Digital Data Flow (DDF) Workshop: Mastering USDM

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Dave Iberson-Hurst (CDISC)
Berber Snoeijer (CDISC)
John Owen (CDISC)

PHUSE EU Connect,
5 November 2023

Today's Speakers

Sumesh Kalappurakal

Senior Director, Technology Solutions

Johnson and Johnson

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CDISC DDF Technical Lead

Dave Iberson-Hurst

CDISC DDF Product Owner

John Owen

DDF Project Manager

TransCelerate's Digital Data Flow Initiative aims to break the document paradigm

Re-Cap from Webinar

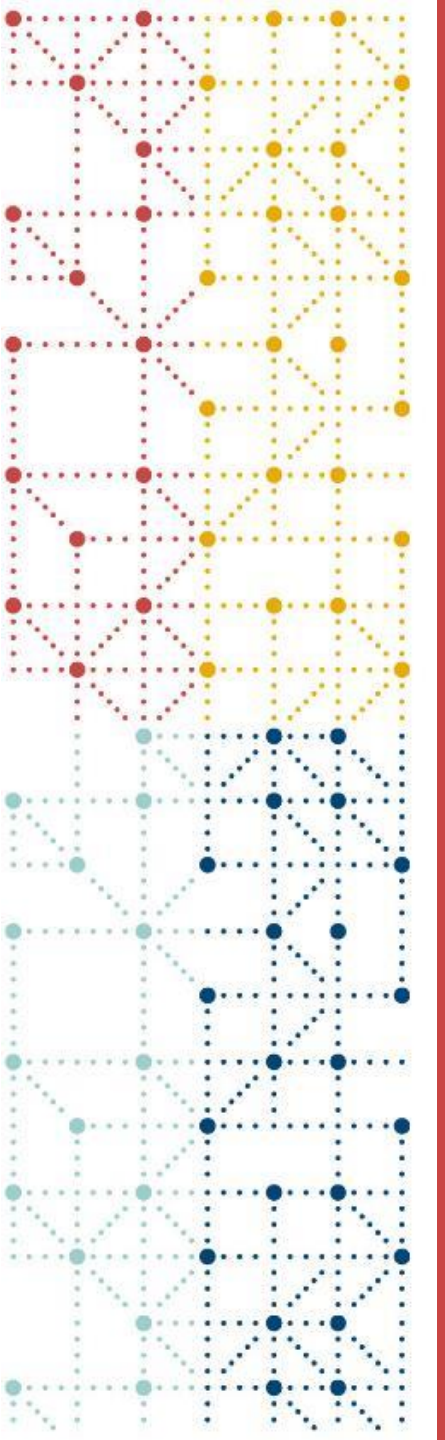
The DDF technical solution consists of two key components
USDM represents the standards aspect

Unified Study Definitions Model (USDM) v2.0 – **developed with CDISC**; this is a published industry standard for specifying and structuring study definitions (design & protocol information) in a digital, machine-readable format promulgated and maintained by CDISC.

Study Definitions Repository (SDR) v2.0.1 – Type of repository that is conformant with USDM and acts as a functioning, example approach to store protocol information and connect other producing and consuming systems to achieve interoperability. **Source code is available under an open-source license on the DDF Github** (see QR code at right).

https://transcelerate.github.io/ddf-home/

TransCelerate BIOPHARMA INC.



Agenda

1. Introduction (John)
2. Overview of model (Dave)
3. Inclusion / Exclusion Criteria (Berber)
4. SoA & Timelines (Dave)
5. Biomedical Concepts (Dave)
6. Footnotes (Berber)
7. Unstructured text & the ICH M11 document template (Dave)
8. Hands-on exercises & discussion (All)

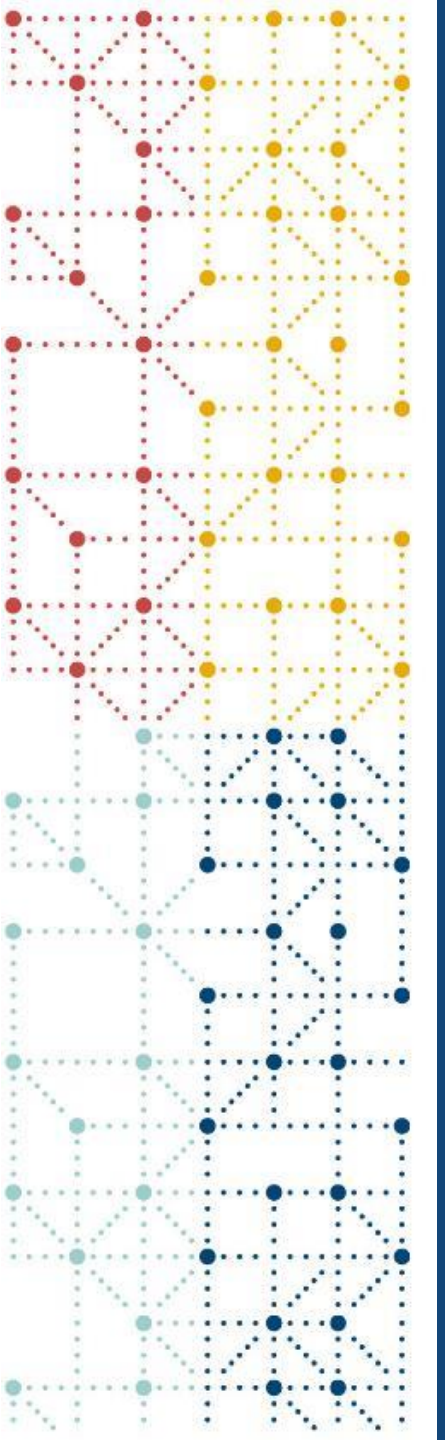
Welcome to Birmingham

MICHELIN STAR

Cadbury

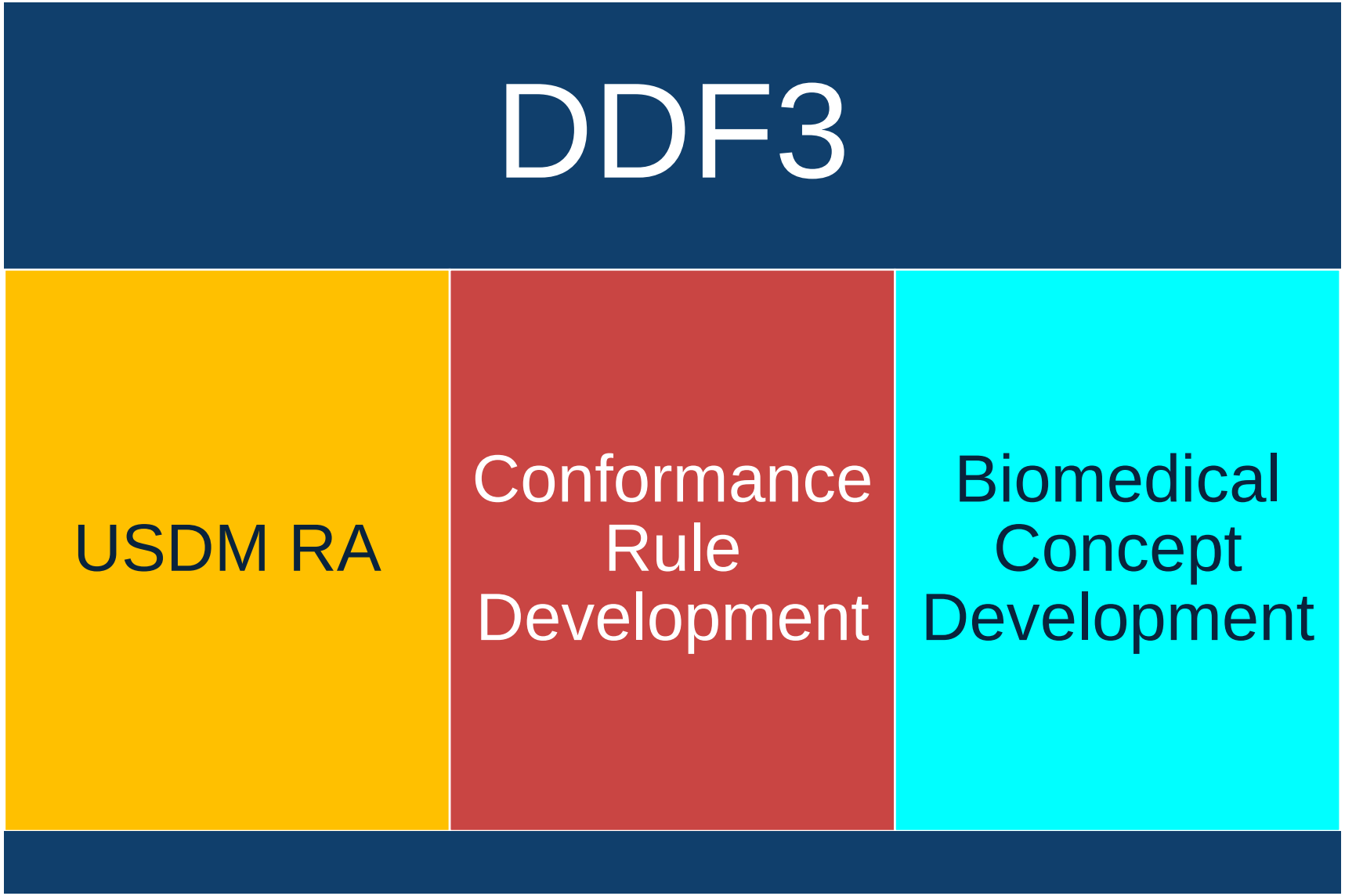
Ty·Phoo TEA

cdisc



Introduction

Work Areas


DDF3
USDM RA
Conformance Rule Development
Biomedical Concept Development

DDF 3 USDM Scope

- Represent ICH M11 in USDM
- SDTM Trial Design Population
- Clinical Trial Registry Population
- Complex Studies/Cohorts
- Model Enhancements

CDISC Study Definition Repository RA Deliverables

- Unified Study Definitions Model (USDM) Class Diagram
- Application Programming Interface (API) Specification
- CDISC Controlled Terminology
- USDM Implementation Guide

Development and Review

2023

Date	Week #		Stage	Sprint #
05-Jul-23	1	Scoping	Development Sprints	1
12-Jul-23	2	Scoping	Development Sprints	1
19-Jul-23	3	Scoping	Development Sprints	2
26-Jul-23	4	Scoping	Development Sprints	2
02-Aug-23	5	Scoping	Development Sprints	3
09-Aug-23	6	Scoping	Development Sprints	3
16-Aug-23	7	Scoping	Development Sprints	4
23-Aug-23	8	Scoping	Development Sprints	4
30-Aug-23	9	Scoping	Development Sprints	5
06-Sep-23	10	Scoping	Development Sprints	5
13-Sep-23	11	Scoping	Development Sprints	6
20-Sep-23	12	Scoping	Development Sprints	6
27-Sep-23	13	Scoping	Development Sprints	7
04-Oct-23	14		Development Sprints	7
11-Oct-23	15		Development Sprints	8
18-Oct-23	16		Development Sprints	8
25-Oct-23	17		Development Sprints	9
01-Nov-23	18		Development Sprints	9
08-Nov-23	19		Development Sprints	10
15-Nov-23	20		Development Sprints	10
22-Nov-23	21		Development Sprints	11
29-Nov-23	22		Development Sprints	11
06-Dec-23	23		Development Sprints	12
13-Dec-23	24		Development Sprints	12
20-Dec-23	25		Development Sprints	13
27-Dec-23	26		Development Sprints	13

Development

Continuous Internal Review

2024

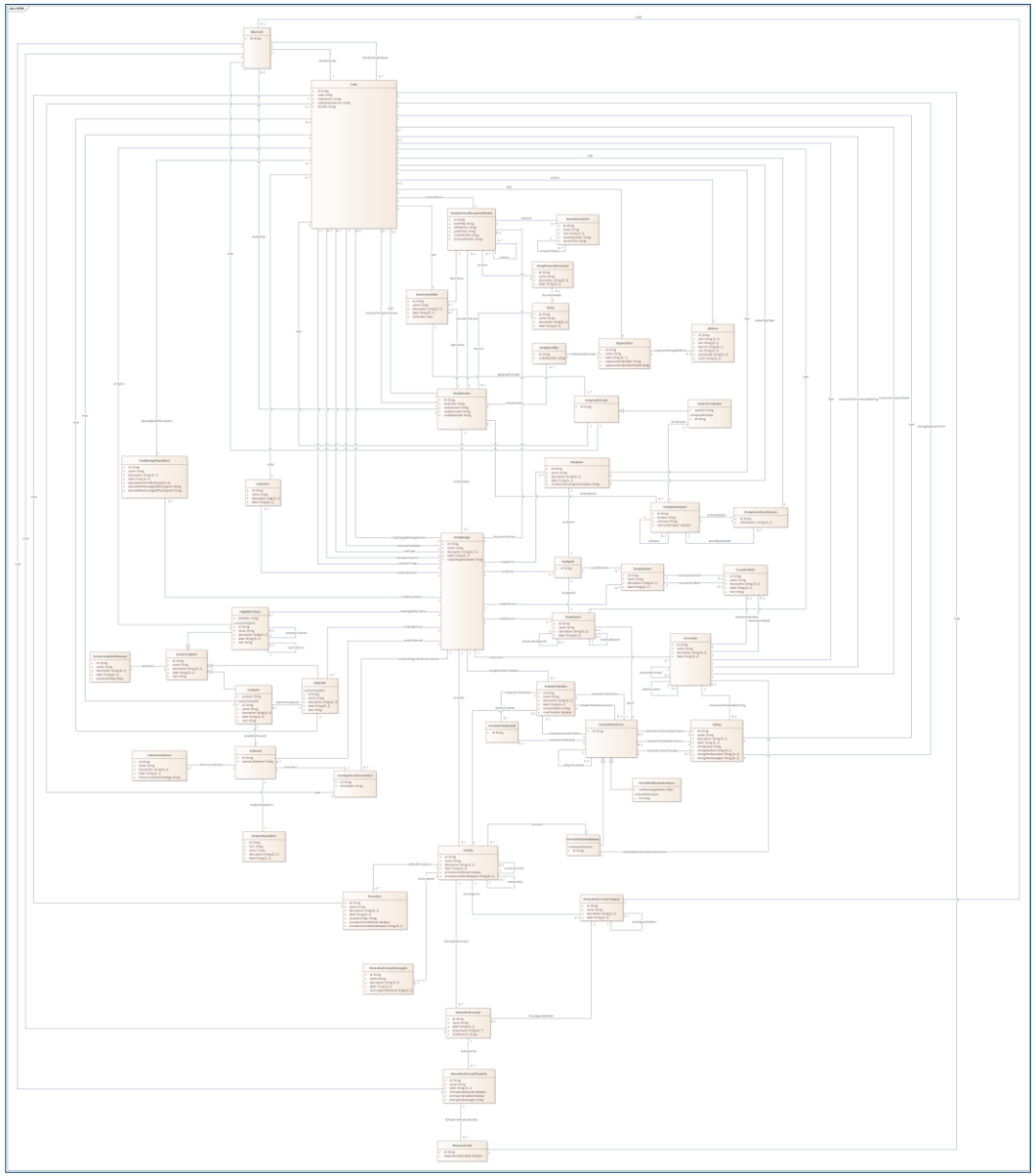
Date	Week #		Stage	Sprint #
03-Jan-24	27		Public Review	14
10-Jan-24	28		Public Review	14
17-Jan-24	29		Public Review	15
24-Jan-24	30		Public Review	15
31-Jan-24	31		Public Review	16
07-Feb-24	32		Public Review	16
14-Feb-24	33		Public Review	17
21-Feb-24	34		Public Review	17
28-Feb-24	35		Public Review	18
06-Mar-24	36		Public Review	18
13-Mar-24	37		Publication	19
20-Mar-24	38		Publication	19
27-Mar-24	39		Publication	20
03-Apr-24	40		Publication	20

Public Review

USDM v3.0

Purpose

- Provide an understanding of the USDM model
- To do this we will use a MS Excel tool to “make it real”
- Not the purpose of this workshop to give you all the detail on using the MS Excel tool



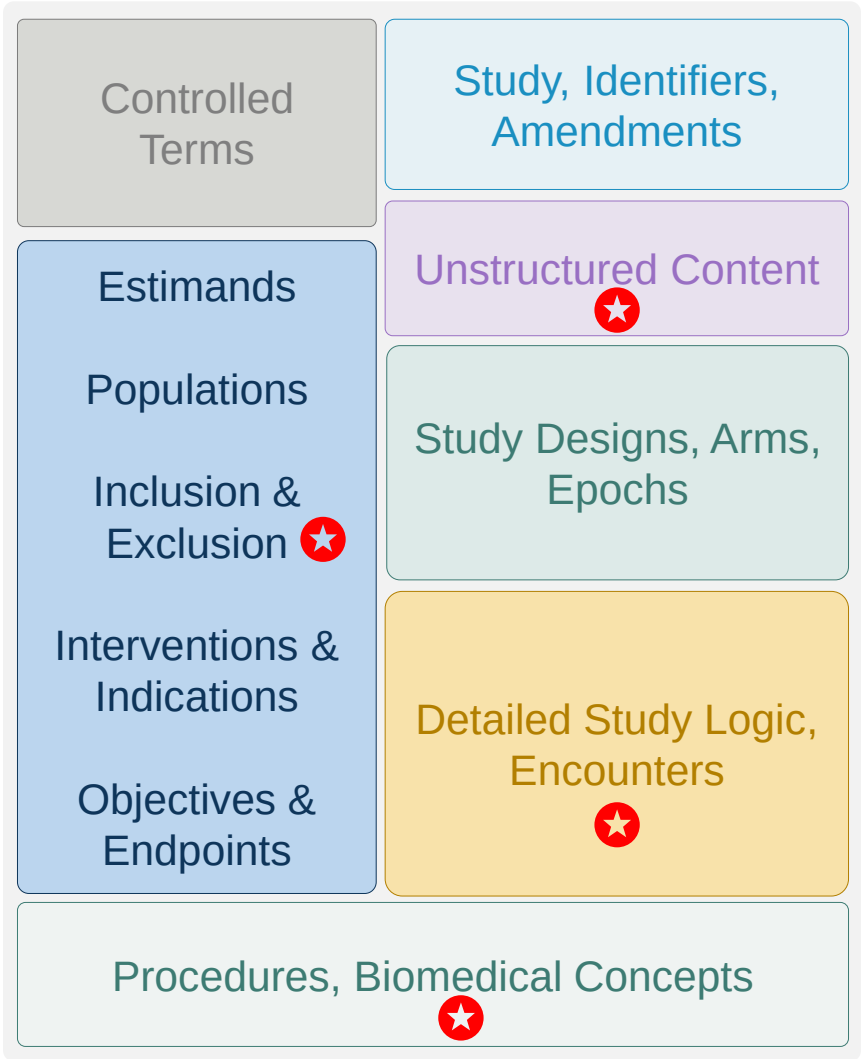
Focus Areas

Cannot cover every aspect in detail in an hour and a half. We will provide an overview and focus on some of the interesting aspects of the model

- Overview of model
- Inclusion / Exclusion Criteria
- SoA & Timelines
- Biomedical Concepts
- Footnotes
- Unstructured text & the ICH M11 document template
- Hands-on exercises & discussion

We will try and give you the most up-to-date information. We will be looking at release 2.5 of the USDM.

Remember this is "work in progress".



Prereads

Materials to look at prior to the workshop if you wish to. NOT compulsory!

Item	Link	Notes
Model (UML)	https://github.com/cdisc-org/DDF-RA/blob/main/Deliverables/UML/USDM_UML.png	Release 2.5
Controlled Terminology (XLSX)	https://github.com/cdisc-org/DDF-RA/blob/main/Deliverables/CT/USDM_CT.xlsx	Release 2.5
Implementation Guide (PDF)	https://github.com/cdisc-org/DDF-RA/blob/main/Deliverables/IG/USDM-IG.pdf	Work in progress
Informative Diagram (PNG)	https://github.com/cdisc-org/DDF-RA/blob/main/Documents/DDF%20USDM%20Model%20Informative.png	Release 2.5
Miro Board (Web)	https://miro.com/app/board/uXjVPl5X2AY=/	P: CDISC-DDF-SME

Tools For The Workshop

- Laptop!
- Tools on Laptop
  - MS Excel
  - Text editor (e.g. VS Code)
- Web tools
  - USDM Web Tool
  - Web Text/JSON Comparison

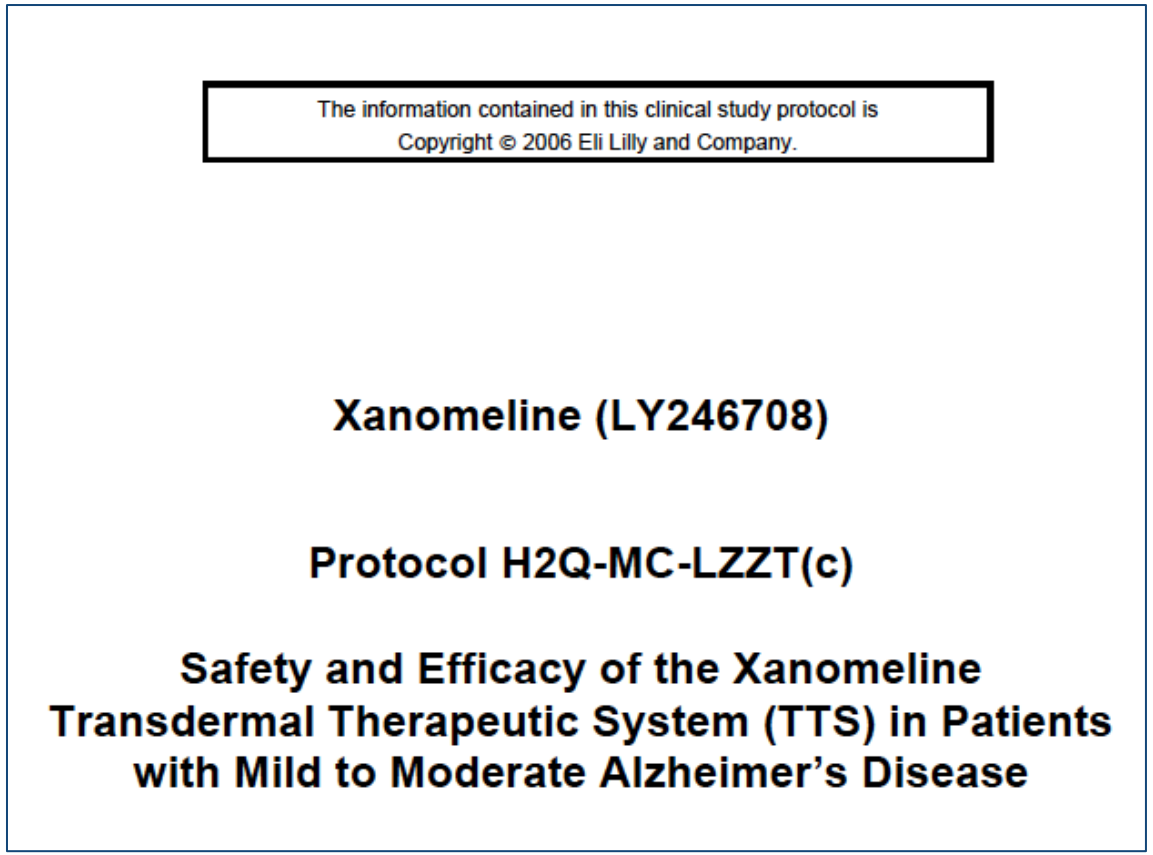
Web Tools

No need to install any tools on your laptop other than MS Excel

Item	Link	Notes
Excel To JSON Tool	https://usdm-service.fly.dev/	U: PHUSE P: learning_usdm
Excel to JSON Tool readme	https://github.com/data4knowledge/usdm	
Excel to JSON Tool Infographic	https://github.com/data4knowledge/usdm/blob/main/docs/sheets.png	
JSON Comparison	https://www.textcompare.org/json/	Useful to see changes in the resulting JSON outputs

Example Protocol

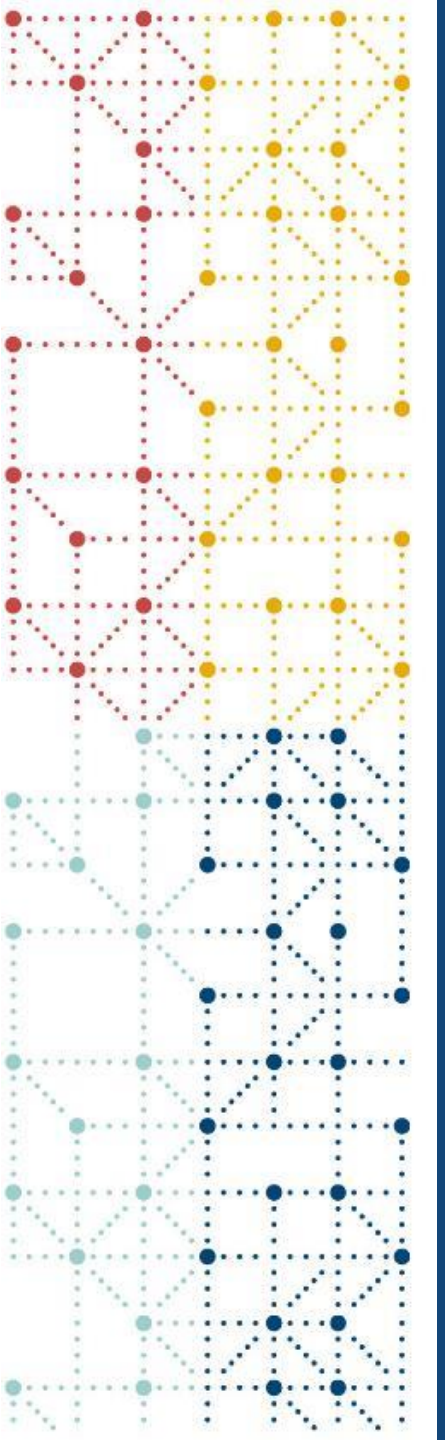
- We will use the CDISC Pilot Study Protocol for the workshop
- This was donated by Eli Lilly many years ago
- It has served CDISC well
- Download from here
  - https://github.com/cdisc-org/DDF-RA/blob/main/Documents/Examples/CDISC_Pilot/CDISC_Pilot_Study.pdf



Presentations During EU Connect

Tuesday 7 November

Time (GMT)	Hall 6a	Hall 7	Hall 9	Hall 10A
06:30	**PHUSE 5k Run Around Birmingham – Meet Outside the ICC** *All abilities welcome*			
09:00 - 10:30	**Keynote Speaker – Gareth Thomas** | Plenary Room – Hall 1			
10:30–11:00	**Morning Break**			
11:00–11:30	**TT06: Red Pill or Blue Pill? Assessing the Impact of Artificial Intelligence on Pharmaceutical Programming** *Katalyze Data*	**PM04: Navigating Unprecedented Challenges: Journey Through a Pandemic and International Conflict** *Veramed*	**Panel Discussion** Let's Discuss Open Source Openly: A New Path in Pharma	**Connect Theme Presentations (DS)** Digital Data Flow – From Vision to Reality
11:30–12:00	**TT14: Automation and Orchestration of Data Science Applications Using OpenAPI** *Entimo*	**PM05: An Agile Approach to Onboarding** *GSK*		**DS01: ICH M11 Clinical Electronic Structured Harmonized Protocol (CeSHarP) and CDISC: Making the Electronic Protocol a Reality** *CDISC*
12:00–12:30	**TT16: Taking Down the Fence Between Biostatistics and Medical Writing** *GSK*	**PM06: Statistical Programming – Hiring Mission Made Possible** *Johnson & Johnson*		**DS02: The TransCelerate/CDISC Digital Data Flow Project: Practical Electronic Study Designs** *data4knowledge & CDISC* **DS03: The Digital Protocol Is Just the Beginning. Or Is It?** *Instem*



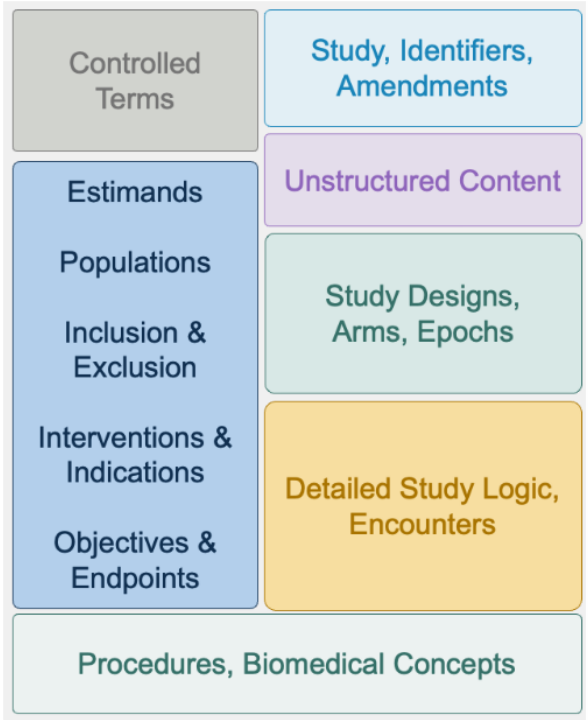
Model Overview

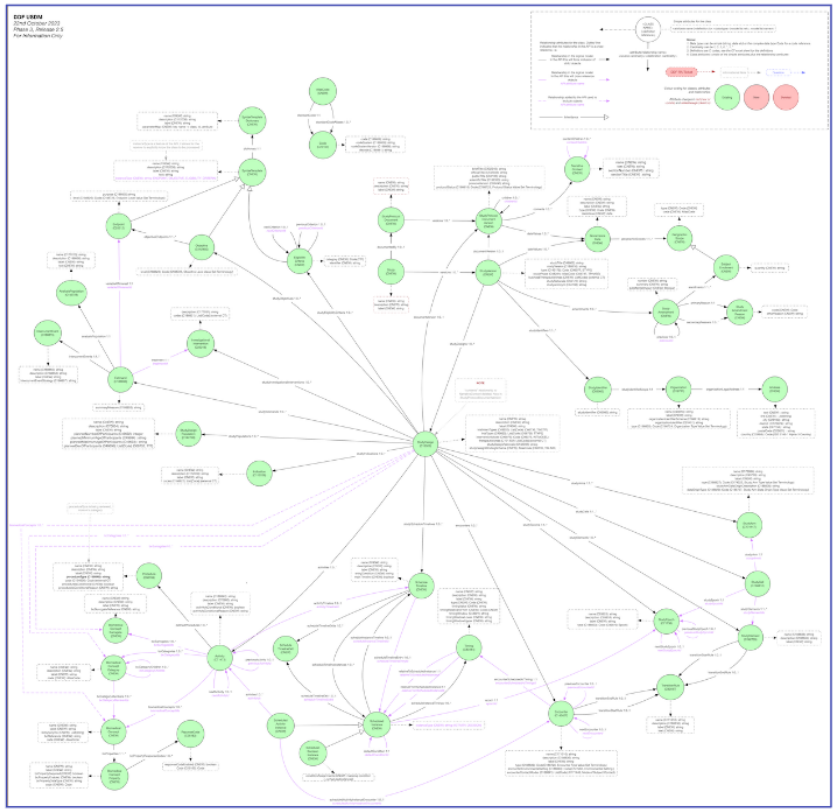
Model Overview

Overview

Main Areas

- Study
  - Study Versions
  - Document Versions
  - Study Identifiers
  - Amendments
- Study Design
  - Arms, Epochs ...
  - Study Logic and Timing
  - Biomedical Concepts
  - Populations (Cohorts coming)
  - Objectives & Endpoints
  - Inclusion / Exclusion
  - Estimands
  - Interventions
  - Indications
- Utility
  - CT References



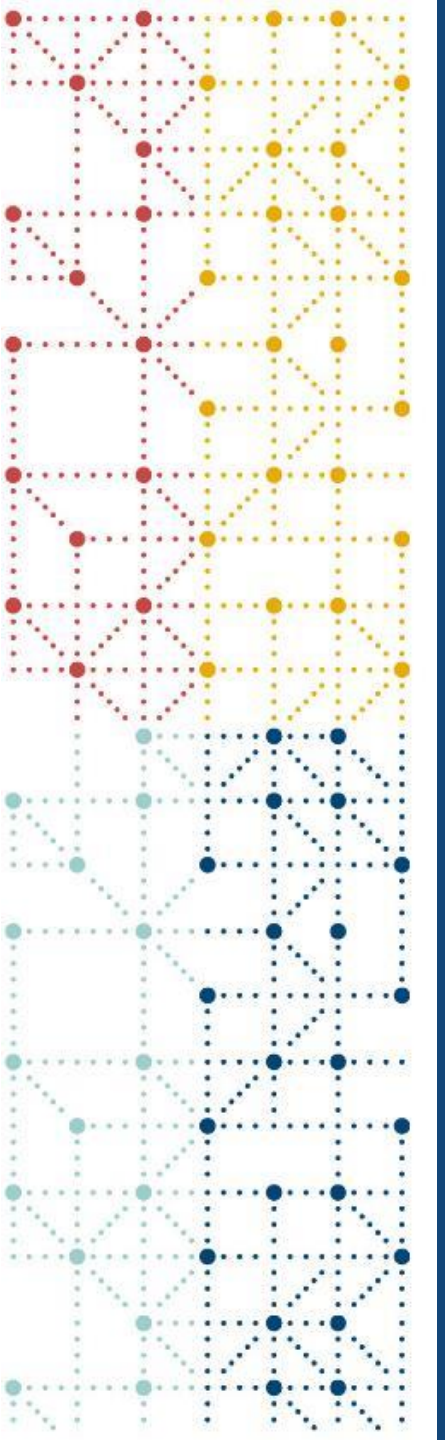


"Green Blob" Diagram

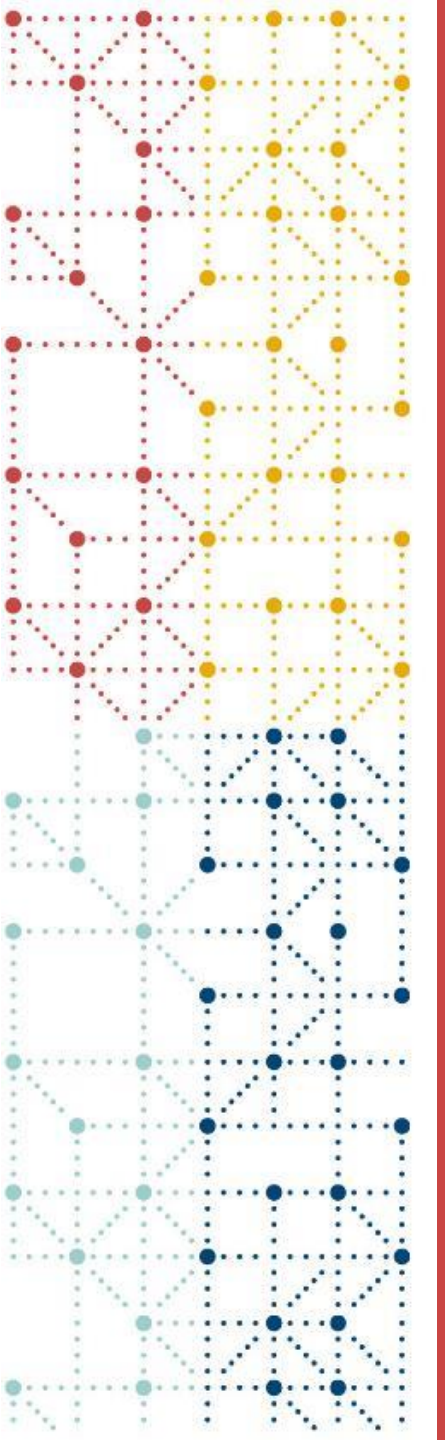
- **Informative. The UML is the Normative form**
- Informative view of the model
- Used to discuss ideas before putting into normative UML
- Used as a cross-check of normative deliverables at end of sprints

Page from the Miro Board

Link on the wiki along with password
https://miro.com/app/board/uXjVPl5X2AY=/



Focus Areas



Inclusion / Exclusion

Inclusion / Exclusion

- Model Class EligibilityCriteria
- Inherits SyntaxTemplates class
- References to structured elements stored elsewhere in the data model like:
  - Population characteristics
  - Activities
  - …

3.4.2.1. Inclusion Criteria

Patients may be included in the study only if they meet **all** the following criteria:

[1] Males and postmenopausal females at least 50 years of age.

[2] Diagnosis of probable AD as defined by National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) guidelines (Attachment LZZT.7).

[3] MMSE score of 10 to 23.

[4] Hachinski Ischemic Scale score of ≤4 (Attachment LZZT.8).

[5] CNS imaging (CT scan or MRI of brain) compatible with AD within past 1 year.

	A	B	C	D	E	F	G
1	**category**	**identifier**	**name**	**description**	**label**	**text**	**dictionary**
2	Inclusion	01	Age Criteria	The study age criterion		Males and postmenopausal females at least of [min_age] of age	IE_Dict
3	Inclusion	02	Pop Criteria	The study population criterion		[StudyPopulation] as defined by the NINCDS and the ADRDA guidelines (Attachment LZZT.7)	IE_Dict
4	Inclusion	03	Diag Criteria	The study diagnosis criterion		[Activity1] score of 10 to 23	AS_Dict
5							
6							

studyIdentifiers | studyDesign | studyDesignEligibilityCriteria | studyDesignArms | studyDesi…

Ready | Accessibility: Good to go | Display Settings | 105%

Inclusion / Exclusion

Sample Excel:

	A	B	C	D	E	F	G
1	**name**	**description**	**label**	**key**	**class**	**xref**	**attribute**
2	IE_Dict	Dictionary for IE	IE Dictionary	min_age	StudyDesignPopulation	POP1	plannedMinimumAgeOfParticipants
3				max_age	StudyDesignPopulation	POP1	plannedMaximumAgeOfParticipants
4				StudyPopulation	StudyDesignPopulation	POP1	populationDescription
5	AS_Dict	Dictionary for Study Assessments	Assessment Dictionary	Activity1	Activity	MMSE	label
6							
7							

studyDesignElements | dictionaries | studyDesignContent | configuration

	A	B	C	D	E	F	G
1	**category**	**identifier**	**name**	**description**	**label**	**text**	**dictionary**
2	Inclusion	01	Age Criteria	The study age criterion		Males and postmenopausal females at least of [min_age] of age	IE_Dict
3	Inclusion	02	Pop Criteria	The study population criterion		[StudyPopulation] as defined by the NINCDS and the ADRDA guidelines (Attachment LZZT.7)	IE_Dict
4	Inclusion	03	Diag Criteria	The study diagnosis criterion		[Activity1] score of 10 to 23	AS_Dict
5							
6							

studyIdentifiers | studyDesign | studyDesignEligibilityCriteria | studyDesignArms | studyDesi

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Inclusion / Exclusion

json


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    "label": "",
    "description": "The study age criterion",
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      "codeSystem": "http://www.cdisc.org",
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    "nextCriterionId": null,
    "previousCriterionId": null
  }
],
```



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      "max_age": {
        "klass": "StudyDesignPopulation",
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        "attribute": "plannedMaximumAgeOfParticipants"
      }
    }
  }
```
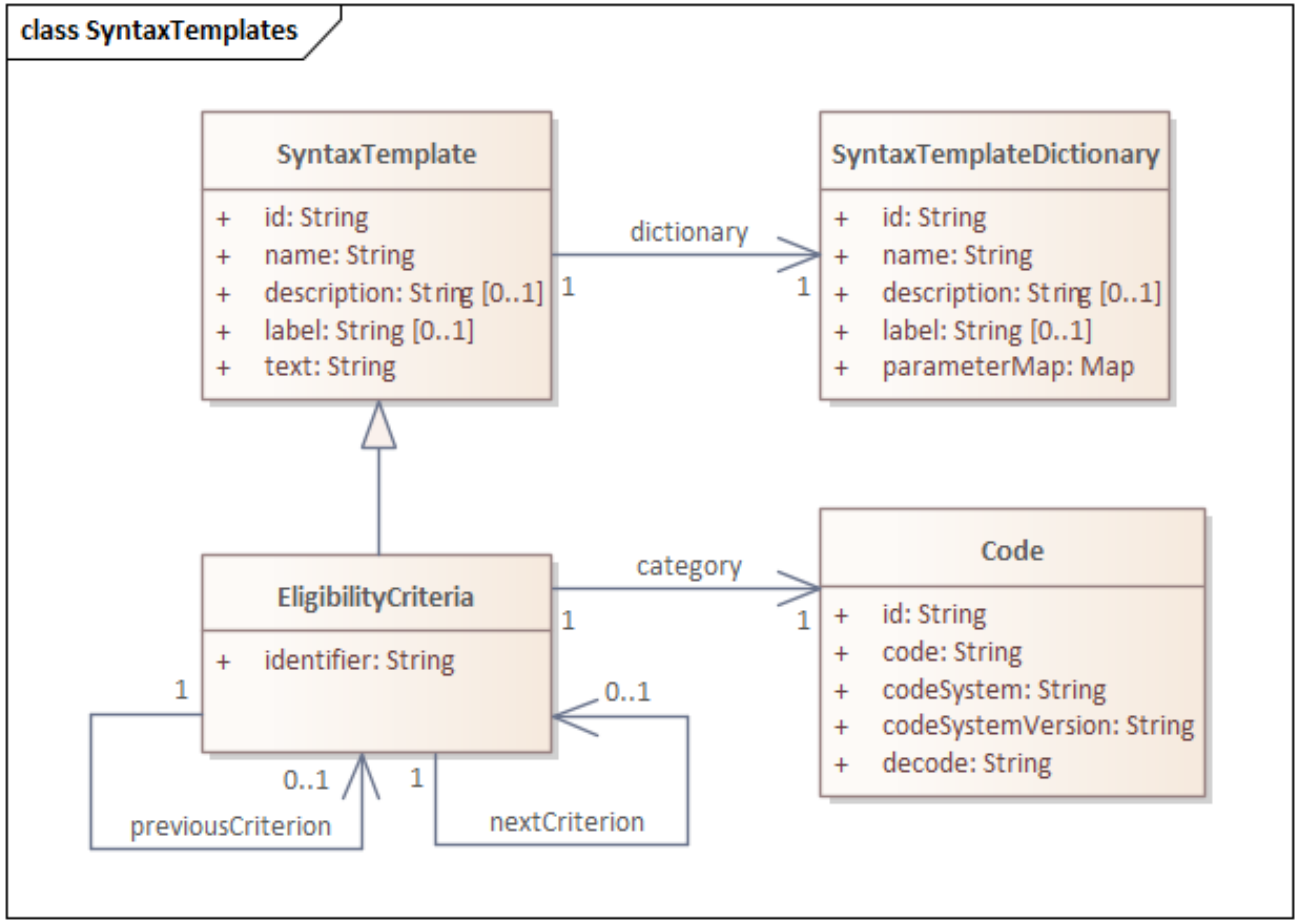
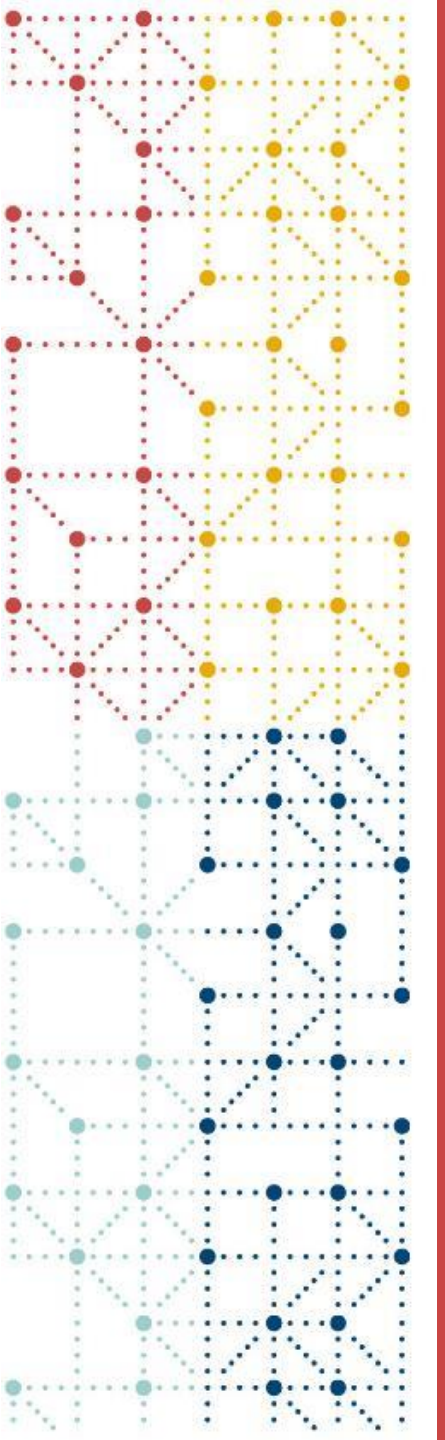


uml





Timelines

LZZT - Schedule of Activities

Protocol Attachment LZZT.1
Schedule of Events for Protocol H2Q-MC-LZZT(c)

	VISIT	1	2	3	4	5		7	8
ACTIVITY	WEEK	-2	-3	0	2	4		6	8
Informed consent		X							
Patient number assigned		X							
Hachinski ≤4		X							
MMSE 10-23		X							
Physical examination		X							
Medical History		X							
Habits		X							
Chest x-ray		X							
Apo E genotyping					X				
Patient randomized				X					
Vital signs/Temperature		X	X	X	X	X		X	X
Ambulatory ECG placed			X						
Ambulatory ECG removed				X					
ECG		X			X	X		X	X
Placebo TTS test		X							
CT Scan (if not within last year and patient passes all other screens)		X							
Concomitant Medications		X		X	X	X		X	X
Laboratory (Chem/Hemat):		X			X	X		X	X
Laboratory (Urinalysis)		X			X				
Plasma Specimen (Xanomeline)				X	X	X		X	
Hemoglobin A_{1C}		X[a]							
Study drug record Medications dispensed Medications returned				X	X	X		X	X
TTS Acceptability Survey									
ADAS-Cog		P		X					X
CIBIC+		P		X					X
DAD		P		X					X
NPI-X		P		X	X	X		X	X[b]
Adverse events		X	X	X	X	X		X	X

Abbreviations: CT = computed tomography; ECG = electrocardiogram
X = Performed at this visit.
X[a] = Performed at this visit if patient is an insulin-dependent diabetic.
X[b] = Performed at this visit and via telephone interview 2 weeks following this visit.
P = Practice only - It is recommended that a sampling of the CIBIC+, ADAS-Cog, DAD, and NPI-X be administered at Visit 1. Data from this sampling would not be considered as study data and would not be collected.

Schedule of Events for Protocol H2Q-MC-LZZT(c) (concluded)

	VISIT	9	10	11	12	13	ET	RT
ACTIVITY	WEEK	12	16	20	24	26		
Informed consent								
Patient number assigned								
Hachinski ≤4								
MMSE 10-23								
Physical examination						X	X	
Medical History								
Habits								
Chest x-ray								
Apo E genotyping								
Patient randomized								
Vital signs/Temperature		X	X	X	X	X	X	X
Ambulatory ECG placed								
Ambulatory ECG removed								
ECG		X	X	X	X	X	X	
Placebo TTS test								
CT Scan (if not within last year and patient passes all other screens)								
Concomitant Medications		X	X	X	X	X	X	X
Laboratory (Chem/Hemat):		X	X	X	X	X	X	
Laboratory (Urinalysis)		X			X		X	
Plasma Specimen (Xanomeline)		X		X			X	
Hemoglobin A_{1c}								
Study drug record Medications dispensed Medications returned		X	X	X	X	X	X	
TTS Acceptability Survey						X	X	
ADAS-Cog			X		X		X	X
CIBIC+			X		X		X	X
DAD			X		X		X	X
NPI-X		X[b]	X[b]	X[b]	X	X	X	X
Adverse events		X	X	X	X	X	X	X

Abbreviations: CT = computed tomography; ECG = electrocardiogram; ET = Early Termination; RT = Retrieval
X = Performed at this visit.
X[b] = Performed at this visit and via telephone interview 2 weeks following this visit.

Timeline

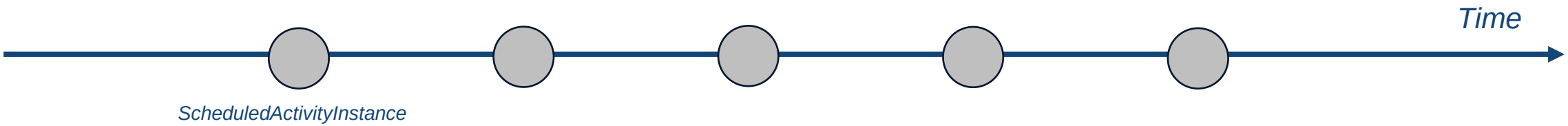
Timeline - SoA

Time

Small excerpt from LZZT, for purposes of explanation

	VISIT	1	2	3	4	5
ACTIVITY	WEEK	-2	-.3	0	2	4
Informed consent		X				
Patient number assigned		X				

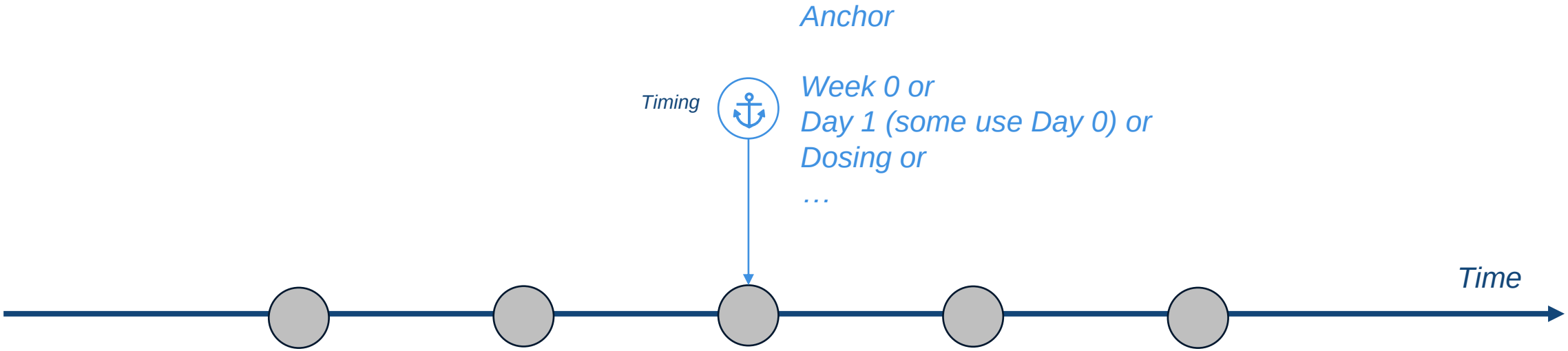
Timeline - Timepoints



ScheduledActivityInstance

	VISIT	1	2	3	4	5
ACTIVITY	WEEK	-2	-.3	0	2	4
Informed consent		X				
Patient number assigned		X				

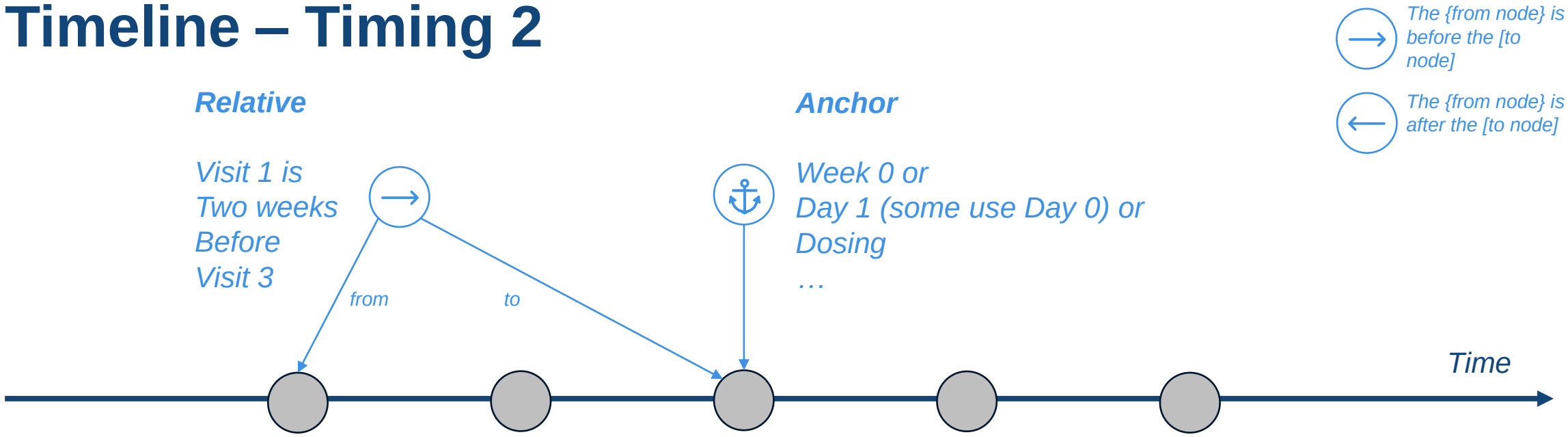
Timeline – Timing I



Anchor

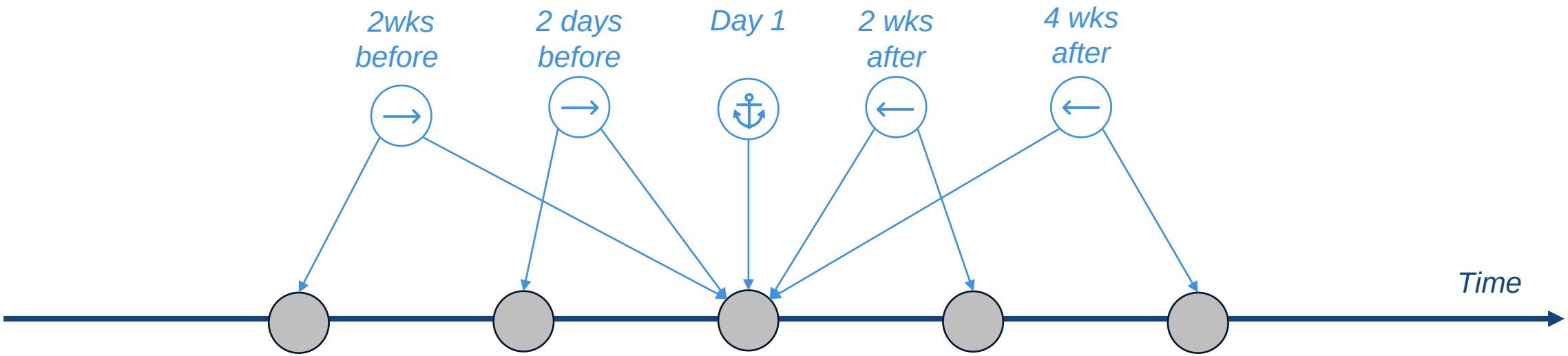
	VISIT	1	2	3	4	5
ACTIVITY	WEEK	-2	-.3	0	2	4
Informed consent		X				
Patient number assigned		X				

Timeline – Timing 2



		Relative		Anchor		
	VISIT	1	2	3	4	5
ACTIVITY	WEEK	-2	-.3	0	2	4
Informed consent		X				
Patient number assigned		X				

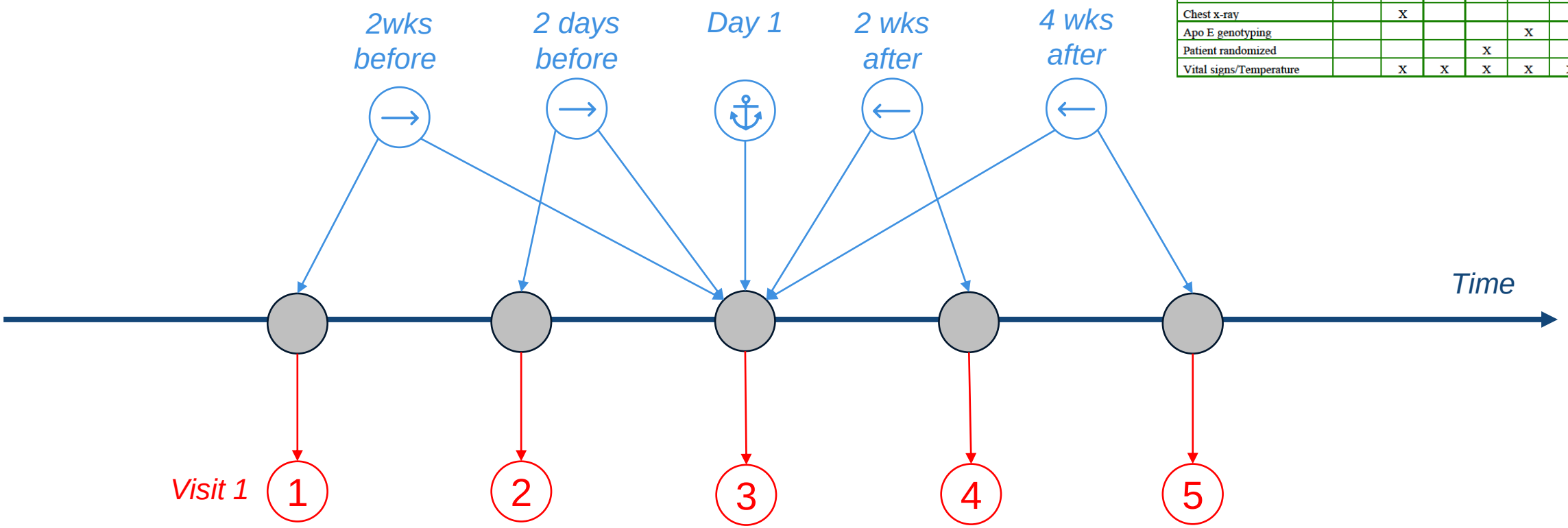
Timeline – Timing 3



	VISIT	1	2	3	4	5
ACTIVITY	WEEK	-2	-.3	0	2	4
Informed consent		X				
Patient number assigned		X				

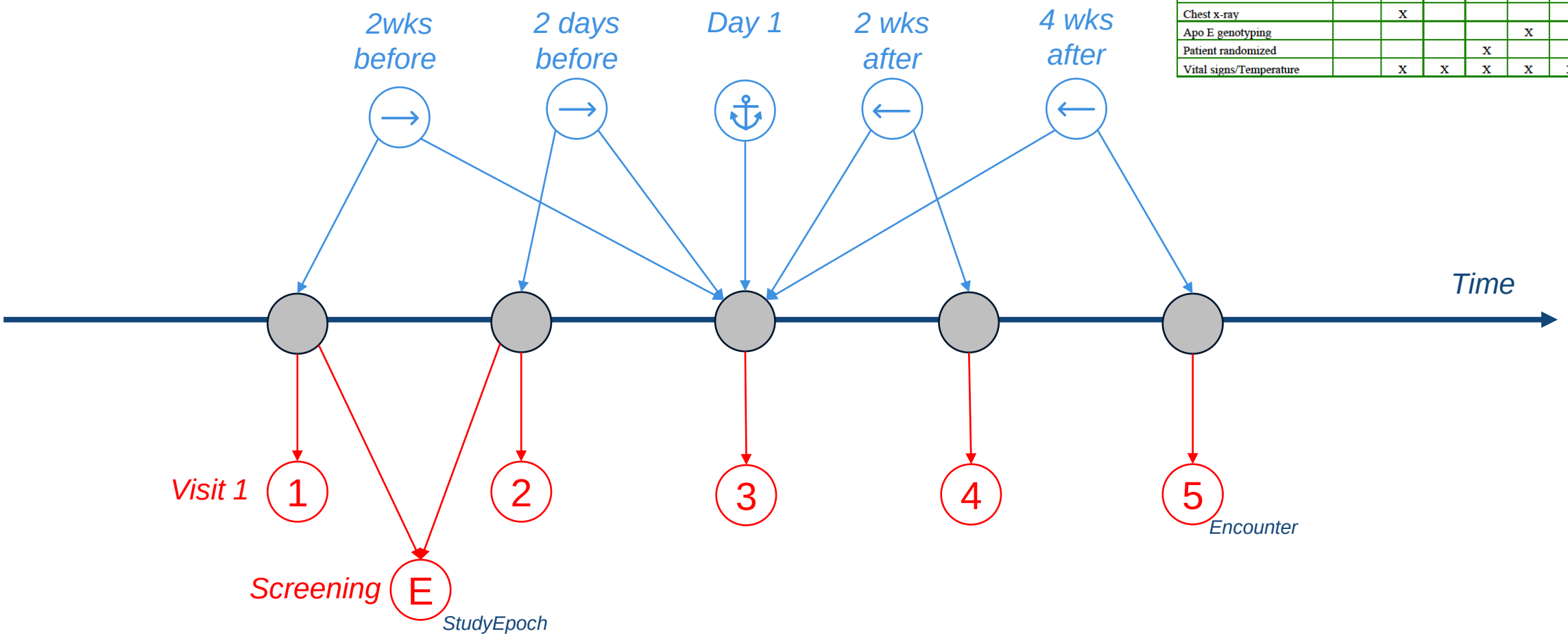
Timeline – Encounters (Visits)

	VISIT	1	2	3	4	5
ACTIVITY	WEEK	-2	-.3	0	2	4
Informed consent		X				
Patient number assigned		X				
Hachinski ≤4		X				
MMSE 10-23		X				
Physical examination		X				
Medical History		X				
Habits		X				
Chest x-ray		X				
Apo E genotyping					X	
Patient randomized				X		
Vital signs/Temperature		X	X	X	X	X



Timeline – Epochs

	VISIT	1	2	3	4	5
ACTIVITY	WEEK	-2	-.3	0	2	4
Informed consent		X				
Patient number assigned		X				
Hachinski ≤4		X				
MMSE 10-23		X				
Physical examination		X				
Medical History		X				
Habits		X				
Chest x-ray		X				
Apo E genotyping					X	
Patient randomized				X		
Vital signs/Temperature		X	X	X	X	X

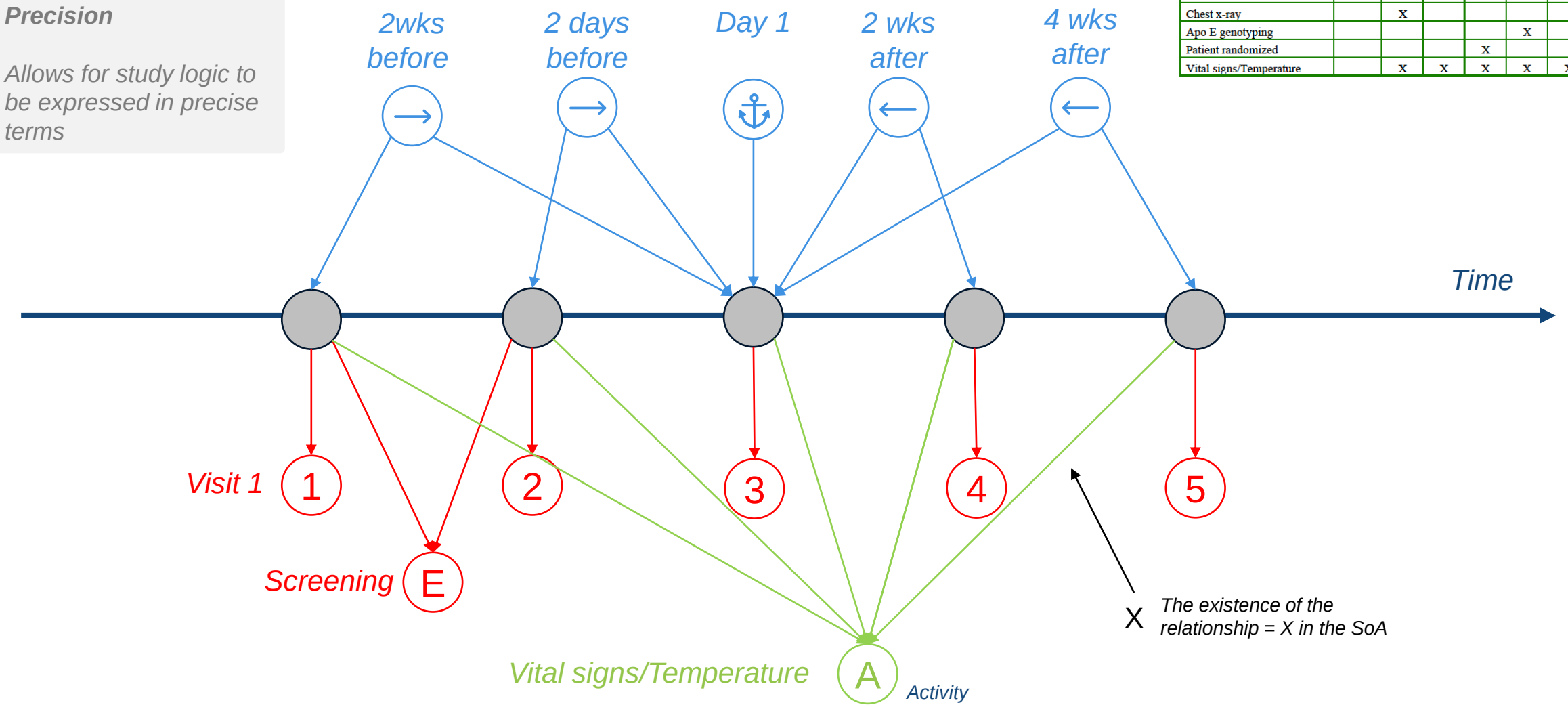


Timeline – Activities

	VISIT	1	2	3	4	5
ACTIVITY	WEEK	-2	-.3	0	2	4
Informed consent		X				
Patient number assigned		X				
Hachinski ≤4		X				
MMSE 10-23		X				
Physical examination		X				
Medical History		X				
Habits		X				
Chest x-ray		X				
Apo E genotyping					X	
Patient randomized				X		
Vital signs/Temperature		X	X	X	X	X

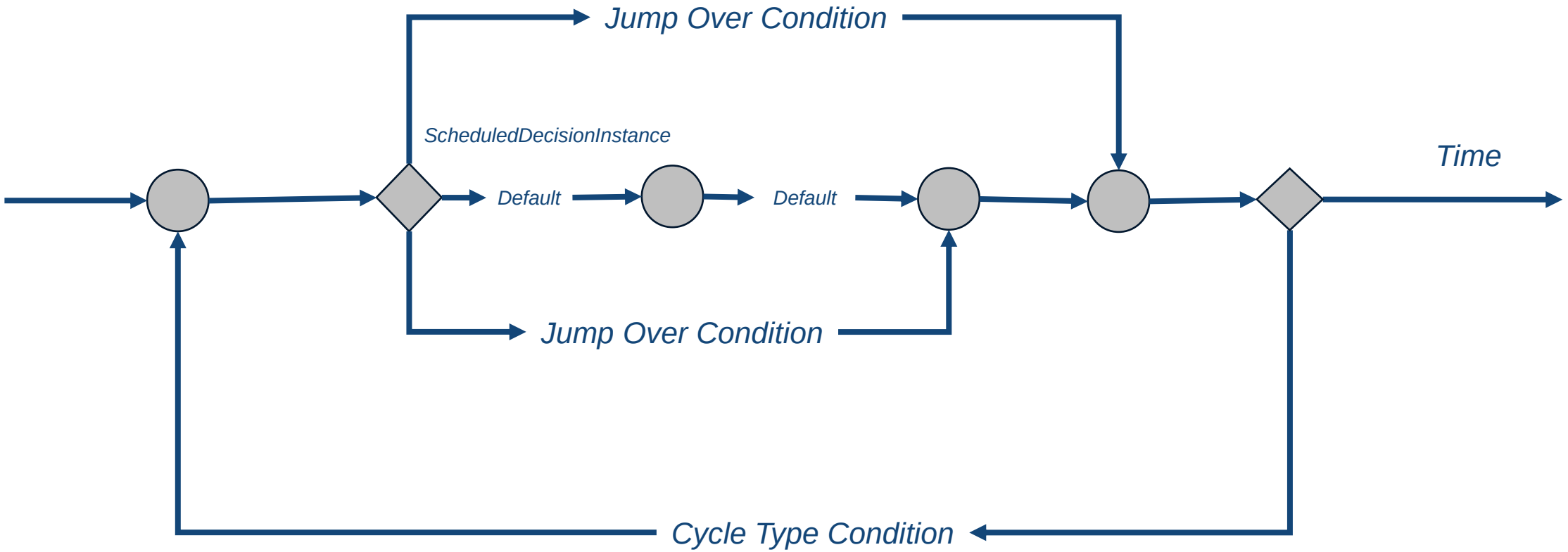
Precision

Allows for study logic to be expressed in precise terms

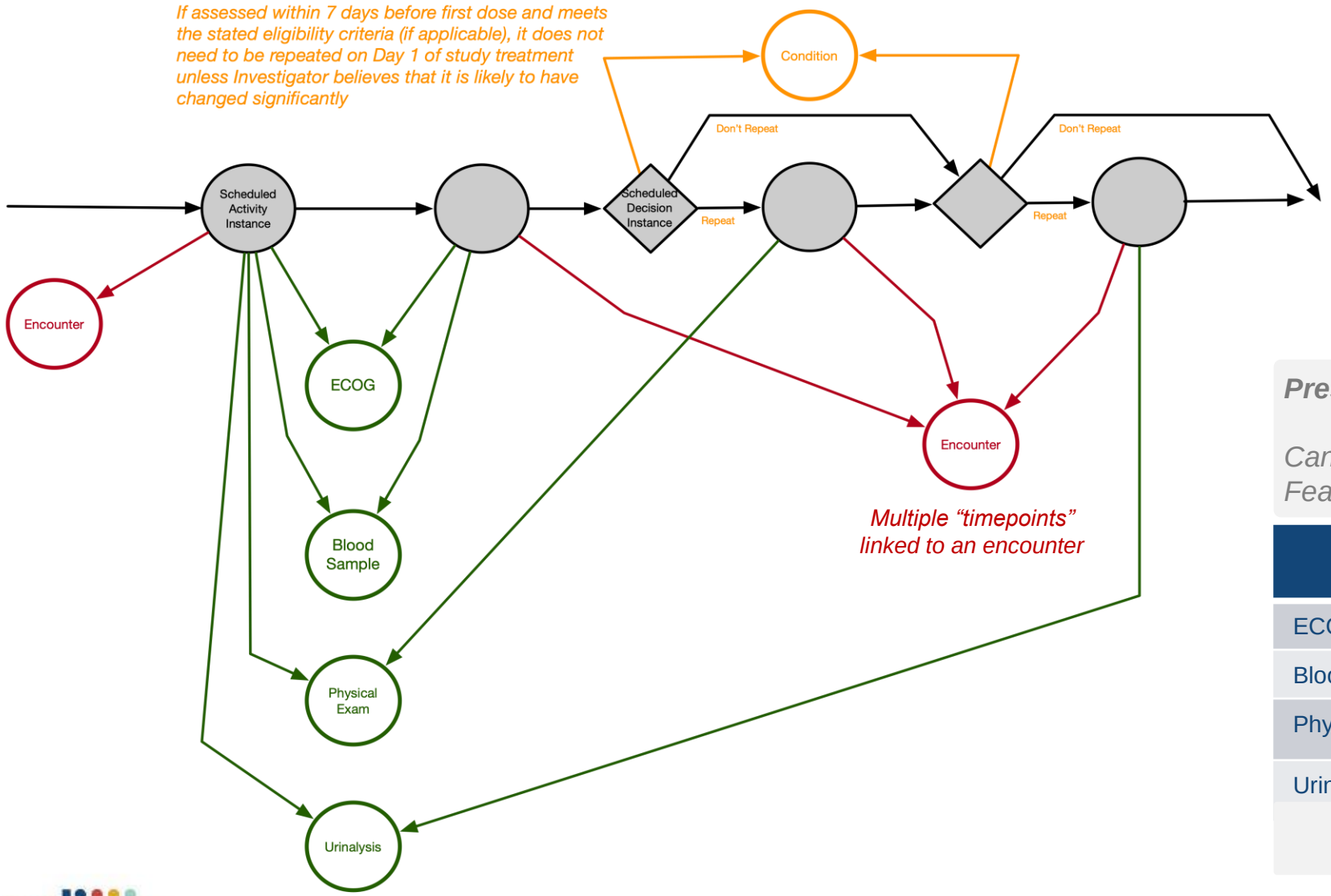


Vital signs/Temperature		X	X	X	X	X

Timeline – Decision



Timelines - Conditions



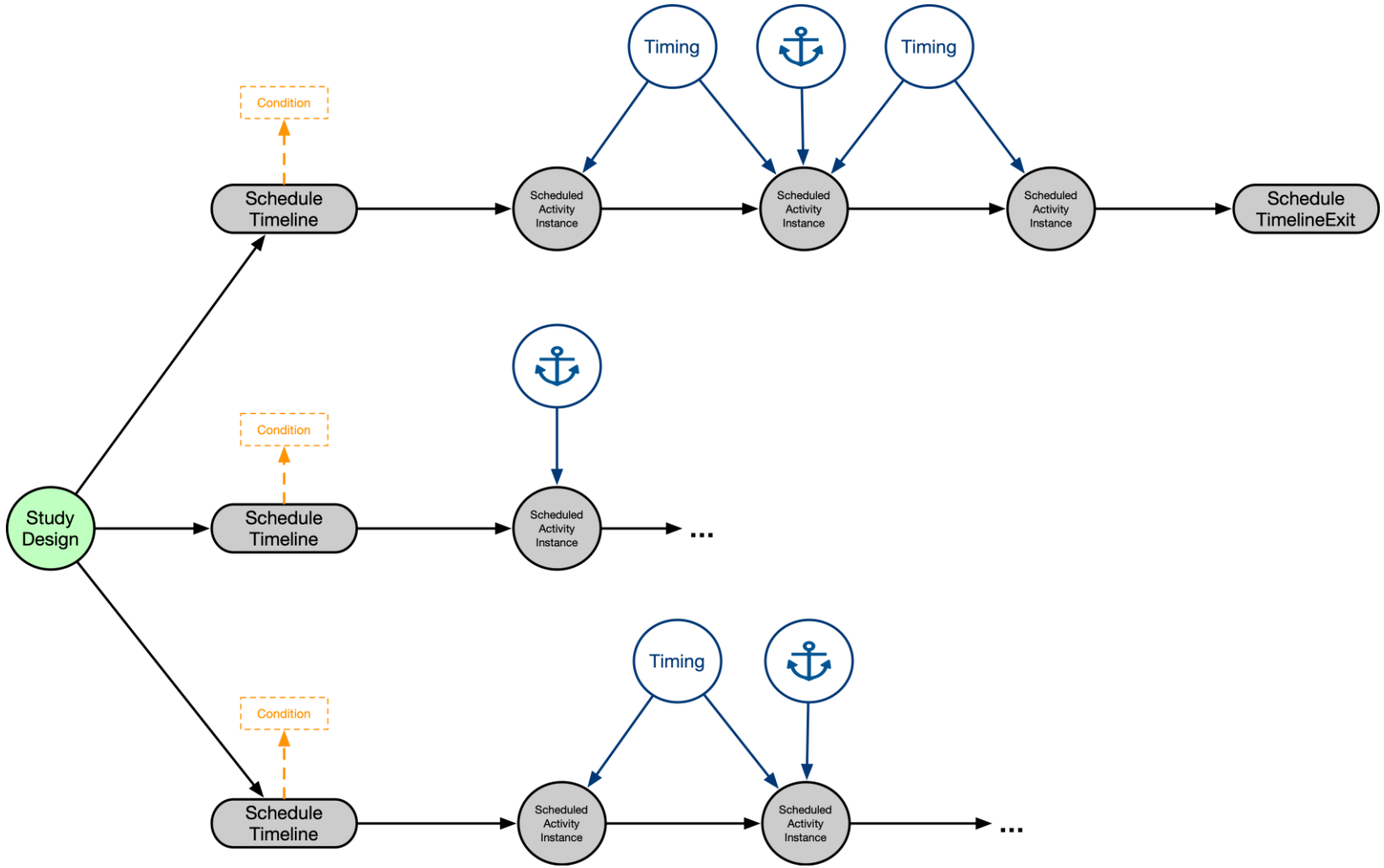
Presentation

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

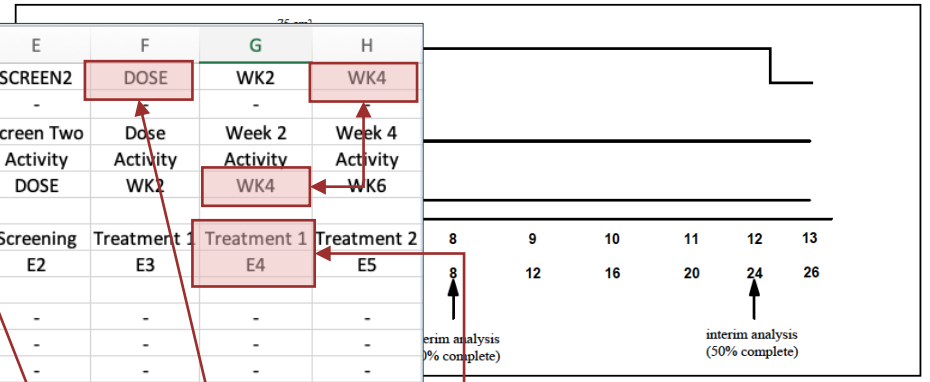
Timeline – Sub timelines



Timeline – LZZT Excel

	A	B	C	D	E	F	G	H
1	**Name**	Main Timeline	**name**	SCREEN1	SCREEN2	DOSE	WK2	WK4
2	**Description**	This is the main timeline for the study design.	**description**		-		-	
3	**Condition**	Potential subject identified	**label**	Screen One	Screen Two	Dose	Week 2	Week 4
4			**type**	Activity	Activity	Activity	Activity	Activity
5			**default**	SCREEN2	DOSE	WK2	WK4	WK6
6			**condition**					
7			**epoch**	Screening	Screening	Treatment 1	Treatment 1	Treatment 2
8			**encounter**	E1	E2	E3	E4	E5
9	**Parent Activity**	**Child Activity**	**BC/Procedure/Timeline**					
10		Informed consent		X	-	-	-	-
11		Inclusion/exclusion criteria		X	-	-	-	-
12		Patient number assigned		X	-	-	-	-
13		Demographics	BC:Date of Birth, BC:Sex, BC:Race	X	-	-	-	-
14		Hachinski <= 4		X	-	-	-	-
15		MMSE 10-23		X	-	-	-	-
16		Physical examination		X	-	-	-	-
17		Medical history		X	-	-	-	-
18		Habits		X	-	-	-	-
19		Chest X-ray		X	-	-	-	-
20		Apo E genotyping		-	-	-	X	-
21		Patient randomised		-	-	X	-	-
22		Vital signs / Temperature	BC:Systolic blood pressure, BC:Diastolic blood	X	X	X	X	X

Visits 1 through 13 should be scheduled relative to Visit 3 (Week 0 - randomization). Visits 4, 5, 7, 8, and 13 should occur within 3 days of their scheduled date. Visits 9, 10, 11, and 12 should occur within 4 days of their scheduled date. At Visit 13 patients will be given the option to enter the open-label extension phase (see Section 3.10.3. Study Extensions).

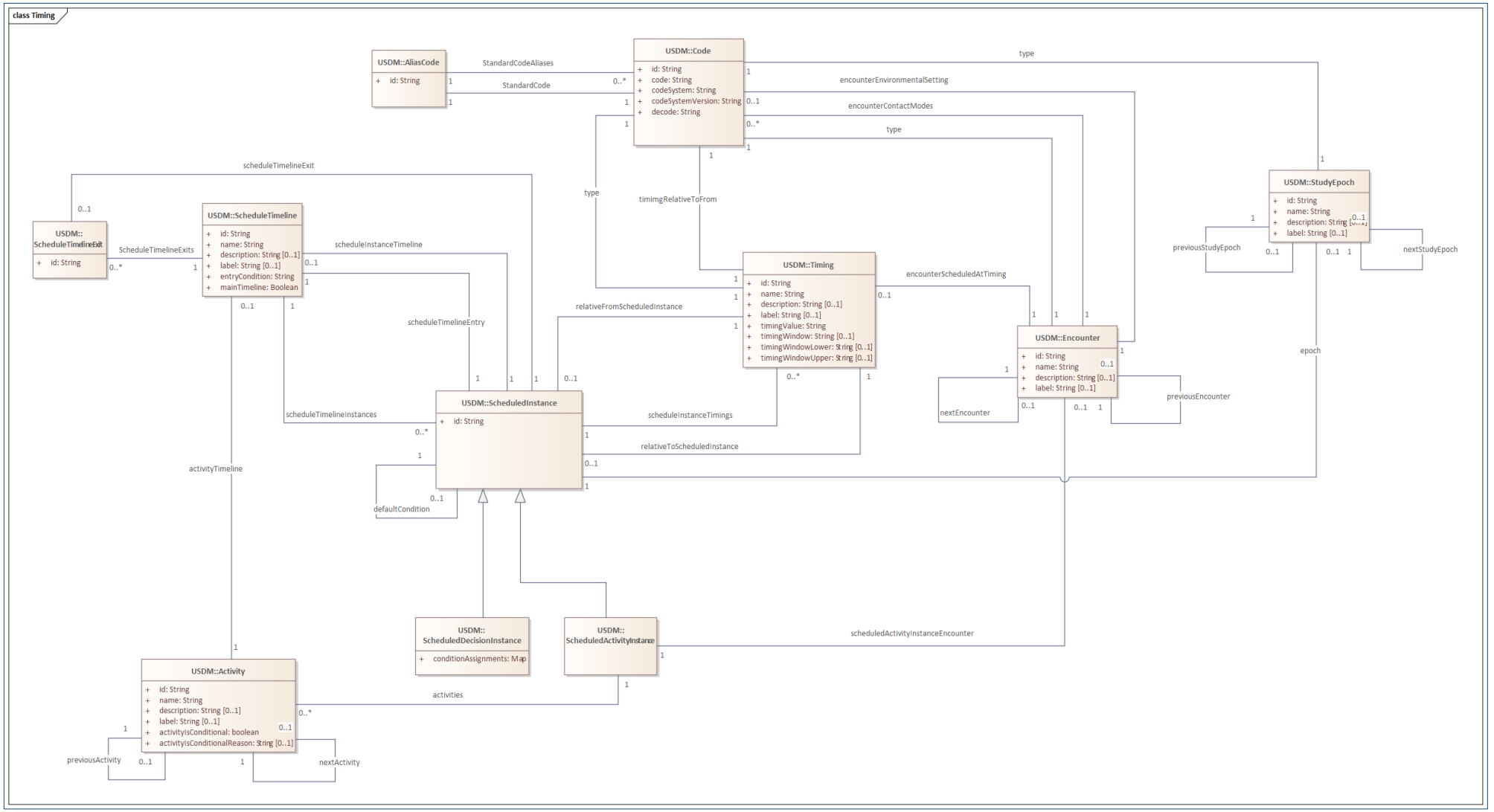


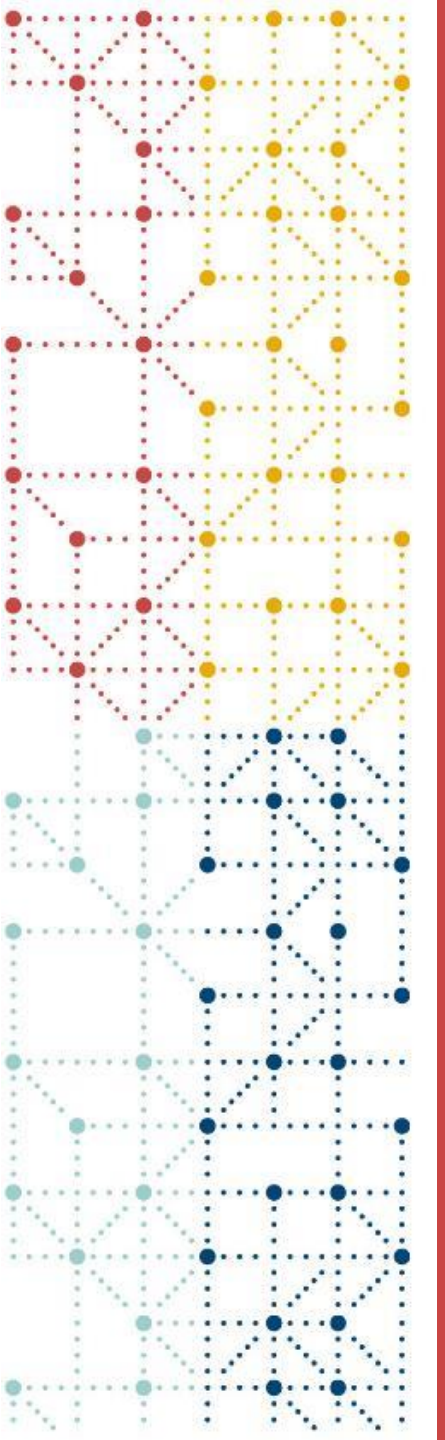
y design for Protocol H2Q-MC-LZZT(c).

Epochs & Encounters

	A	B	C	D	E	F	G	H	I
1	**name**	**description**	**label**	**type**	**from**	**to**	**timingValue**	**toFrom**	**window**
2	TIM1	Screening timing	Screening	BEFORE	SCREEN1	DOSE	2 weeks	S2S	
3	TIM2	Pre dose timing	Pre dose	BEFORE	SCREEN2	DOSE	2 days	S2S	-4..0 hours
4	TIM3	Dosing anchor	Dosing	FIXED	DOSE	DOSE	1 Day		
5	TIM4	Week 2 timing	Week 2	AFTER	WK2	DOSE	2 Weeks	S2S	-3..3 days
6	TIM5	Week 4 timing	Week 4	AFTER	WK4	DOSE	4 Weeks	S2S	-3..3 days
7	TIM6	Week 6 timing	Week 6	AFTER	WK6	DOSE	6 Weeks	S2S	-3..3 days
8	TIM7	Week 8 timing	Week 8	AFTER	WK8	DOSE	8 Weeks	S2S	-3..3 days
9	TIM8	Week 8 at home timing	Week 8 Home	AFTER	WK8N	WK8	2 Weeks	S2S	
10	TIM9	Week 12 timing	Week 12	AFTER	WK12	DOSE	12 Weeks	S2S	-4..4 days
11	TIM10	Week 12 at home timing	Week 12 Home	AFTER	WK12N	WK12	2 Weeks	S2S	
12	TIM11	Week 16 timing	Week 16	AFTER	WK16	DOSE	16 Weeks	S2S	-4..4 days
13	TIM12	Week 16 at home timing	Week 16 Home	AFTER	WK16N	WK16	2 Weeks	S2S	
14	TIM13	Week 20 timing	Week 20	AFTER	WK20	DOSE	20 Weeks	S2S	-4..4 days
15	TIM14	Week 20 at home timing	Week 20 Home	AFTER	WK20N	WK20	2 Weeks	S2S	
16	TIM15	Week 24 timing	Week 24	AFTER	WK24	DOSE	24 Weeks	S2S	-4..4 days
17	TIM16	Week 26 timing	Week 26	AFTER	WK26	DOSE	26 Weeks	S2S	-3..3 days
18	TIM17	Adverse Event	Adverse Event	FIXED	AE	AE	1 Day		
19	TIM18	Early Termination	Early Termination	FIXED	ET	ET	1 Day		

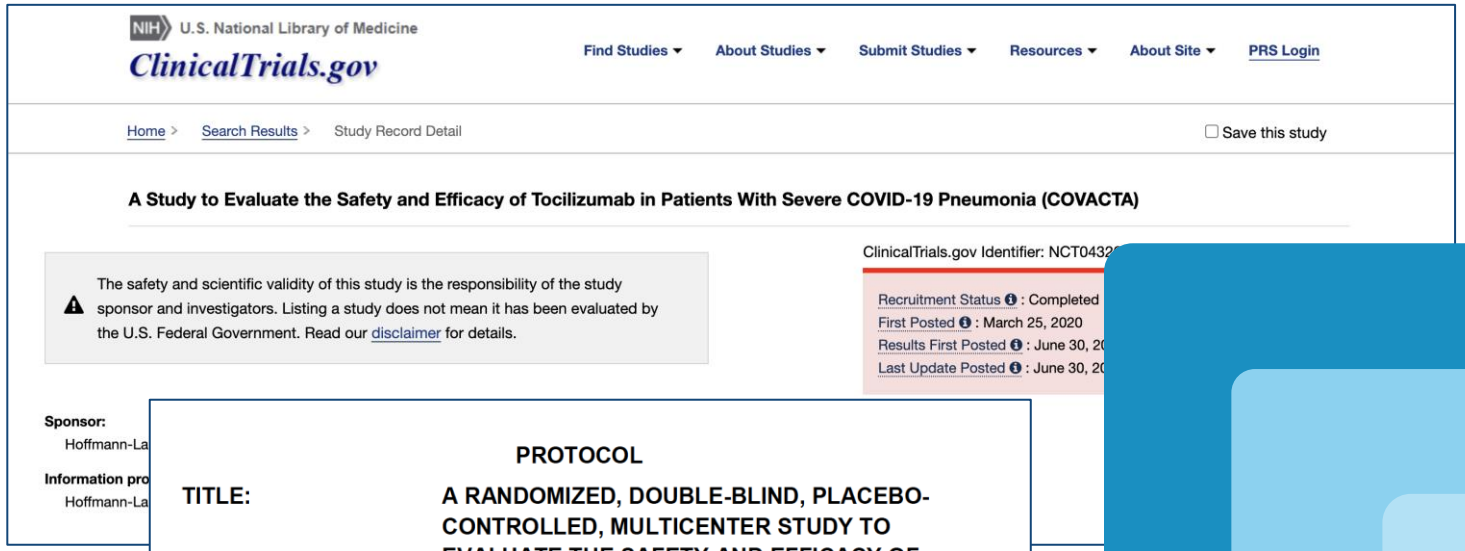
Timing – UML

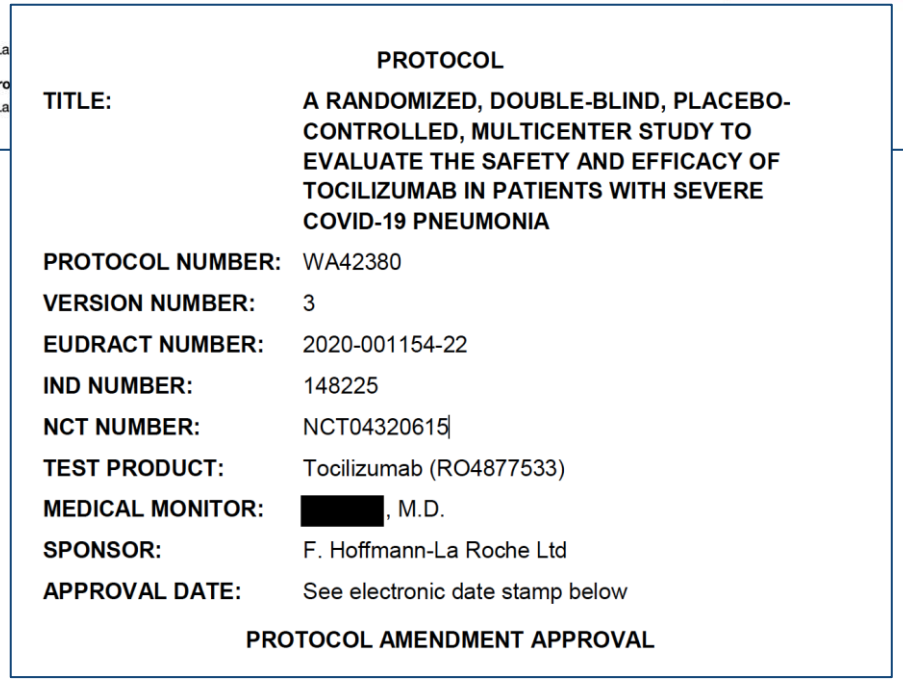

class Timing
USDM::AliasCode
+ id: String
StandardCodeAliases
StandardCode
USDM::Code
+ id: String
+ code: String
+ codeSystem: String
+ codeSystemVersion: String
+ decode: String
type
encounterEnvironmentalSetting
encounterContactModes
type
USDM::StudyEpoch
+ id: String
+ name: String
+ description: String [0..1]
+ label: String [0..1]
previousStudyEpoch
nextStudyEpoch
epoch
scheduleTimelineExit
USDM::ScheduleTimelineExit
+ id: String
ScheduleTimelineExits
USDM::ScheduleTimeline
+ id: String
+ name: String
+ description: String [0..1]
+ label: String [0..1]
+ entryCondition: String
+ mainTimeline: Boolean
scheduleInstanceTimeline
scheduleTimelineEntry
scheduleTimelineInstances
type
timimgRelativeToFrom
USDM::Timing
+ id: String
+ name: String
+ description: String [0..1]
+ label: String [0..1]
+ timingValue: String
+ timingWindow: String [0..1]
+ timingWindowLower: String [0..1]
+ timingWindowUpper: String [0..1]
encounterScheduledAtTiming
relativeFromScheduledInstance
USDM::Encounter
+ id: String
+ name: String
+ description: String [0..1]
+ label: String [0..1]
previousEncounter
nextEncounter
USDM::ScheduledInstance
+ id: String
scheduleInstanceTimings
relativeToScheduledInstance
activityTimeline
defaultCondition
USDM::ScheduledDecisionInstance
+ conditionAssignments: Map
USDM::ScheduledActivityInstance
scheduledActivityInstanceEncounter
USDM::Activity
+ id: String
+ name: String
+ description: String [0..1]
+ label: String [0..1]
+ activityIsConditional: boolean
+ activityIsConditionalReason: String [0..1]
activities
previousActivity
nextActivity



Biomedical Concepts

Biomedical Concepts


NIH U.S. National Library of Medicine
ClinicalTrials.gov
Find Studies | About Studies | Submit Studies | Resources | About Site | PRS Login
Home > Search Results > Study Record Detail
Save this study
A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA)
The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.
ClinicalTrials.gov Identifier: NCT0432
Recruitment Status : Completed
First Posted : March 25, 2020
Results First Posted : June 30, 2
Last Update Posted : June 30, 2
Sponsor:
Hoffmann-La
Information pro
Hoffmann-La

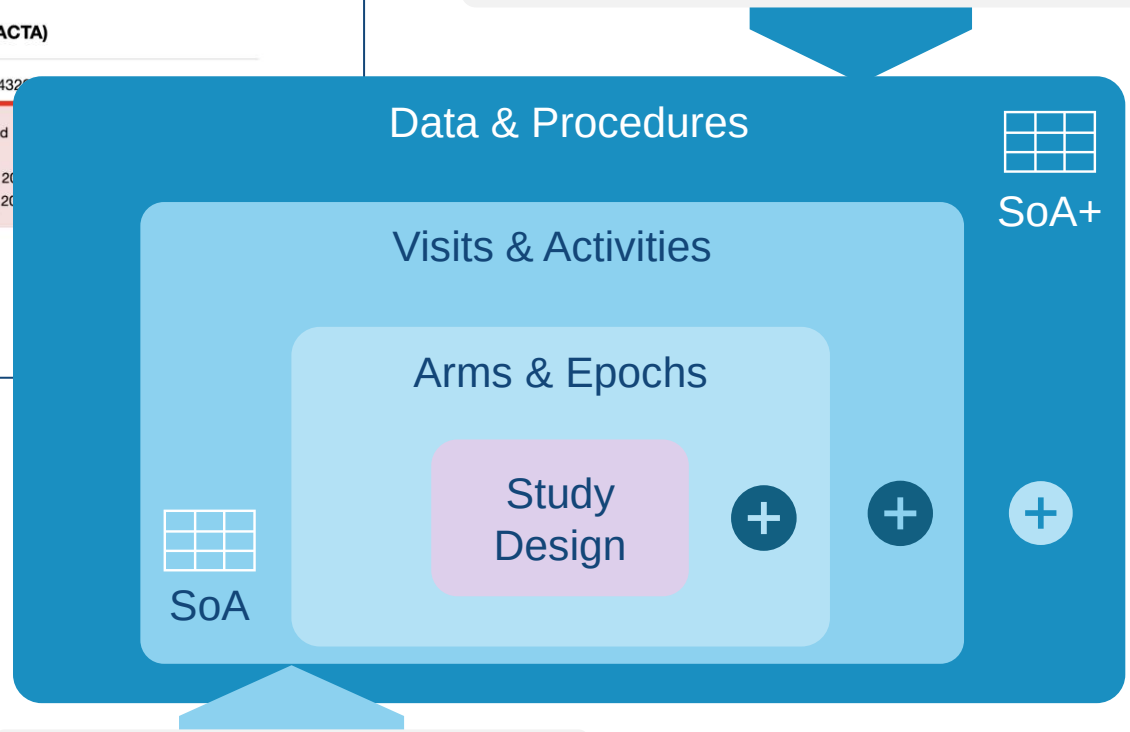

PROTOCOL

TITLE:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF TOCILIZUMAB IN PATIENTS WITH SEVERE COVID-19 PNEUMONIA
PROTOCOL NUMBER:	WA42380
VERSION NUMBER:	3
EUDRACT NUMBER:	2020-001154-22
IND NUMBER:	148225
NCT NUMBER:	NCT04320615
TEST PRODUCT:	Tocilizumab (RO4877533)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

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+



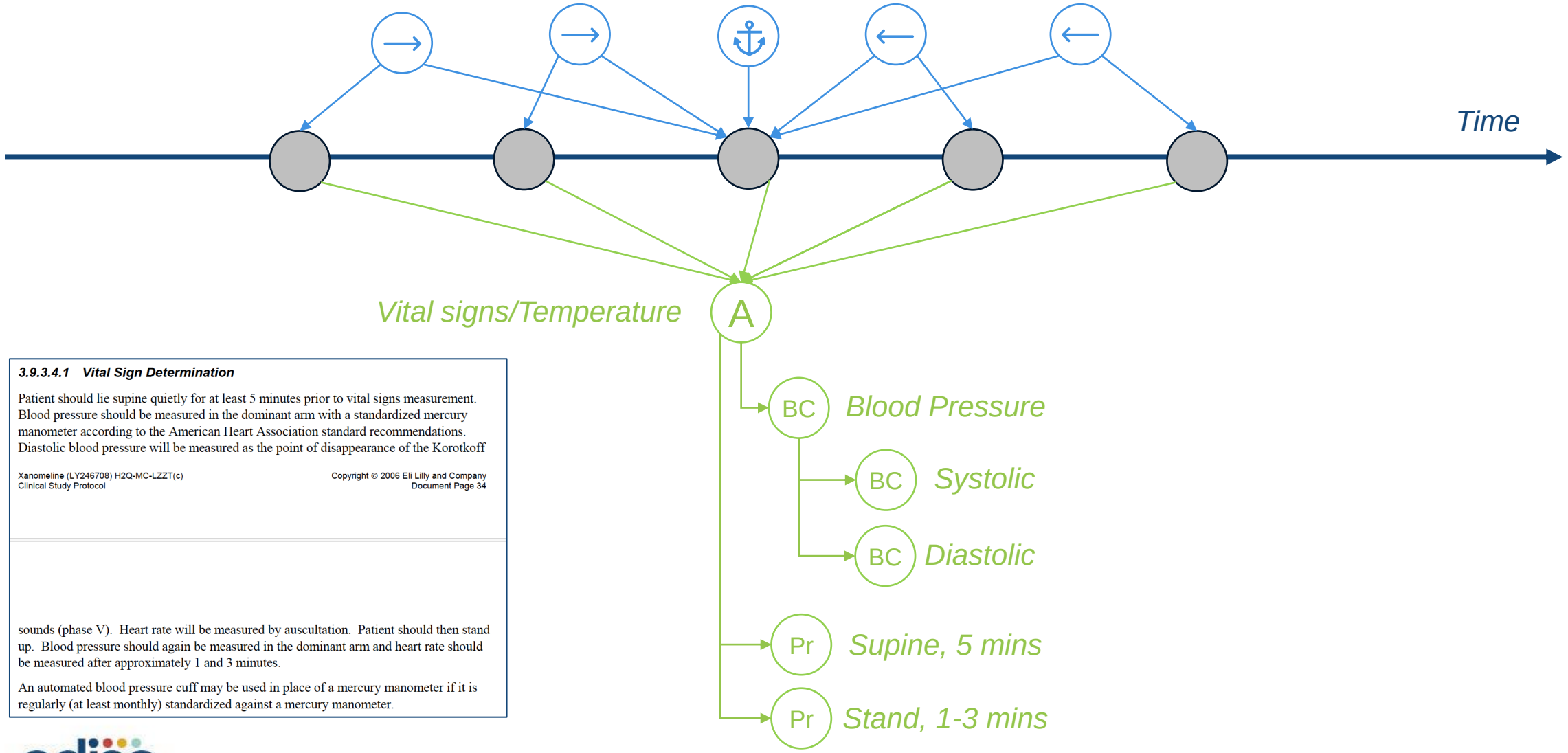
Current "Limit"

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

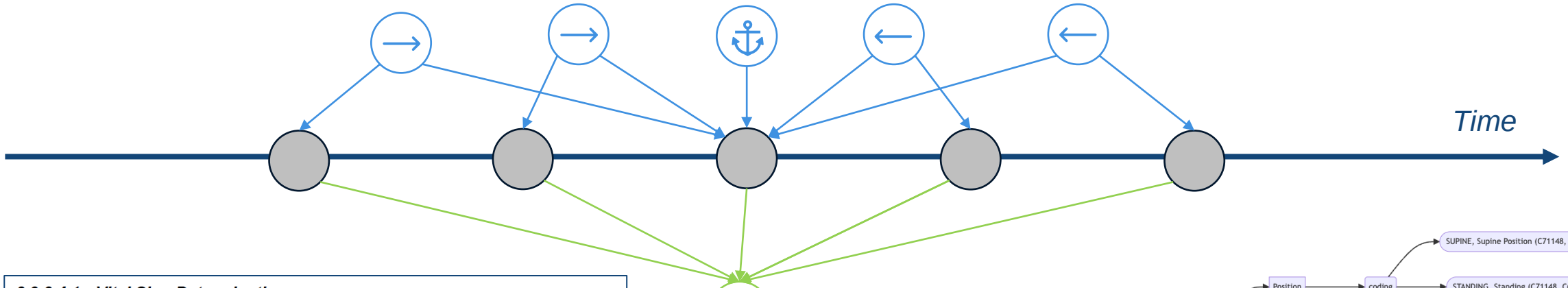
sounds (phase V). Heart rate will be measured by auscultation. Patient should then stand up. Blood pressure should again be measured in the dominant arm and heart rate should be measured after approximately 1 and 3 minutes.

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 – Precision

Precision

Allows for study logic to be expressed in precise terms



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Xanomeline (LY246708) H2Q-MC-LZZT(c)
Clinical Study Protocol

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Document Page 34

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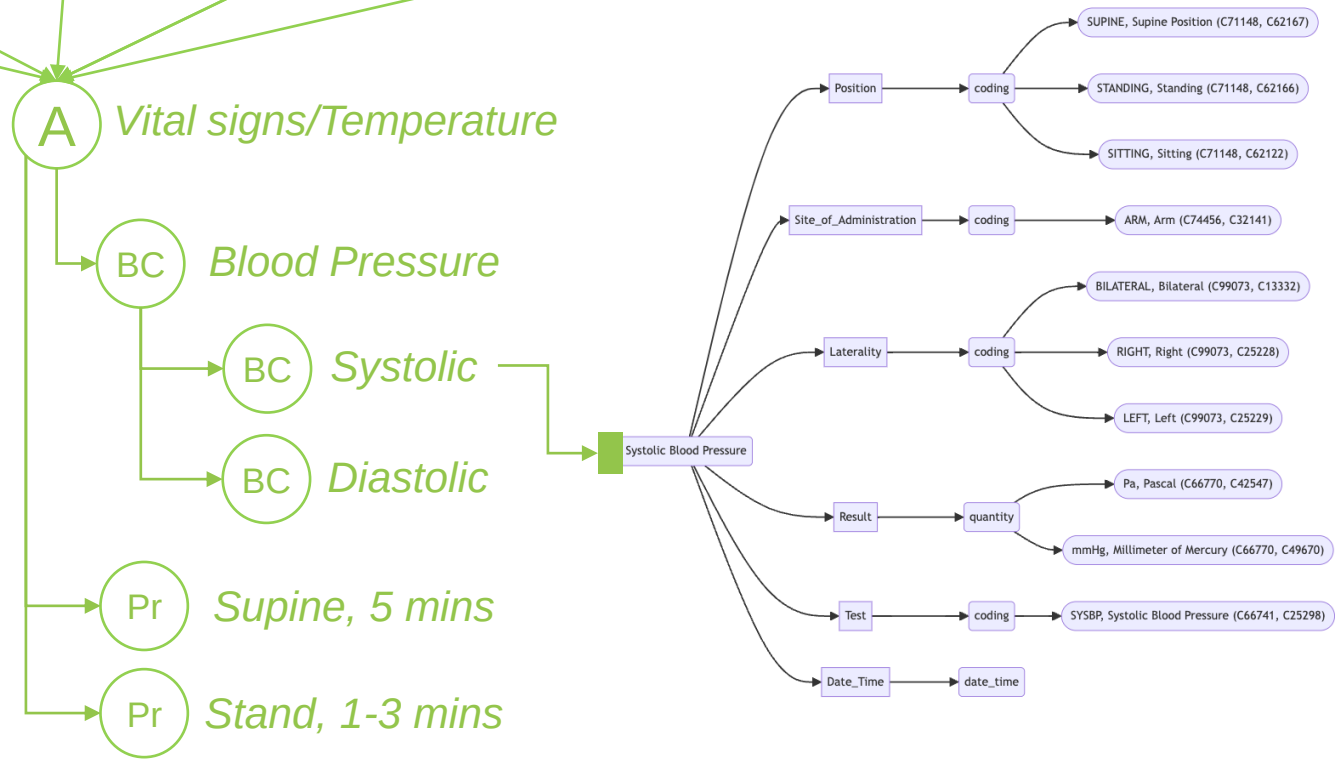
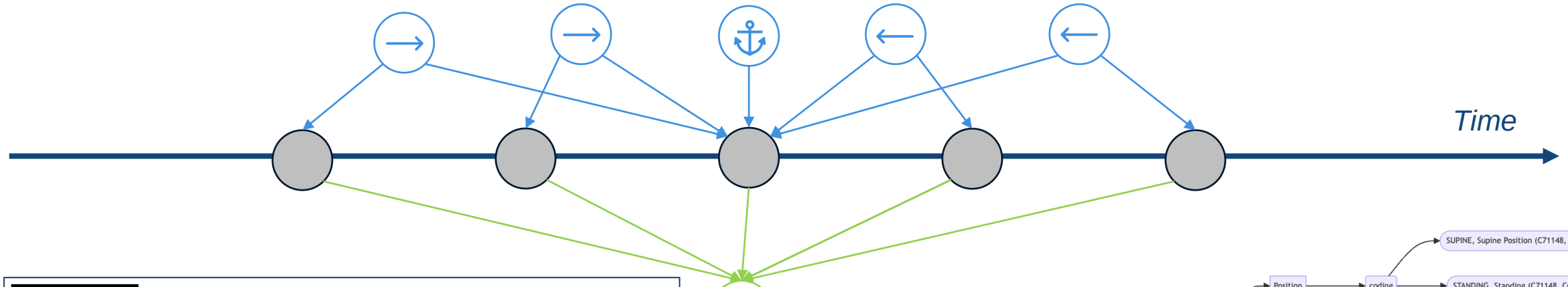
An automated blood pressure cuff may be used in place of a mercury manometer if it is regularly (at least monthly) standardized against a mercury manometer.



Biomedical Concepts – CRF



VITAL SIGNS : HEART RATE AND BLOOD PRESSURE

INFORMATION NOT OBTAINED ☐ Not Entered In Database

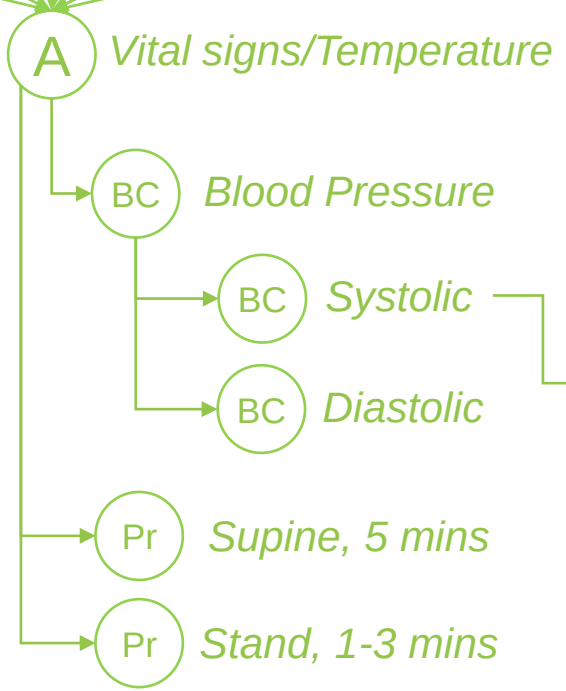
NOTE: Blood pressure and pulse must be taken after the patient has been lying down for 5 minutes (supine) and after standing for 1 minute (standing) and 3 minutes.

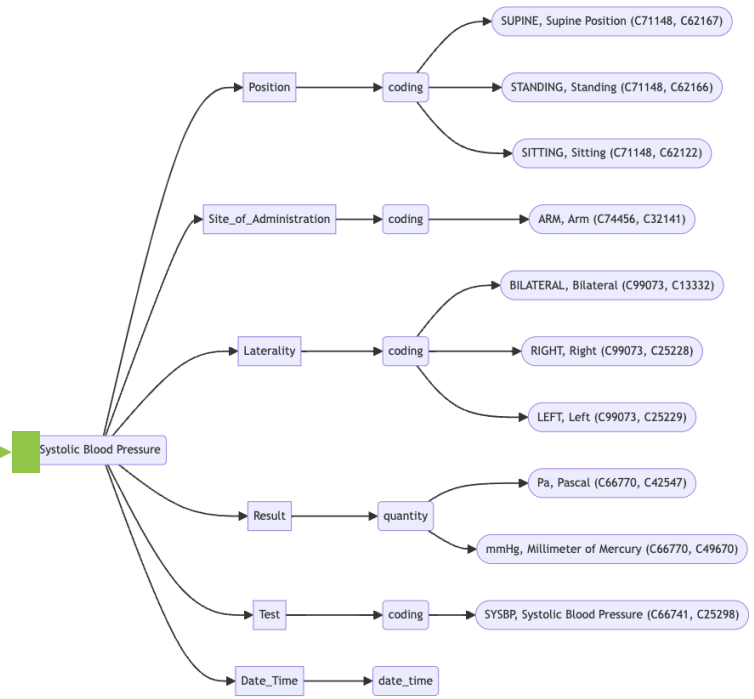
	(DNDE) Reference Time	Timing Code	Position (SU = Supine, ST = Standing)	Heart Rate (bpm)	Blood Pressure (mmHg) Systolic/Diastolic
0.	5 minutes	815	SU		/
1.	1 minute	816	ST		/
2.	3 minutes	817	ST		

VSTPTNUM VSTPT VSPOS VSTESTCD VSORRESU VSORRES VSTESTCD VSORRESU VSORRES VSTESTCD VSORRESU

Automation

Getting close to building this from the eProtocol





Biomedical Concepts – LZZT Spreadsheet

	A	B	C	D	E	F	G	H	I
1	**Name**	Main Timeline	**name**	SCREEN1	SCREEN2	DOSE	WK2	WK4	WK6
2	**Description**	This is the main timeline for the study design.	**description**	-	-	-	-	-	-
3	**Condition**	Potential subject identified	**label**	Screen One	Screen Two	Dose	Week 2	Week 4	Week 6
4			**type**	Activity	Activity	Activity	Activity	Activity	Activity
5			**default**	SCREEN2	DOSE	WK2	WK4	WK6	WK8
6			**condition**						
7			**epoch**	Screening	Screening	Treatment 1	Treatment 1	Treatment 2	Treatment 2
8			**encounter**	E1	E2	E3	E4	E5	E7
9	**Parent Activity**	**Child Activity**	**BC/Procedure/Timeline**						
10		Informed consent		X	-	-	-	-	-
11		Inclusion/exclusion criteria		X	-	-	-	-	-
12		Patient number assigned		X	-	-	-	-	-
13		Demographics		X	-	-	-	-	-
14		Hachinski <= 4		X	-	-	-	-	-
15		MMSE 10-23		X	-	-	-	-	-
16		Physical examination		X	-	-	-	-	-
17		Medical history		X	-	-	-	-	-
18		Habits		X	-	-	-	-	-
19		Chest X-ray		X	-	-	-	-	-
20		Apo E genotyping		-	-	-	X	-	-
21		Patient randomised		-	-	X	-	-	-
22		Vital signs / Temperature	BC:Systolic blood pressure, BC:Diastolic blood pressure, BC:Body temperature, BC:Body Weight, BC:Body Height	X	X	X	X	X	X

BC *Systolic*

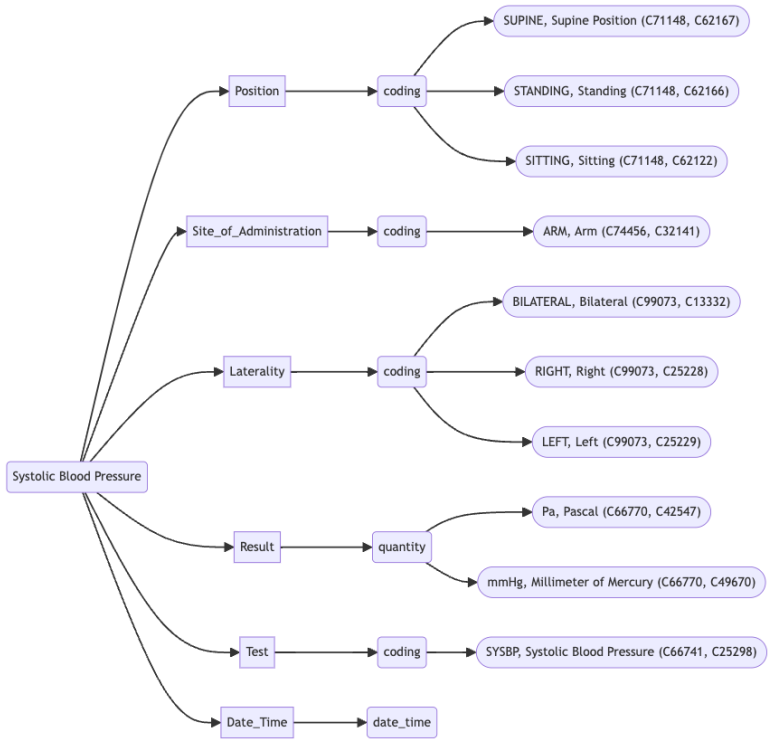
CDISC Library & Biomedical Concepts

d4k BC Browser BCS STATUS

SYSTOLIC BLOOD PRESSURE

Owner: d4k, Version: 1.0.0

Graphical View



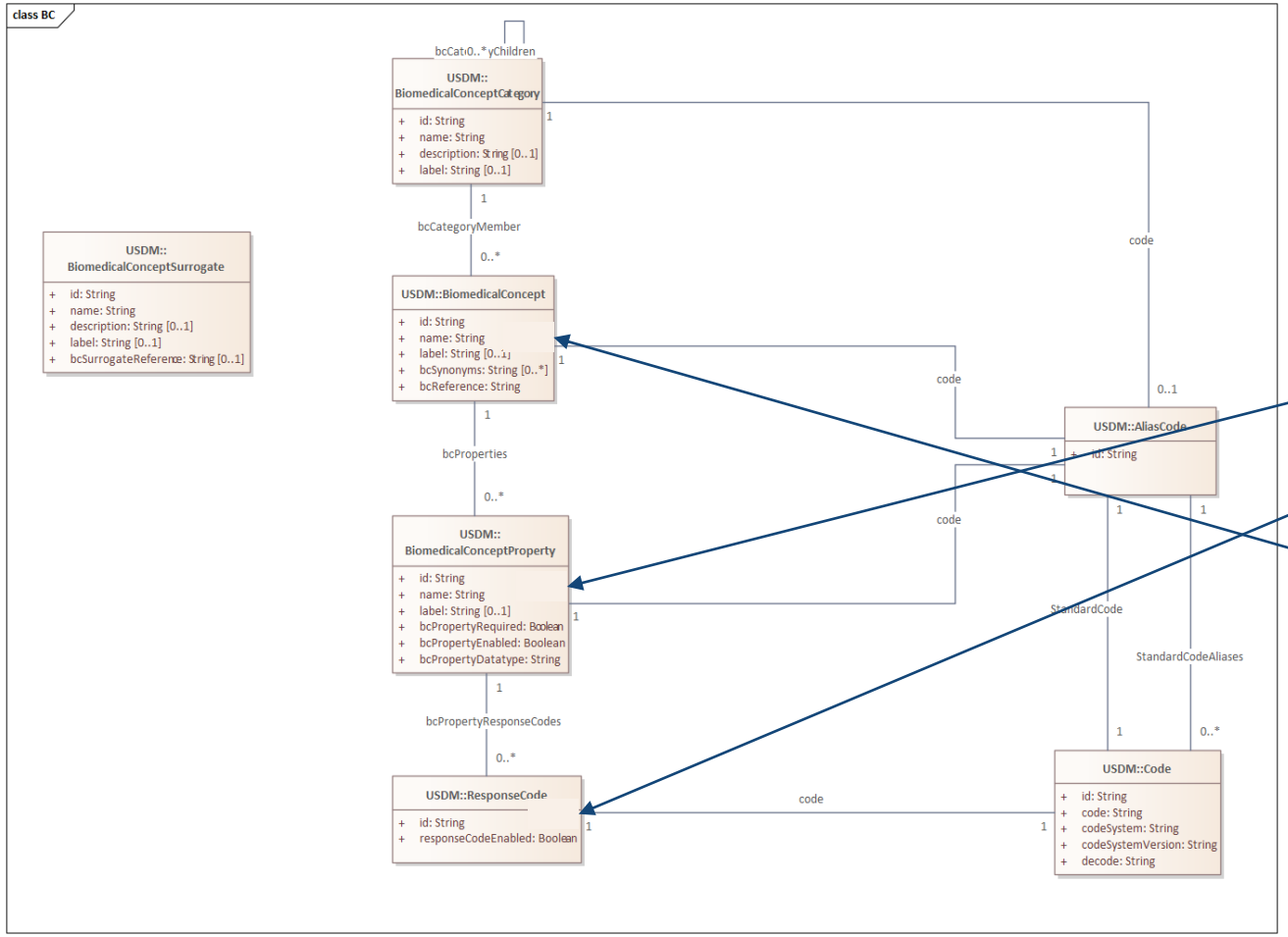
Tabular View

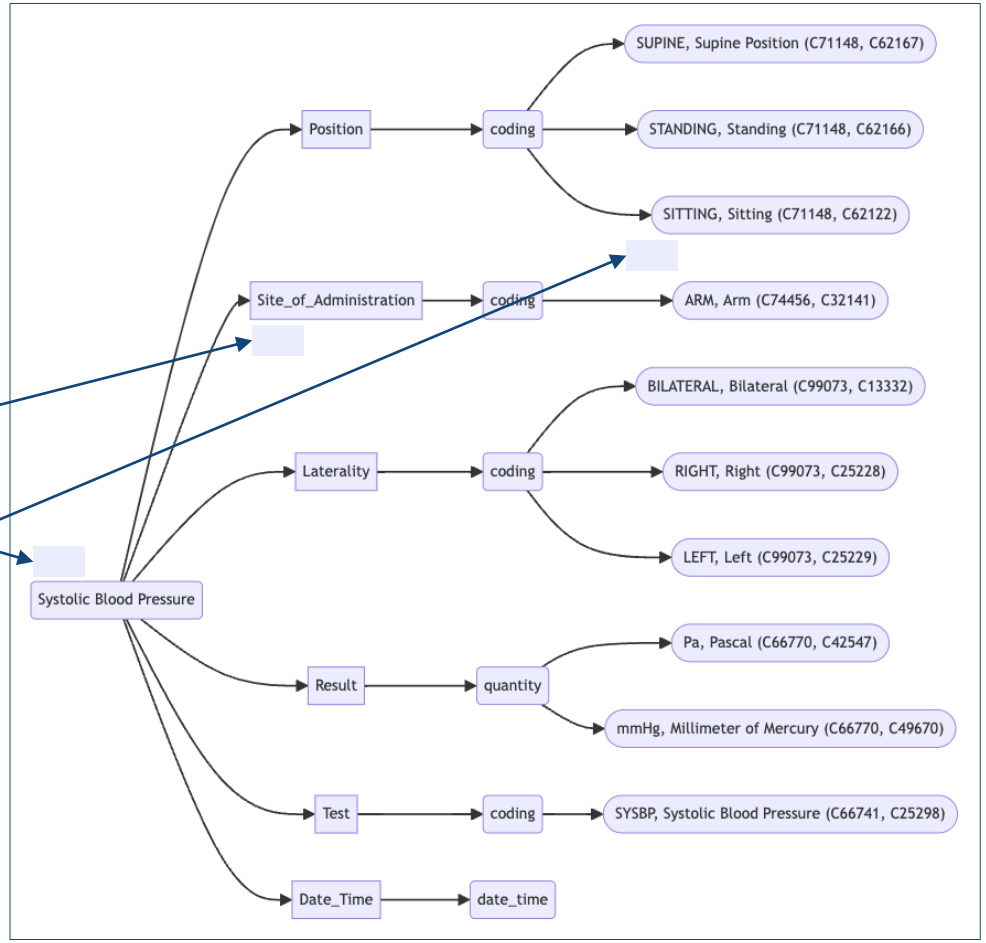
Item Name	Identifier	Data Type	Terms
Position		coding	SUPINE, Supine Position (C71148, C62167) STANDING, Standing (C71148, C62166) SITTING, Sitting (C71148, C62122)
Site of Administration		coding	ARM, Arm (C74456, C32141)
Laterality		coding	BILATERAL, Bilateral (C99073, C13332) RIGHT, Right (C99073, C25228) LEFT, Left (C99073, C25229)
Result		quantity	Pa, Pascal (C66770, C42547) mmHg, Millimeter of Mercury (C66770, C49670)
Test	✓	coding	SYSBP, Systolic Blood Pressure (C66741, C25298)
Date Time		date_time	

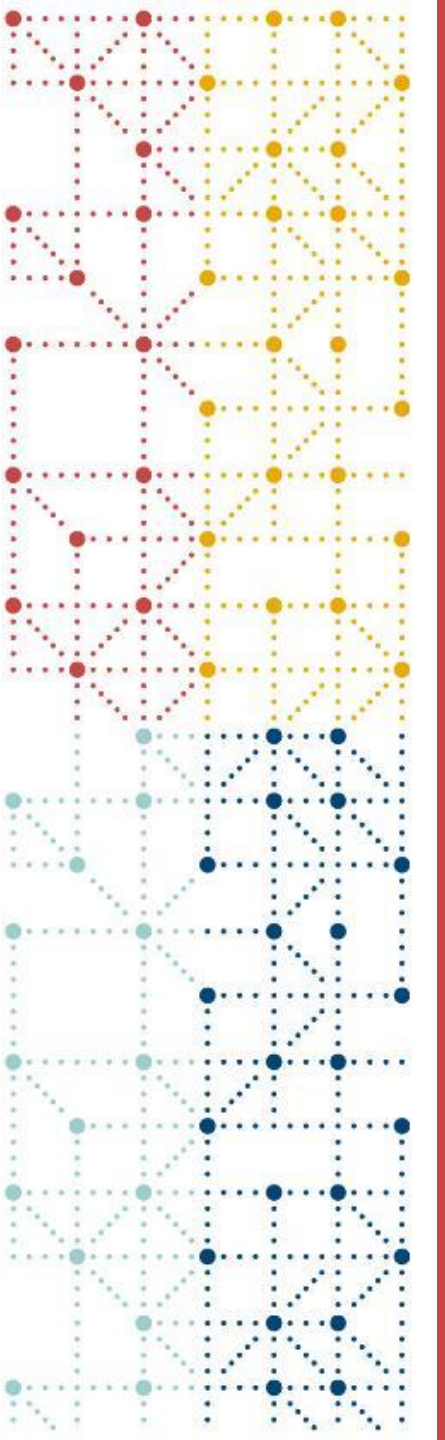
Excel - Some Restrictions

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







Footnotes

Footnotes

1. Footnotes representing sub-timelines
2. Footnotes representing timing and/or order of activities
3. Footnotes representing alternative visit schedules
4. Repeated activities not presented in the SoA
5. Footnotes representing conditional activities and procedures
6. Footnotes representing optional/alternative encounter methods
7. Footnotes representing optional alternative measurement methods
8. Additional instructions for procedures and assessments
9. Specification of actual measurements for an activity
10. Visit windowing information
11. Eligibility requirements
12. Complex combinations of the above

=> timepoints: predose, 30 minutes, 1h, 2h, …

=> before all other, on day of admission, during admission, until end of …

=> visits in case of withdrawal, adverse events, optional visits …

=> online questionnaire, every 3 cycles, during wash-out...

=> only women with childbearing potential, discretion of investigator, when criteria are met, for cohort B, …

=> or perfomed by telephone, visits may take at home, …

=> urine or plasma pregnancy test, either Chest X-reay or CT scan

=> Assessed by a blinded asessor, samples will be send to, instructions for inhaler use, …

=> heamatology must include WBC differential count

=> plus or minus 3 days

=> assessment must demonstrate a value of …

=> the initial measurement should be … then repeated … within a timewindow of ...

Footnotes

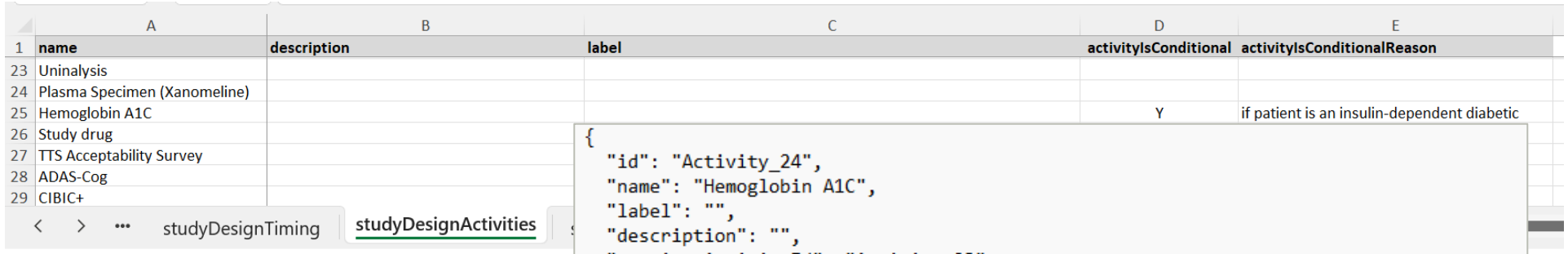
	VISIT	1	2	3	4	5		7	8
ACTIVITY	WEEK	-2	-.3	0	2	4		6	8
Hemoglobin A_{1C}		X^a							
Study drug record Medications dispensed Medications returned				X	X	X		X	X
TTS Acceptability Survey									
ADAS-Cog		P		X					X
CIBIC+		P		X					X
DAD		P		X					X
NPI-X		P		X	X	X		X	X^b
Adverse events		X	X	X	X	X		X	X

Abbreviations: CT = computed tomography; ECG = electrocardiogram
X = Performed at this visit.
X^a = Performed at this visit if patient is an insulin-dependent diabetic.
X^b = Performed at this visit and via telephone interview 2 weeks following this visit.
P = Practice only - It is recommended that a sampling of the CIBIC+, ADAS-Cog, DAD, and NPI-X be administered at Visit 1. Data from this sampling would not be considered as study data and would not be collected.

- X_a: if patient is an insulin-dependent diabetic
  => conditional
- X_b: and via telephone interview 2 weeks following this visit
  => repeated but not presented in SoA
- P: Practice only
  => additional instructions

Conditional footnotes

1. Define on what level they are conditional/optional?
   - Activity
   - Procedure
   - Assessment
2. Add conditionality/optionality information to corresponding class
3. Can be parsed as footnote by implementation



	A	B	C	D	E
1	**name**	**description**	**label**	**activityIsConditional**	**activityIsConditionalReason**
23	Uninalysis				
24	Plasma Specimen (Xanomeline)				
25	Hemoglobin A1C			Y	if patient is an insulin-dependent diabetic
26	Study drug				
27	TTS Acceptability Survey				
28	ADAS-Cog				
29	CIBIC+				

studyDesignTiming | studyDesignActivities

	A	B	C	D
1	**name**	**description**	**label**	**procedureType**
2	PR1	CT Scan	CT Scan	CT Scan
3				
4				
5				
6				
7				

studyDesignProcedures | studyDesignEncounters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{
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  "name": "Hemoglobin A1C",
  "label": "",
  "description": "",
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  "definedProcedures": [],
  "activityIsConditional": true,
  "activityIsConditionalReason": "if patient is an insulin-dependent diabetic",
  "biomedicalConceptIds": [],
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    "BiomedicalConceptSurrogate_2"
  ],
  "activityTimelineId": ""
},
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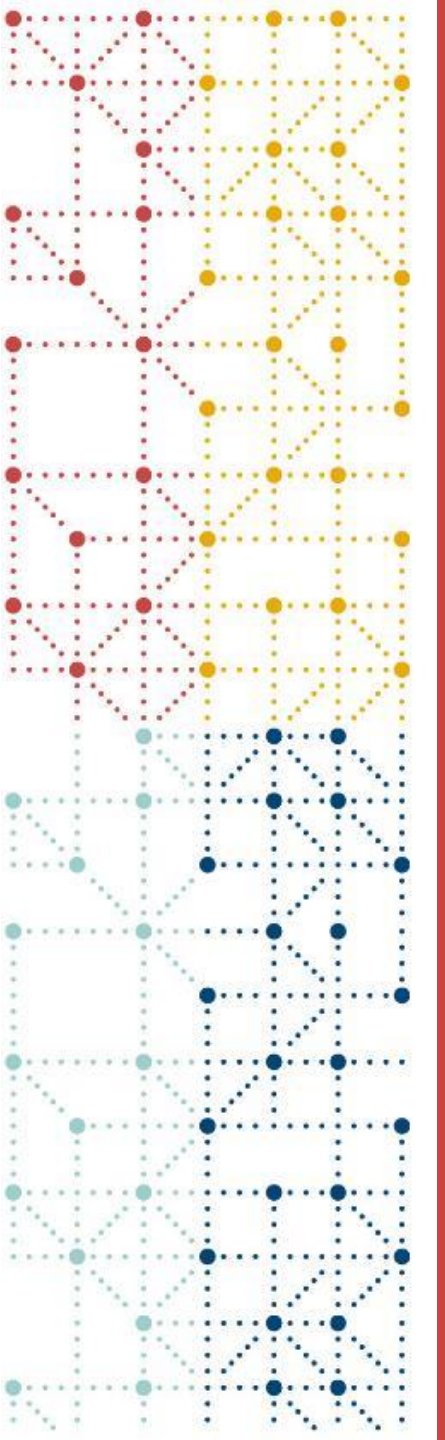
Footnotes: Repeated activities not presented in the SoA

1. Identify the extra timepoints mentioned in the footnote
2. Add as instances to the timeline
3. Optionally link to encounter
   - By defining new encounter
   - By linking to existing encounter

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
1	**Name**	Main Timeline	**name**	SCREEN1	SCREEN2	DOSE	WK2	WK4	WK6	WK8	WK8N	WK12	WK12N	WK16	WK16N
2	**Description**	This is the main timeline for	**description**	-	-	-	-	-	-	-	-	-	-	-	-
3	**Condition**	Potential subject identified	**label**	Screen One	Screen Two	Dose	Week 2	Week 4	Week 6	Week 8	Week NPI	Week 12	Week 12 NPI	Week 16	Week 16 N
4			**type**	Activity	Activity	Activity	Activity	Activity	Activity	Activity	Activity	Activity	Activity	Activity	Activity
5			**default**	SCREEN2	DOSE	WK2	WK4	WK6	WK8	WK8N	WK12	WK12N	WK16	WK16N	WK20
6			**condition**												
7			**epoch**	Screening	Screening	Treatment 1	Treatment 1	Treatment 2	Treatment 2	Treatment 2	Treatment 2	Treatment 2	Treatment 2	Treatment 2	Treatment
8			**encounter**	E1	E2	E3	E4	E5	E7	E8	E8	E9	E9	E10	E10
9	**Parent Activity**	**Child Activity**	**BC/Procedure/Timeline**												
33		Hemoglobin A1C	BC:HbA1c	X	-	-	-	-	-	-	-	-	-	-	-
34		Study drug		-	-	X	X	X	X	X	-	X	-	X	-
35		TTS Acceptability Survey		-	-	-	-	-	-	-	-	-	-	-	-
36	-	ADAS-Cog		X	-	X	-	-	-	X	-	-	-	X	-
37		CIBIC+		X	-	X	-	-	-	X	-	-	-	X	-
38		DAD		X	-	X	-	-	-	X	-	-	-	X	-
39		NPI-X		X	-	X	X	X	X	X	X	X	X	X	X
40															
41															

studyDesignArms | studyDesignEpochs | mainTimeline | adverseEventTimeline | ea



USDM and the ICH M11 Document

M11 Document & Unstructured Text

	A	B	C	D
45	6.6.3		Blinding and Unblinding	The study will be double-blind. To further preserve the blinding of the study, only a minimum number of Lilly and CRO personnel will see the randomization table and codes before the study is complete. Emergency codes generated by a computer drug-labeling system will be available to the investigator. These codes, which reveal the patients treatment group, may be opened during the study only if the choice of follow-up treatment depends on the patient's therapy assignment. The investigator should make every effort to contact the clinical research physician prior to unblinding a patient's therapy assignment. If a patient's therapy assignment is unblinded, Lilly must be notified immediately by telephone. After the study, the investigator must return all sealed and any opened codes.

Text "blobs"

Model allows for "unstructured" text to be include to allow the entire protocol to be held.

6.6.3 Blinding and Unblinding

The study will be double-blind. To further preserve the blinding of the study, only a minimum number of Lilly and CRO personnel will see the randomization table and codes before the study is complete.

Emergency codes generated by a computer drug-labeling system will be available to the investigator. These codes, which reveal the patients treatment group, may be opened during the study only if the choice of follow-up treatment depends on the patient's therapy assignment.

The investigator should make every effort to contact the clinical research physician prior to unblinding a patient's therapy assignment. If a patient's therapy assignment is unblinded, Lilly must be notified immediately by telephone. After the study, the investigator must return all sealed and any opened codes.

Excel Tool

Excel too can build the document and produce a PDF

M11 Document & Structured Text

Excel Tool

Some simple macros to build M11 standard content.
Uses references to the structured content

	A	B	C	D
1	sectionNumber	name	sectionTitle	text
2	0		TITLE PAGE	<usdm:section name="M11-title-page">

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  <tr>
    <th style="vertical-align: top; text-align: left">
      <p>Protocol Full Title:</p>
    </th>
    <td style="vertical-align: top; text-align: left">
      <p>
        <usdm:ref klass="StudyProtocolDocumentVersion"
id="StudyProtocolDocumentVersion_1" attribute="officialTitle" />
      </p>
    </td>
  </tr>
  …
  <tr>
    <th style="vertical-align: top; text-align: left">
      <p>Sponsor Name and Address:</p>
    </th>
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      <p>
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        <usdm:ref klass="Address" id="Address_1" attribute="text" />
      </p>
    </td>
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Protocol Full Title:	Safety and Efficacy of the Xanomeline Transdermal Therapeutic System (TTS) in Patients with Mild to Moderate Alzheimer's Disease
Protocol Number:	H2Q-MC-LZZT
Version:>	2
Amendment Number:	1
Amendment Scope:	
Compound Number(s):	
Compound Name(s):	
Trial Phase:	Phase II Trial
Acronym:	H2Q-MC-LZZT
Short Title:	Xanomeline (LY246708)
Sponsor Name and Address:	Eli Lilly Lilly Corporate Ctr, Indianapolis, -, IN, 4628, United States of America

M11 Document & Structured Text

M11 Template Specification

Protocol Full Title:	[Protocol Full Title] The protocol should have a descriptive title that identifies the scientific aspects of the trial sufficiently to ensure it is immediately evident what the trial is investigating and on whom, and to allow retrieval from literature or internet searches.
Sponsor Confidentiality Statement:	[Sponsor Confidentiality Statement] Insert the Sponsor's confidentiality statement, if applicable, otherwise delete.
Protocol Number:	[Protocol Number] A unique alphanumeric identifier for the trial, designated by the Sponsor, is a standard part of trial data, and should be included for most trials.
Version:	[Version] An optional field for use by the Sponsor at their discretion.
Amendment Number:	[Amendment Number] Enter the amendment number. If this is the original instance of the protocol, indicate Not Applicable.
Amendment Scope:	[Amendment Scope] [Country/Region Identifier] Acceptable entries for amendment scope are: "global" or "Country-specific/Regional" Use the ISO-3166 region or country identifier (for example, DE or EU). For global trials delete the Country/Region Identifier field.
Compound Number(s):	[Compound Number] Enter the Sponsor's unique identifier for investigational compound(s) in the trial. Add or delete additional fields as needed.
Compound Name(s):	[Nonproprietary Name]. [Proprietary Name]. [Additional Proprietary Name] Delete this line from the table if a nonproprietary name has not yet been assigned. Omit proprietary name fields if not yet established.
Trial Phase:	[Trial Phase] [Description of Trial Phase Other] Acceptable entries are: "Early Phase 1", "Phase 1", "Phase 1/Phase 2", "Phase 2", "Phase 2/Phase 3", "Phase 3", "Phase 4",

Protocol Full Title:	Safety and Efficacy of the Xanomeline Transdermal Therapeutic System (TTS) in Patients with Mild to Moderate Alzheimer's Disease
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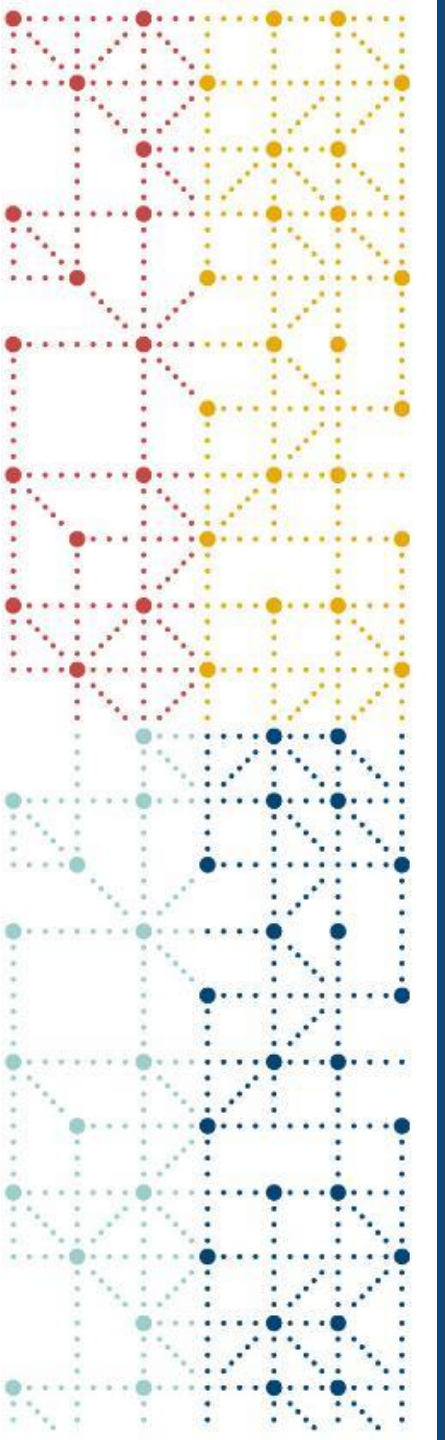
Excel Tool

1. *No effort made to make it look pretty! ☺*
2. *Still work in progress and some alignment needed with structured text*

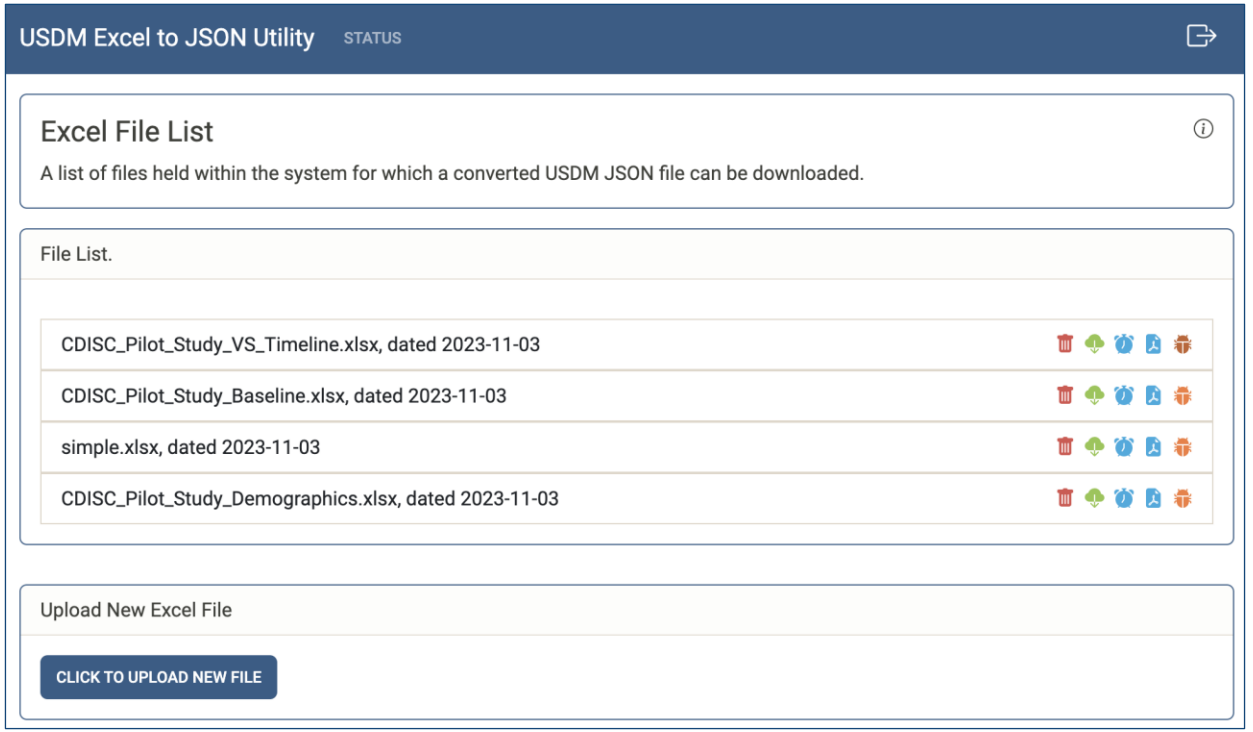
USDM & Excel



Exercises

Exercises

- Footnote X[a] Hemoglobin
- IE, add a new one
- BCs, add in demography activity BCs
  - Date of Birth,
  - Sex,
  - Race
- Make one of the telephone NPI-X collection an extra visit rather part of the previous visit
- Vital Signs Sub timeline



Want to learn more?

TransCelerate BIOPHARMA INC.
Accelerating Answers.

TransCelerate Public Webinars

"Modernizing Clinical Trials Using Digitized Protocol Information: An Exploration of New Tools for Digital Transformation"

Presentation Overview:

Join us for a presentation and panel Q&A to explore the newly released resources developed by TransCelerate's Digital Data Flow (DDF) Initiative. DDF, in collaboration with CDISC and other industry stakeholders, has built the foundational capabilities and is helping enable a digital transformation that unlocks efficiencies in the design and conduct of clinical studies, while modernizing pharma to healthcare interoperability.

This webinar will include:

- An overview of the available tools and resources from different stakeholder perspectives.
- Exploration of various implementation scenarios that provide optionality towards greater USDM conformance.
- Focused discussion on several model implementation resources that may be used as a catalyst in your digitalization journey – solutions include the Study Definitions Repository (SDR) and prototype Common Protocol Template (CPT) Utility Tool.

Ideal Attendees:

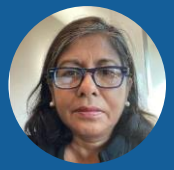
Solution Providers: Study builders and authoring platforms, EDCs, CTMSs and CDMSs, RTs, Central laboratories, EHR systems

Sponsors/CROs: involved in processes that consume protocol information, Clinical Trial Operations, Clinical Trial Digital and Technology Support, Data Manager; Innovation Manager, Infrastructure Manager; Programmers in Clinical Development, Health Authorities, Industry Group or Consortium

Featured Panelists:

Craig Galan (BMS)
Director of Digital Capability Management, Solution Architecture

William Illis (Novartis)
Global Head of Collaboration & Technology Strategy, Clinical Development & Analytics



Renu Shukla (J&J)
Statistical Programming TA Head Oncology

Michael Vesik (Genentech)
Senior Project Manager, Industry Collaborations

Gernot Weber (Merck KGaA)
Head of Data Strategy & Digital Innovation

December 13, 2023

10:00AM to 11:00AM EST

TransCelerate webinars may be recorded in whole or in part.

Scan QR code or click here to sign up.

Additional Opportunities to Stay Involved with DDF?

Scan QR Code to explore DDF GitHub

- Download the SDR source code available on the Github
- Review the videos, newsletters and other archived materials available on the GitHub
- Contribute and interact on the open discussion forums
- If you work for a TransCelerate member company, volunteer to join our core team
- Volunteer to join the CDISC USDM team (via CDISC website)

https://transcelerate.github.io/ddf-home/