

CDISC 360

Session 4, Track C: CDISC 360, Part II



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1. Introduction, Future State, Process and Architecture of the PoC – *Bhavin and Mikkel* 10 mins
2. **PoC for Study Design and Configuration using CDISC 360 Concept-based Standards – Mikkel and Nicolas** 20 mins
3. Automation of SDTM & ADaM Generation and Artifacts using CDISC 360 Enriched Metadata – Bhavin and Jimmy 20 mins
4. Automation of TFL Generation using CDISC 360 Enriched Metadata – *Bhavin, Prasanna & Stuart* 20 mins
5. Concluding Remarks and Next Steps – *Bhavin and Mikkel* 5 mins
6. Q & A session 15 mins



PoC for Study Design and Configuration using CDISC 360 Concept-based Standards

Mikkel Traun, *Novo Nordisk*
Nicolas de Saint Jorre, *XClinical*

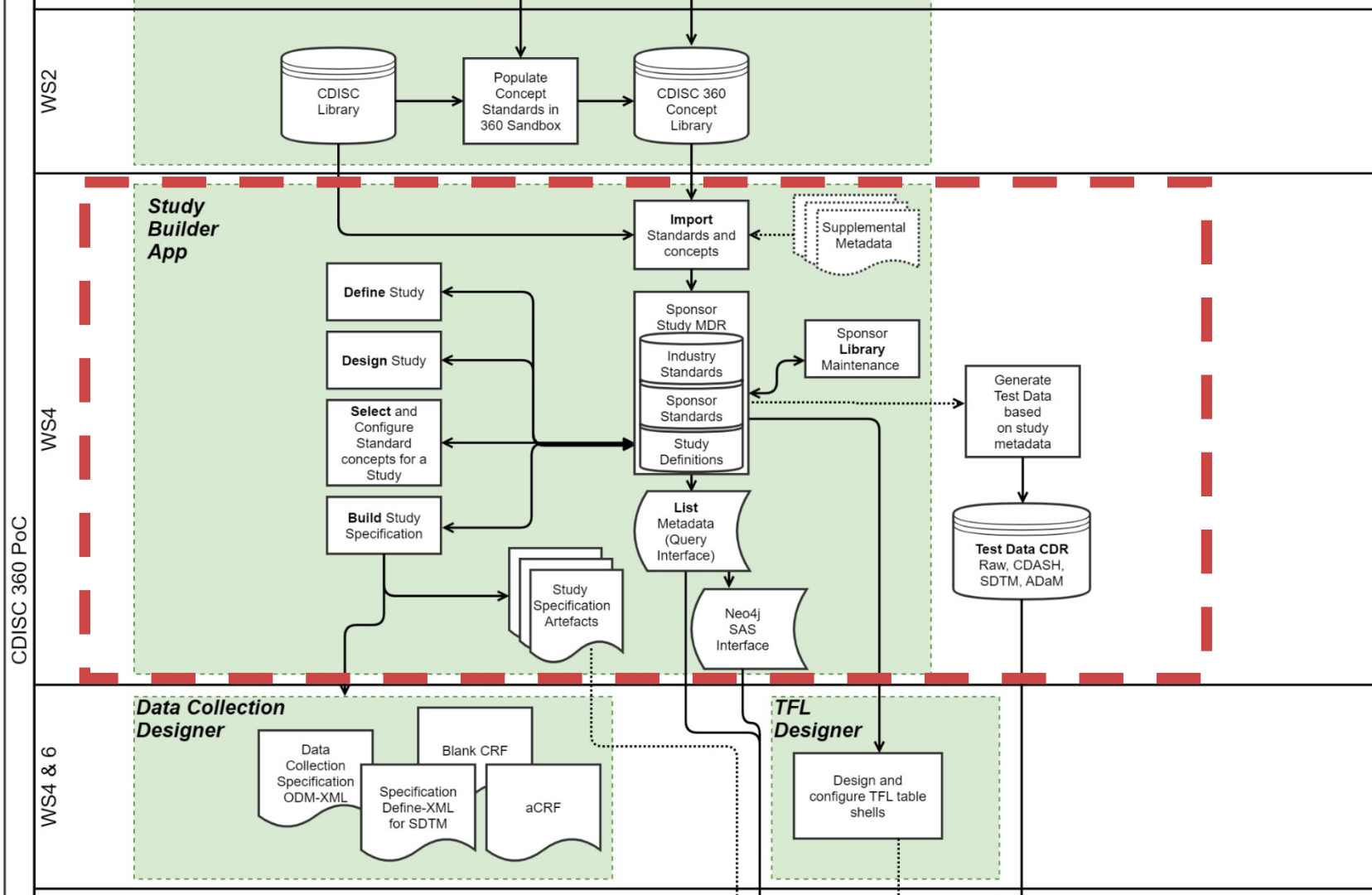
CDISC US Interchange, October 2020





Agenda

- General Introduction to Study Builder App & MDR
- Demo
 - Define – Design – Select – Build
 - List and interface study metadata
- BC's for Activities and Assessment
 - Linked Graph Data Model
- API for Sponsor Study MDR
- Neo4j to SAS Interface



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.



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)

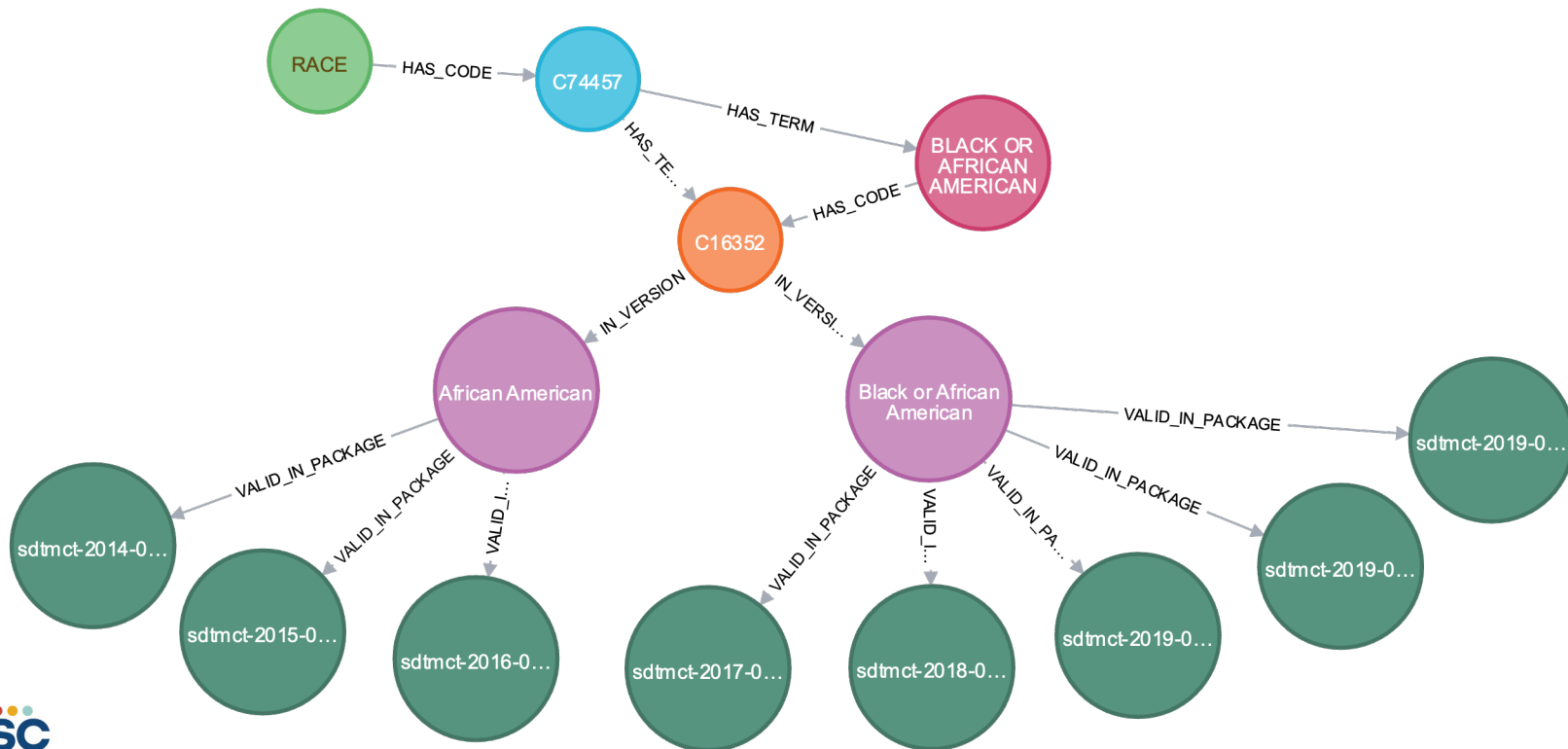
RootCTCodeList(1)

RootCTCodeListName(1)

CTPackage(8)

TerminologyStandard(8)

RootCTTermName(1)



Demo

Library – Import and manage sponsor standards


Define – Design – Select – Build

List and interface study metadata

How do you work with a 360 enabled Sponsor Study MDR



Study Designer App - Library




cdisc360 Study Designer Library Studies Help mt


Summary
Objectives
Endpoints
Activities & Assessments
TA - TAUGs & Indications






Objectives Templates & Objectives

Templates Objectives

 [New Template](#)

Templates available in the library



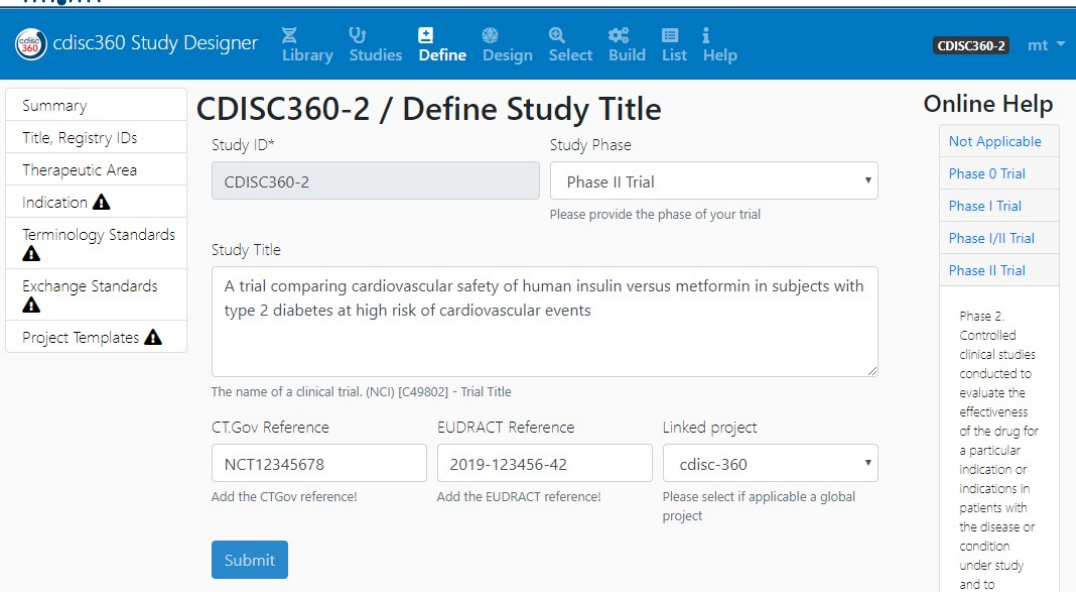
Library	Template	DateFrom	DateTo	Status	Mdv	Edit
CDISC	To demonstrate superiority in the efficacy of [StudyIntervention] to [ComparatorIntervention] in [Assessment]	2020-04-24 20:52:26	2286-11-20 17:46:39	Final	1.0 	
CDISC	To assess the safety in each treatment group	2020-04-24 20:52:26	2286-11-20 17:46:39	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



Study Designer App - Define



The screenshot shows the 'Define' menu of the CDISC360 Study Designer application. The interface is divided into several sections:

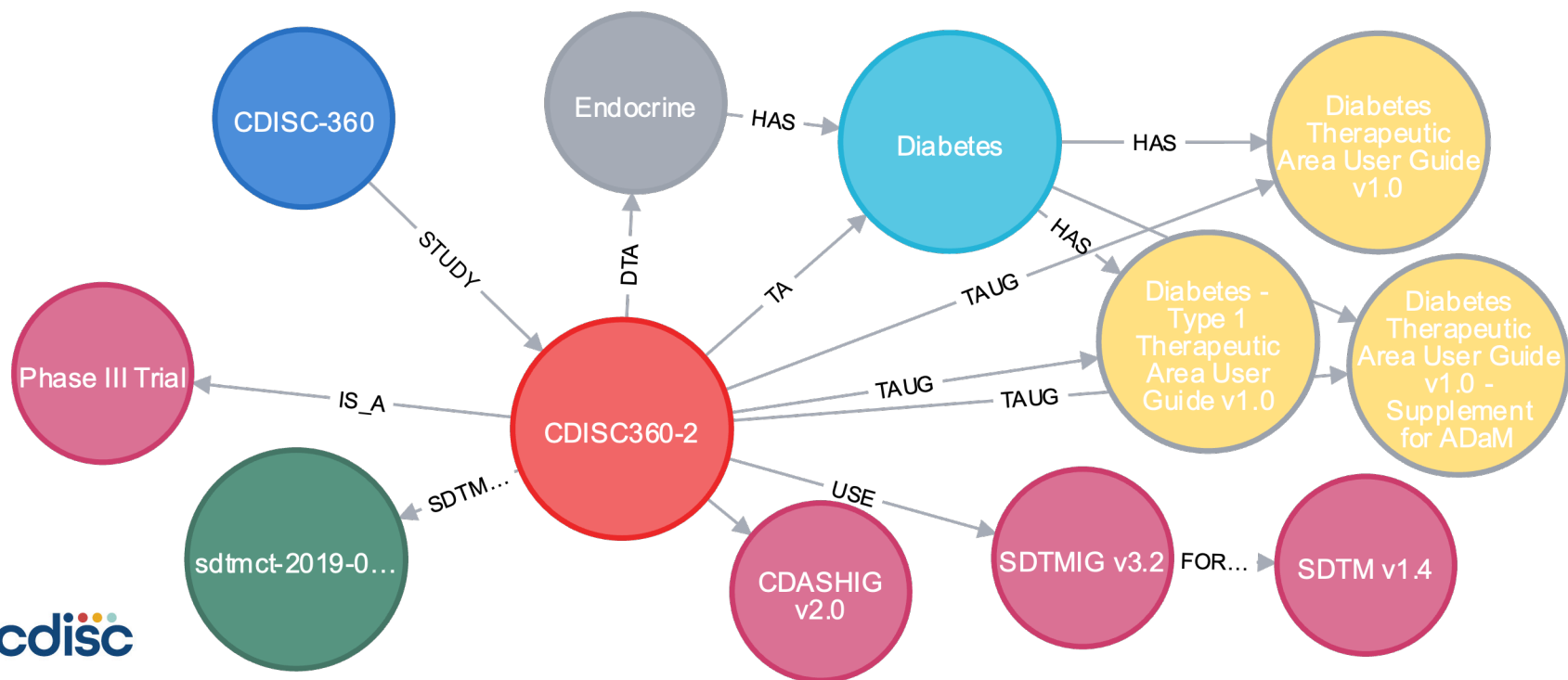
- Navigation Bar:** Includes icons for Library, Studies, Define (active), Design, Select, Build, List, and Help. The user is logged in as 'mt'.
- Left Sidebar:** Contains links to Summary, Title, Registry IDs, Therapeutic Area, Indication (with a warning icon), Terminology Standards (with a warning icon), Exchange Standards (with a warning icon), and Project Templates (with a warning icon).
- Main Content Area:**
 - CDISC360-2 / Define Study Title:** The current view.
 - Study ID*:** A text input field containing 'CDISC360-2'.
 - Study Phase:** A dropdown menu currently showing 'Phase II Trial'. Below it is a note: 'Please provide the phase of your trial'.
 - Study Title:** A large text area containing the text: 'A trial comparing cardiovascular safety of human insulin versus metformin in subjects with type 2 diabetes at high risk of cardiovascular events'.
 - Help Text:** Below the title field, it says: 'The name of a clinical trial. (NCI) [C49802] - Trial Title'.
 - References:** Three input fields for 'CT.Gov Reference' (NCT12345678), 'EUDRACT Reference' (2019-123456-42), and 'Linked project' (cdisc-360). Each has a corresponding instruction below it: 'Add the CTGov reference!', 'Add the EUDRACT reference!', and 'Please select if applicable a global project'.
 - Submit Button:** A blue button labeled 'Submit'.
- Online Help:** A sidebar on the right with a list of links: 'Not Applicable', 'Phase 0 Trial', 'Phase I Trial', 'Phase I/II Trial', and 'Phase II Trial' (which is highlighted). Below the links, there is a description for '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

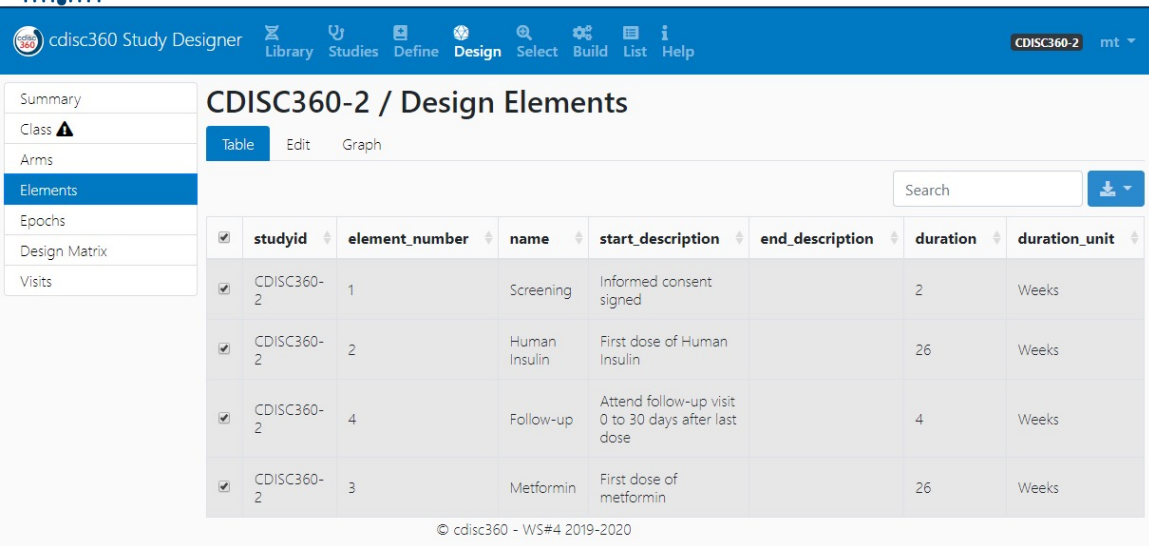
- Enter the basic description of the trial like the study phase, title, registry identifiers
- Therapeutic Area of the study and CDISC TAUGs used
- Version of terminology standards
- Version of exchange standards

Linked graph domain model for Study Define

*(24) CDASHIGVersion(1) ExchangeStandard(3) CTPackage(1) TerminologyStandard(1) RootTSParmValue(6) SDTMIGVersion(1) RootCTTermName(1)
RootTPhase(1) RootTSParmValueCT(1) Project(1) SDTMVersion(1) DiseaseArea(1) TherapeuticArea(1) CDISCTAUG(3) Study(1)



Study Designer App - Design



The screenshot shows the CDISC360 Study Designer application interface. The top navigation bar includes tabs for Library, Studies, Define, Design (selected), Select, Build, List, and Help. The main header displays "CDISC360-2 / Design Elements". On the left, a sidebar menu lists Summary, Class, Arms, Elements (selected), Epochs, Design Matrix, and Visits. The main content area features a table with columns: studyid, element_number, name, start_description, end_description, duration, and duration_unit. The table contains four rows of design elements, each with a checkbox in the first column. A search bar and a download icon are located at the top right of the table.

	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





Library
Studies
Define
Design
Select
Build
List
Help
CDISC360-2
mt

Summary
Objectives / Endpoints
Derived Assessments
Collected Assessments
Schedule of Activities
Data Collection
Tables, Figures and Listings

CDISC360-2 / Schedule of Activities

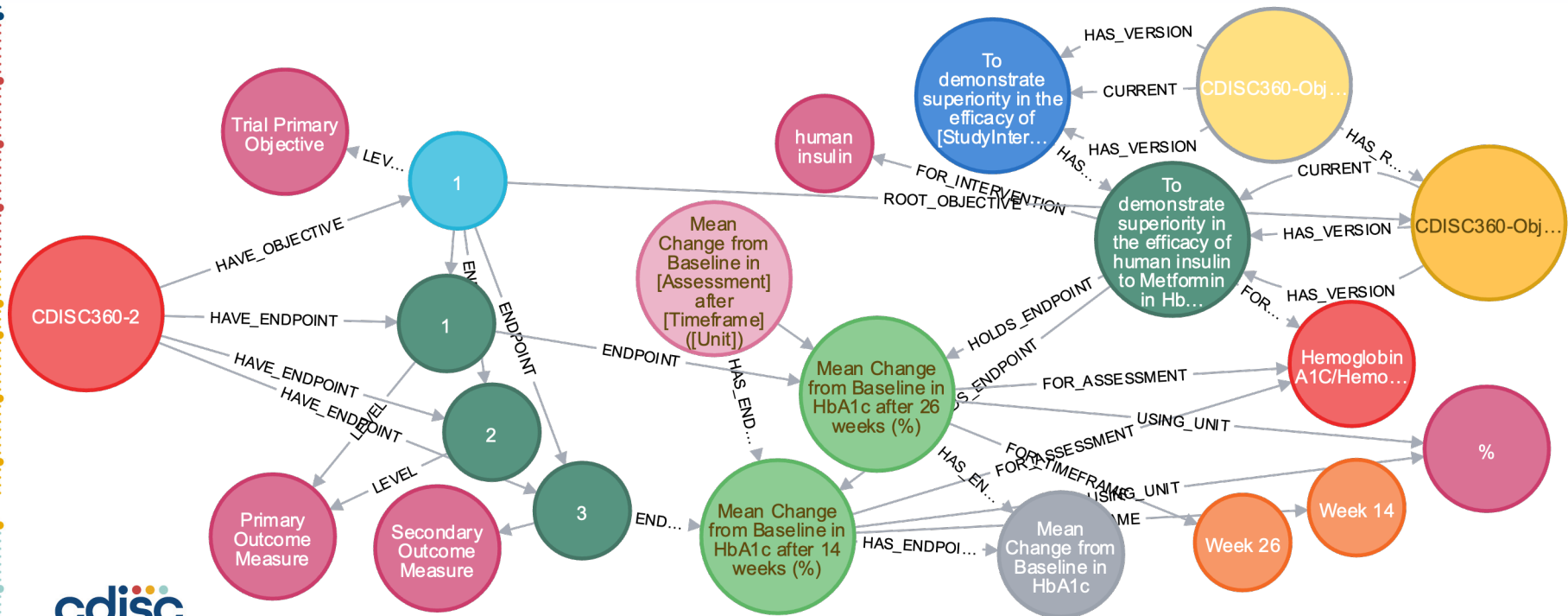
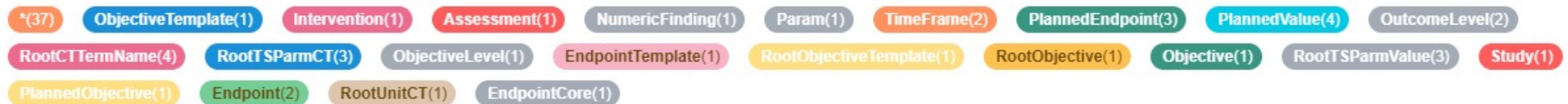
We have for this study the following visits and the following Activities: [i](#)

	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	✓	✓	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗	✓	✗	✗	✗	✗

Visit using this Domain
 Visit not using this Domain

- 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

Linked graph domain model for Study Select



Study Designer App - Build


The screenshot shows the 'Build' menu in the cdisc360 Study Designer application. The top navigation bar includes 'Library', 'Studies', 'Define', 'Design', 'Select', 'Build' (highlighted), 'List', and 'Help'. The 'Build' menu is open, showing three main sections:

- Summary**: Includes 'Study Data Standardization Plan', 'Common Protocol Template', 'ODM Tree', 'SDTM Tree & Define', and 'ODM SDTM Mapping' (highlighted).
- ODM Tree**: A hierarchical tree structure for ODM data. It includes 'CDISC360-2', 'Visit 1 (Week -2)', 'Adverse Events', 'Disposition', 'Labs', 'Medical History', 'Vital Signs', and 'VS [Vital Signs]' with sub-items like 'Height', 'Body Weight', 'Systolic Blood Pressure', 'Diastolic Blood Pressure', 'Pulse', and 'Body Temperature'. It also lists visits from 'Visit 2 (Week 0)' to 'Visit 25 (Week 23)'.
- ODM2SDTM - Just an example**: A text box showing 'Item : Systolic Blood Pressure' and 'From ODM Will go into the SDTM variable' and 'Variable : VSORRES'.
- SDTM Tree**: A hierarchical tree structure for SDTM data. It includes 'CDISC360-2', '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]' with sub-items like 'STUDYID', 'DOMAIN', 'USUBJID', 'VSSEQ', 'VSGRPID', 'VSSPID', 'VSTESTCD', 'VSTEST', 'VSCAT', 'VSSCAT', 'VSPOS', 'VSORRES', 'VSORRESU', 'VSSSTRESC', 'VSSSTRESU', 'VSSTAT', 'VSREASND', 'VSLOC', 'VSLAT', 'VSBFL', '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 – Select Activities & Assessments



cdisc360 Study Builder

Library Studies Define Design **Select** Build List Help

CDISC360-2 mikkel traun

Summary CDISC360-2 / Select Activities / Assessments for this Study

Objectives / Endpoints We have for this study the following Activities / Assessments: ⓘ

Derived Assessments ⓘ

Collected Assessments ⓘ

Select Activity / Assessment

Schedule of Assessments

Schedule SDTM Datasets

Data Collection ⓘ

Tables, Figures and Listings ⓘ

Study

Search ⓘ

Order	Activity	Info / Edit ⓘ ⓘ ⓘ	Assessment	Info / Edit ⓘ ⓘ ⓘ	Linked with CDISC360-2
1 / 1	Randomisation	ⓘ ⓘ ⓘ	Randomisation Date	ⓘ ⓘ ⓘ	✓
21 / 24	Demography	ⓘ ⓘ ⓘ	Date of Birth	ⓘ ⓘ ⓘ	✓
25 / 25	Body Measurement	ⓘ ⓘ ⓘ	Height	ⓘ ⓘ ⓘ	✓
25 / 26			Body Weight	ⓘ ⓘ ⓘ	✓
30 / 29	Glucose metabolism	ⓘ ⓘ ⓘ	Hemoglobin A1C/Hemoglobin	ⓘ ⓘ ⓘ	✓

On the **Select** menu the user

- Selects BC's in the form of Activities and Assessments
- Configure these in context of the study
- Schedule the Activities and Assessments in Study Design



Summary

Objectives /
EndpointsDerived
Assessments
Collected
Assessments
Select
Activity /
AssessmentSchedule of
AssessmentsSchedule
SDTM
DatasetsData
Collection
Tables,
Figures and
Links 

CDISC360-2 / Schedule of Assessments

We have for this study the following visits and the following Assessments:

Epoch		Screening	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment
Activity	Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Randomisation	Randomisation Date	⊗	✓	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗
Demography	Date of Birth	✓	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗
Vital signs	Systolic Blood Pressure	✓	✓	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗
	Diastolic Blood Pressure	✓	✓	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗
	Pulse	✓	✓	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗
	Body Temperature	✓	✓	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗
Glucose metabolism	Hemoglobin A1C/Hemoglobin	⊗	✓	✓	✓	⊗	⊗	⊗	⊗	✓	⊗	⊗
	Glucose, Plasma	⊗	⊗	✓	✓	✓	✓	✓	✓	✓	✓	✓

Study Builder API Documentation!!!

[Base URL: cdisc360poc.azurewebsites.net]

Schemes

HTTP

Authorize



api



GET

/api/objectives-templates/

GET

/api/objectives/

GET

/api/schedule-of-assessment/

POST

/api/schedule-of-assessment/schedule/ Schedule an assessment for a visit.

POST

/api/schedule-of-assessment/unschedule/ Unschedule an assessment for a visit.

GET

/api/studies/



Study Designer App - List

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

SDTM Trial Design ODM SDTM Listing ADaM Define CTR TOC DTE

SDTM Trial Design Model

Trial Summary Trial Arms Trial Elements Trial Inclusion/Exclusion Criteria Trial Visits

Trial Summary (TS)

Search [Download]

	studyid	tsparm	tsparmcd	tsval	tsvcdref	tsvcdver
<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 (%)		

cdisc360 Study Builder Library Studies Define Design Select Build List Help CDISC360-2 mikkel traun

CDASH to SDTM SDTM Trial Design ODM SDTM Listing SDTM Define P21 SDTM Define CST ADaM Define CTR TOC DTE

CDASH to SDTM

Study Datasets Variables ValueLevel

Datasets

Search [Download]

STUDYID	ASSESSMENT	SRCSEQ	SRCLIB	SRCDSN	TGTSEQ	TGTLIB	TGTDSN	WHERE	I
CDISC360-2	['BODY_WEIGHT', 'HEIGHT', 'BP_DIASTOLIC', 'BODY_TEMPERATURE', 'PULSE']	1	CDASH	VS	5	SDTM	VS		
CDISC360-2	['FIRST_TRIAL_PROD_DATE', 'FIRST_TRIAL_PROD_DATE']	3	CDASH	DS_FDRUGDT	4	SDTM	DM		
CDISC360-	['BODY_WEIGHT', 'HEIGHT', 'BP_DIASTOLIC']	2	SDTM	DM	5	SDTM	VS		

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
- This include CDASH2SDTM and SDTM2ADaM Bindings



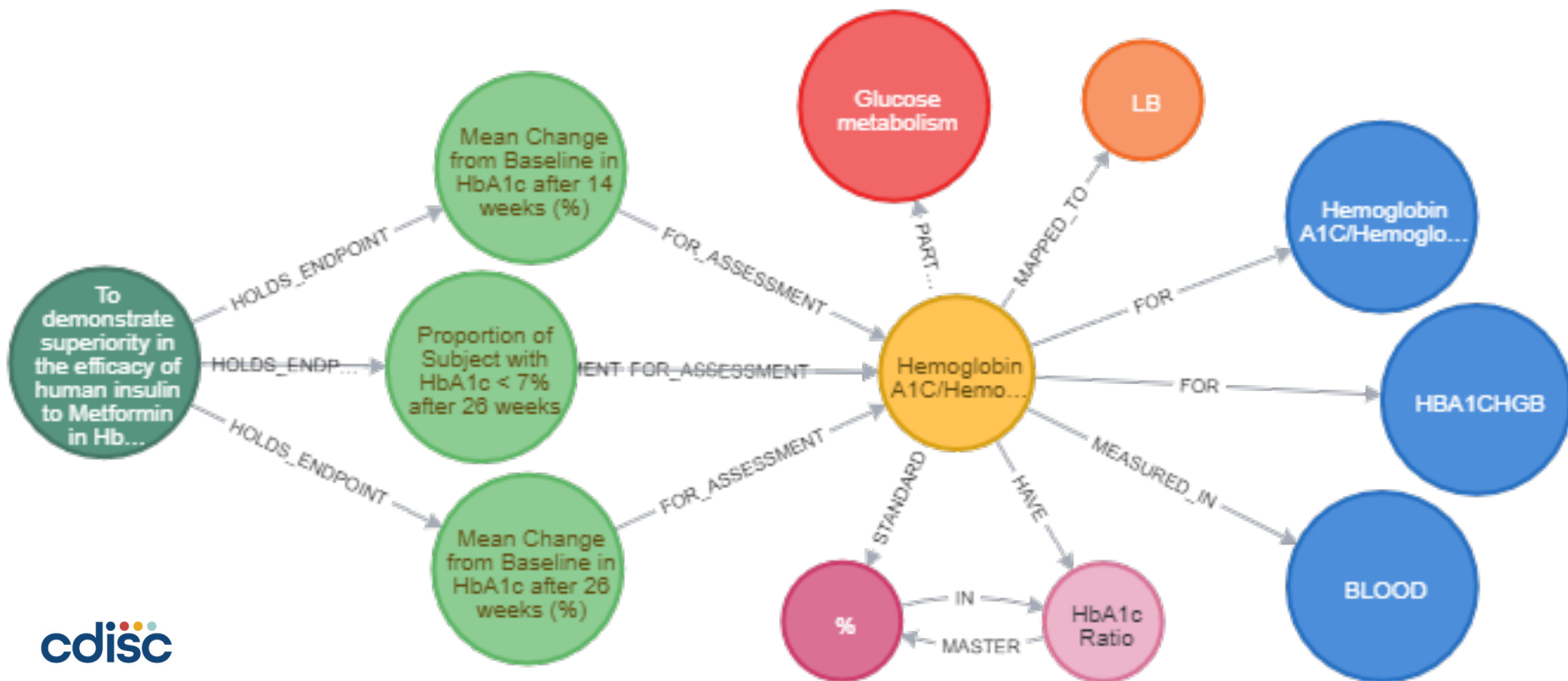
BC's for Activities and Assessment

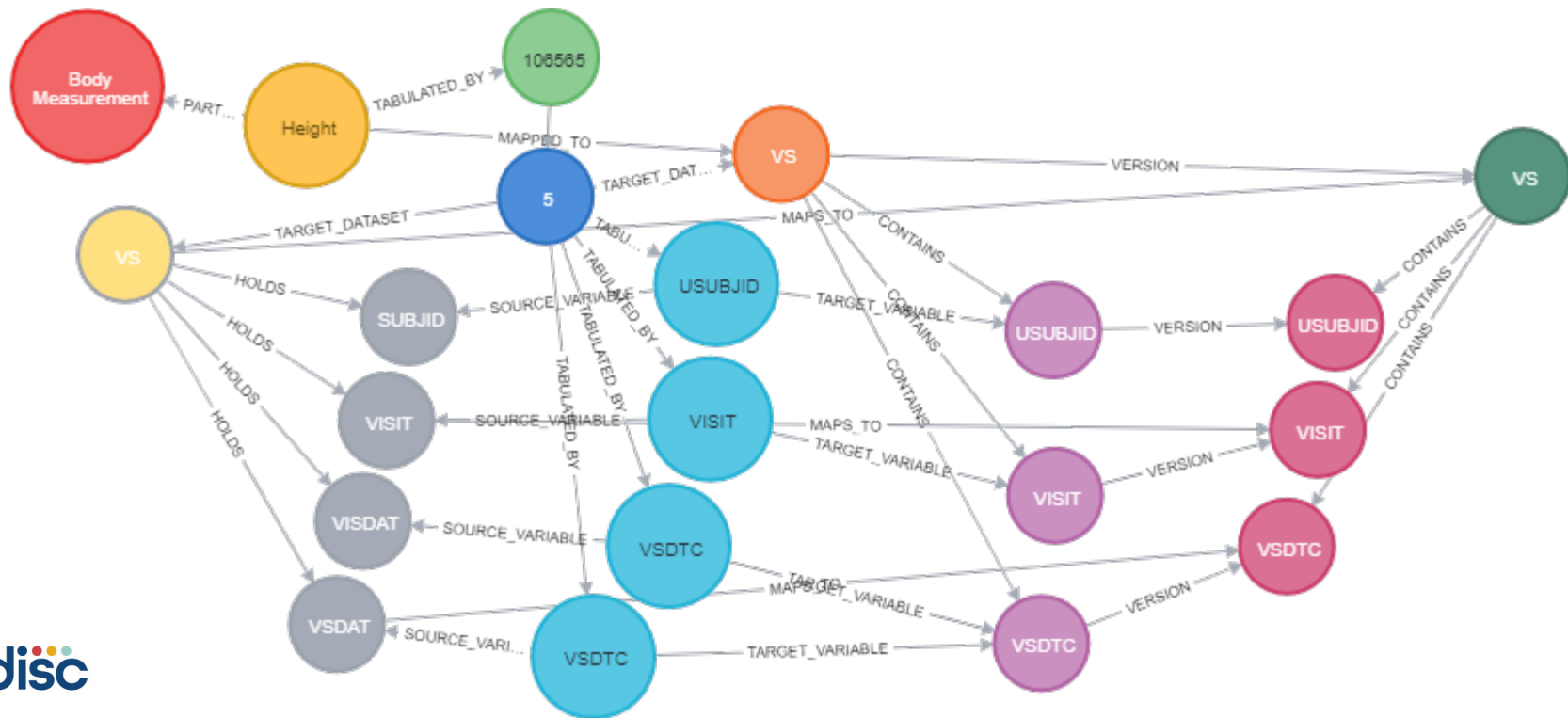
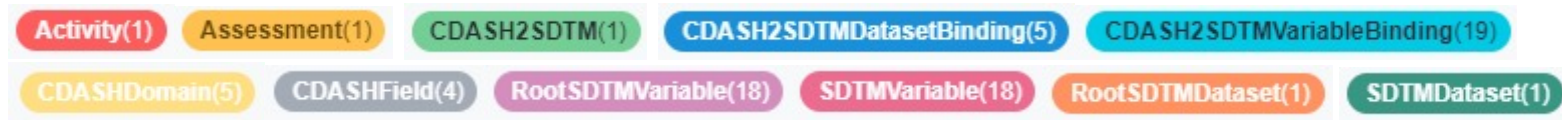
Linked Graph Data Model

Linked graph domain model for Activities and Assessments

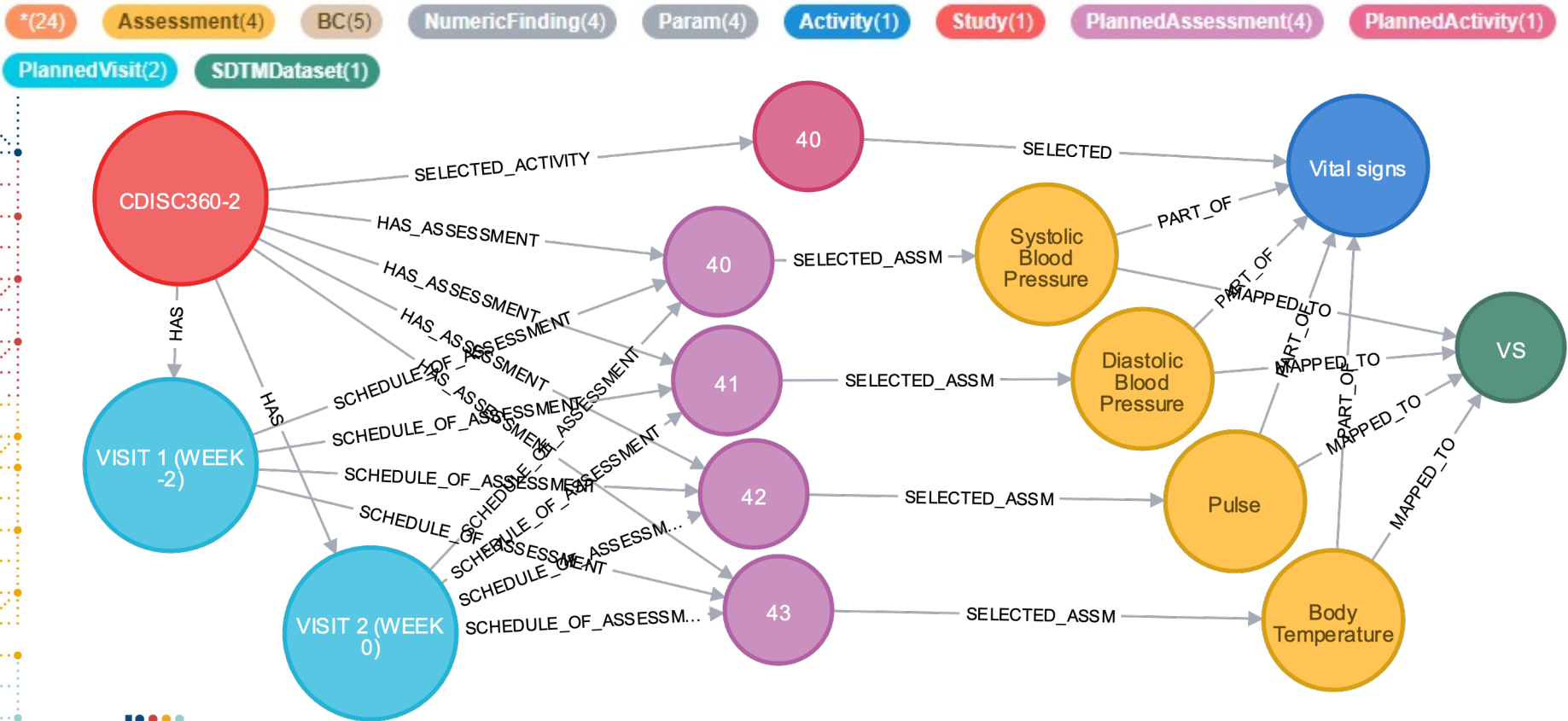
The Concept Definition

Objective(1) Endpoint(3) Activity(1) Assessment(1) RootSDTMDataset(1) UnitDefinition(1) UnitDimension(1) RootCTTermName(3)





Linked graph domain model for Schedule of Assessment



Sample Cypher Query Schedule of Assessments

\$ MATCH (s:Study {id: \$studyid})→(v:PlannedVisit)→(pm:PlannedAssessment)→(a:Assessment)→(ac:A...

	study_id	activity	assessment	visitnum	pa.order	pm.order
1	"CDISC360-2"	"Vital signs"	"Systolic Blood Pressure"	100	40	40
2	"CDISC360-2"	"Vital signs"	"Diastolic Blood Pressure"	100	40	41
3	"CDISC360-2"	"Vital signs"	"Pulse"	100	40	42
4	"CDISC360-2"	"Vital signs"	"Body Temperature"	100	40	43
5	"CDISC360-2"	"Vital signs"	"Systolic Blood Pressure"	200	40	40

// List Schedule of Activity and Assessment for a Study

```
MATCH (s:Study {id: $studyid})-->(v:PlannedVisit)-->
(pm:PlannedAssessment)-->(a:Assessment)-->(ac:Activity)<--
(pa:PlannedActivity)<--(s)
```

```
RETURN s.id as study_id, ac.name as activity, a.name as assessment,
v.visitnum as visitnum, pa.order, pm.order
ORDER BY s.id, v.visitnum, pa.order, pm.order;
```

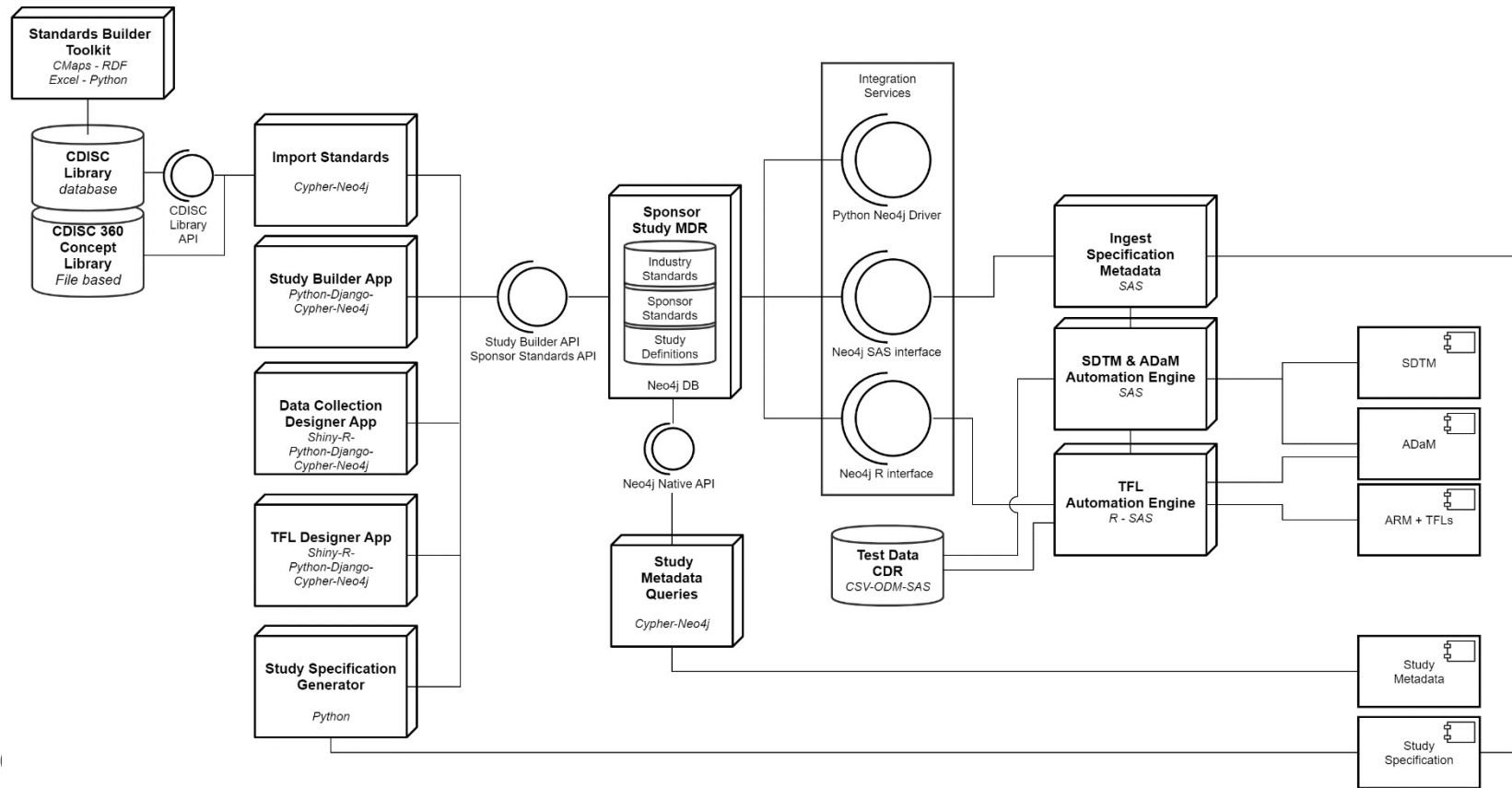


API for Sponsor Study MDR

PoC implementation of API endpoints

API for Sponsor MDR managing the Study Metadata

This component diagram will be described in the CDISC 360 PoC Yellow-paper





Neo4j to SAS Interface

All metadata in Sponsor Study MDR Neo4j database can be access directly from SAS

Access Neo4j Sponsor Study MDR from SAS

- The Neo4j transactional HTTP endpoint allows you to execute Cypher statements
- Using SAS PROC LUA to easily interface with the Neo4j REST API from SAS
- Neo4j to SAS Interface manage SAS Dataset metadata

ASSESSMENT	SRCSEQ	SRCLIB	SRCDSN	SRCVAR	SRCTYPE	ORIGIN	METHOD	CODELIST	TGTLIB
["BODY_WEIGHT", "HEIGHT", "BP_DIASTOLIC", "BODY_TEMPERATURE", "PULSE"]	1	CDASH	VS	SUBJID	text	Assigned	ALL.USUBJID		SDTM
["BODY_WEIGHT", "HEIGHT", "BP_DIASTOLIC", "BODY_TEMPERATURE", "PULSE"]	1	CDASH	VS	VISIT	text	Predecessor		VISIT	SDTM
["BODY_WEIGHT", "HEIGHT", "BP_DIASTOLIC", "BODY_TEMPERATURE", "PULSE"]	1	CDASH	VS	VSDAT	text	Assigned	VS.VSDTC		SDTM
["BODY_WEIGHT", "HEIGHT", "BP_DIASTOLIC", "BODY_TEMPERATURE", "PULSE"]	1	CDASH	VS	VISDAT	text	Assigned	VS.VSDTC		SDTM
["BODY_WEIGHT", "HEIGHT", "BP_DIASTOLIC", "BODY_TEMPERATURE", "PULSE"]	1	CDASH	DM	SUBJID	text	Assigned	ALL.USUBJID		SDTM
["BODY_WEIGHT", "HEIGHT", "BP_DIASTOLIC", "BODY_TEMPERATURE", "PULSE"]	1	CDASH	DM	RACE	text	Predecessor		RACE	SDTM
2" ["FIRST_TRIAL_PROD_DATE", "FIRST_TRIAL_PROD_DATE"]	3	CDASH	DS_FDRUGDT	DSSTDAT	date	Assigned	DM.RFSTDTC	ISO 8601	SDTM



Reflections from WS4

What have we accomplished in the cdisc360 PoC

Machine-readable Study Specification Metadata

- Study Design
 - Implemented basic Study Definition and Design in Study Repository linked to Schedule of Assessment
- CDASH & SDTM
 - Implemented Assessment BC's in a Label Property Graph Model linked with versioned metadata from the CDISC Library
 - Including sample CDASH2SDTM bindings
- ADaM
 - Implemented basic ADaM Sponsor model in a Label Property Graph Model linked with versioned metadata from the CDISC Library
 - Including sample SDTM2ADaM bindings
- Study Builder & Sponsor Study MDR
 - Standard API based to enable tool and vendor agnostic system integrations





Thank You!

Mikkel Traun, *Novo Nordisk*

Nicolas de Saint Jorre, *XClinical*

