

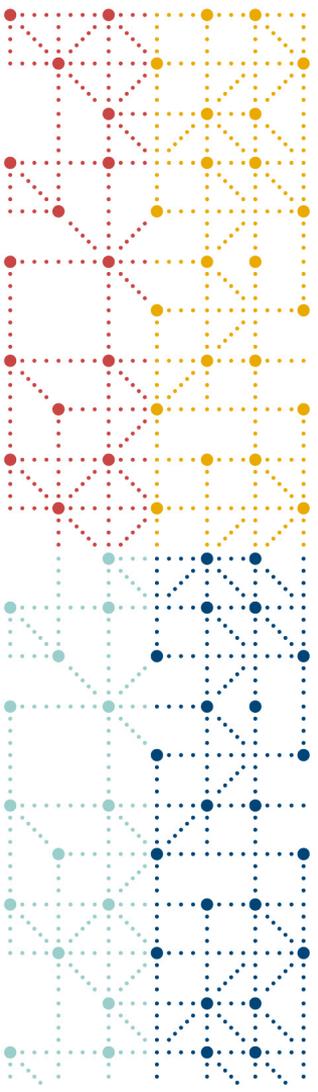


# Study Design and Configuration using CDISC 360 concept based standards

Mikkel Traun, *Novo Nordisk*  
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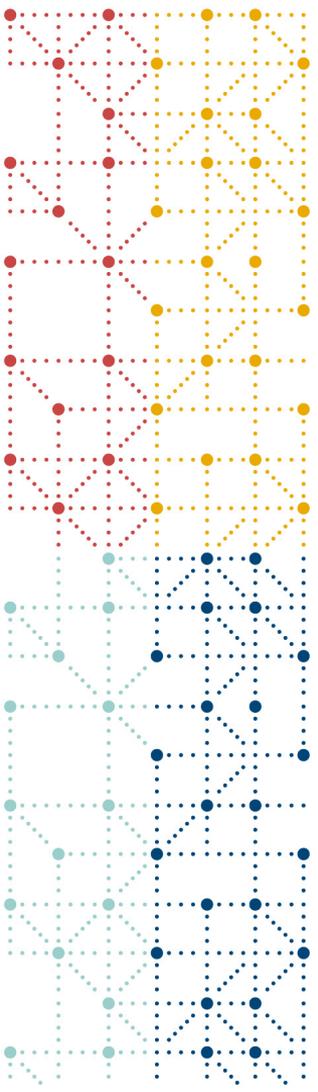
CDISC EU Interchange, April 2020



A decorative graphic on the left side of the slide. It consists of a grid of small dots connected by thin lines. The dots are colored in a gradient from yellow at the top to blue at the bottom. The lines are also colored in a gradient, matching the dots. The overall effect is a complex, interconnected network of points and lines.

# Study Design and Configuration using CDISC 360 concept based standards

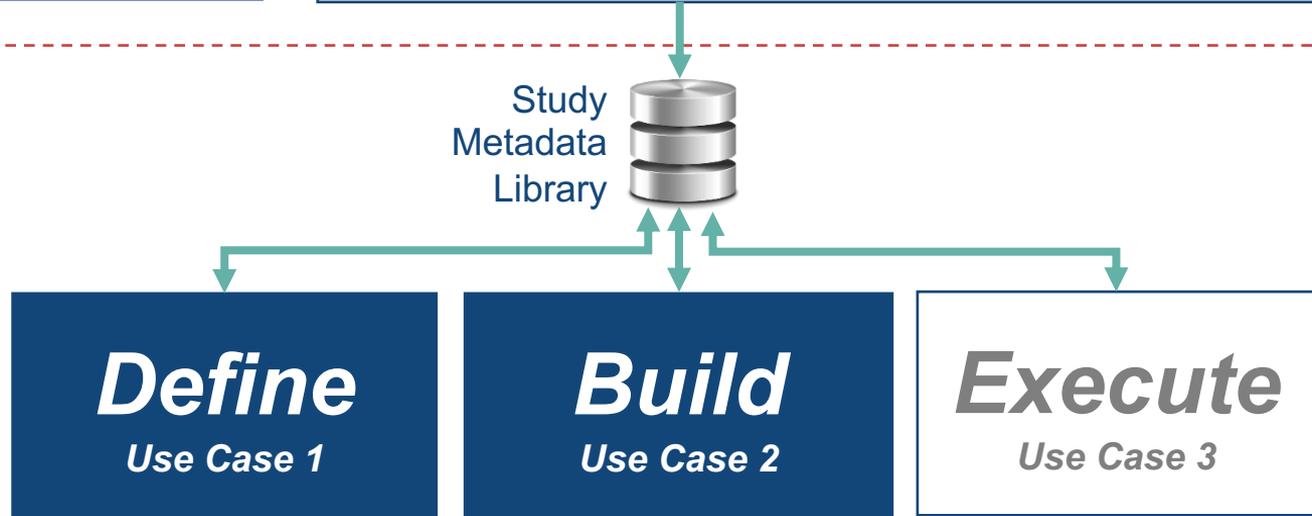
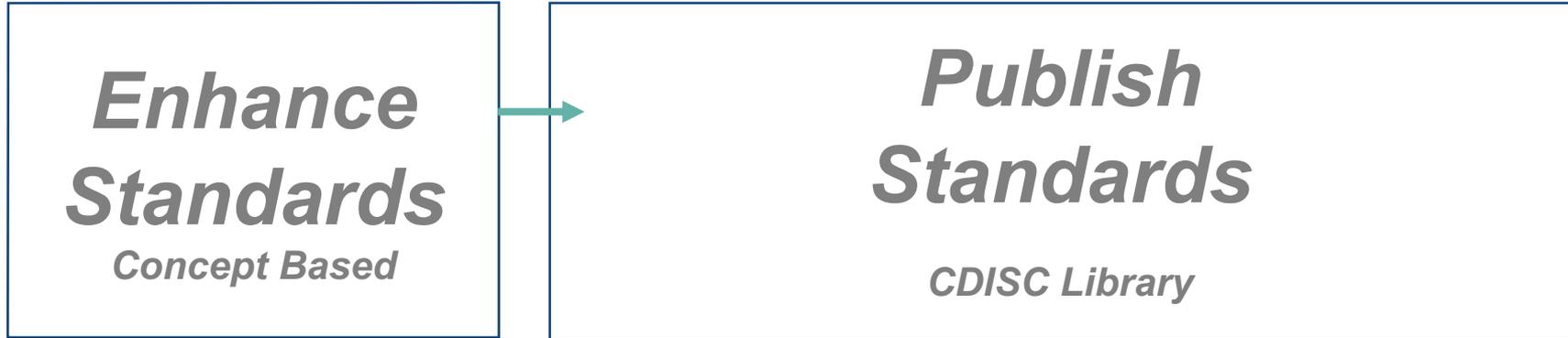
- CDISC 360 Use Case 1 & 2
  - Using a Study Metadata Library
- Approach for the Proof of Concept prototype
- Demo
  - Import Concept Based Standards
  - Define – Design – Select – Build
  - List and interface study metadata
- Learnings so far
  - Linked Graph Data Model for Study Metadata Library
- Next Step



## **CDISC 360 Use Case 1 & 2 Using a Study Metadata Library**

*How the Study Metadata Library fit in the overall CDISC360 vision*

# CDISC 360 Use Case 1 and 2

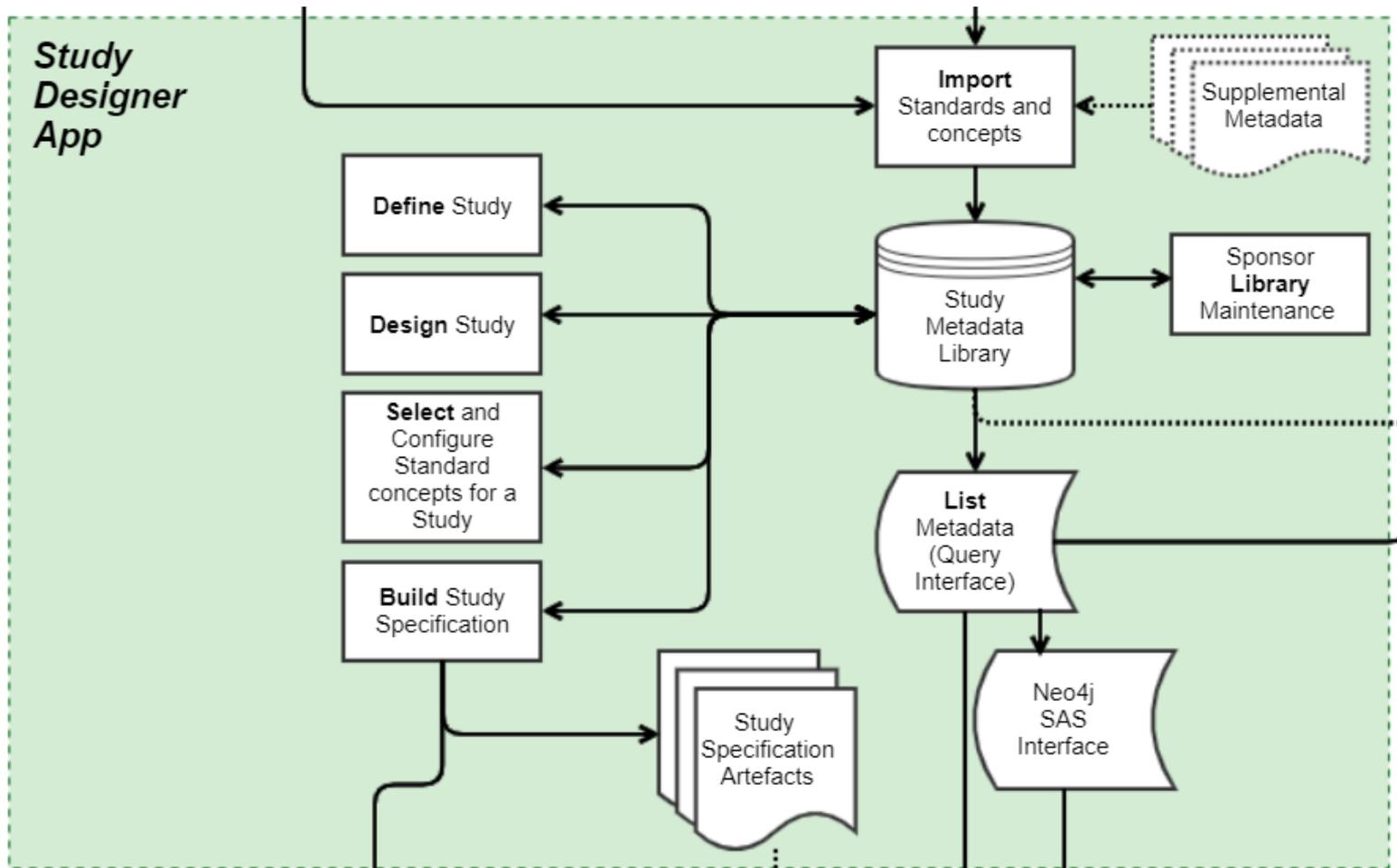


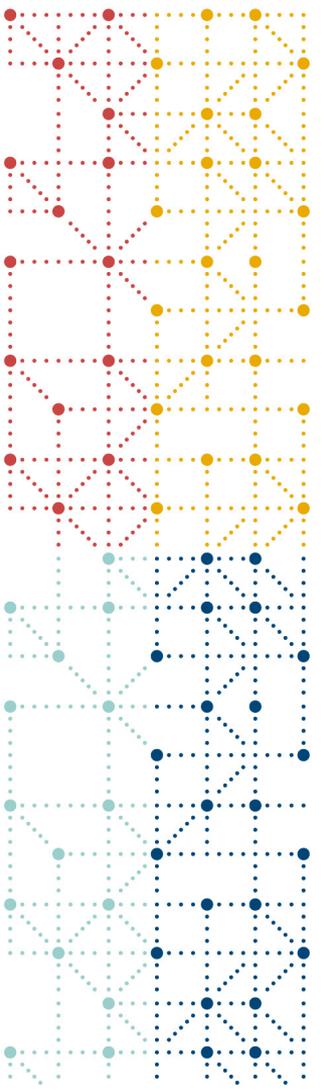


# Goal for Study Metadata Library PoC prototype

- Import Concept Based standards
  - Including end-to-end definitions
- Select Concept Based standards to be used in a study
  - Search and select concept standards for a study
- Deliver selection of Concept standards to support study configuration
  - Concepts will drive CDASH-SDTM-ADaM-Output automation
- To limit scope
  - Started in the middle with SDTM, adding relationship downstream to ADaM and TFL's
  - Added upstream relationship to Endpoints, Objectives and Trial Design
  - Next add relationship to data collection and specifications for study setup

# Process flow for Study Metadata Library PoC prototype





# Approach for the Study Metadata Library Proof of Concept prototype

*What is the main design elements of a Study Metadata Library solution*



# Study Metadata Library in Label Property Graph Model

- What is a Label Property Graph
  - A linked graph model where nodes have labels, relationships and properties
  - Invented by Neo4j
- Why
  - Representing study metadata close to our logical model
  - Enable dynamic linking between study definition and standards metadata
  - Cypher Query language very efficient for PoC development
- How
  - In program scripts
  - Simple listing exports in CSV files
  - Simple Browser Guide Apps
  - Generic GUI (Bloom)
  - Interface with Python and SAS
  - Rapid application developments for prototyping

# 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

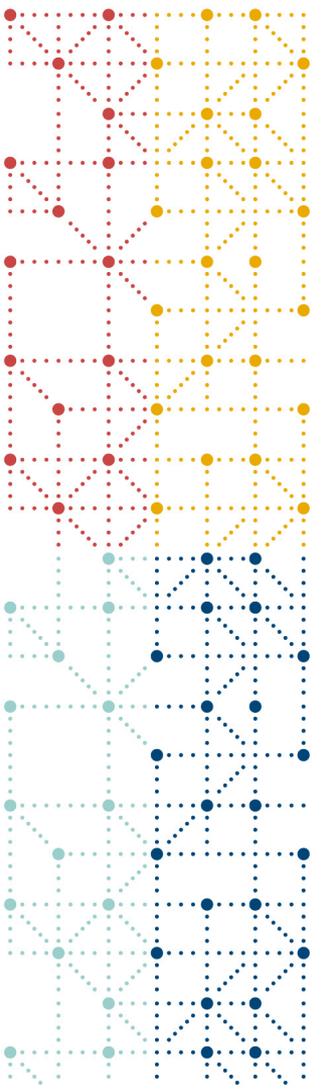
**Select** Search and select concept-based standards and define schedule of activities and assessments

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

## List

Extract study metadata in tabular format for downstream usage.

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



# Demo

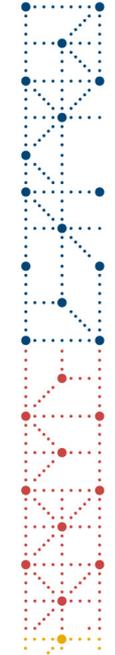
Import Concept Based Standards

Library – manage templates and standards

Define – Design – Select – Build

List and interface study metadata

*How do you work with a Study Metadata Library*



# Import Concept Based Standards

- Currently the Concept Based Standards are imported as a combination of data from
  - Current CDISC Library
  - Supplemental Metadata
- This is done in Cypher program scripts loading data into the Neo4j based Study Metadata Library
- Each CT term is stored once and Neo4j enable version tracking over time

```
"https://library.cdisc.org/api/mdr/ct/packages"
```

```
// Load Scope of CT packages
CALL apoc.load.jsonParams("https://library.cdisc.org/api/mdr/ct/packages",{Authorization:
  "Basic Y2xxx", Accept: "application/json"}, null) YIELD value AS link
UNWIND link._links.packages AS package
WITH DISTINCT SPLIT(package.title, ' ')[0] AS model
MERGE (mdl:Model {name: model})
RETURN mdl.name;
```

# Linked graph domain model for CDISC CT

\*(22)

RootCTTerm(1)

CTTerm(2)

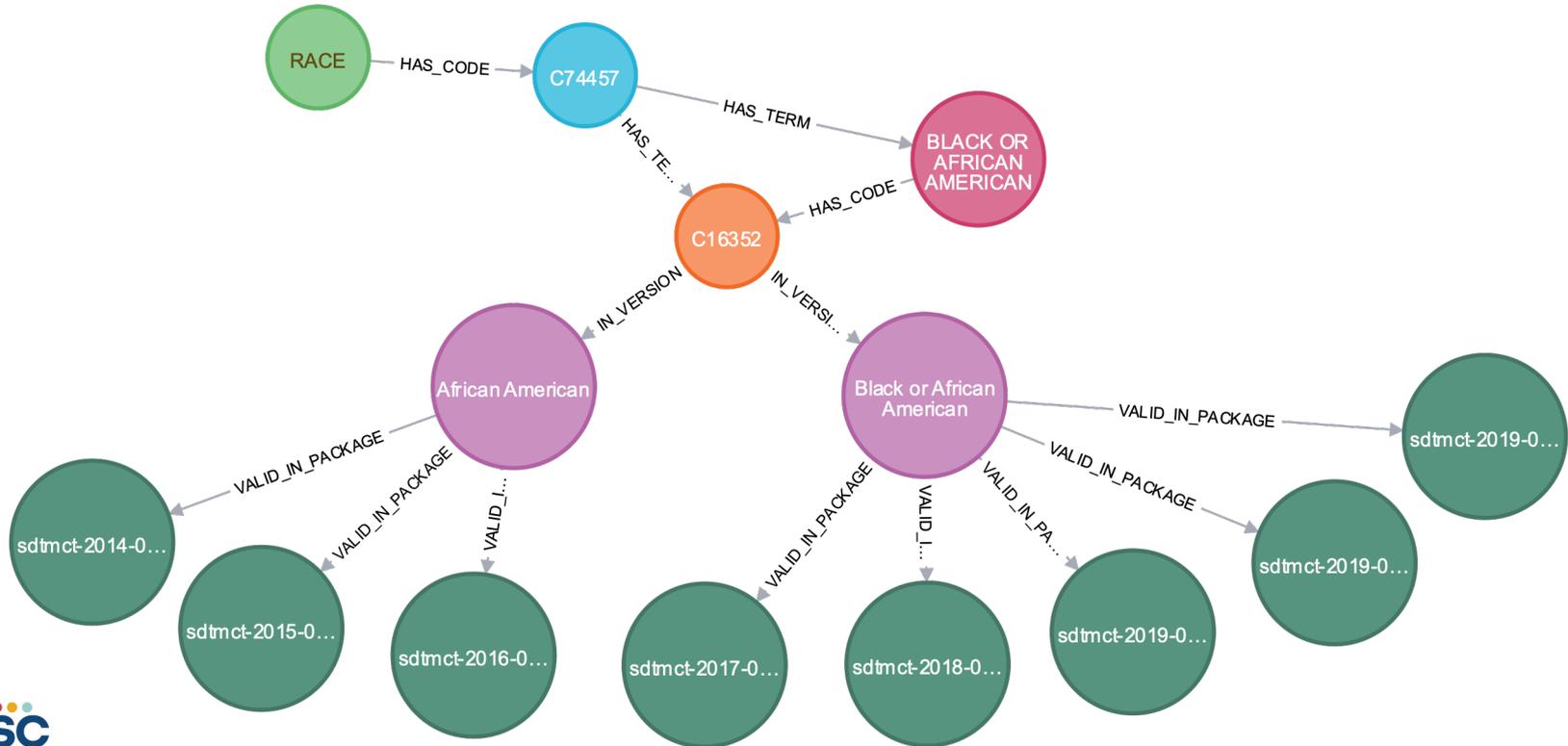
RootCTCodeList(1)

RootCTCodeListName(1)

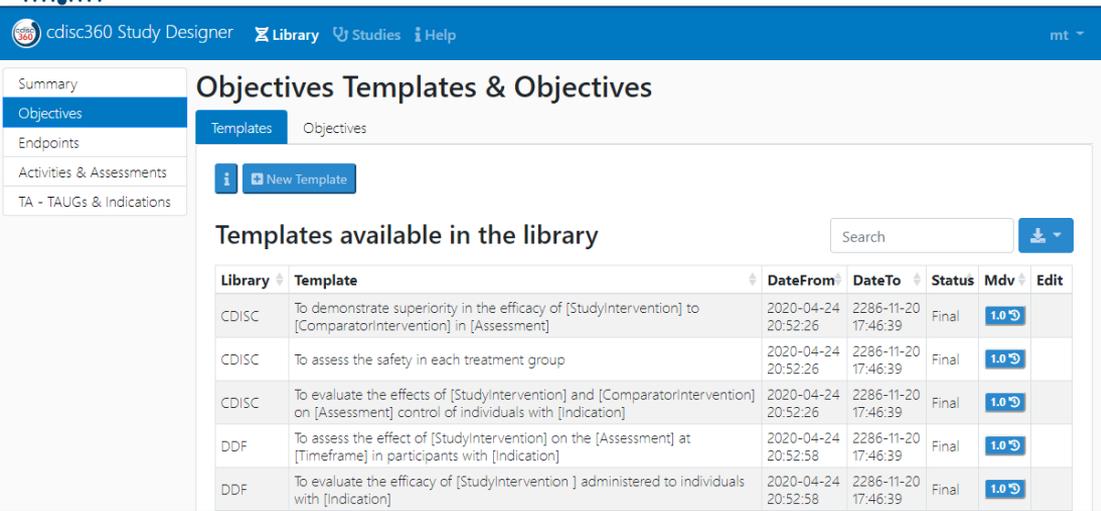
CTPackage(8)

Terminology Standard(8)

RootCTTermName(1)



# Study Designer App - Library



The screenshot shows the 'Library' menu in the Study Designer app. The main heading is 'Objectives Templates & Objectives'. Below this, there are tabs for 'Templates' and 'Objectives'. A 'New Template' button is visible. A search bar and a download icon are also present. The table below lists five templates available in the library.

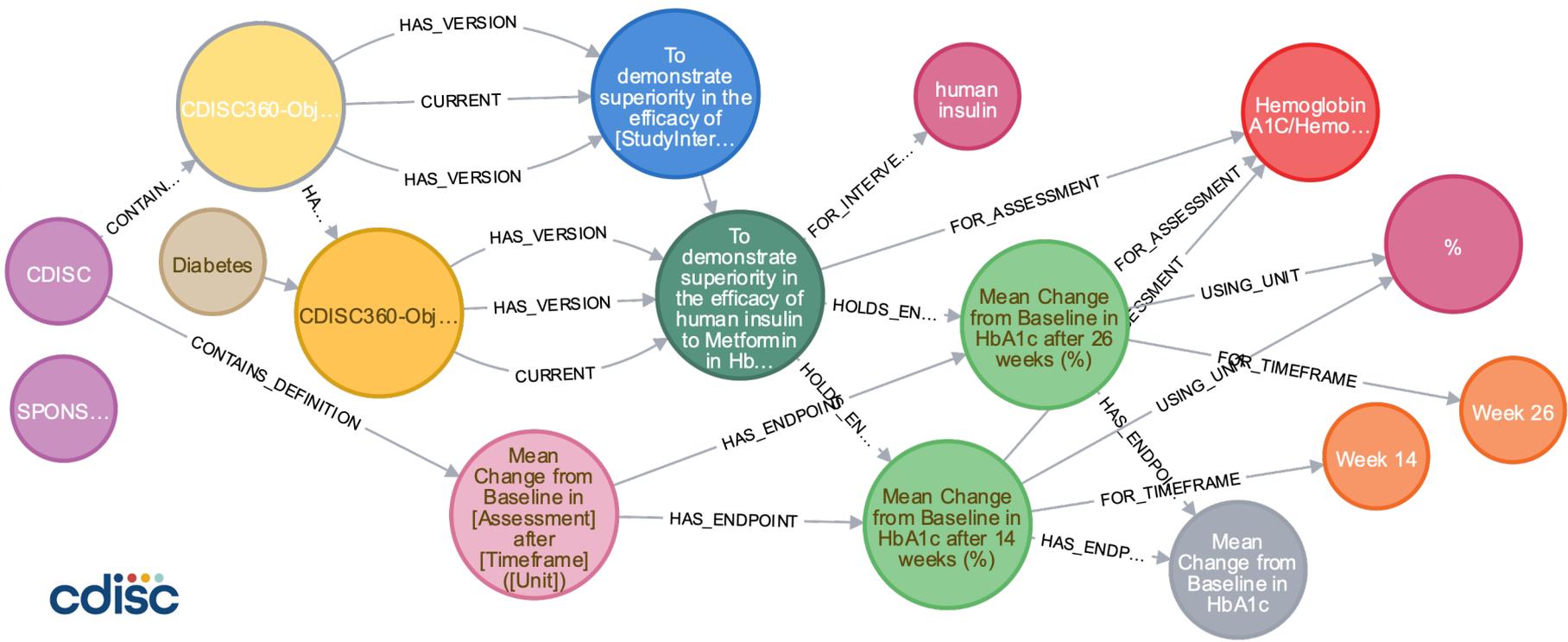
Library	Template	DateFrom	DateTo	Status	Mdv	Edit
CDISC	To demonstrate superiority in the efficacy of [StudyIntervention] to [ComparatorIntervention] in [Assessment]	2020-04-24 20:52:26	2286-11-20 17:46:39	Final	1.0	
CDISC	To assess the safety in each treatment group	2020-04-24 20:52:26	2286-11-20 17:46:39	Final	1.0	
CDISC	To evaluate the effects of [StudyIntervention] and [ComparatorIntervention] on [Assessment] control of individuals with [Indication]	2020-04-24 20:52:26	2286-11-20 17:46:39	Final	1.0	
DDF	To assess the effect of [StudyIntervention] on the [Assessment] at [Timeframe] in participants with [Indication]	2020-04-24 20:52:58	2286-11-20 17:46:39	Final	1.0	
DDF	To evaluate the efficacy of [StudyIntervention ] administered to individuals with [Indication]	2020-04-24 20:52:58	2286-11-20 17:46:39	Final	1.0	

On the **Library** menu the user

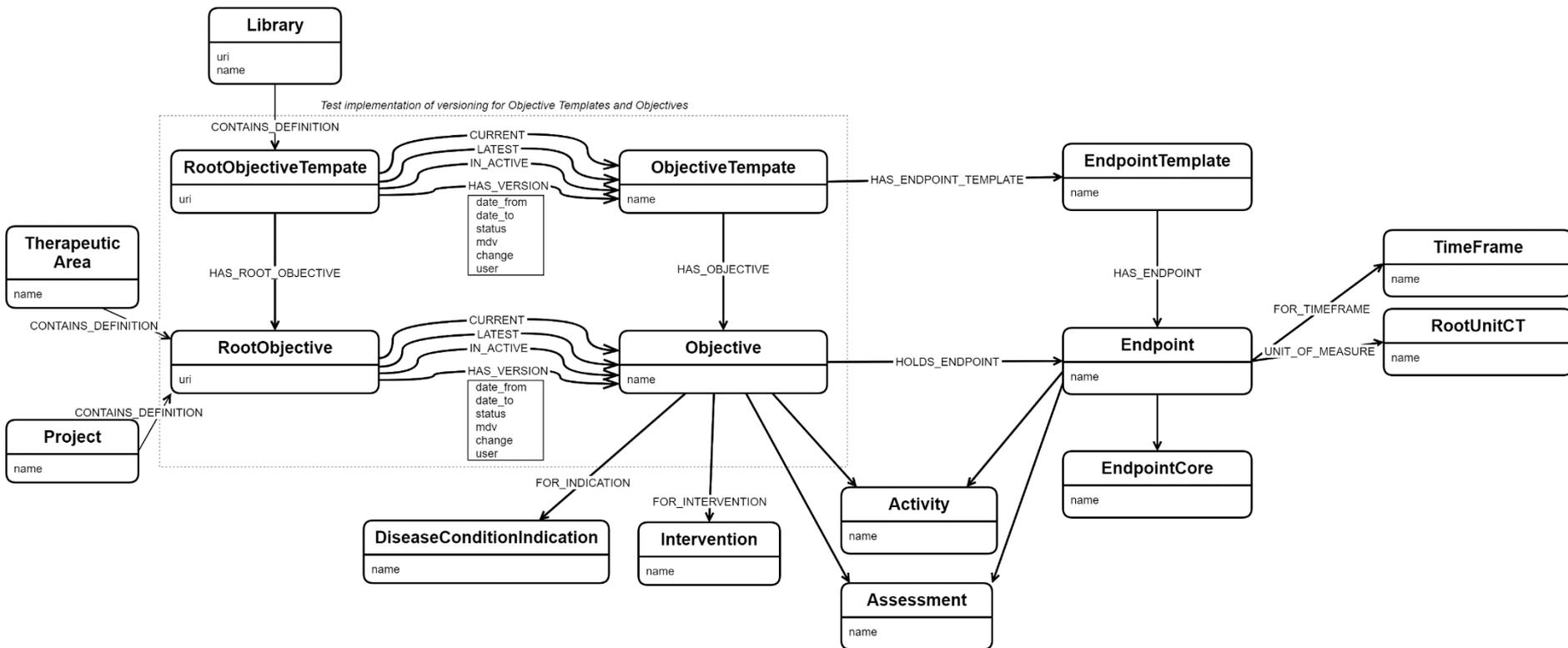
- Create additional templates for Objectives and Endpoints
- Create instantiations of imported or sponsor defined templates
- Instances of Objectives and Endpoints include reference to dependent parameters

# Linked graph domain model for Library

- \*(23)
- Library(2)
- EndpointTemplate(1)
- RootObjectiveTemplate(1)
- ObjectiveTemplate(1)
- RootTSParmValue(4)
- TherapeuticArea(1)
- Intervention(1)
- Objective(1)
- Assessment(1)
- NumericFinding(1)
- Param(1)
- RootCTTermName(1)
- RootUnitCT(1)
- EndpointCore(1)
- TimeFrame(2)
- Endpoint(2)
- RootObjective(1)



# Linked graph domain model for Objective with versioning



# Study Designer App - Define

cdisc360 Study Designer Library Studies **Define** Design Select Build List Help CDISC360-2 mt

## CDISC360-2 / Define Study Title

Summary

Title, Registry IDs

Therapeutic Area

Indication ▲

Terminology Standards ▲

Exchange Standards ▲

Project Templates ▲

Study ID\*

Study Phase

Please provide the phase of your trial

Study Title

The name of a clinical trial. (NCI) [C49802] - Trial Title

CT.Gov Reference

EUDRACT Reference

Linked project

Add the CTGov reference!

Add the EUDRACT reference!

Please select if applicable a global project

### Online Help

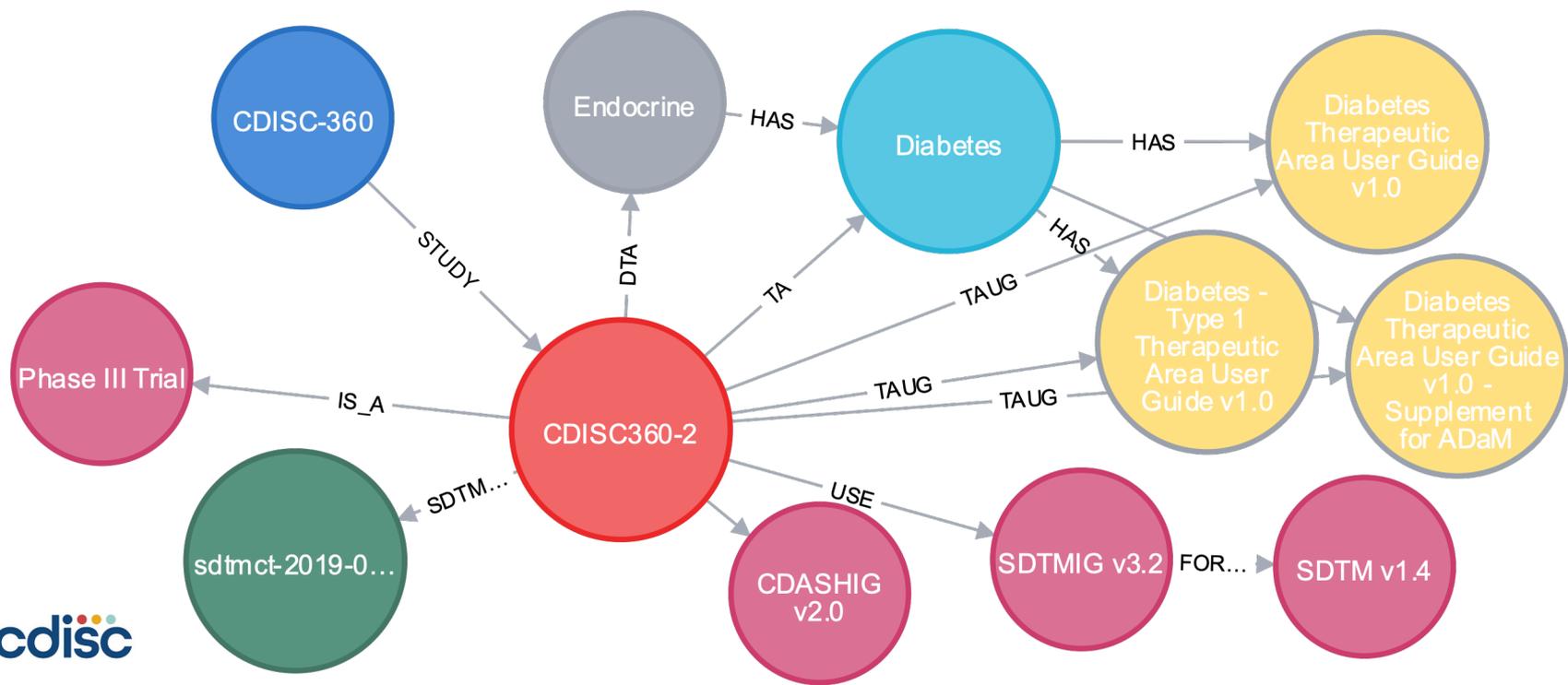
- [Not Applicable](#)
- [Phase 0 Trial](#)
- [Phase I Trial](#)
- [Phase I/II Trial](#)
- [Phase II Trial](#)

Phase 2. Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to

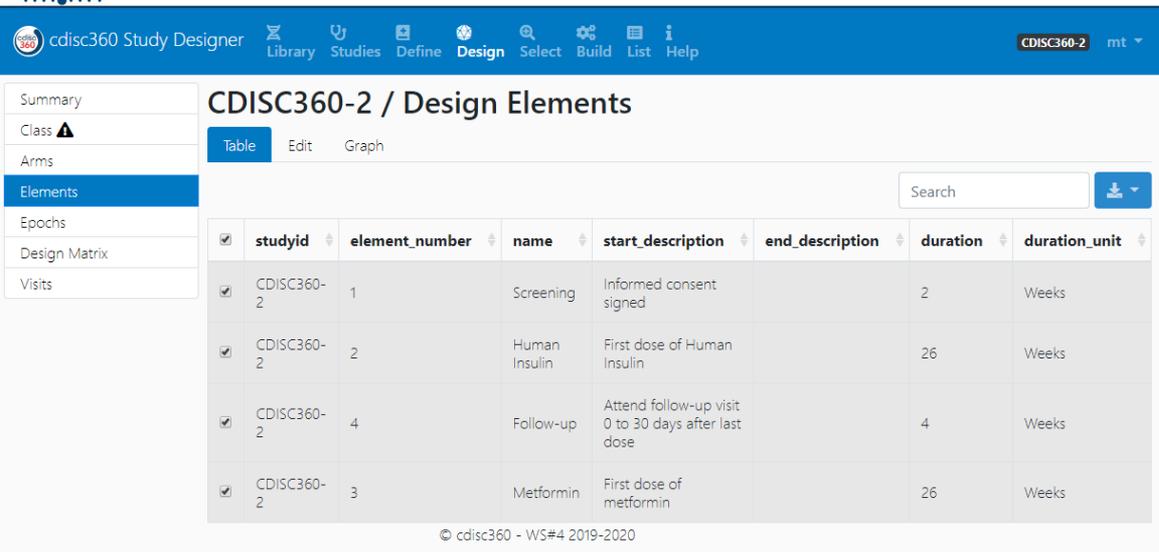
On the **Define** menu the user

- Enter the basic description of the trial like the study phase, title, registry identifiers
- Therapeutic Area of the study and CDISC TAUGs used
- Version of terminology standards
- Version of exchange standards

# Linked graph domain model for Study Define



# Study Designer App - Design



The screenshot shows the CDISC360 Study Designer interface. The top navigation bar includes 'Library', 'Studies', 'Define', 'Design', 'Select', 'Build', 'List', and 'Help'. The 'Design' menu is active, and the current study is 'CDISC360-2'. The main content area displays 'CDISC360-2 / Design Elements' with a table view selected. The table lists four design elements with columns for studyid, element\_number, name, start\_description, end\_description, duration, and duration\_unit.

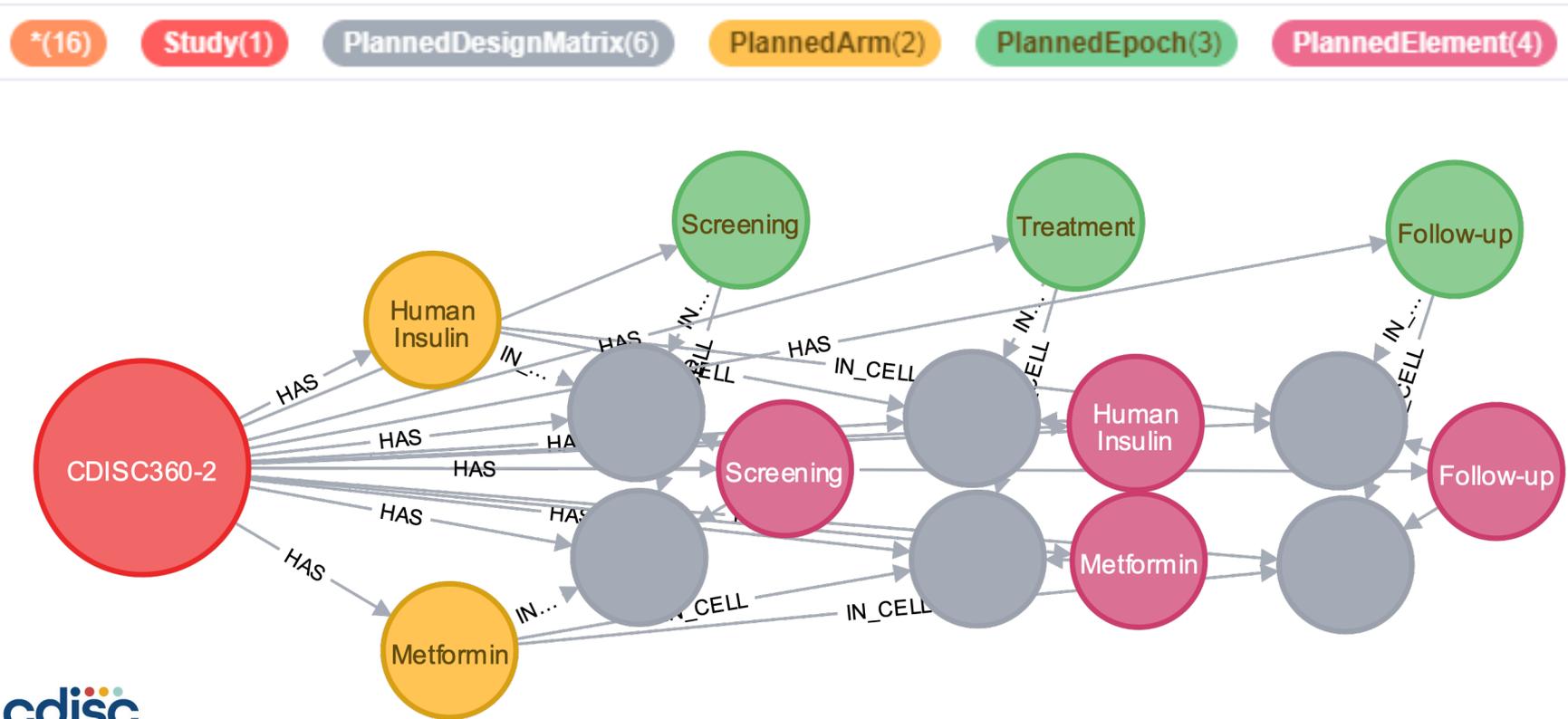
<input checked="" type="checkbox"/>	studyid	element_number	name	start_description	end_description	duration	duration_unit
<input checked="" type="checkbox"/>	CDISC360-2	1	Screening	Informed consent signed		2	Weeks
<input checked="" type="checkbox"/>	CDISC360-2	2	Human Insulin	First dose of Human Insulin		26	Weeks
<input checked="" type="checkbox"/>	CDISC360-2	4	Follow-up	Attend follow-up visit 0 to 30 days after last dose		4	Weeks
<input checked="" type="checkbox"/>	CDISC360-2	3	Metformin	First dose of metformin		26	Weeks

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On the **Design** menu the user

- Make basic selection of trial design related trial summary parameters like Intervention Type, Intervention Model etc.
- Define the Trial Arms, Epochs, Elements and the Design matrix
- Define the visit schedule
- Define the planned interventions

# Linked graph domain model for Study Design



# Study Designer App - Select

The screenshot shows the 'Select' menu in the CDISC360 Study Designer application. The 'Objectives and Endpoints' section is active, displaying a table of objectives for the study. The table includes columns for Study, Order, Level, Objective, DateFrom, DateTo, Status, Mdv, and Unlink. Three objectives are listed, all with a status of 'Final' and a metadata value of '1.0'. A search bar and a plus icon are located above the table.

Study	Order	Level	Objective	DateFrom	DateTo	Status	Mdv	Unlink
CDISC360-2	1	Trial Primary Objective	To demonstrate superiority in the efficacy of human insulin to Metformin in HbA1c	2020-04-24 20:52:26	2286-11-20 17:46:39	Final	1.0	
CDISC360-2	2	Trial Secondary Objective	To assess the safety in each treatment group	2020-04-24 20:52:26	2286-11-20 17:46:39	Final	1.0	
CDISC360-2	3	Trial Secondary Objective	To evaluate the effects of human insulin and Metformin on glucose control of individuals with Type 2 Diabetes Mellitus	2020-04-24 20:52:26	2286-11-20 17:46:39	Final	1.0	

The screenshot shows the 'Schedule of Activities' section in the CDISC360 Study Designer application. It displays a grid of activities (AE, DS, LB, MH, VS) across 17 visits. Checkmarks indicate activities using the domain, and 'X' marks indicate activities not using the domain. A legend at the bottom explains the symbols.

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17
AE	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DS	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
LB	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MH	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
VS	✓	✓	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗

Legend: ✓ Visit using this Domain, ✗ Visit not using this Domain

On the **Select** menu the user

- Selects the concept based standards from the libraries that are to be used in the study
  - These can be based on templates that are instantiated in the local library
- Objectives and Endpoints
- Activities and Assessments
- Schedule of Activities and Assessments
- TFL metadata



# Study Designer App - Build

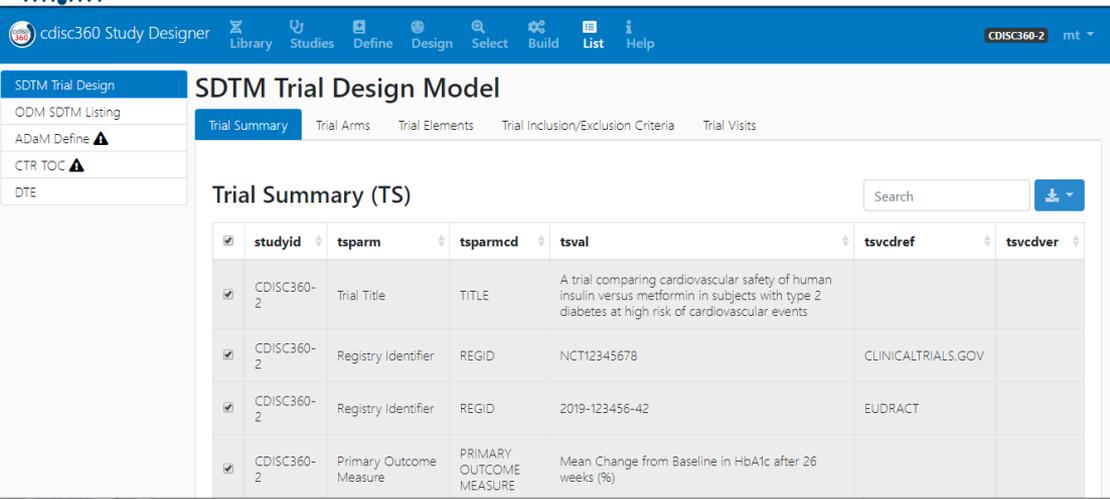
The screenshot shows the CDISC360 Study Designer application in the 'Build' menu. The interface is divided into three main sections:

- Summary:** A sidebar on the left with a 'Summary' section containing 'Study Data Standardization Plan', 'Common Protocol Template', 'ODM Tree', 'SDTM Tree & Define', and 'ODM SDTM Mapping' (which is highlighted).
- ODM Tree:** A tree view on the left showing the study structure. It includes 'CDISC360-2' with sub-items for 'Visit 1 (Week -2)', 'Adverse Events', 'Disposition', 'Labs', 'Medical History', 'Vital Signs', and 'VS [Vital Signs]'. Under 'VS', there are items for 'Height', 'Body Weight', 'Systolic Blood Pressure', 'Diastolic Blood Pressure', 'Pulse', and 'Body Temperature'. Below this are 25 visits from 'Visit 2 (Week 0)' to 'Visit 25 (Week 23)'.
- ODM2SDTM - Just an example:** A central text box containing:
  - Item : Systolic Blood Pressure
  - From ODM Will go into the SDTM variable
  - Variable : VSORRES
- SDTM Tree:** A tree view on the right showing the SDTM structure. It includes 'CDISC360-2' with sub-items for 'DM [Demographics]', 'SE [Subject Elements]', 'DS [Disposition]', 'TA [Trial Arms]', 'TE [Trial Elements]', 'TV [Trial Visits]', 'TD [Trial Disease Assessments]', 'TI [Trial Inclusion/Exclusion Criteria]', 'TS [Trial Summary]', 'AE [Adverse Events]', 'MH [Medical History]', 'LB [Labs]', and 'VS [Vital Signs]'. Under 'VS', there is a list of variables: STUDYID, DOMAIN, USUBJID, VSSEQ, VSGRPID, VSSPID, VSTESTCD, VSTEST, VSCAT, VSSCAT, VSPPOS, VSORRES, VSORRESU, VSSTRESC, VSSTRESN, VSSTRESU, VSSTAT, VSREASND, VSLOC, VSLAT, VSBLFL, VSDRVFL, VISITNUM, and VISIT.

On the **Build** menu the user can generate:

- Study data standards plan
- Protocol metadata report
  - To be copy paste into CPT
  - As XML to be imported into eCPT
  - As tables that can be exported
- Data collection specification
  - ODM-XML
  - Blank CRF, techCRF and aCRF
- Tabulation Specification
  - Define-XML specification
- Analysis Specification

# Study Designer App - List



The screenshot displays the CDISC360 Study Designer interface. The top navigation bar includes 'Library', 'Studies', 'Define', 'Design', 'Select', 'Build', 'List', and 'Help'. The 'List' menu is active, showing options for 'SDTM Trial Design', 'ODM SDTM Listing', 'ADaM Define', 'CTR TOC', and 'DTE'. The main content area is titled 'SDTM Trial Design Model' and features a 'Trial Summary' tab. Below this, a table titled 'Trial Summary (TS)' is displayed with a search bar and a download icon. The table contains the following data:

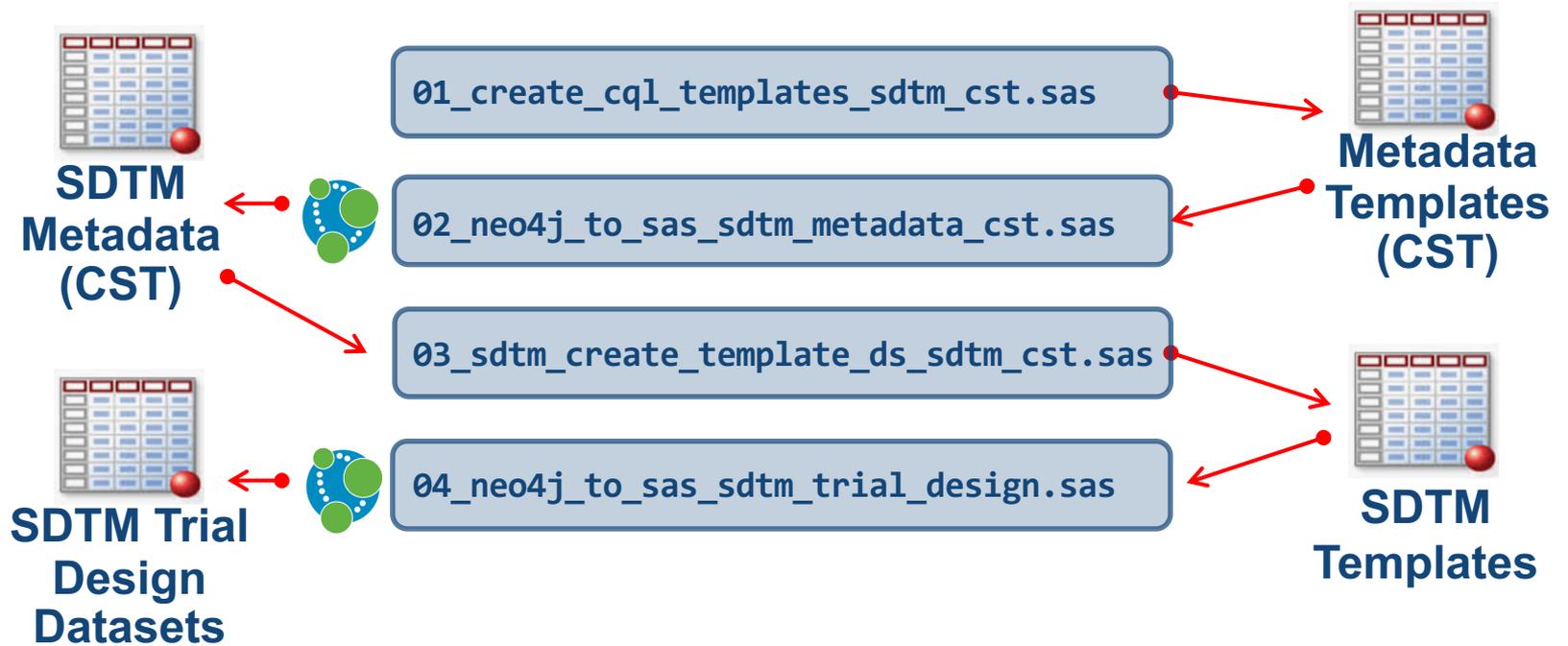
<input checked="" type="checkbox"/>	studyid	tsparm	tsparmcd	tsval	tsvcdrref	tsvcdrver
<input checked="" type="checkbox"/>	CDISC360-2	Trial Title	TITLE	A trial comparing cardiovascular safety of human insulin versus metformin in subjects with type 2 diabetes at high risk of cardiovascular events		
<input checked="" type="checkbox"/>	CDISC360-2	Registry Identifier	REGID	NCT12345678	CLINICALTRIALS.GOV	
<input checked="" type="checkbox"/>	CDISC360-2	Registry Identifier	REGID	2019-123456-42	EUDRACT	
<input checked="" type="checkbox"/>	CDISC360-2	Primary Outcome Measure	PRIMARY OUTCOME MEASURE	Mean Change from Baseline in HbA1c after 26 weeks (%)		

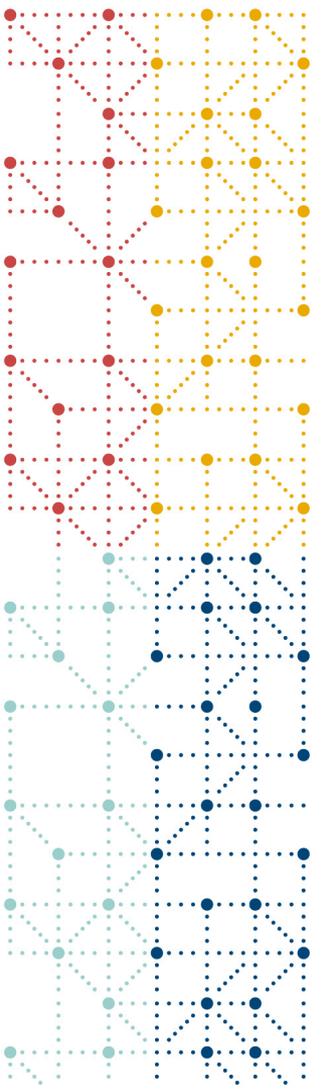
On the **List** menu the user can generate:

- Browse all study metadata in tabular form
- Export these into various file formats
- Will correspond to the SAS based interface to the Study Metadata Library enabling extract of study metadata into SAS datasets

# Neo4j to SAS Interface – Engine CST

Using SAS PROC LUA to easily interface with the Neo4j REST API from SAS





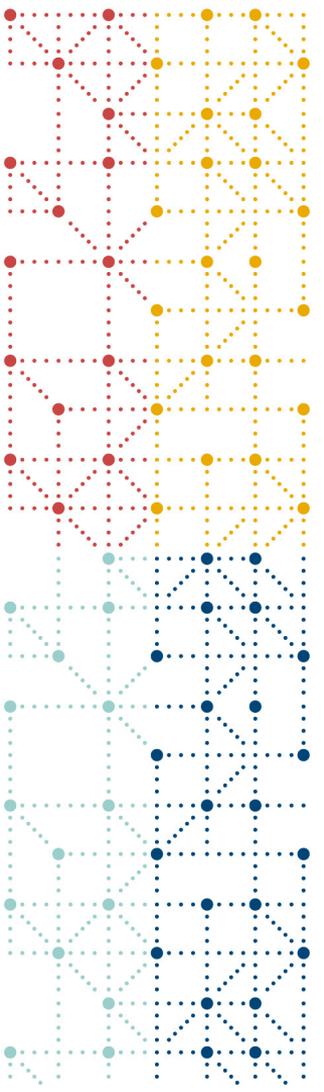
## Learnings so far

*Experience using Linked Graph Data Model for Study Metadata Library*



# Learnings from initial implementation of Study Library in a Property Label Graph database (Neo4j)

- Very efficient to load JSON data from API's into Neo4j with no duplication of metadata
- Intuitive to represent BCs in a Property Label Graph Model linked with metadata from the CDISC Library
- Intuitive to define and query standards selections for a study in Property Label Graph Model
- Difficult to articulate and agree on what a BC is
  - Iterations are needed to learn and evolve definitions of a BC
- Learning new tools takes time
- Working and setting things up in Azure require support
  - Big thanks to Microsoft, Neo4j and CDISC IT



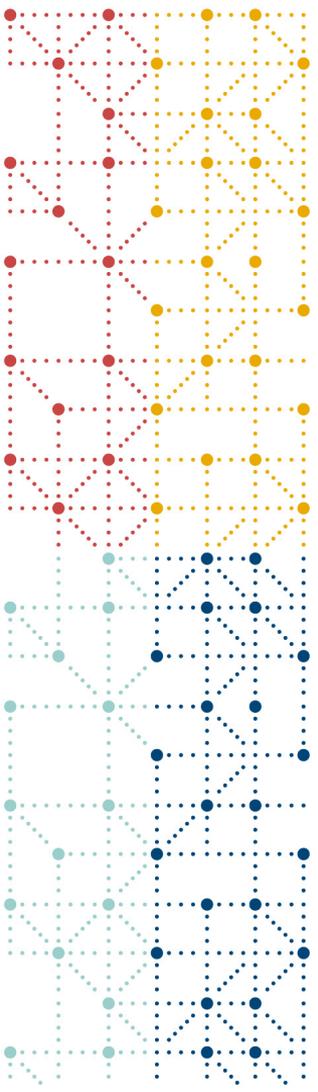
## Next Steps

*Our plans for remaining part of PoC*



# Next Steps in Study Design and Configuration

- Configuring BCs as Assessments and Activities in Study
- Data Collection Specification as ODM.XML
- Metadata for transformations
- Metadata for TFLs



# Thank You!

Mikkel Traun, *Novo Nordisk*

Nicolas de Saint Jorre, *XClinical*

