 Display and Result elements to support TFL that repeat an analysis (e.g., by cohort, by visit, etc.). The ByVar works 'within' the display, so a single Display can repeat its results for each value in APERIOD.
- **CodeReference**. New attribute added to ARM v1 Display and Results to support automation. This new attribute is a machine-readable field intended to pass information as to what type of analysis will be performed to create the results and could include parameters for the specific TFL.

R-Shiny Programs

R-Shiny-application-related-UI packages are stored under the designated UI_SERVER location.

This PC > Data (F:) > CDISC360 > CDISC360-2 > tfl-automation > dev > script > RProg > UI_SERVER >

Name	Date modified	Type	Size
www	5/22/2020 2:46 PM	File folder	
	5/22/2020 2:46 PM	R History Source F...	1 KB
generate_sas_code_ae2tier	5/22/2020 2:46 PM	R Source File	4 KB
generate_sas_code_demog	5/22/2020 2:46 PM	R Source File	6 KB
generate_sas_code_eff1421	5/22/2020 2:46 PM	R Source File	4 KB
generate_xml_code_ae2tier	5/22/2020 2:46 PM	R Source File	5 KB
generate_xml_code_demog	5/22/2020 2:46 PM	R Source File	4 KB
generate_xml_code_eff1421	5/22/2020 2:46 PM	R Source File	5 KB
server	5/22/2020 2:46 PM	R Source File	124 KB
ui	5/22/2020 2:46 PM	R Source File	31 KB

Output Programs

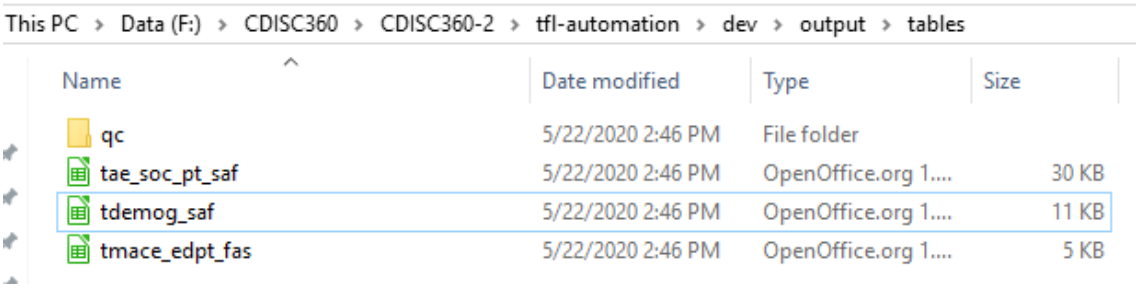
Generated SAS programs for outputs are stored under designated study program location.

This PC > Data (F:) > CDISC360 > CDISC360-2 > tfl-automation > dev > program > tables >

Name	Date modified	Type	Size
tmace_edpt_fas	5/22/2020 2:46 PM	SAS System Progr...	3 KB
tdemog_saf	5/22/2020 2:46 PM	SAS System Progr...	4 KB
tae_soc_pt_saf	5/22/2020 2:46 PM	SAS System Progr...	3 KB

Outputs

Automation-execution-generated outputs are stored under designated study output location.



This PC › Data (F:) › CDISC360 › CDISC360-2 › tfl-automation › dev › output › tables

Name	Date modified	Type	Size
qc	5/22/2020 2:46 PM	File folder	
tae_soc_pt_saf	5/22/2020 2:46 PM	OpenOffice.org 1....	30 KB
tdemog_saf	5/22/2020 2:46 PM	OpenOffice.org 1....	11 KB
tmace_edpt_fas	5/22/2020 2:46 PM	OpenOffice.org 1....	5 KB

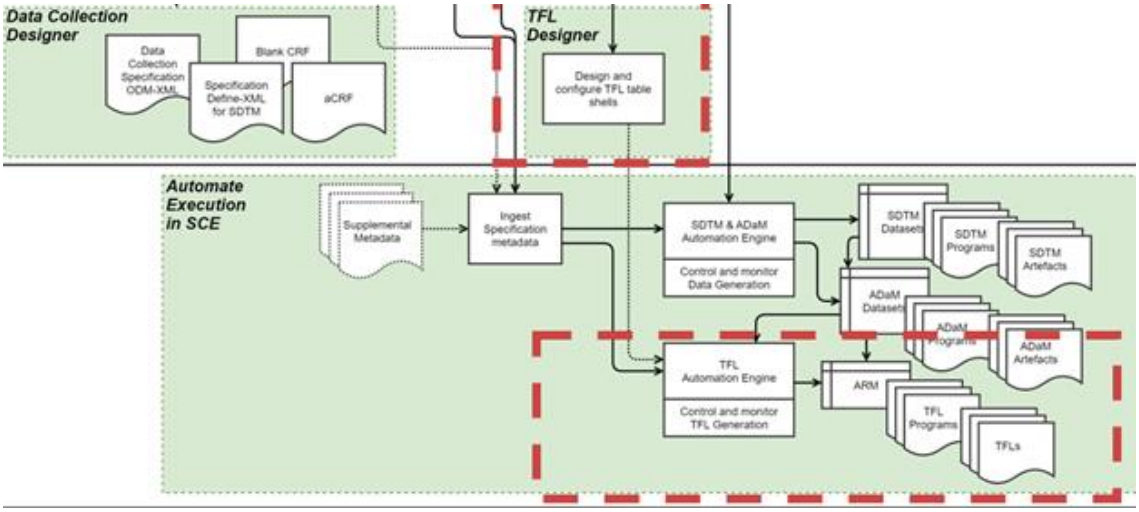
Project status

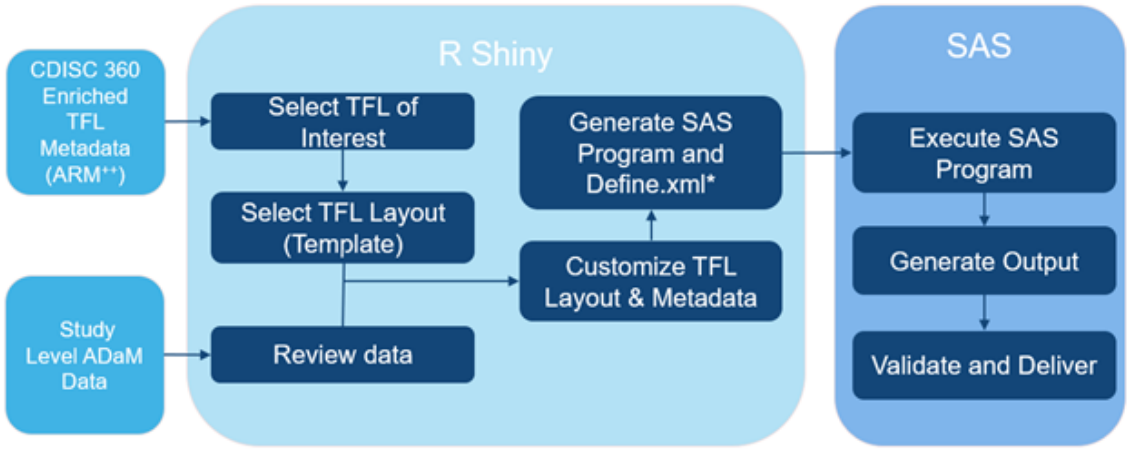
Both front and back-end applications are fully functional with the current TFL metadata structure.

Sources/Reference documents

- WS6 – TFL Automation
- WS6-360-Automation-ADaM-to-TFL-Final-v1.0.pptx
- Live demo: http://youtube.com/watch?v=FxQJvG-1R2M

Illustrations





** ARM to be combined with ADaM Define*

Limitations and Assumptions

Assumptions

- TFL metadata follows designated structure.
- Output layout template is available.

Limitations

- Not all the ARM++ metadata extensions have been implemented - only sufficient to create the Proof of Concept shells.
- The Proof of Concept only includes Tables, no figures or listing.
- Metadata is loaded from an Excel file; no direct connection to the metadata repository.

Programs and Metadata file:

- generate_xml_code_demog.R
- generate_xml_code_eff1421.R
- server.R
- ui.R
- generate_sas_code_ae2tier.R
- generate_sas_code_demog.R
- generate_sas_code_eff1421.R
- generate_xml_code_ae2tier.R
- WS6_TFL_Metadata_Views_Final_v1.0.xlsx

Execution dependencies:

Input files needed:
1. TFL metadata file - WS6_TFL_Metadata_Views_Final_v1.0.xlsx

2. R programs needed
    a. ui.R
    b. server.R
    c. generate_sas_code_ae2tier.R
    d. generate_sas_code_demog.R
    e. generate_sas_code_eff1421.R
    f. generate_xml_code_ae2tier.R
    g. generate_xml_code_demog.R
    h. generate_xml_code_eff1421.R

Software requirements:
1. R Studio 3.6.3
2. Packages: Shiny, Shinyjs, tidyverse, xlsxjars,
3. SAS 9.3 or higher

Data Transformation Engine 360 Proof of Concept Component

The purpose of this Component is to show and document how an agile metadata design can help in augmenting the conceptual-level information into the metadata allowing anyone to programmatically select the content of the standards and apply them to their study-specific requirements. The Data Transformation Engine (DTE) software was used by the 360 Proof of Concept project as a parallel workstream to ascertain the completeness of the 360 project metadata and the level of effort that would be required for a future implementation (i.e., the gaps).

Sub-components

- DTE Metadata Design (DTE Metadata-Concept)
    - Data State Metadata
    - Data Map Metadata
- CDISC 360 Metadata Model (C360 MDR- Define.xml v 2.1 extension SDTM Define-XML files Based on WS 1 Cmaps)
    - XML based C360 MDR Schemas

Technologies

- DTE Software based on SAS (CDISC360 Proof of Concept DTE Component Diagram)
- MindMap
- Excel templates
- DTE environment running on Microsoft Azure DevLab VM (SAS Execution Environment)

Scope of Functionalities

The component is not intended to describe or detail the software that uses DTE agile metadata to achieve the data transformation from one state to another state. However, this points out the

technical description of the metadata design and its use cases wherever required. Metadata design becomes crucial as it becomes the framework in providing full transparency and content availability programmatically, simplifying the integration of standards for automation.

As a result, a concise, agile metadata design is essential to store all required data attributes and mapping information based on the CDISC Standard Models beyond the submission scope by leveraging higher and more consistent quality.

Deployment of Component

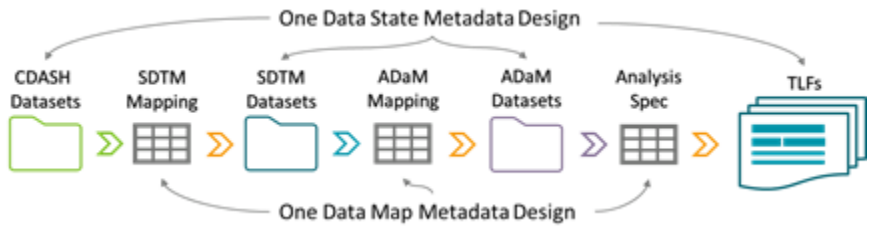
The component concentrated on covering the following segments, which are aligned with this project.

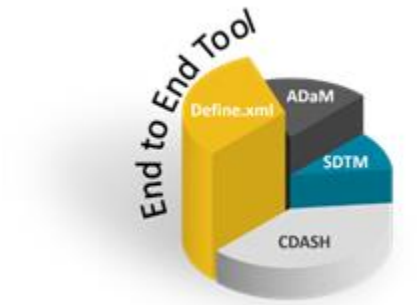
- Understanding how an adequate metadata design can accelerate metadata-driven automation for the CDISC Standards Data Model
- Providing a gap analysis for CDISC Standards Metadata Model
- Documenting the proposed metadata design for the different use case that demonstrates the ability of the DTE metadata in processing and transforming the data from one state to other
- Gauging the practicality of scaling from the proposed metadata design

Examples

High-level Technical Description of the DTE Metadata

Data state metadata comprises six metadata elements that describe the states of data as stored in CDASH, SDTM, ADaM or SEND. Data map metadata also includes six metadata elements that will link each source data state to its target data state.





The six metadata elements that describe each data state include:

- Tables – Describe domain-level data attributes
- Columns – Describe element-level data attributes
- Row Definition – Describe value-level data attributes
- Row Columns – Describe value-level data attributes
- Values – Describe codelists and valid values
- Descriptions – Store plain-language descriptions that can be attached to any table, column, or VLM element

The six metadata elements that describe dataflow include:

- Source Prepare – Describes domain-level mapping information
- Columns Map – Describes element-level mapping information
- Wide Thin Map – Describes value-level mapping information
- Values Map – Describes mapping information to redefine values
- Text Snippet – Describes derivation logic in plain language
- Code Snippet – Describes derivation code

Gap analysis for CDISC Standards Metadata Model

This gap analysis is a commendable example of standardization of the metadata design. It will exhibit the control of data state standards by inhabiting a standard metadata design whose content can drive all aspects of data exchange requirements from data state level to dataflow level. This analysis will craft our working proficiency to decide a standard metadata design. The findings will eventually stretch the boundary to yield an end-to-end description of the dataflow between CDASH, SDTM, ADaM, TFLs, and much more.

The real and original objective of having robust adequate metadata is to enable regulatory agencies to integrate study data across studies and organizations in order to more thoroughly understand the safety and efficacy of a drug or drug class. The gap analysis is conducted by file schema, comparing and associating the define elements and their nested elements against the DTE.

Scope DTE Data Map Metadata 18-11-2020, 00:03:45	Gap Analysis for CDISC Metadata Model (C360 MDR-Define-XML V2.1.0 Extension) WS6- DTE Team			
DTE Section	**DTE Associated name**	**DTE Name Description**	**CDISC 360 Define MDR**	**CDISC Define XML 2.1.0**
Source_Prepare	source_table	Value of TABLE variable in source metadata TABLES		
Source_Prepare	target_table	Value of TABLE variable in target metadata TABLES		
Source_Prepare	table_map_sequence	Table Map identifier		
Source_Prepare	tdescription_map	Name of description describing the table mapping		
Source_Prepare	merge_type	Type of match merge to execute for the source and target		
Source_Prepare	source_torder	Order that the source_table is processed for a target		
Source_Prepare	source_prep	Name of preprocessing code to apply to source data set		
Columns_Map	source_table	Value of TABLE variable in source metadata COLUMNS	MethodDef.OID{ItemRef.MethodOID}>mdr:InputVariables>mdr:InputVariable.Dataset	
Columns_Map	source_column	Value of COLUMN variable in source metadata COLUMNS	MethodDef.OID{ItemRef.MethodOID}>mdr:InputVariables>mdr:InputVariable.VarName	
Columns_Map	target_table	Value of TABLE variable in target metadata COLUMNS		
Columns_Map	target_column	Value of COLUMN variable in metadata COLUMNS		
Columns_Map	table_map_sequence	value of TABLE_MAP_SEQUENCE in TABLES_MAP		
Columns_Map	cdescription_map	Name of description describing the column mapping		
Columns_Map	cinclude_map	Name of code source entry to support the mapped derivation		
Columns_Map	corder_map	Order that the column is processed for a target		
Values_Map	source_values_name	Value of FORMAT in source metadata VALUES		
Values_Map	source_start	Value of START in source metadata VALUES		
Values_Map	source_end	Value of END in source		

From the gap analysis, it is evident that there is a need for information in the metadata beyond what is available in the Define-XML schema.

Scope DTE Data State Metadata 18-11-2020, 00:03:45	Gap Analysis for CDISC Metadata Model (C360 MDR-Define-XML V2.1.0 Extension) WS6- DTE Team			
DTE Section	**DTE Associated name**	**DTE Name Description**	**CDISC 360 Define MDR**	**CDISC Define XML 2.1.0**
Tables	table	Table Name	ItemGroupDef.Name ItemGroupDef.SASDatasetName ItemGroupDef>Alias.Name	ItemGroupDef.Name ItemGroupDef.SASData ItemGroupDef>Alias.Na
Tables	tshort	Table Short Name		
Tables	tlabel	Table Label	ItemGroupDef>Description>TranslatedText	ItemGroupDef>Descri
Tables	tlabellong	Table Long Label		
Tables	torder	Table Order in define file		
Tables	ttype	Table Type - view/table		
Tables	tdescription	Catalog Entry Containing Description of Table	ItemGroupDef.def:CommentOID	ItemGroupDef.def:Com.
Tables	tlocation	Table Location	ItemGroupDef>def:leaf [ID{ItemGroupDef.def:ArchiveLocationID}]	ItemGroupDef>def: [ID{ItemGroupDef.def:A
Tables	tcrf_loc	Blank CRF location for table		
Tables	tcrf_note	Note about CRF location for table		
Tables	structure	ODM Structure	ItemGroupDef.def:Structure	ItemGroupDef.def:Struc
Tables	repeating	ODM Repeating	ItemGroupDef.Repeating	ItemGroupDef.Repeati.
Tables	is_reference_data	ODM IsReferenceData	ItemGroupDef.IsReferenceData	ItemGroupDef.IsRefere
Tables	purpose	ODM Purpose	ItemGroupDef.Purpose	ItemGroupDef.Purpose
Tables	class	ODM Class	ItemGroupDef>def:Class.Name	ItemGroupDef>def:Class
Columns	table	Table Name	ItemGroupDef.Name ItemGroupDef.SASDatasetName	ItemGroupDef.Name ItemGroupDef.SASDataset
Columns	column	Column Name	ItemDef.Name[OID{ItemGroupDef >ItemRef.ItemOID}]	ItemDef.Name[OID{ItemG >ItemRef.ItemOID}]
Columns	cshort	column Short Name	ItemDef.SASFieldName[OID{ItemGroupDef >ItemRef.ItemOID}]	ItemDef.SASFieldName[>ItemRef.ItemOID}]
Columns	cpkey	Primary Key Rank	ItemGroupDef>ItemRef.KeySequence	ItemGroupDef>ItemRef.K
Columns	corder	column Order	ItemGroupDef>ItemRef.OrderNumber	ItemGroupDef>ItemRef.O
Columns	clabel	column Label	ItemDef.OID{ItemGroupDef>ItemRef.ItemOID} >Description>TranslatedText	ItemDef.OID{ItemGroupD >Description>Translated
Columns	clabellong	column Long label		
Column	ctype			

Use Case Demo Data Against the DTE Metadata Model

Source Data State Metadata

Dataset Name	Variable Name	Key	Variable Label	Data Type	Variable Length	Values List Name	Values Column Name	SAS Informat
Demog	AGE			N	8	V250_	START	3
Demog	AGEU			C	18	V251_	START	
Demog	AGEU_STD		AGEU	C	18	V252_	START	
Demog	SEX			C	48	V294_	START	
Demog	SEX_STD		SEX Coded Value	C	6	V295_	START	
Demog	SITEID	2	Site ID information	N	8	V298_	START	10
Demog	STUDYID	1	Study ID Information	N	8	V304_	START	10
Demog	SUBJECT	3	Subject name	C	150	V306_	START	

Source to Target Data Map Metadata

Source Dataset	Source Variable	Target Dataset	Target Variable	Derivation Syntax Name
Demog	AGE	DM	AGE	
Demog	AGEU_STD	DM	AGEU	
Demog	SEX_STD	DM	SEX	
Demog	STUDYID	DM	USUBJID	USUBJID
Demog	SITEID	DM	USUBJID	USUBJID
Demog	SUBJECT	DM	USUBJID	USUBJID

Dataset Name	Variable Name	Key	Variable Order	Variable Label	Data Type	Variable Length	Values List Name	Values Column Name	Values Description Name	CRF Page Number	Variable Role	Variable Origin
DM	AGE		15	Age	N	8			DMAGE	1	Record Qualifier	CRF
DM	AGEU		16	Age Units	C	5	AGEUSUB	START	DMAGEU	1	Variable Qualifier	CRF
DM	SEX		17	Sex	C	16	SEX	START	DMSEX	1	Record Qualifier	CRF
DM	STUDYID	0	1	Study Identifier	C	4	STUDYID	START	DMSTUDYID		Identifier	Protocol
DM	SUBJID		4	Subject Identifier for the Study	C	200			DMSUBJID		Topic	Assigned
DM	USUBJID	2	3	Unique Subject Identifier	C	200			DMUSUBJID		Identifier	Derived

Target Data State Metadata

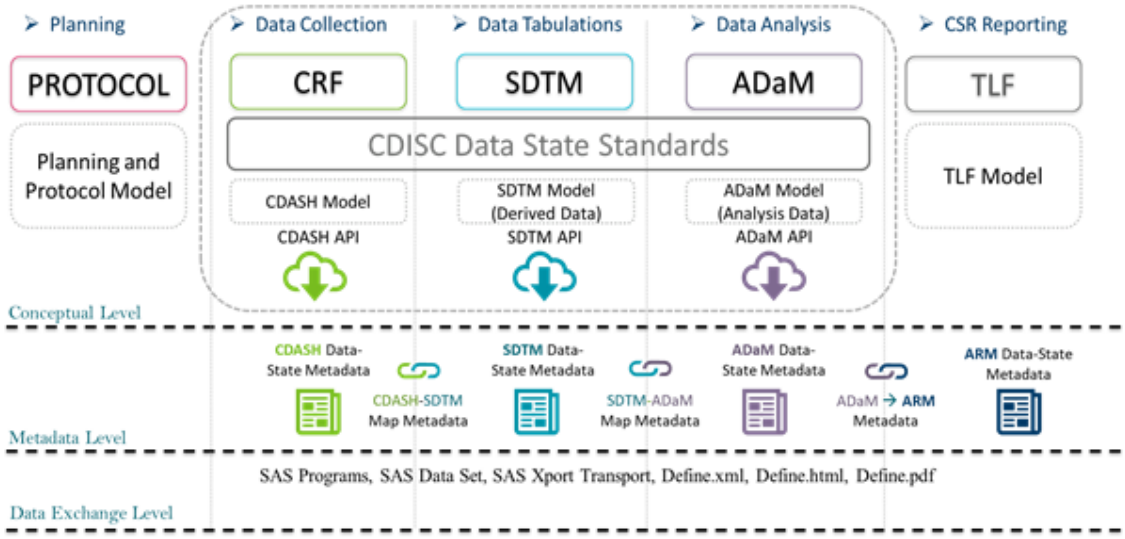
Project Status

From the principles followed in the DTE metadata design, it is clear that this design structure is unique. It does not assume any standards; therefore, it is a unified metadata design, not only for all CDISC Foundational Standards, but also for a broad range of implementations, which can describe any relational data. Additionally, the design bridges the gap in the Foundational Standards. The DTE team presented the unified metadata design to project workstreams and demonstrated it using DTE software, which carried out the data transformation from one data state to another using this metadata design.

Sources/Reference documents

- DTE Metadata-Concept
- DTE Documentations

Illustrations



Suggested Next Steps

A next step could be to publish the Foundational Standards in this standard DTE metadata design. This solution would help us attain efficiency and could serve as a standard way to communicate data and dataflow specifications with CROs, labs, PRO, and other third-party data sources. Additional components are necessary, but a shared metadata design is the logical next step.