DDF USDM Workshop – EU Interchange

Presented by

Dave Iberson-Hurst, DDF Technical Product Owner, CDISC
Berber Snoeijer, DDF Technical Team Lead, CDISC

23rd April 2024

Agenda

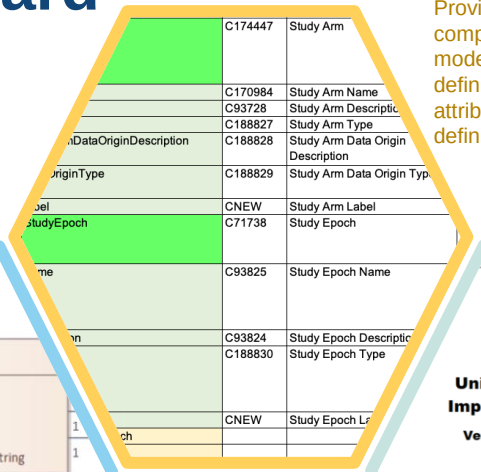
1. Introduction
2. Overall framework, structured/unstructured content
3. Inclusion & Exclusion, Objectives & Endpoints
4. Population & Cohorts
5. SOA Timelines & Timing
6. SOA Biomedical Concepts, Procedures & conditions
7. Amendments
8. Narrative Content, Protocol document and M11
9. Wrap-up

Introduction

The USDM Standard

CDISC Controlled Terminology

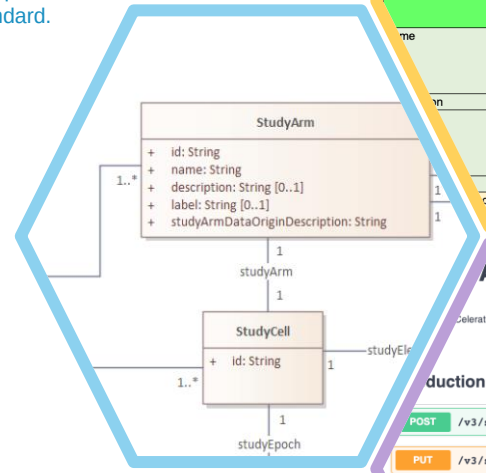
Provides further semantics, complementing the UML model. Includes the definition of classes and attributes along with the definition of value sets



	C174447	Study Arm
	C170984	Study Arm Name
	C93728	Study Arm Descriptio
	C188827	Study Arm Type
nDataOriginDescription	C188828	Study Arm Data Origin Description
riginType	C188829	Study Arm Data Origin Typ
el	CNEW	Study Arm Label
tudyEpoch	C71738	Study Epoch
me	C93825	Study Epoch Name
n	C93824	Study Epoch Descriptio
	C188830	Study Epoch Type
	CNEW	Study Epoch La
ch		

Logical Model

The UML logical model (a class diagram) that provides the basis for the USDM standard.



Examples

Example protocols implemented in the USDM with associated JSON files and visualisations

```
tudyArms": [
{
  "id": "StudyArm_1",
  "name": "Placebo",
  "label": "",
  "description": "Placebo",
  "type": {
    "id": "Code_61",
    "code": "C174268",
    "codeSystem": "http://www.cdisc.org",
    "codeSystemVersion": "2022-12-16",
    "decode": "Placebo Comparator Arm"
  },
  "studyArmDataOriginDescription": "Data collec
  "dataOriginType": {
    "id": "Code_62",
    "code": "C188866",
    "codeSystem": "http://www.cdisc.org",
    "codeSystemVersion": "2022-12-16",
    "decode": "Data Generated Within Study"
  }
},
{
  "id": "StudyArm_2",
  "name": "Xanomeline Low Dose",
  "label": "",
  "description": "Active Substance",
  "type": {
    "id": "Code_63",
    "code": "C174267",
    "codeSystem": "http://www.cdisc
    "codeSystemVersion": "2022-12-
```

API for DDF

2.4 Provisional (0.39)

elerate Digital Data Flow (DDF) Study Definitions Repository API.

duction Routes that form the production specification.

POST /v3/studyDefinitions Create a study

PUT /v3/studyDefinitions/{studyId} Update a study

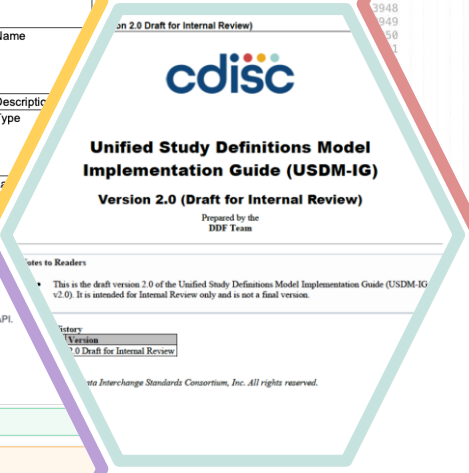
GET /v3/studyDefinitions/{studyId} Return a study

ET /v3/studyDefinitions/{studyId}/history Returns the study

/v3/studyDesigns Study designs for a study

API Specification

Provides the means to exchange a single study between machines using a JSON API



Implementation Guide

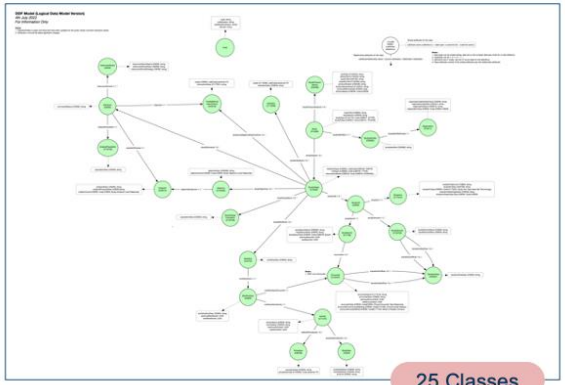
Guidance on using the USDM model and ensuring conformance with the standard

USDM Status

	PHASE ONE *July 2021 – July 2022*	PHASE TWO *Oct 2022 – June 2023*	PHASE THREE *July 2023 – Apr 2024*
Unified Study Definitions Model (USDM)	✓	✓	✓
Application Programming Interface (API) Specification	✓	✓	✓
CDISC Controlled Terminology	✓	✓	✓
Reference Architecture Conformance Tests	✓		*Being replaced by CDISC CORE rules*
Essential Users Stories	✓		
Architecture Principles	✓	*Still applicable*	*Still applicable*
Test Files		✓	✓
Implementation Guide		✓	✓

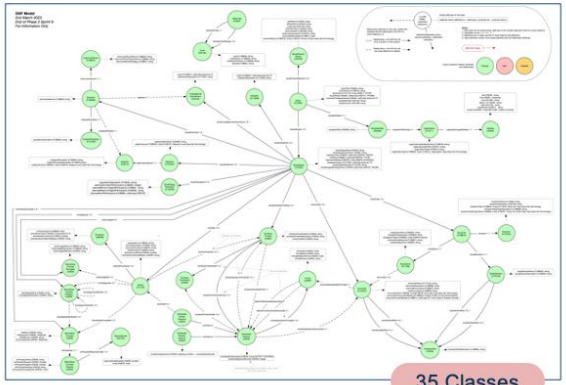
CDISC DDF / USDM: Phases One, Two and Three

Phase One



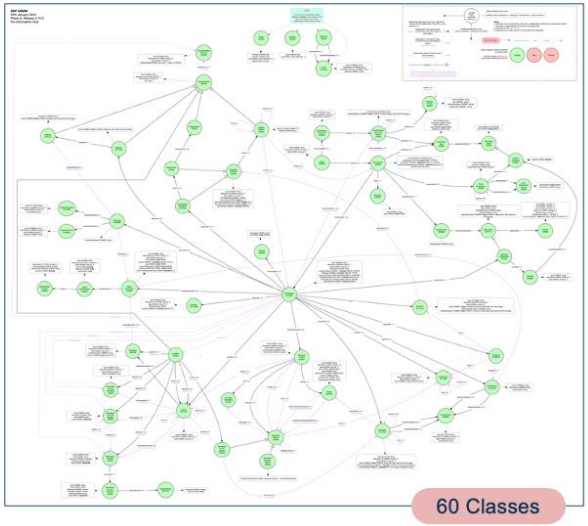
- Solid foundation
- The protocol document was an external entity into which the structured content could be exported

Phase Two



- Focused on the structured elements of the protocol, e.g. the Schedule of Activities (SoA) & Biomedical Concepts (BCs)
- The protocol document still an external entity

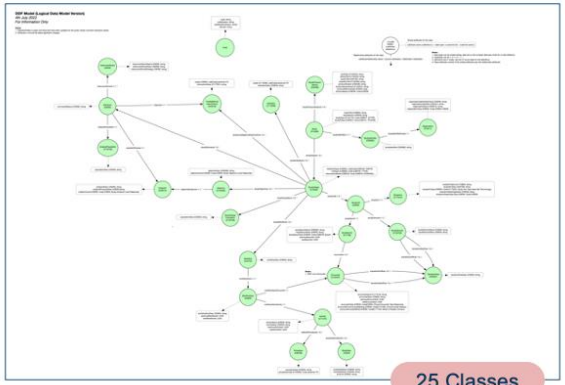
Phase Three



- Now contains structured and unstructured elements
- The entire protocol document can be held within the USDM
- Allows for the protocol document to be generated from the model

CDISC DDF / USDM: Phases One, Two and Three

Phase One



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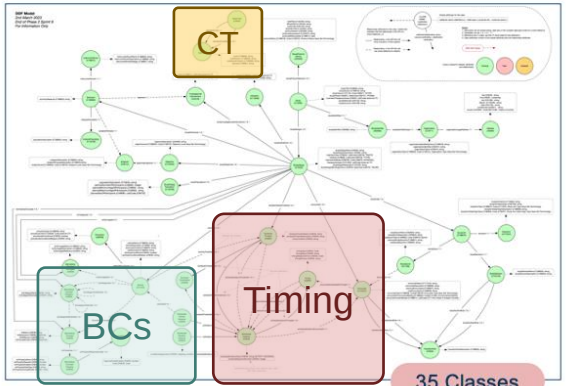
Phase Two



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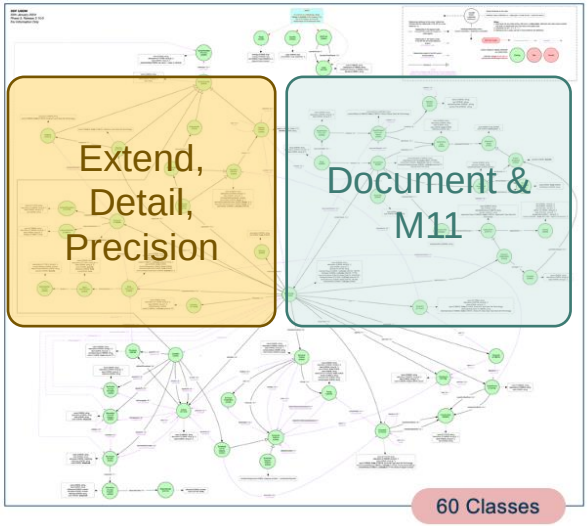
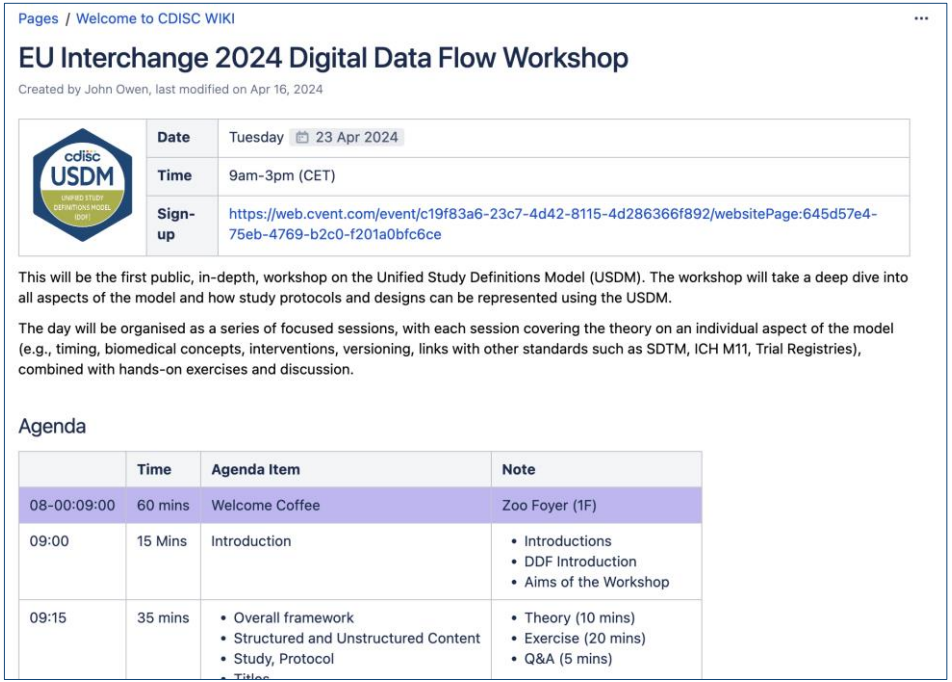
Phase Three



- Now contains structured and unstructured elements
- The entire protocol document can be held within the USDM
- Allows for the protocol document to be generated from the model

Wiki Page

- Make sure you have access
- Base file for the exercises
- We will provide a complete Excel workbook after the workshop
- We will also put the slides used on the wiki



Pages / Welcome to CDISC WIKI

EU Interchange 2024 Digital Data Flow Workshop

Created by John Owen, last modified on Apr 16, 2024

Date	Tuesday 23 Apr 2024
Time	9am-3pm (CET)
Sign-up	https://web.cvent.com/event/c19f83a6-23c7-4d42-8115-4d286366f892/websitePage:645d57e4-75eb-4769-b2c0-f201a0bfc6ce

This will be the first public, in-depth, workshop on the Unified Study Definitions Model (USDM). The workshop will take a deep dive into all aspects of the model and how study protocols and designs can be represented using the USDM.

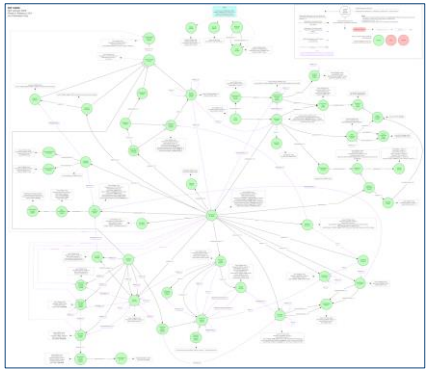
The day will be organised as a series of focused sessions, with each session covering the theory on an individual aspect of the model (e.g., timing, biomedical concepts, interventions, versioning, links with other standards such as SDTM, ICH M11, Trial Registries), combined with hands-on exercises and discussion.

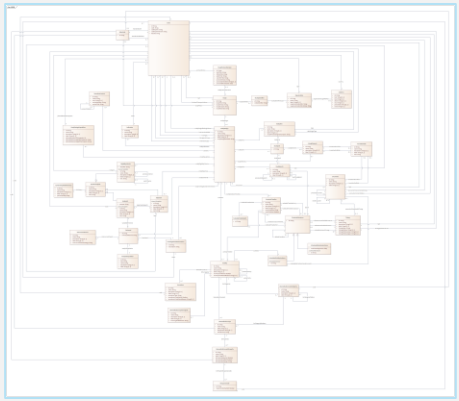
Agenda

	Time	Agenda Item	Note
08-00:09:00	60 mins	Welcome Coffee	Zoo Foyer (1F)
09:00	15 Mins	Introduction	• Introductions • DDF Introduction • Aims of the Workshop
09:15	35 mins	• Overall framework • Structured and Unstructured Content • Study, Protocol	• Theory (10 mins) • Exercise (20 mins) • Q&A (5 mins)

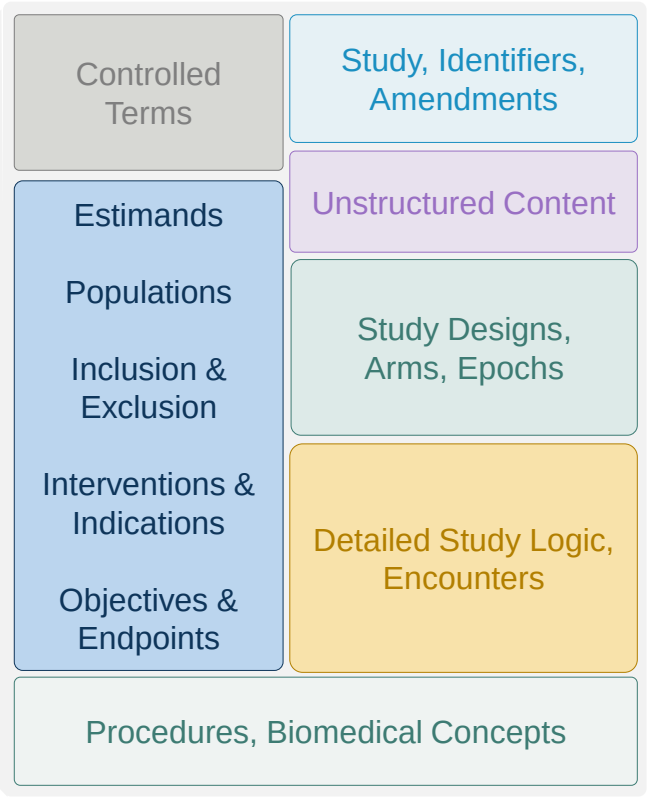
https://wiki.cdisc.org/display/PUB/EU+Interchange+2024+Digital+Data+Flow+Workshop

USDM Model Overview



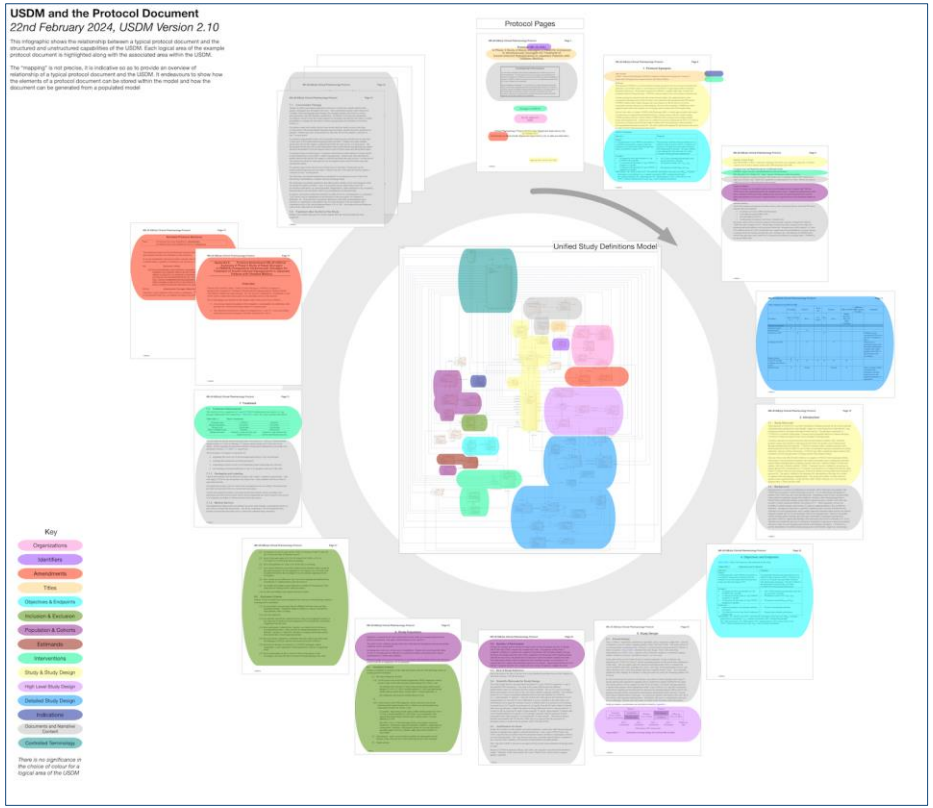


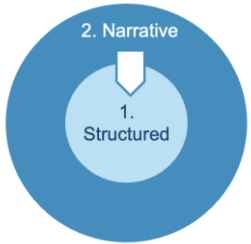
- Wiki page has
  - The UML diagram (normative)
  - An informative diagram
  - The Controlled Terminology
- Aim of today is to educate as to
  - What the model can do
  - What it cannot do
  - How it works, what goes where



USDM and the Protocol

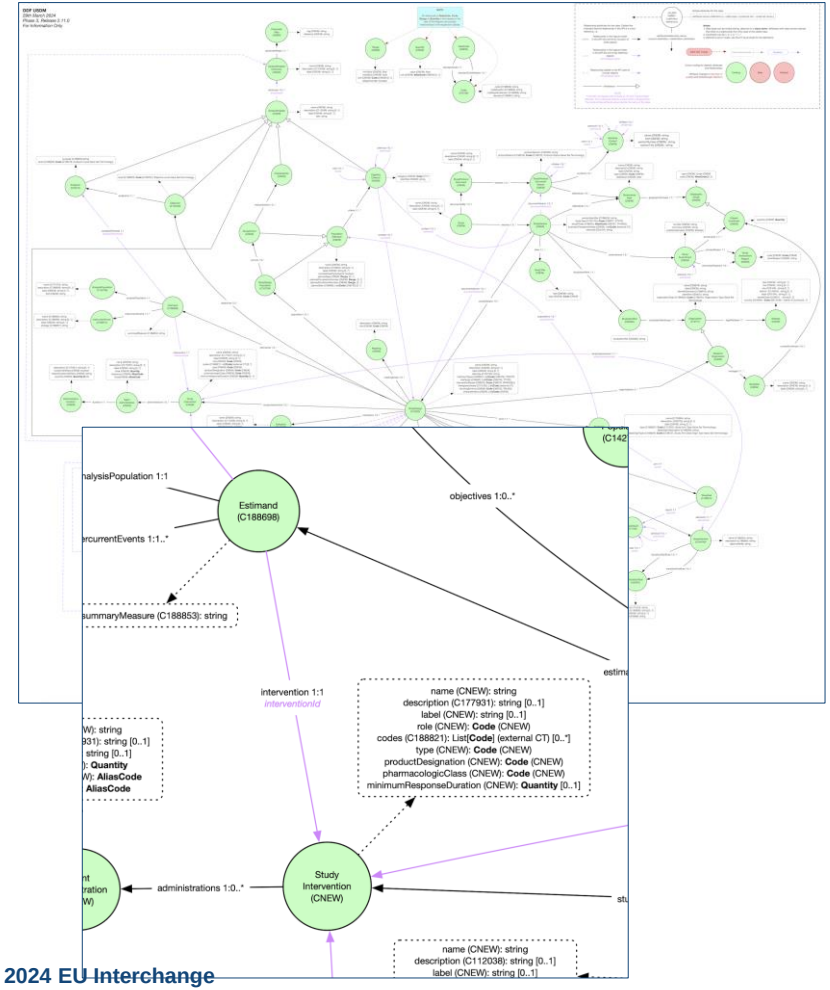
- Download the infographic from the wiki
- You can zoom in to see the detail
- Gives an overview of how a protocol is structured within the USDM
- How the USDM can support generation of a complete protocol





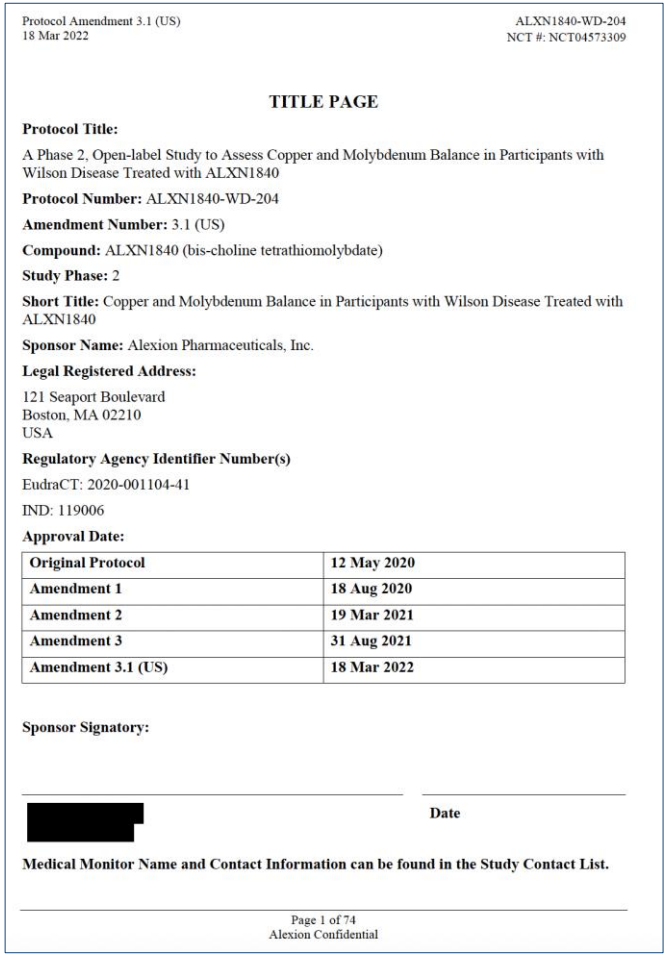
The API and JSON

- Informative Diagram available on the wiki
- JSON is a serialization of the model content
- Holds a single version of a study
- Need to not duplicate information so JSON includes references
- These are shown in the informative diagram
- Sometimes useful to see differences in the JSON when adding or removing content



Protocol

- Using protocol from Alexion as the basis of the workshop
- Used to help in answering the question “how do I put a protocol into USDM?”
- File is on the wiki
- Use of this protocol is not a reflection of this protocol or of Alexion
- The protocol was one of several chosen from CT.gov because of features within the protocol and study design



Protocol Amendment 3.1 (US)
18 Mar 2022

ALXN1840-WD-204
NCT #: NCT04573309

TITLE PAGE

Protocol Title:

A Phase 2, Open-label Study to Assess Copper and Molybdenum Balance in Participants with Wilson Disease Treated with ALXN1840

Protocol Number: ALXN1840-WD-204

Amendment Number: 3.1 (US)

Compound: ALXN1840 (bis-choline tetrathiomolybdate)

Study Phase: 2

Short Title: Copper and Molybdenum Balance in Participants with Wilson Disease Treated with ALXN1840

Sponsor Name: Alexion Pharmaceuticals, Inc.

Legal Registered Address:

121 Seaport Boulevard
Boston, MA 02210
USA

Regulatory Agency Identifier Number(s)

EudraCT: 2020-001104-41

IND: 119006

Approval Date:

Original Protocol	**12 May 2020**
Amendment 1	**18 Aug 2020**
Amendment 2	**19 Mar 2021**
Amendment 3	**31 Aug 2021**
Amendment 3.1 (US)	**18 Mar 2022**

Sponsor Signatory:

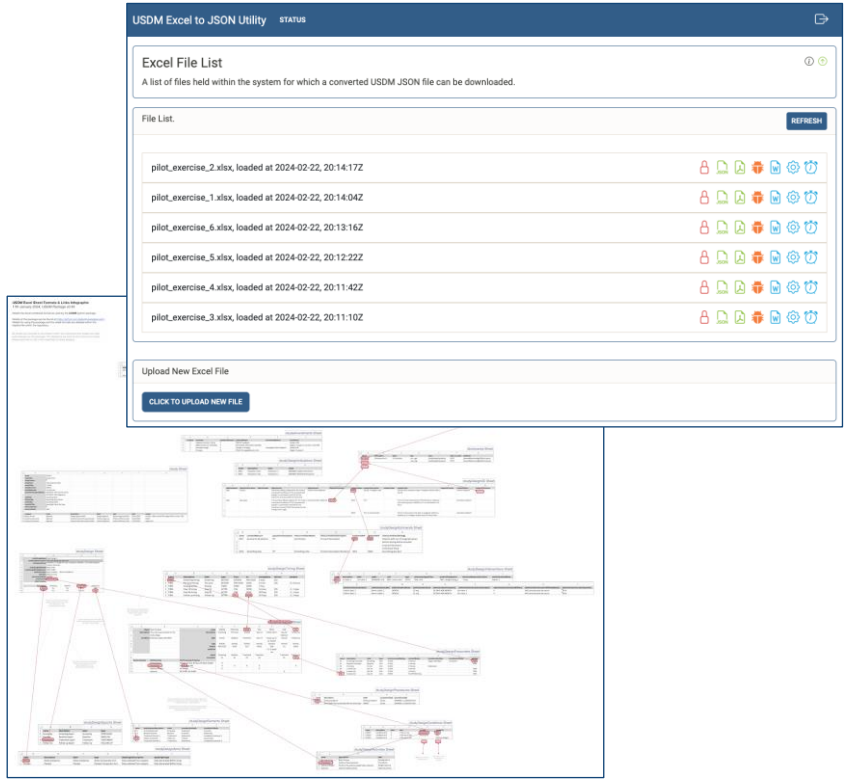
[redacted] **Date**

Medical Monitor Name and Contact Information can be found in the Study Contact List.

Page 1 of 74
Alexion Confidential

Check We Can Work

- Simple exercise to check everybody can do the remaining exercises
- Steps
  - Take base example and rename the file to something unique to you
  - Upload your renamed file to the online tool
  - Examine the outputs
  - Have a look at the Excel sheet
  - Have a look at the Excel infographic
- There is a readme at https://github.com/cdisc-org/usdm

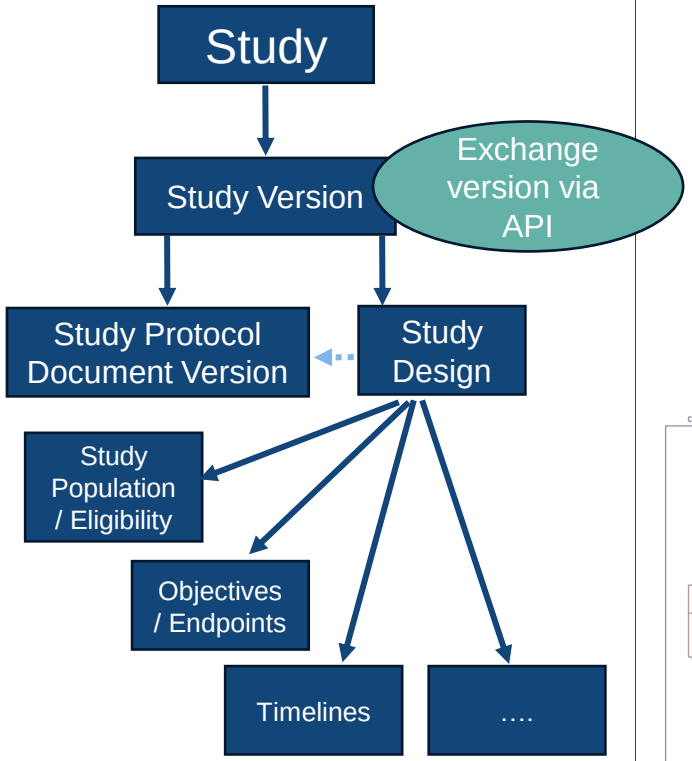


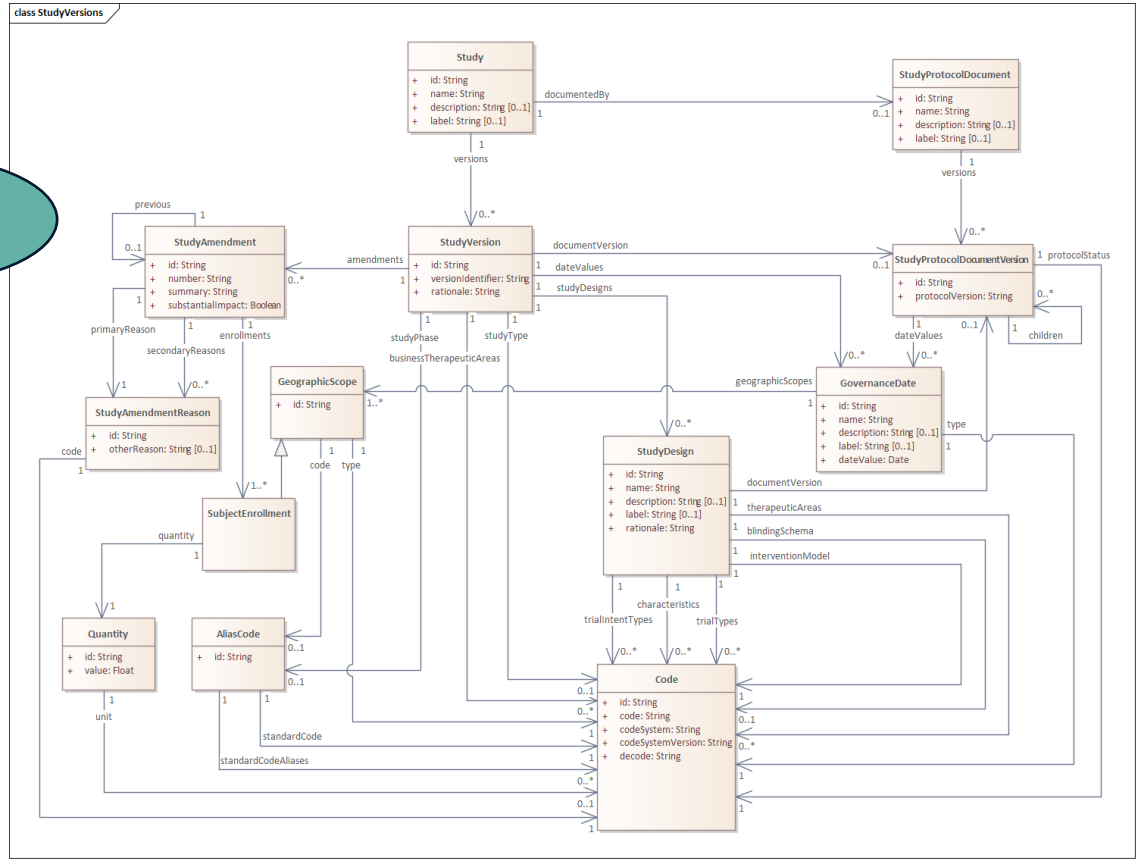
The Excel tool is a TEST TOOL.

We should **NEVER** use it for production work or protocol writing!

Overall framework
Titles & Identifiers

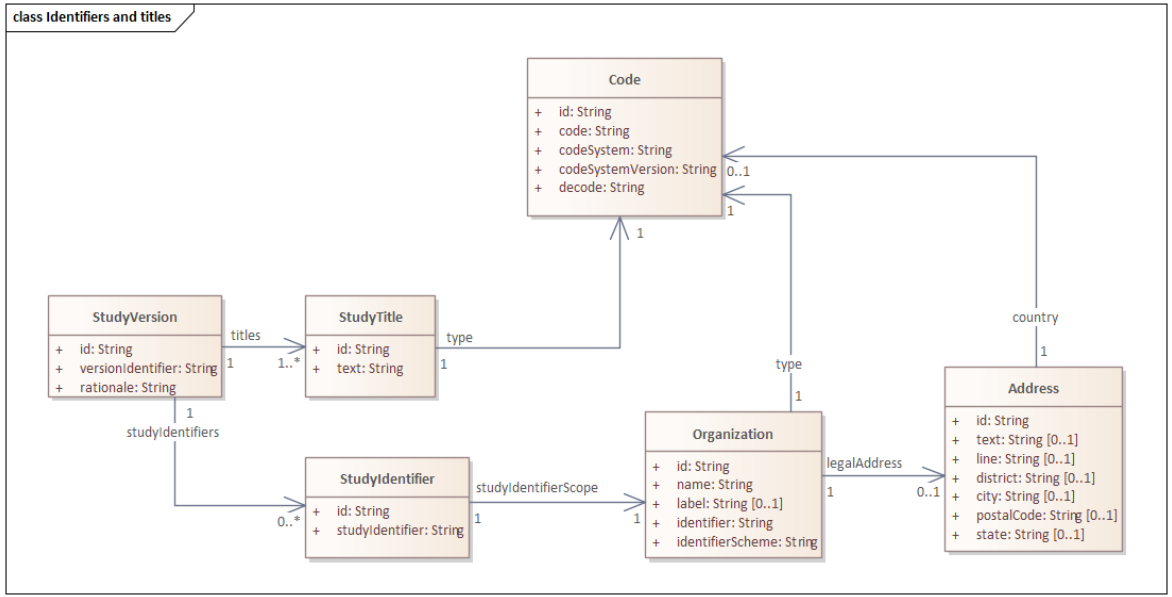
Study and Protocol





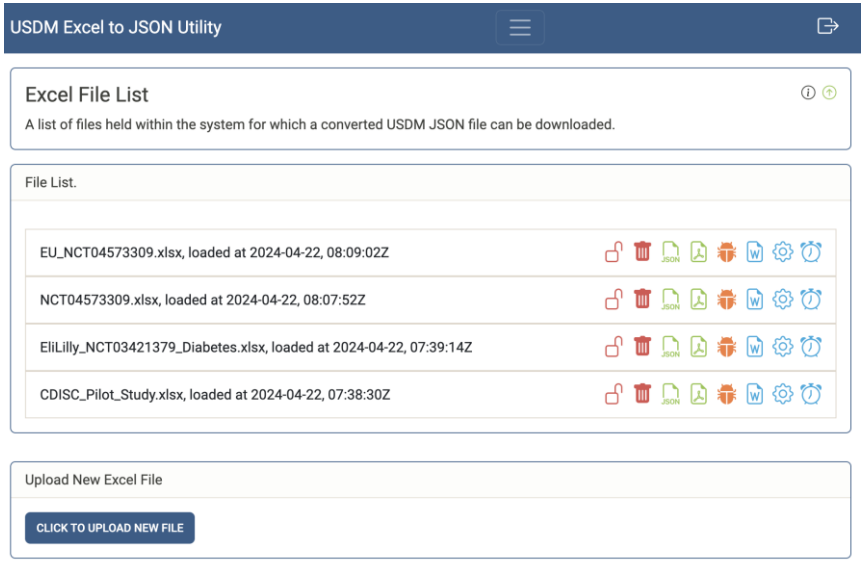
Titles and Identifiers

- Title Types
  - Brief Study Title
  - Official Study Title
  - Public Study Title
  - Scientific Study Title
  - Study Acronym
- Identifier Organization types
  - Clinical Study Sponsor (1 required!!)
  - Clinical Study Registry
  - Regulatory Agency
  - Research Organization



Exercise

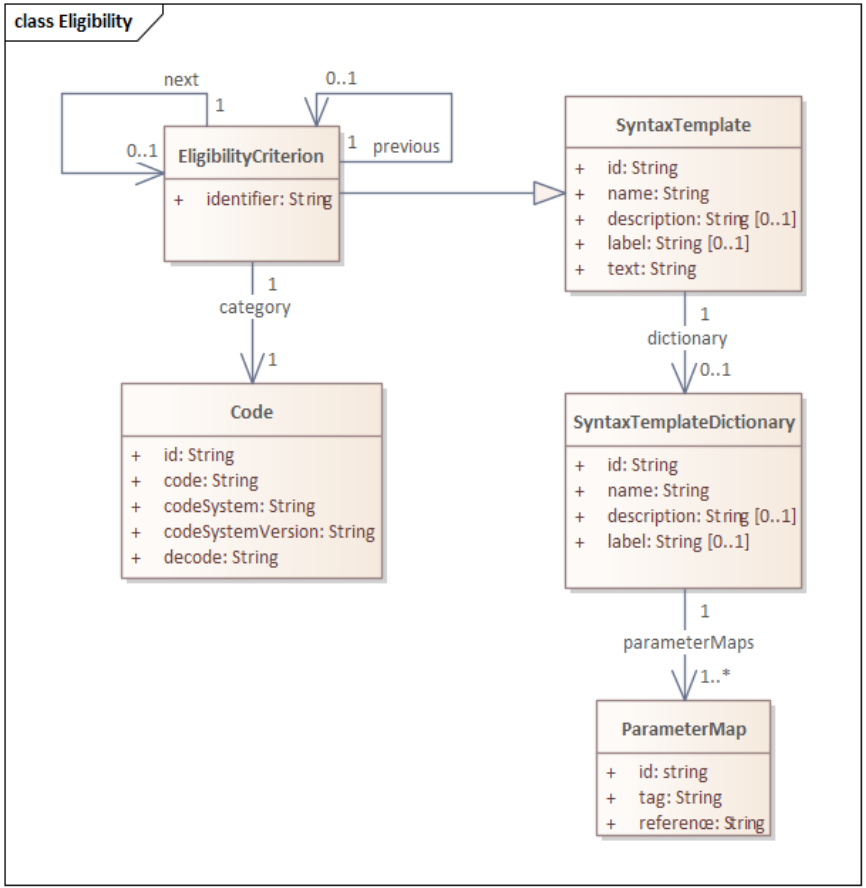
- Add in the brief and official titles
  - Edit the “study” sheet
- Add in the EUDRACT and IND identifiers
  - Edit the “studyIdentifiers” sheet
  - The organization “type” column is coded



Inclusion & Exclusion Objectives & Endpoints

Inclusion / Exclusion

- Model Class EligibilityCriterion
- Inherits from SyntaxTemplate class
  - Includes references to structured elements stored elsewhere in the data model like:
    - Population characteristics
    - Activities
    - …
  - Structured elements in dictionary can be reused across the study design
- Categories
  - SDTM terminology C66797
    - INCLUSION
    - EXCLUSION



Inclusion / Exclusion

- Tag elements in text of criteria

<usdm:tag name="parametername"/>

5.1. Inclusion Criteria

Age

1. Participants aged ≥18 at the time of signing the ICF.

Type of Participants and Disease Characteristics

2. Diagnosis of WD by Leipzig Criteria ≥ 4 documented by testing as outlined in the 2012 European Association for the Study of Liver WD Clinical Practice Guidelines (Ferenci, 2003; EASL, 2012) or by historical test results for WD including some or all of the following:
   - Presence of Kayser Fleischer rings,

	A	B	C	D	E	F	G
1	**category**	**identifier**	**name**	**description**	**label**	**text**	**dictionary**
2	Inclusion	01	Age Criteria	The study age criterion		Participants aged ≥ <usdm:tag name="min_age"/> at the time of signing ICF	IE_Dict
3	Inclusion	02	Indication Criteria	The study indication criterion		Diagnosis of <usdm:tag name="indic_label"/> by Leipzig Criteria ≥ 4 documented by testing as outlined in the 2012 European Association for the Study of Liver WD Clinical Practice Guidelines (Ferenci, 2003; EASL, 2012) or ...	IE_Dict
4	Exclusion	01	Contra Indication 1	Study contra indication 1		Decompensated cirrhosis or model for end-stage liver disease (MELD) score > <usdm:tag name="meld_max"/>	IE_Dict

Example spreadsheet: studyDesignEligibilityCriteria tab

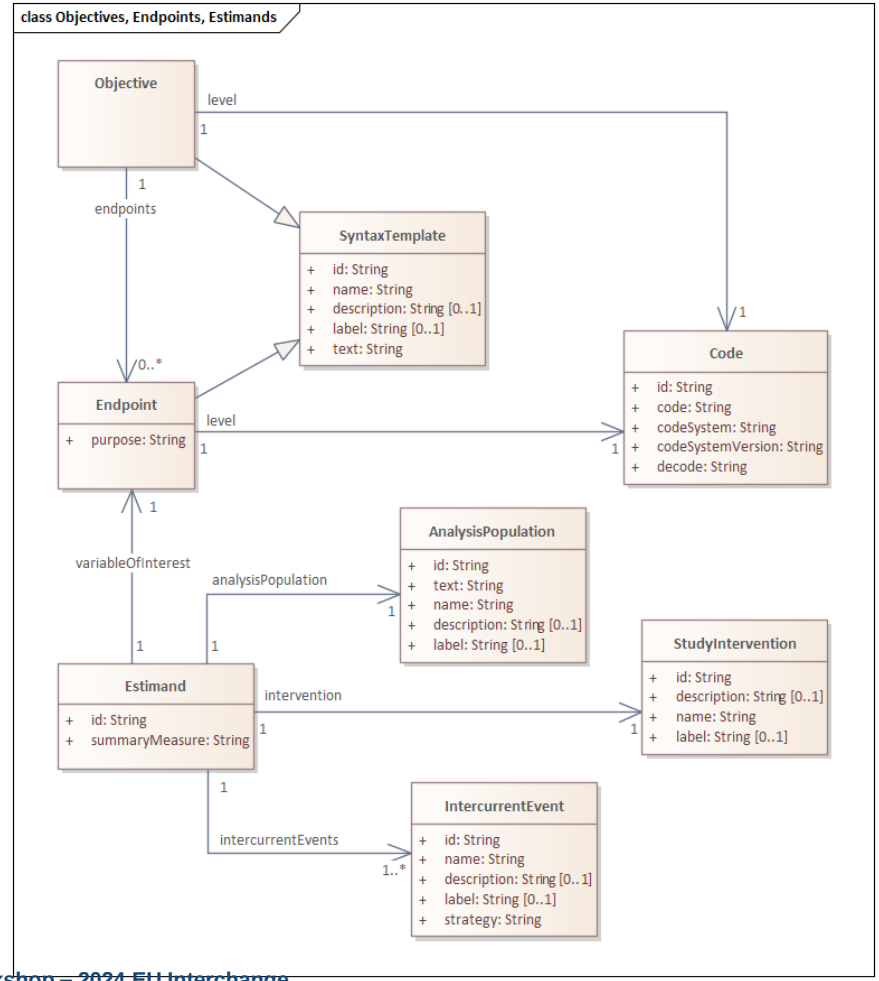
- Define elements in dictionary

	A	B	C	D	E	F	G	H
1	**name**	**description**	**label**	**key**	**class**	**xref**	**attribute**	**value**
2	IE_Dict	Dictionary for IE	IE Dictionary	min_age	StudyDesignPopulation	POP1	plannedAge	
3				max_age	StudyDesignPopulation	POP1	plannedAge	
4				indic_label	Indication	IND1	label	
5	Settings_Dict	Dictionary for value settings	Settings Dictionary	Demo_label	Activity	Demographics	label	
6				meld_max				13

Example spreadsheet: dictionaries

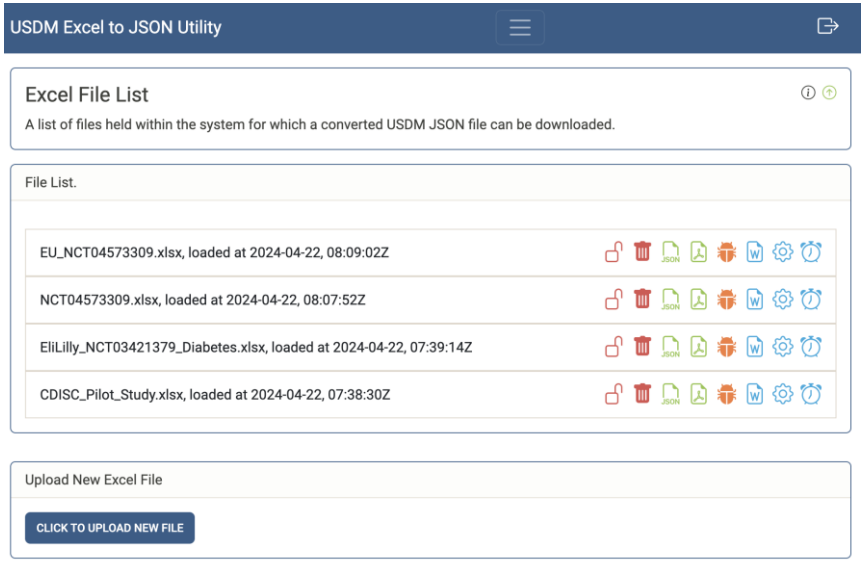
Objectives & Endpoints

- Model classes
  - Objective
  - Endpoint
- Inherit from SyntaxTemplate
  - Use tagging and dictionaries like for Eligibility criteria
- Levels
  - Objectives C188725
    - Primary Objective
    - Secondary Objective
    - Exploratory Objective
  - Endpoints C188726
    - Primary Endpoint
    - Secondary Endpoint
    - Exploratory Endpoint
- (Primary) endpoint can be referred to from Estimand class



Exercise

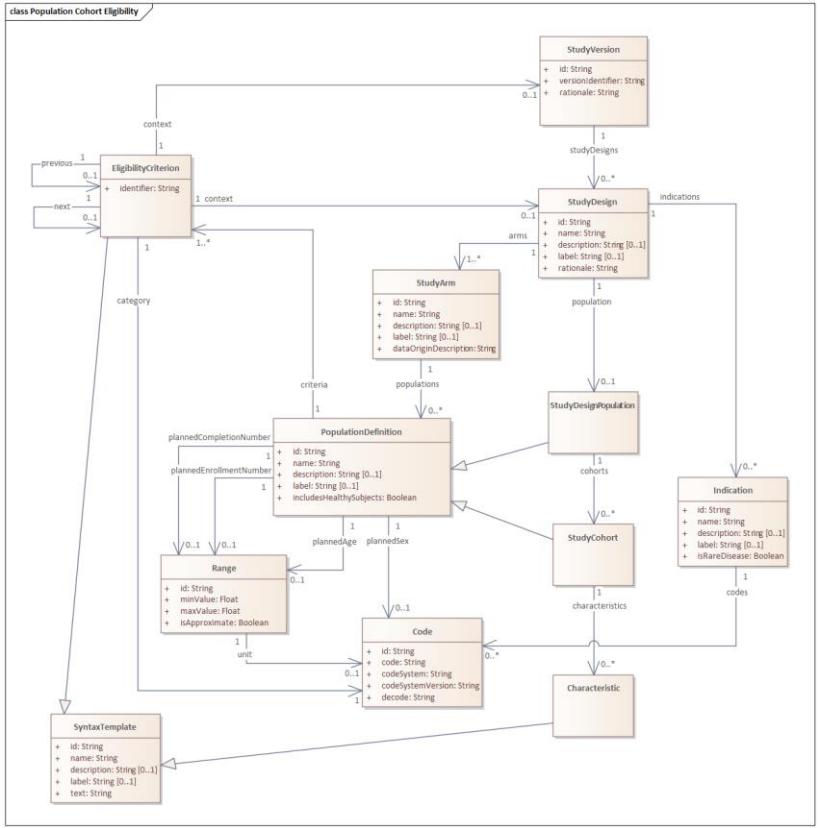
- Add in an inclusion criteria
  - Edit the “studyDesignEligibilityCriteria” sheet
  - “category” column is coded
  - Can choose to use the dictionary sheet
- Add in an objective and associated endpoint
  - Edit the “studyDesignOE” sheet
  - “objectiveLevel” column is coded
  - “endpointLevel” column is coded
  - Can choose to use “dictionary” sheet



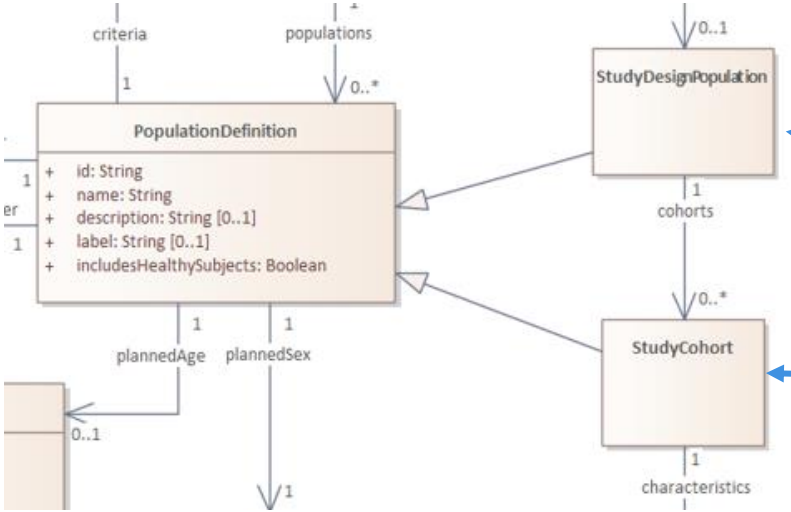
Population & Cohorts

Population & Cohorts

- One Study Design Population!
- May be divided into multiple cohorts
  - StudyDesignPopulation class refers to zero to many StudyCohorts
- Both inherit from PopulationDefinition class
  - Attributes plannedAge, plannedSex need to be filled either at study population or cohort level
- Utilizes Range class
  - plannedAge, plannedEnrollmentNumer, plannedCompletionNumber
- Sex: SDTM CT: C66732
- Additional study Cohort characteristics may be defined
  - Characteristic class inherits syntax templates



Population & Cohorts



4. STUDY DESIGN

4.1. Overall Design

This study will be conducted as an open-label, repeat-dose study to evaluate the effects of ALXN1840 on copper balance in participants with WD.

Treatment-experienced (which includes standard of care therapies or ALXN1840) and treatment-naïve participants are eligible for this study. Eligible patients will be classified into one of two cohorts:

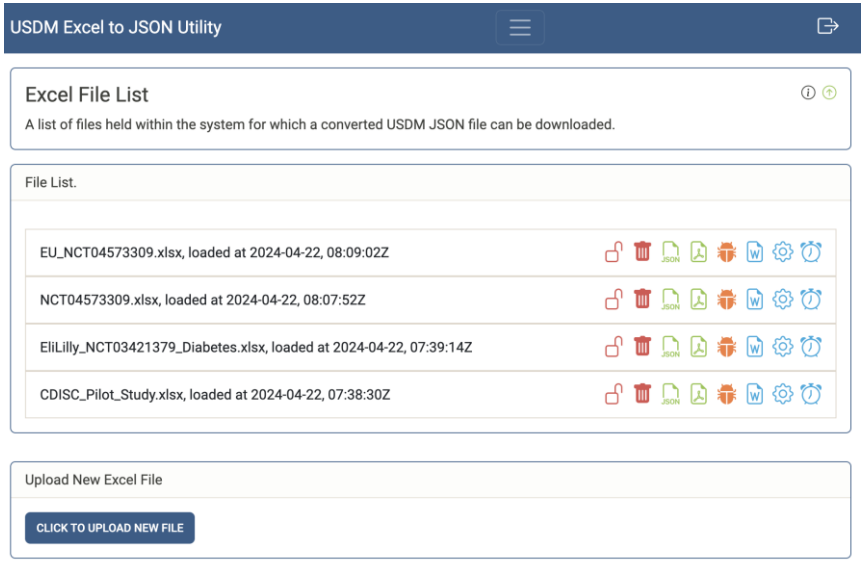
- Cohort 1 (treatment experienced): Patients who have received WD therapy for > 28 days
- Cohort 2 (treatment naïve): Patients who have received WD therapy for ≤ 28 days

	A	B	C	D	E	F	G	H	I
1	level	name	description	label	plannedCompletionNumber	plannedEnrollmentNumber	plannedAge	plannedSexOfParticipants	includesHealthySubjects
2	Main	POP1	Patients with WD		10		18 .. 99 years	BOTH	N
3	Cohort	COHORT1							N
4	Cohort	COHORT2							N

Example spreadsheet: studyDesignPopulations

Exercise

- Add in the cohort definitions
  - Edit the “studyDesignPopulations” sheet
  - “plannedSexOfParticipants” column is coded
  - You will need to consider the “studyDesignCharacteristics” sheet



SOA 1 – Timelines and Timing

Timeline

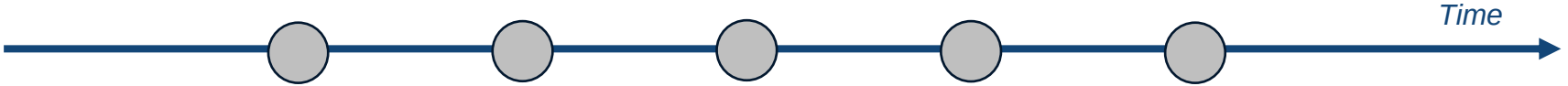
Timeline - SoA

Time

Small excerpt from protocol, for purposes of explanation

Study Procedures	Screening[a]		C-I[b]								
	Screening		C-I	Inpatient Period 1							
Days	-42 to -9	-21	-8	-7	-6 through -5	-4 through -1	1	2-3	4-7	8	9

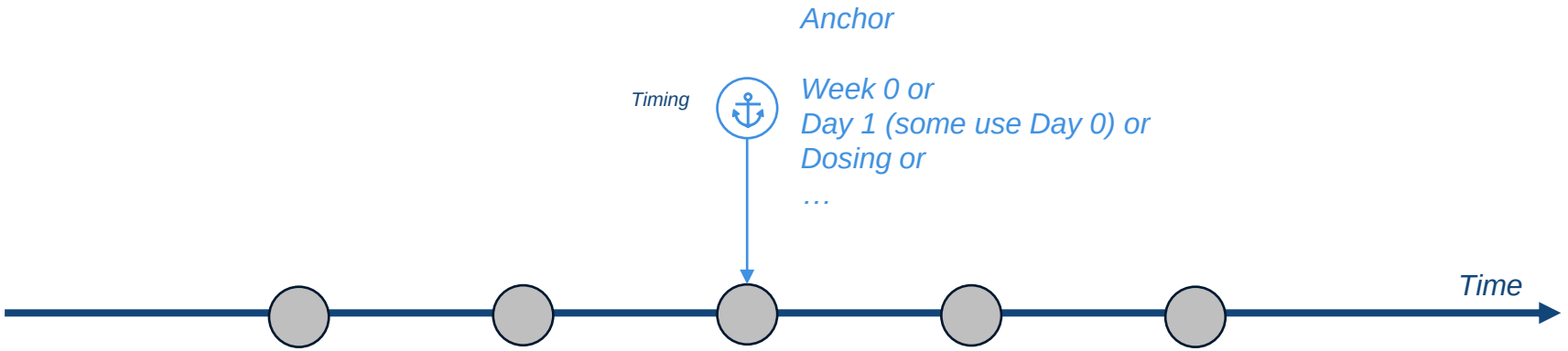
Timeline - Timepoints



ScheduledActivityInstance

Study Procedures	Screening[a]		C-I[b]								
	Screening		C-I	Inpatient Period 1							
Days	-42 to -9	-21	-8	-7	-6 through -5	-4 through -1	1	2-3	4-7	8	9

Timeline – Timing I



Study Procedures	Screening[a]		C-I[b]	Anchor							
	Screening		C-I	Inpatient Period 1							
Days	-42 to -9	-21	-8	-7	-6 through -5	-4 through -1	1	2-3	4-7	8	9

Timeline – Timing 2

The {from node} is before the [to node]

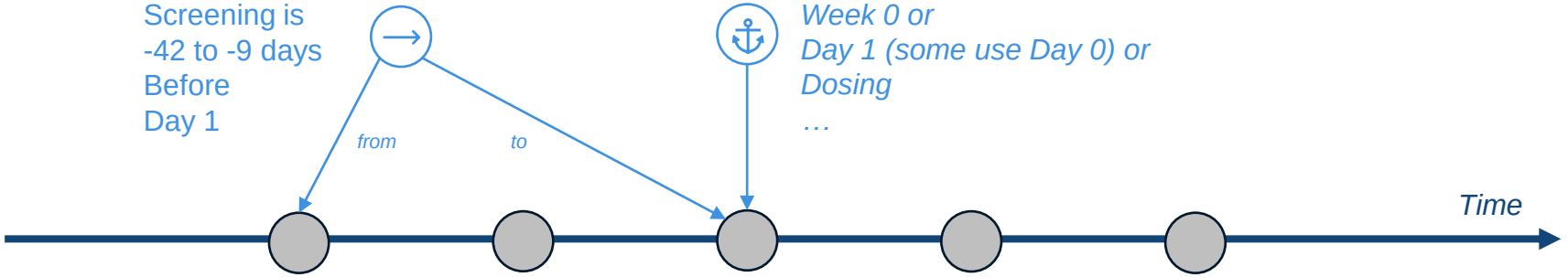
The {from node} is after the [to node]

Relative

Screening is
-42 to -9 days
Before
Day 1

Anchor

Week 0 or
Day 1 (some use Day 0) or
Dosing
…

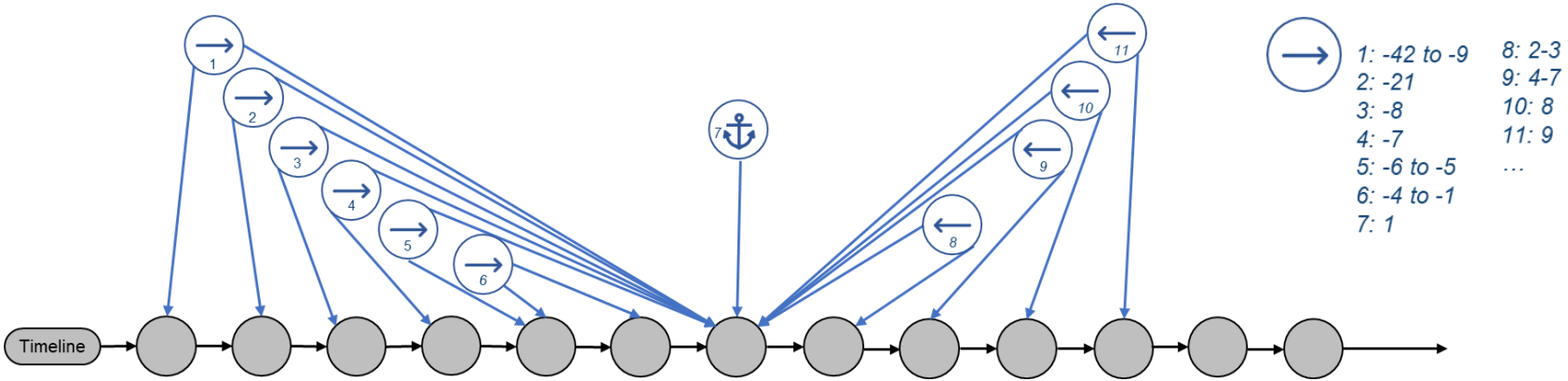


Relative

Anchor

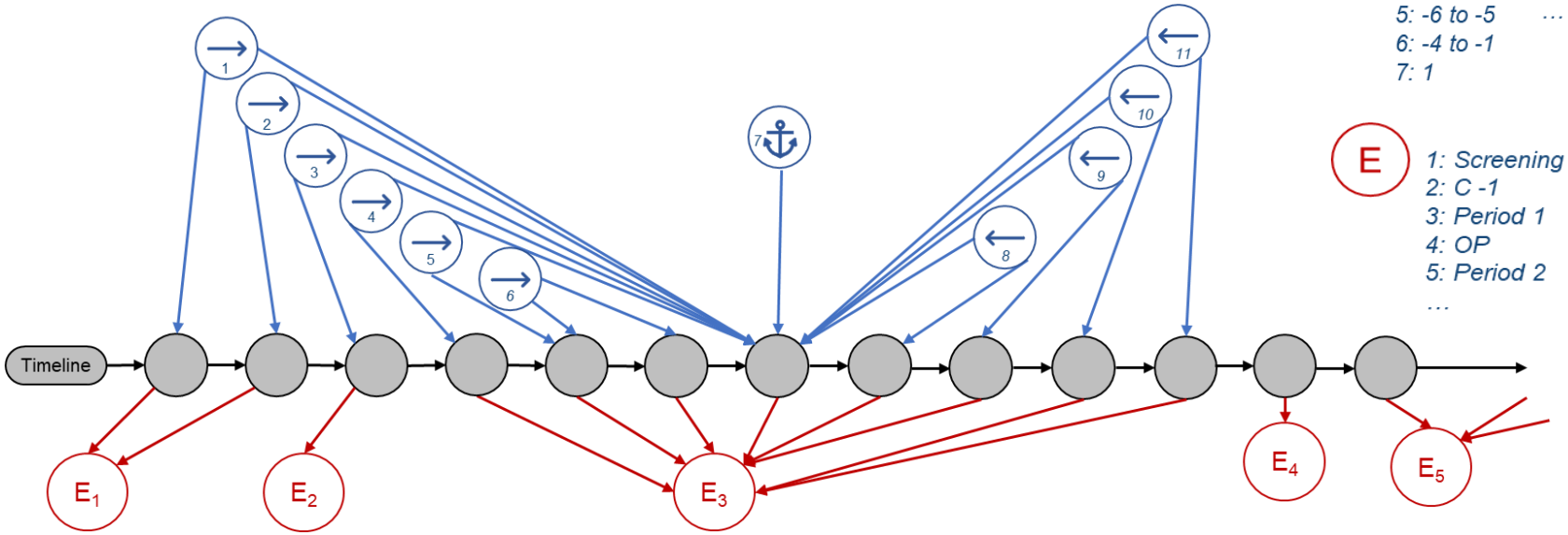
Study Procedures	Screening[a]		C-I[b]								
	Screening		C-I	Inpatient Period 1							
Days	-42 to -9	-21	-8	-7	-6 through -5	-4 through -1	1	2-3	4-7	8	9

Timeline – Timing 3



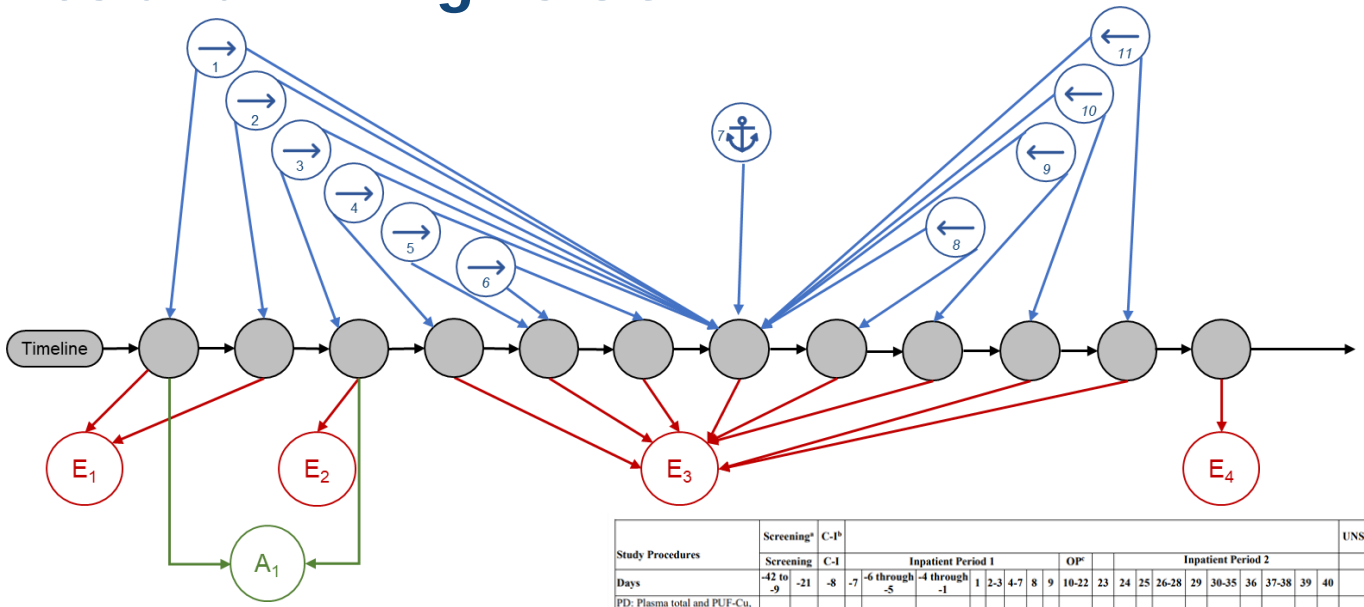
Study Procedures	Screening[a]		C-I[b]								
	Screening		C-I	Inpatient Period 1							
Days	-42 to -9	-21	-8	-7	-6 through -5	-4 through -1	1	2-3	4-7	8	9

Timeline – Encounters (Visits)



Study Procedures	Screening[a]		C-I[b]								
	Screening		C-I	Inpatient Period 1							
Days	-42 to -9	-21	-8	-7	-6 through -5	-4 through -1	1	2-3	4-7	8	9

Timelines and Timing vs SOA

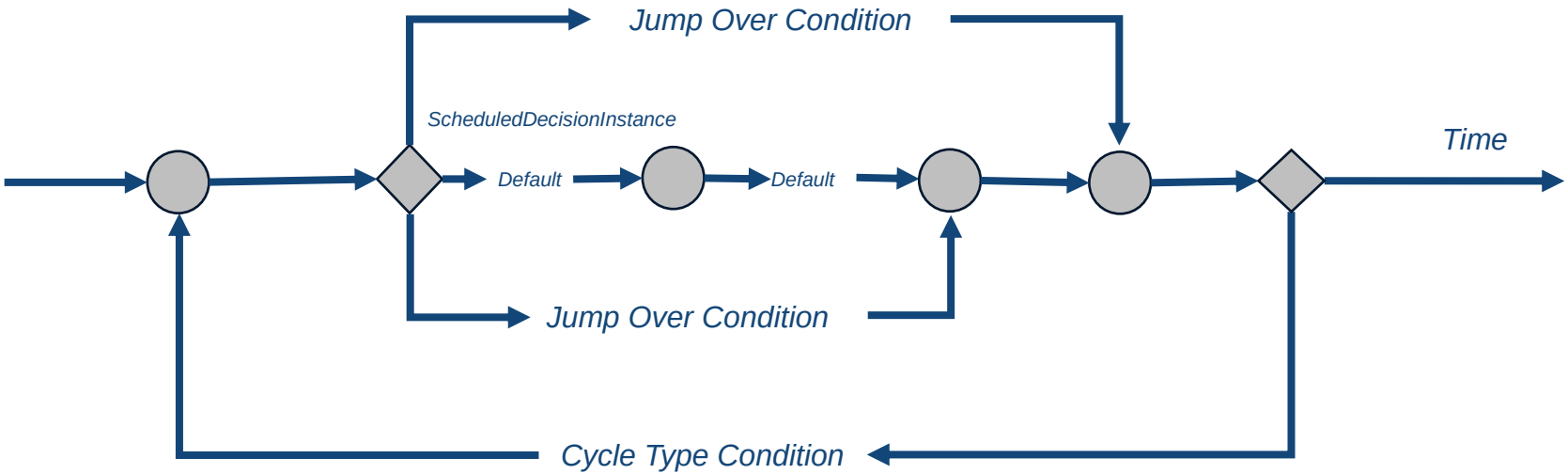


E
1: Screening
2: C -1
3: Period 1
4: OP
5: ..

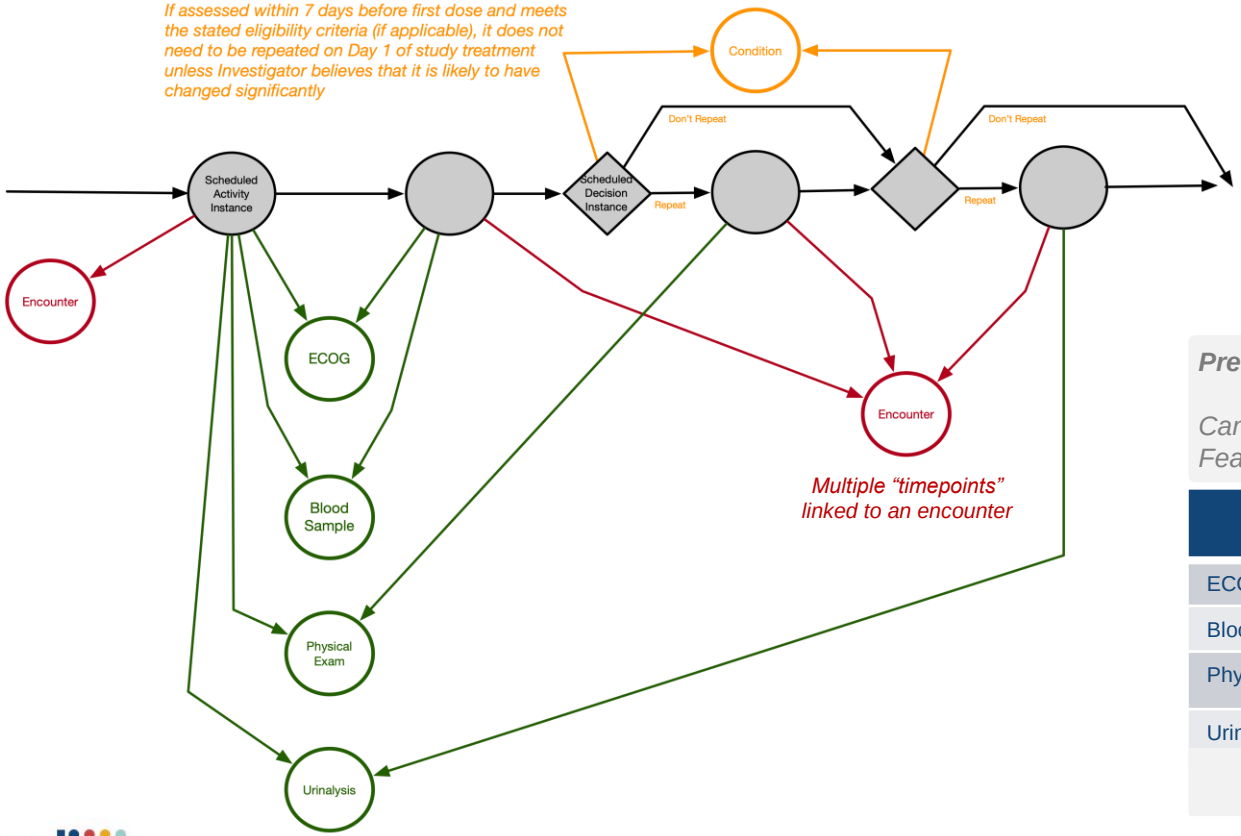
→
1: -42 to -9
2: -21
3: -8
4: -7
5: -6 to -5
6: -4 to -1
7: 1
8: 2-3
9: 4-7
10: 8
11: 9
…

Study Procedures	Screening[a]		C-I[b]	Inpatient Period 1							OP[c]		Inpatient Period 2								UNS[d]	EOS or ET[e]
	Screening		C-I																			
Days	-42 to -9	-21	-8	-7	-6 through -5	-4 through -1	1	2-3	4-7	8	9	10-22	23	24	25	26-28	29	30-35	36	37-38	39	40		EOS Day 54+/-2
PD: Plasma total and PUF-Cu, LBC, ceruloplasmin, ceruloplasmin-bound Cu																								
Safety Assessments / Laboratory Analyses																								
Chemistry[g], hematology, Coagulation	X		X			X[f]				X		X[g]	X			X[f]		X				X		X
Urinalysis	X		X							X		X[g]	X			X						X		X
Urine/serum pregnancy test[a]	X		X										X											X
Retained serum sample (safety)[j]				X																				
Vitals sign measurements[a]	X			X			X				X		X									X		X
12-lead ECG (triplicate)	X			X			X				X		X								X			X
Adverse events	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Balance assessments																								
Cu/Mo-controlled meals[i]				X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X			
Light exercise regimen				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Urination and bowel movement monitoring, menstruation check[k]						X	X	X	X	X					X	X	X	X	X	X	X			
24-hour urine for Cu and Mo[m]						X	X	X	X	X					X	X	X	X	X	X	X			
Feces for Cu and Mo[k]						X	X	X	X	X					X	X	X	X	X	X	X			
Other																								
Concomitant medication and [illegible] therapy/procedure						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Timeline – Decision



Timelines – Repeat conditions



Presentation

Can derive an SoA from the USDM logic. Feature will be added to the Excel utility

	Encounter 1	Encounter 2
ECOG	X	X
Blood Sample	X	X
Physical Exam	X	X[a]
Urinalysis	X	X[b]

Marked as footnotes we would typically see in a protocol, we can do better

Sub-timeline

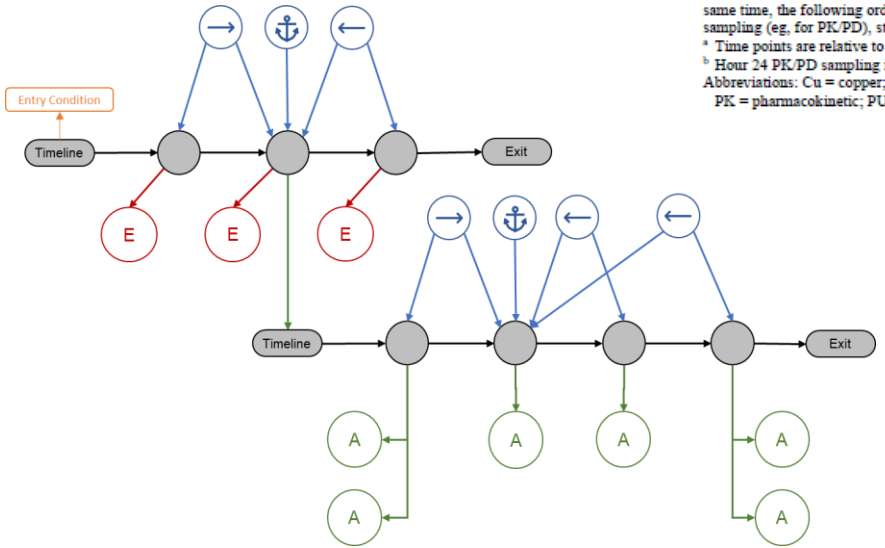


Table 2: Schedule of Pharmacokinetic and Pharmacodynamic Assessments on Days 1, 25, 29, and 39

Time point (hours)[a]	−0.5	0	1	2	3	4	5	6	8	12	24
Blood sampling for PK: Plasma total Mo and PUF-Mo PD: Plasma total and PUF-Cu, LBC, ceruloplasmin, ceruloplasmin-bound Cu	X			X		X	X	X	X	X	X[b]

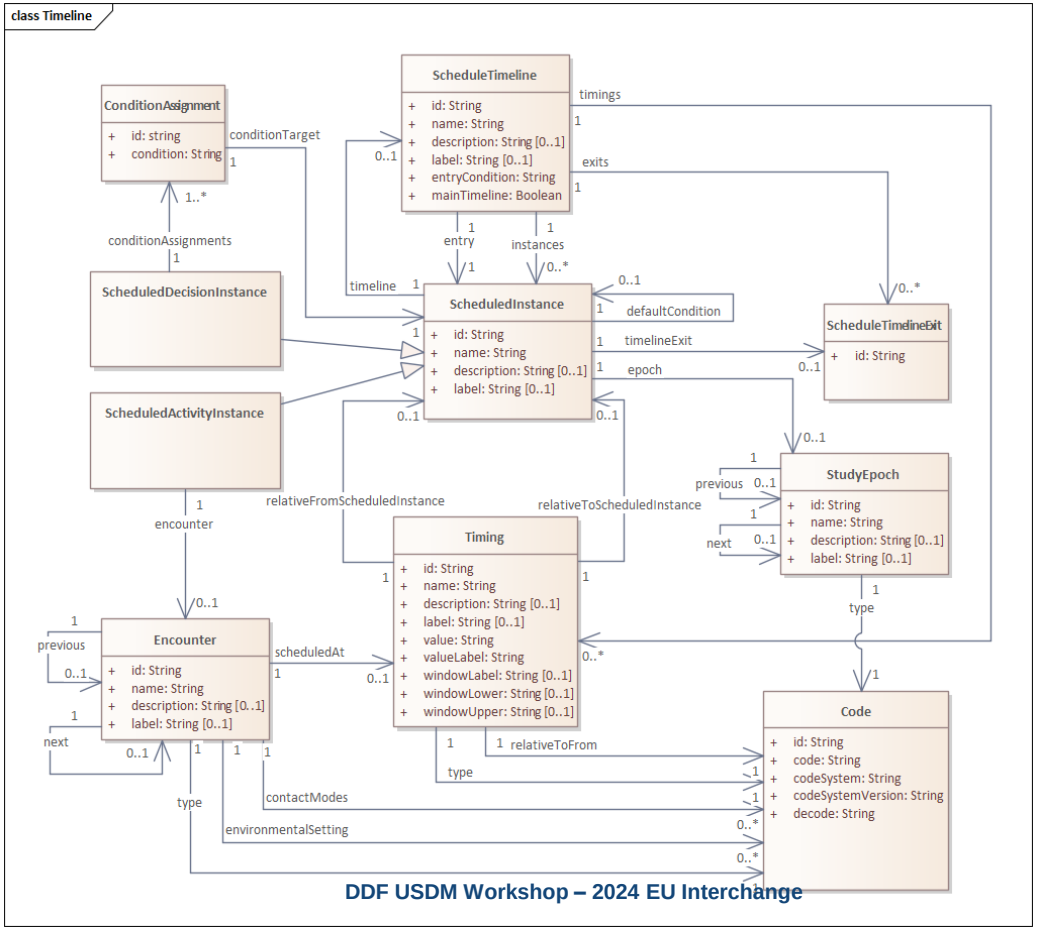
Note: Windows for PK/PD time points will be defined as ±10% of the nominal time point. On Days 1 and 39, triplicate 12-lead ECG will be collected at 4 hours postdose. When multiple procedures are scheduled to occur at the same time, the following order of events should be strictly adhered to whenever possible: ECG, vital signs, blood sampling (eg, for PK/PD), study intervention administration, and meal.

[a] Time points are relative to dosing (0 hours).

[b] Hour 24 PK/PD sampling is to occur just prior to the next-day dose of ALXN1840.

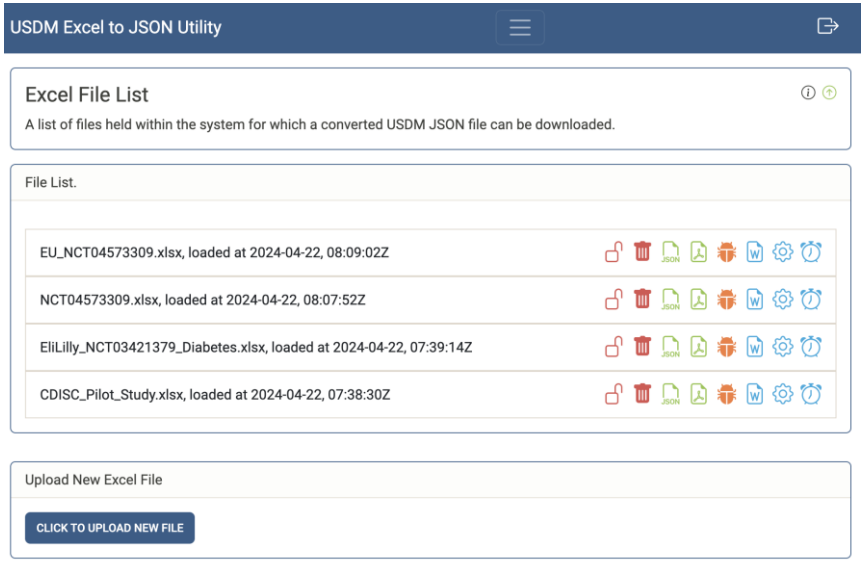
Abbreviations: Cu = copper; LBC = labile bound copper; Mo = molybdenum; PD = pharmacodynamic; PK = pharmacokinetic; PUF = plasma ultrafiltrate.

Timing - UML


class Timeline
ScheduleTimeline
+ id: String
+ name: String
+ description: String [0..1]
+ label: String [0..1]
+ entryCondition: String
+ mainTimeline: Boolean
timings
exits
entry
instances
ConditionAssignment
+ id: string
+ condition: String
conditionTarget
conditionAssignments
ScheduledDecisionInstance
ScheduledActivityInstance
timeline
ScheduledInstance
+ id: String
+ name: String
+ description: String [0..1]
+ label: String [0..1]
defaultCondition
timelineExit
epoch
ScheduleTimelineExit
+ id: String
StudyEpoch
+ id: String
+ name: String
+ description: String [0..1]
+ label: String [0..1]
previous
next
type
relativeFromScheduledInstance
relativeToScheduledInstance
encounter
Timing
+ id: String
+ name: String
+ description: String [0..1]
+ label: String [0..1]
+ value: String
+ valueLabel: String
+ windowLabel: String [0..1]
+ windowLower: String [0..1]
+ windowUpper: String [0..1]
Encounter
+ id: String
+ name: String
+ description: String [0..1]
+ label: String [0..1]
scheduledAt
relativeToFrom
Code
+ id: String
+ code: String
+ codeSystem: String
+ codeSystemVersion: String
+ decode: String
contactModes
environmentalSetting

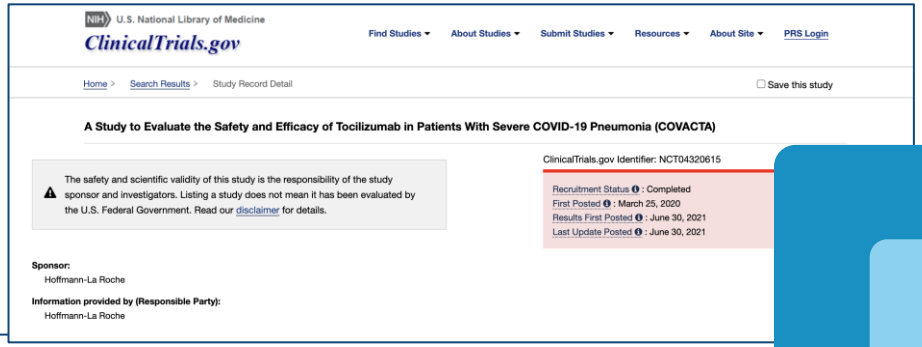
Exercise

- Add in PK / PD profile as a timeline
  - Add a new sheet “pkPdTimeline” sheet
  - Timings are in the ”studyDesignTiming” sheet



SOA 2 – Biomedical Concepts Procedures & Conditions

Detailed Design and the SoA

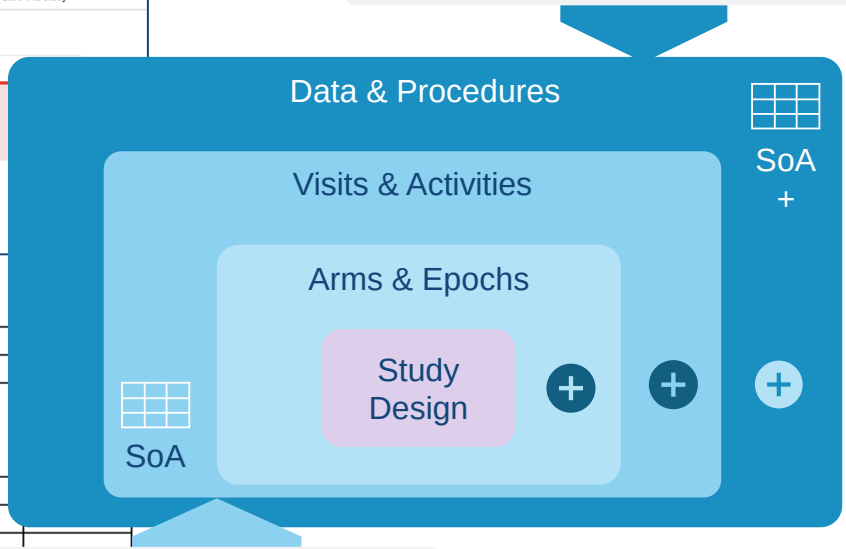


Appendix 1
Schedule of Activities: Days 1 and 2

	Screening [a, b]	Baseline		
Study Day	–2 to 0	1		
Time Post Initial Treatment (Assessment Window)		0 Pre-dose (–4 hrs)	15 min After end of infusion (+1 hr)	24 hrs (±4 hrs)
Informed consent	x			
Inclusion/exclusion criteria	x	x		
Demographic data	x			
Randomization		x		
Medical history		x		

Increasing Detail

Provide precision on the data to be captured to the capture systems in a generic manner to facilitate automation. The data precision has not, typically, been in the "paper" protocol. It is SoA "plus", SoA+



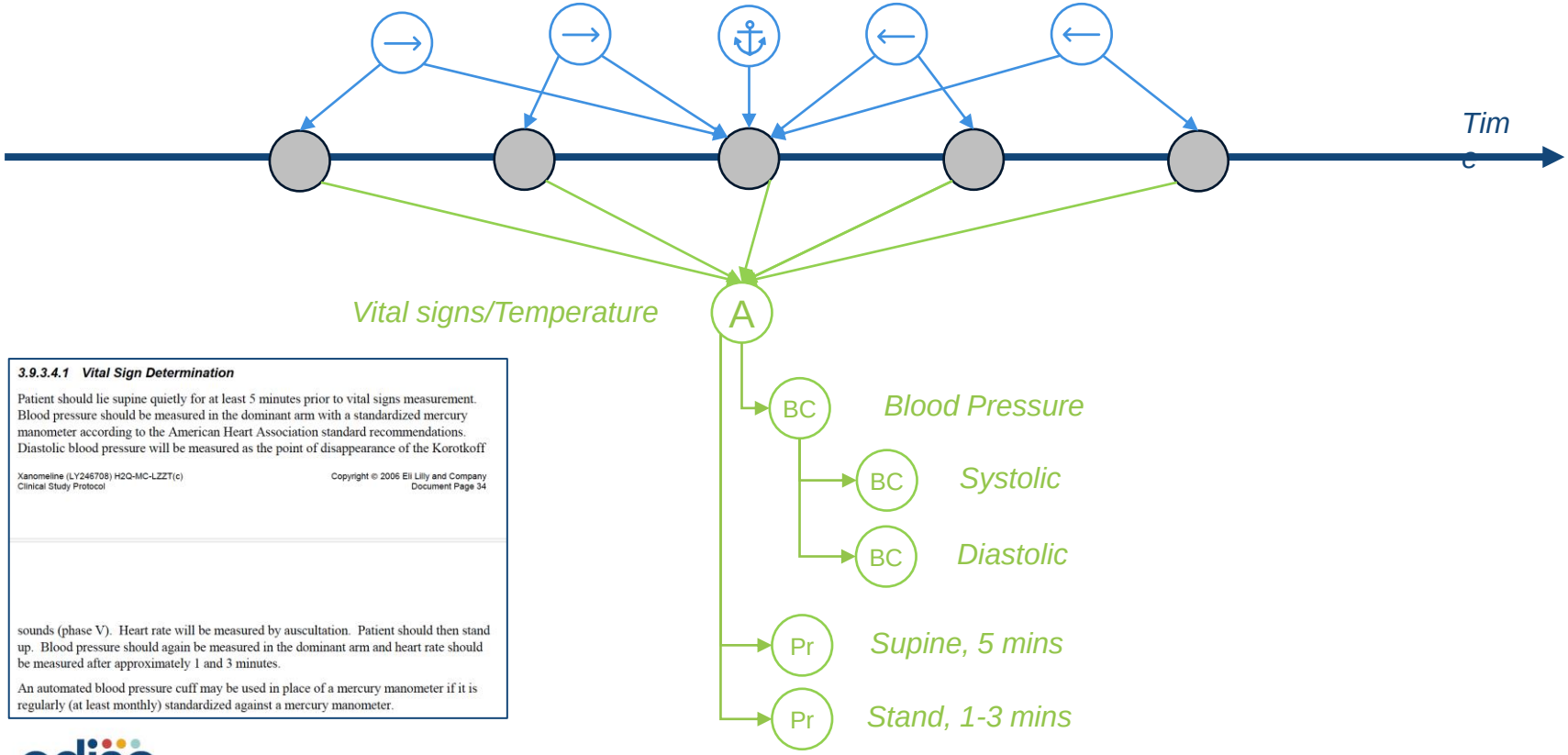
Current "Limit"

SoA is where we are today with associated footnotes and free text. Activities sit at a CRF form "level"

Technology Independent

Definition should be independent of any capture technology

Biomedical Concepts – Timeline



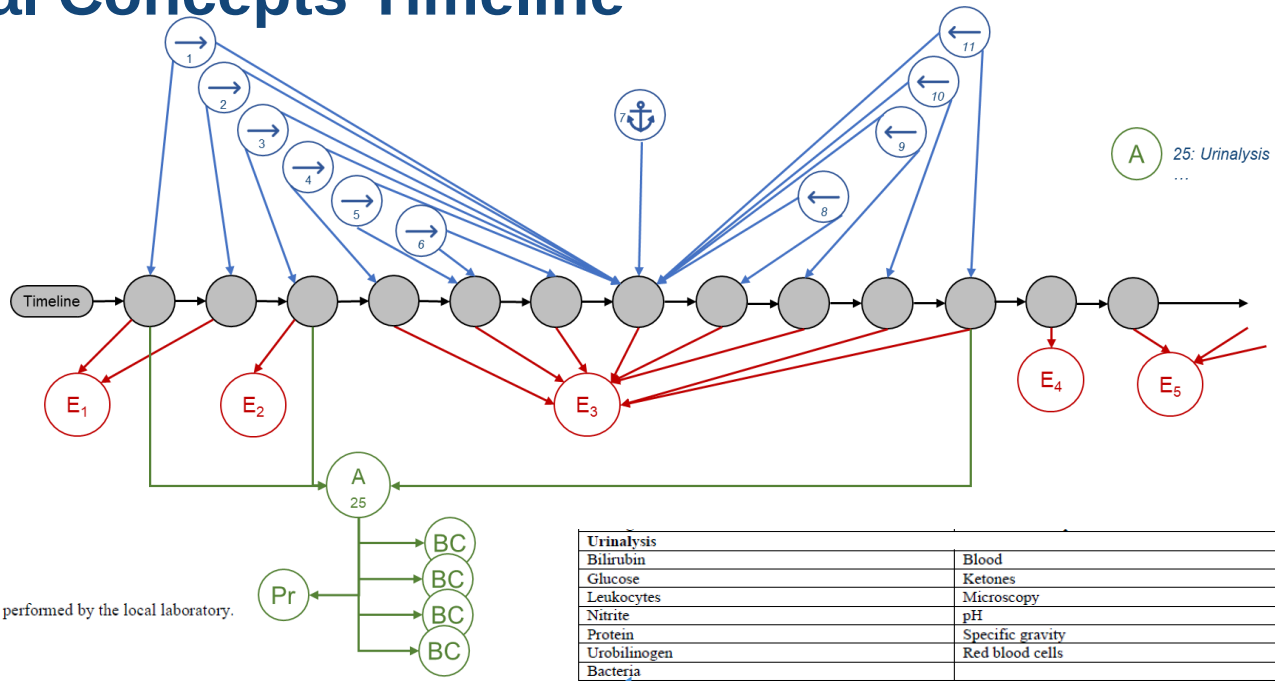
3.9.3.4.1 Vital Sign Determination

Patient should lie supine quietly for at least 5 minutes prior to vital signs measurement. Blood pressure should be measured in the dominant arm with a standardized mercury manometer according to the American Heart Association standard recommendations. Diastolic blood pressure will be measured as the point of disappearance of the Korotkoff

sounds (phase V). Heart rate will be measured by auscultation. Patient should then stand up. Blood pressure should again be measured in the dominant arm and heart rate should be measured after approximately 1 and 3 minutes.

An automated blood pressure cuff may be used in place of a mercury manometer if it is regularly (at least monthly) standardized against a mercury manometer.

Biomedical Concepts Timeline



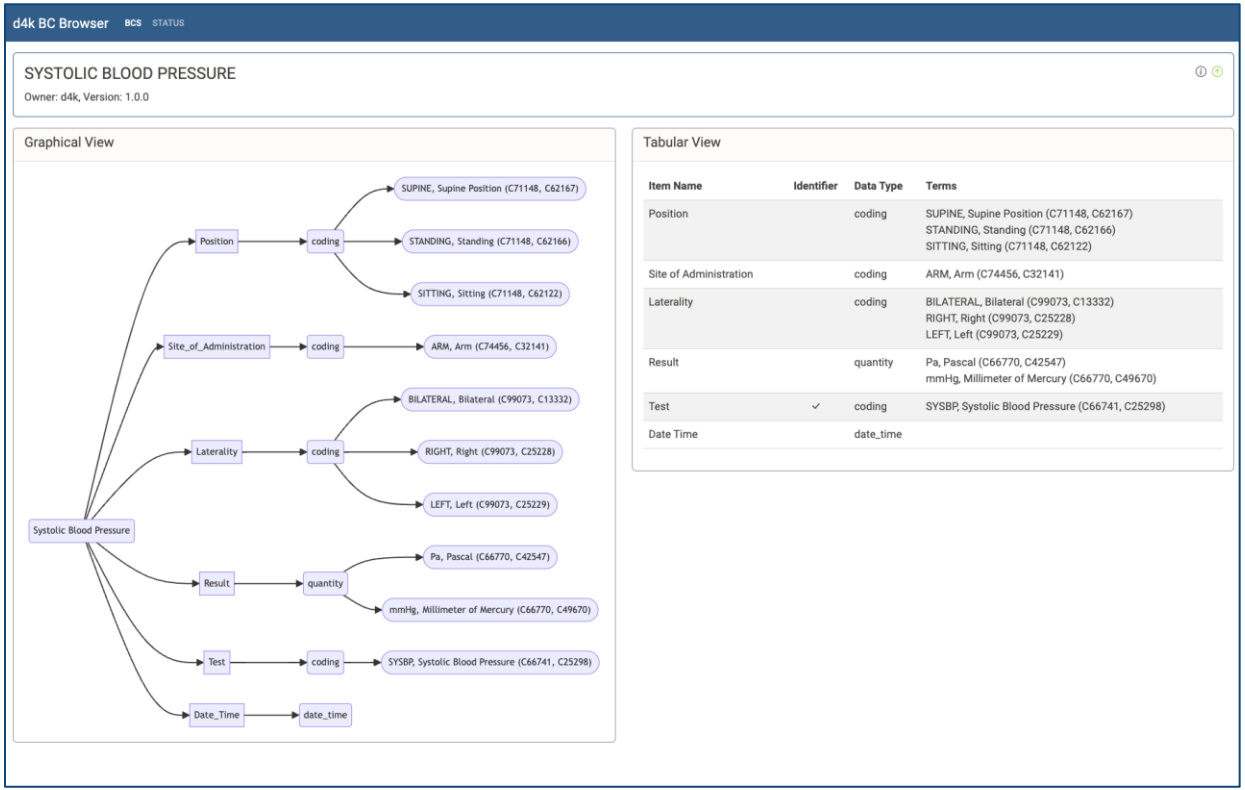
10.2. Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the local laboratory.

Urinalysis	
Bilirubin	Blood
Glucose	Ketones
Leukocytes	Microscopy
Nitrite	pH
Protein	Specific gravity
Urobilinogen	Red blood cells
Bacteria	

Study Procedures	Screening[a]		C-1[b]																				UNS[d]	EOS or ET[e]
	Screening		C-1	Inpatient Period 1							OP[c]		Inpatient Period 2											
Days	-42 to -9	-21	-8	-7	-6 through -5	-4 through -1	1	2-3	4-7	8	9	10-22	23	24	25	26-28	29	30-35	36	37-38	39	40		EOS Day 54+/-2
PD: Plasma total and PUF-Cu, LBC, ceruloplasmin, ceruloplasmin-bound Cu																								
Safety Assessments / Laboratory Analyses																								
Chemistry[g], hematology, Coagulation	X		X			X[f]				X		X[g]	X			X[f]		X				X		X
Urinalysis	X		X							X		X[g]	X			X						X		X

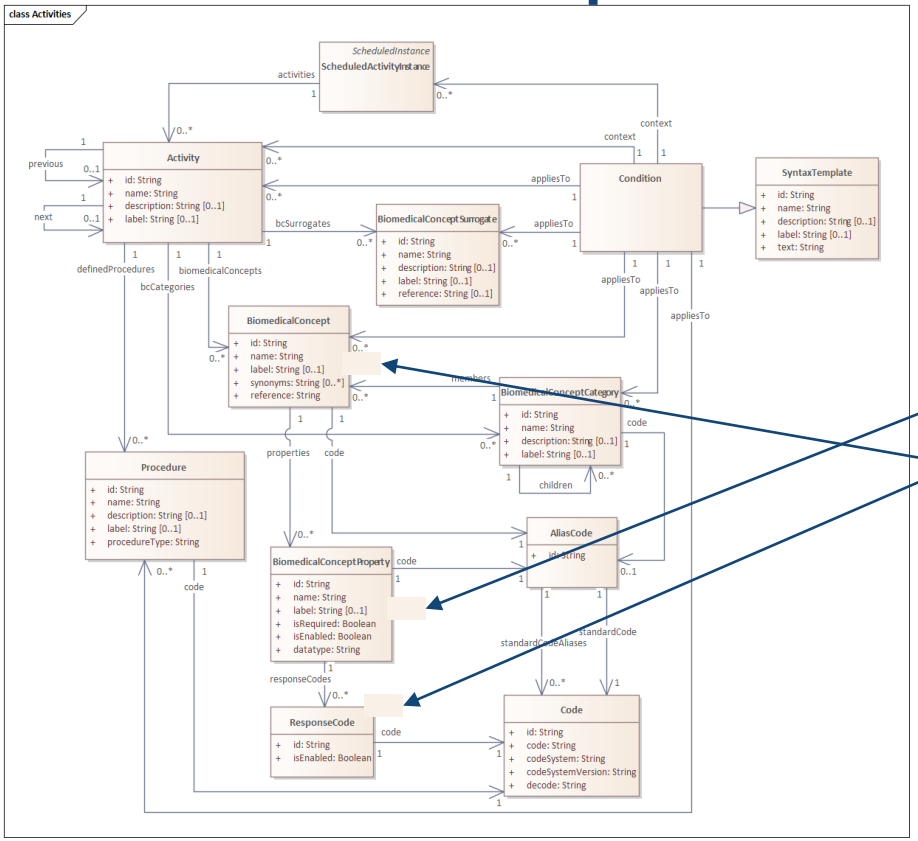
CDISC Library & Biomedical Concepts

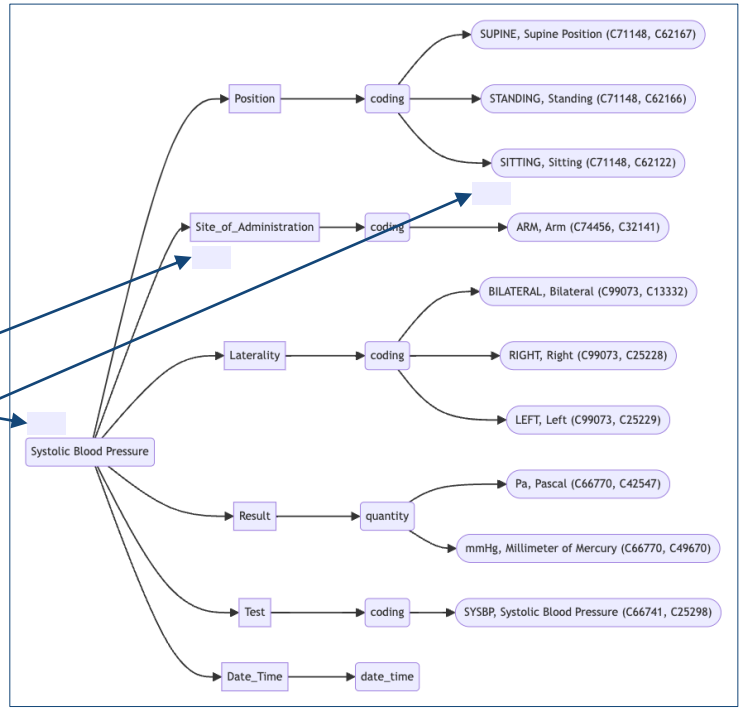


Excel - Some Restrictions

1. *Update to allow for full definition from CDISC Library to be deployed*
2. *Not handling BC categories yet. Only recently exposed by the CDISC Library API, need to catch up*

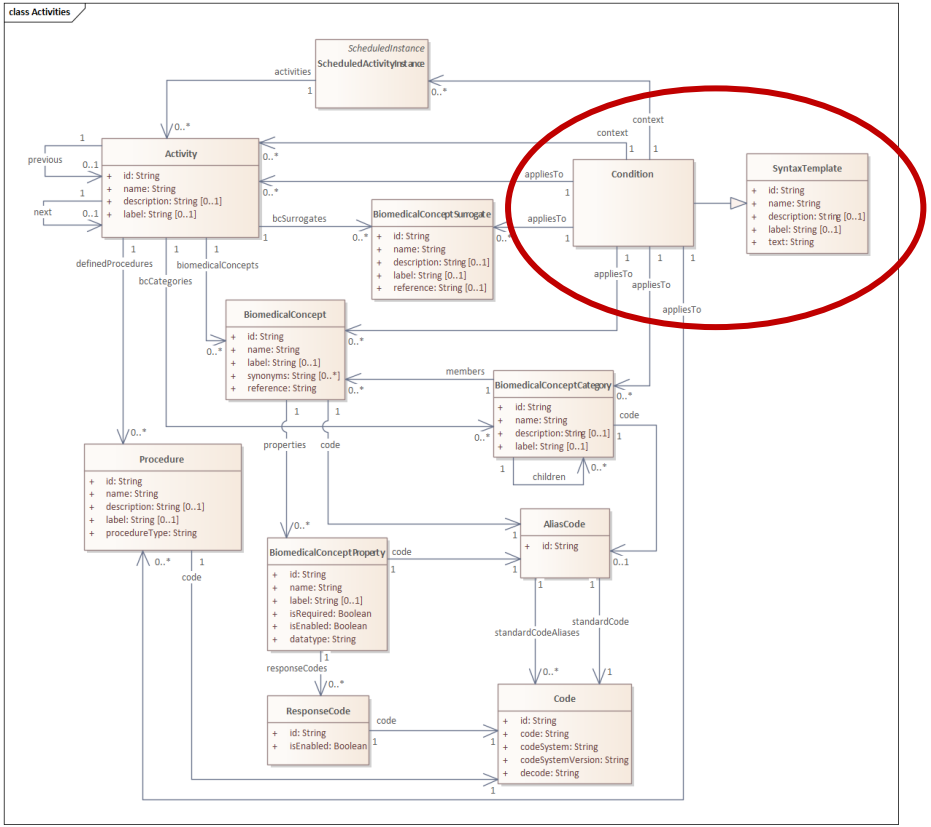
Biomedical Concept – UML





Conditional footnotes

1. Define on what level they are conditional/optional? appliesTo
   - Activity
   - Procedure
   - BiomedicalConcept
   - BiomedicalConceptSurrogate
   - BiomedicalConceptCategory
2. Define the context, for example:
   - BCs within a specific Activity
   - BCs within a specific at a specific timing: ScheduledActivityInstance
3. Condition text can be presented as footnote by implementation



Conditional Footnotes

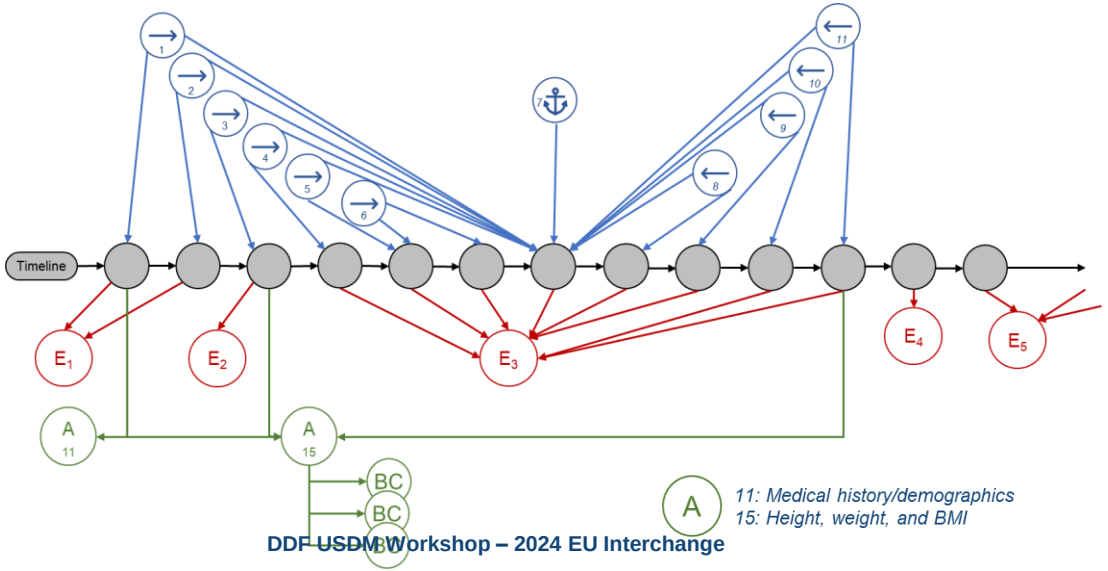
Study Administration
Medical history/demographics[i]
WD history[j]
Prior WD treatment[j]
Physical examination[k]
Height[l], weight, and BMI

[i] Parameters include age and sex. Race and ethnicity will be collected where permitted by local regulations.

[j] Wilson disease history will include diagnosis date, method of diagnosis, history of cirrhosis, details of any previous liver biopsies performed, and treatment received.

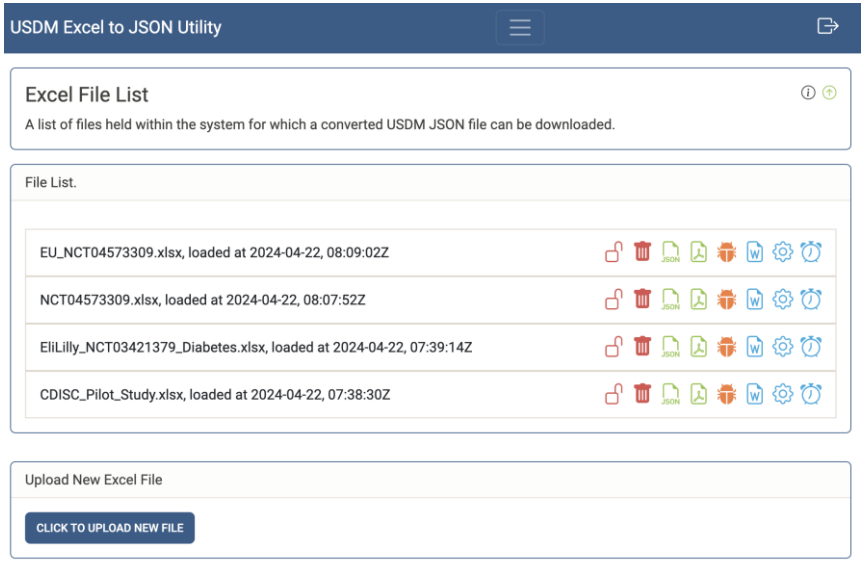
[k] A full physical examination will be performed at Screening, at check-in for the study, and at the End of the study/Early Termination Visit. A physical examination should also be performed on any participants with ongoing adverse events prior to discharge from the unit. Otherwise, a symptom-driven physical examination may be performed at other times, at the Principal Investigator's discretion.

[l] Height at screening only.



Exercise

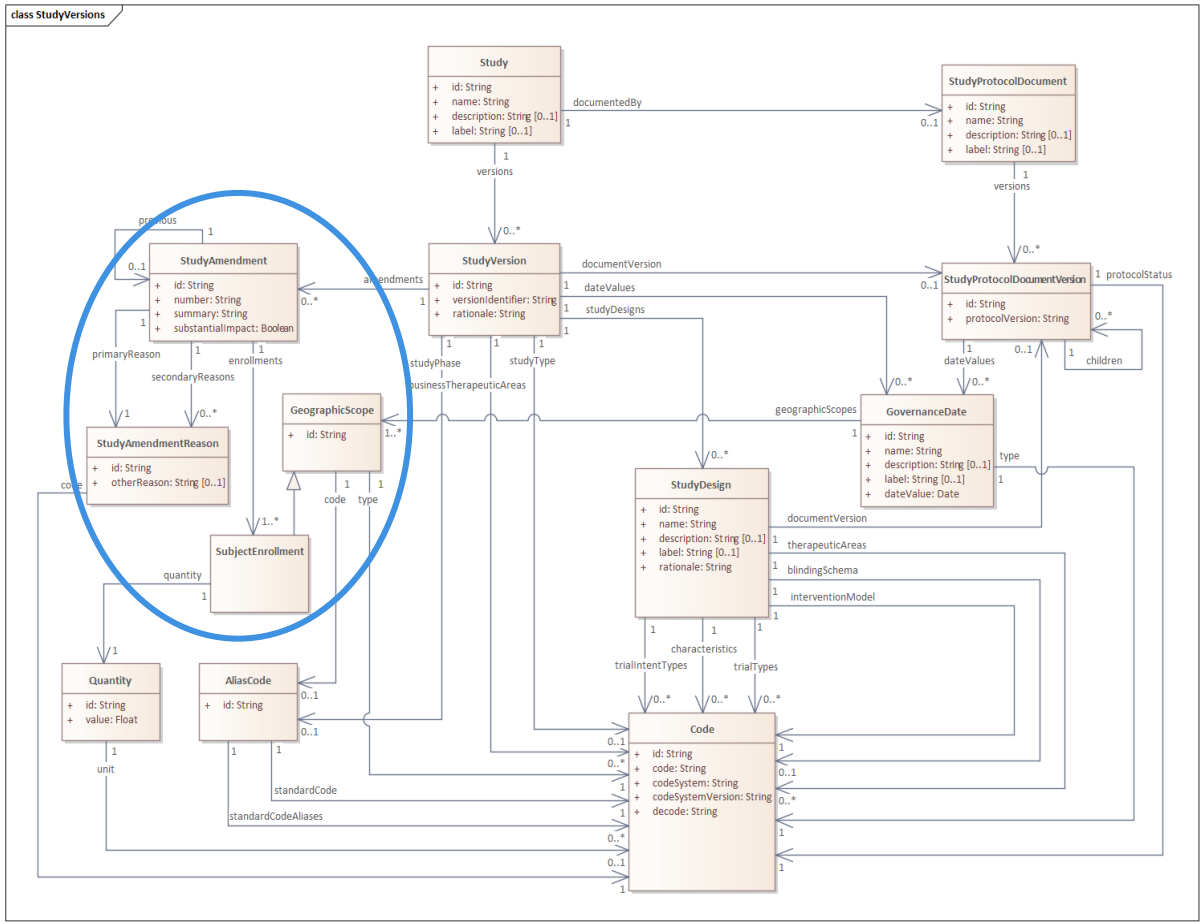
- Add in a condition
  - Edit the “studyDesignConditions” sheet
  - Footnotes c, d or h make for good examples



Amendments

Amendments

- Summary
- Substantial impact?
- Reason (primary/secondary)
  - Regulatory agency request to amend
  - New regulatory guidance
  - IRB/IEC feedback
  - New Safety Information available
  - ….
- Enrollment % or N at time of amendment
  - Geographic scope



Amendments

Approval Date:

Original Protocol	**12 May 2020**
Amendment 1	**18 Aug 2020**
Amendment 2	**19 Mar 2021**
Amendment 3	**31 Aug 2021**
Amendment 3.1 (US)	**18 Mar 2022**

Previous

Previous

Previous

Previous

Amendment 2 (19 Mar 2021)

This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The main reason for preparation of this amendment was to revise the exclusion criterion for a urine drug screen. Changes implemented via Administrative Letter 1 and Administrative Letter 2, as well as COVID vaccination guidance, have also been incorporated.

Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or Clarifications
Section 1.1, Synopsis; Section 9.2, Sample Size Determination	The number of participants changed from "up to 10" to "approximately 10".	Clarification of sample size.
Section 1.1, Synopsis; Section 1.2, Schema; Section 1.3, Schedule of Activities; Section 4.1, Overall Design; Section 6.4, Study	SMS text messaging will replace the dosing diary as the method of confirming treatment compliance during the outpatient period.	Site processes does not allow use of paper diary.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 3.1 (US), 18 Mar 2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, the US Food and Drug Administration's (FDA) regulation at 21 CFR part 312.30(b), and any applicable local regulations.

Overall Rationale for the Amendment

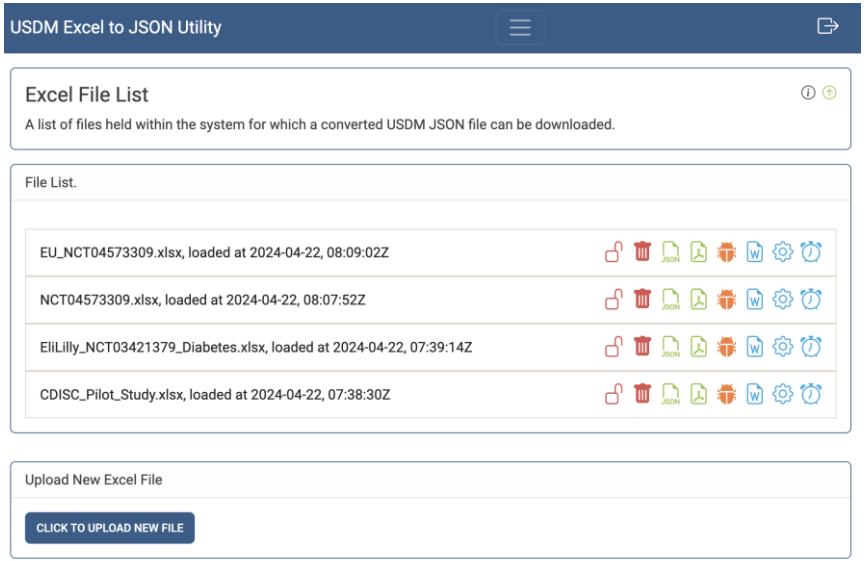
The main reason for preparation of this amendment was to clarify study procedures occurring across different sites in the US, so as to facilitate participant recruitment across different regions of the US, and to lessen inconvenience for participants without compromising the quality of the study.

Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or Clarifications
Section 1.3 Schedule of Activities (SoA), Table 1	Addition of text to the footnote to state that procedures specific to screening sites (only in the US) detailed in Section 8	As per Section 8 (below).
4.2 Scientific Rationale for Study Design	Number of days changed from 30 days to 21 days in the following sentence: • However, the physiologic turnover of human gastrointestinal epithelial cells is 3 - 5 days (Darwich, 2014); therefore, the inhibitory effect of zinc on intestinal copper absorption is expected to be minimal ~~30~~ **21** days after discontinuation of zinc.	To align the number of days with the mention of zinc discontinuation elsewhere in the protocol.
Section 8 Study Assessments and Procedures	Addition of text applicable only to the US that details the possibility for sites in the US to only perform screening procedures and not any of the remaining study procedures.	To facilitate participant recruitment across different regions of the US and to lessen inconvenience for participants without compromising the quality of the study.

Exercise

- Add in amendment two
  - Edit the “studyAmendments” sheet
  - The columns “primaryReason” and “secondaryReason” are coded
  - The column “enrollment” has a particular format, either global, region or country with % or persons
    - “Global: 65%”
    - “Region: Europe=15”
    - “Country: USA=20%”
    - Use “Global: 0”



Narrative content
Protocol document and M11

Narrative content

- 1 class linked to the study Protocol Document Version
- Stores protocol HTML formatted text pieces identified by
  - Name
  - SectionNumber
  - SectionTitle
- Can link to structured elements stored elsewhere in the USDM
- Ordering by next/previous attributes
- Sub-sectioning by children attribute

XHTML Attributes (see Implementation Guide)

'<usdm:ref klass="klassName" id="idValue" attribute="attributeName"/>'

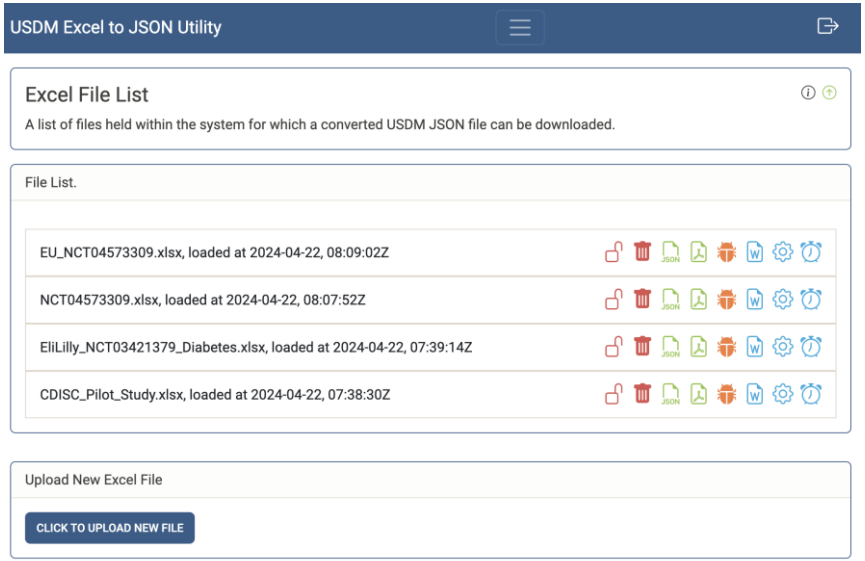
where:

- *klassName* is the name of the class that holds the referenced data element.
- *idValue* is the id value of the referenced data element within *klassName*.
- *attributeName* is the attribute name of the referenced data element within *klassName*.

Further details of the use of these references can be found in Sections 4.20, Unstructured Content, and 4.21, Syntax Template.

Exercise

- Update the amendment info for Amendment 1 on the front sheet of the USDM protocol
  - Edit the “studyDesignContent” sheet, row 1
  - The original document information is already in the right form



Wrap Up