

# Digitizing Therapeutic Areas: Increasing Standardization and Reusability

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# History of Therapeutic Area User Guides

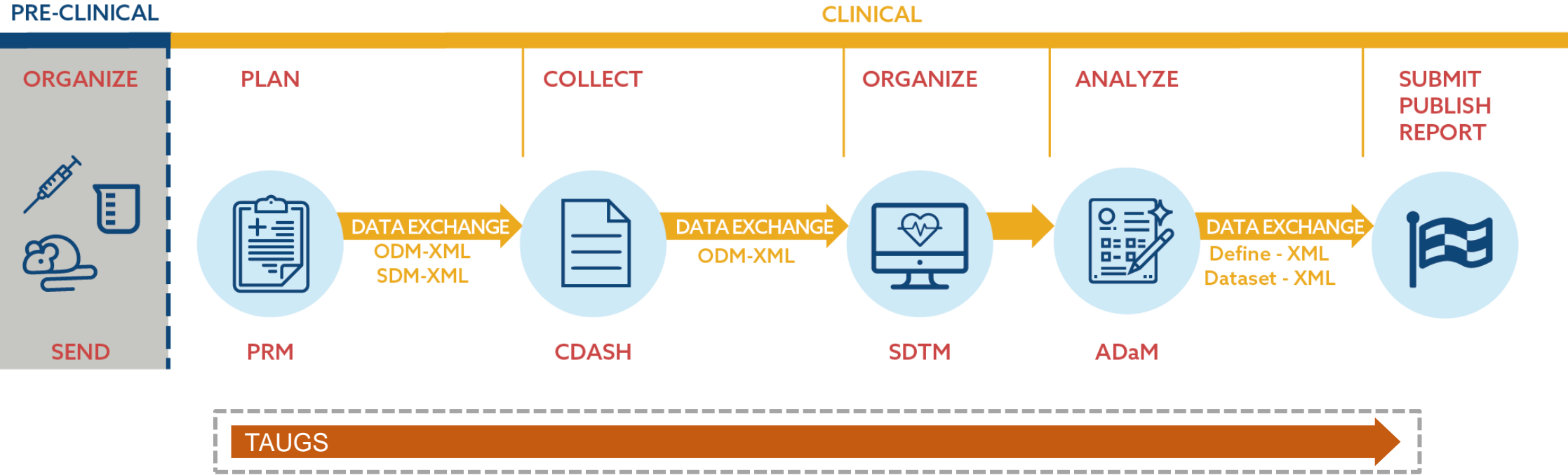
- First one published in 2011 – Alzheimer's Therapeutic Area User Guide v1.0
- CFAST is Launched in 2012



- Original plan: 55 TA Standards in 5 years, today 44 TA Standards in 8 years

# Today we are here

## CDISC Standards in the Clinical Research Process



BRIDG, CONTROLLED TERMINOLOGY AND GLOSSARY



# Current Therapeutic Area User Guide Overview

Therapeutic Area (TA) Standards extend the Foundational Standards to represent data that pertains to specific disease areas. TA Standards include disease-specific metadata, examples and guidance on implementing CDISC standards for a variety of uses, including global regulatory submission.

## Autoimmune

Psoriasis

Rheumatoid Arthritis

## Cardiovascular

Cardiovascular

Heart Failure

QT Studies

Traditional Chinese Medicine - Coronary Artery Disease-

Angina

## Endocrine

Acute Kidney Injury

Diabetes

Diabetes - Type 1

Diabetic Kidney Disease

Dyslipidemia

Kidney Transplant

Polycystic Kidney Disease

## Gastrointestinal

CDAD

Crohn's Disease

## Infectious

COVID-19

Ebola

Hepatitis C

HIV

Influenza

Malaria

Tuberculosis

Virology

## Mental Health

Major Depressive Disorder

Post Traumatic Stress Disorder

Schizophrenia

## Neurology

Alzheimer's

Huntington's Disease

Multiple Sclerosis

Parkinson's Disease

Traumatic Brain Injury

## Oncology

Breast Cancer

Colorectal Cancer

Lung Cancer

Pancreatic Cancer

Prostate Cancer

## Other

Nutrition

Traditional Chinese Medicine - Acupuncture

## Rare Diseases

Duchenne Muscular Dystrophy

## Respiratory

Asthma

COPD

COVID-19

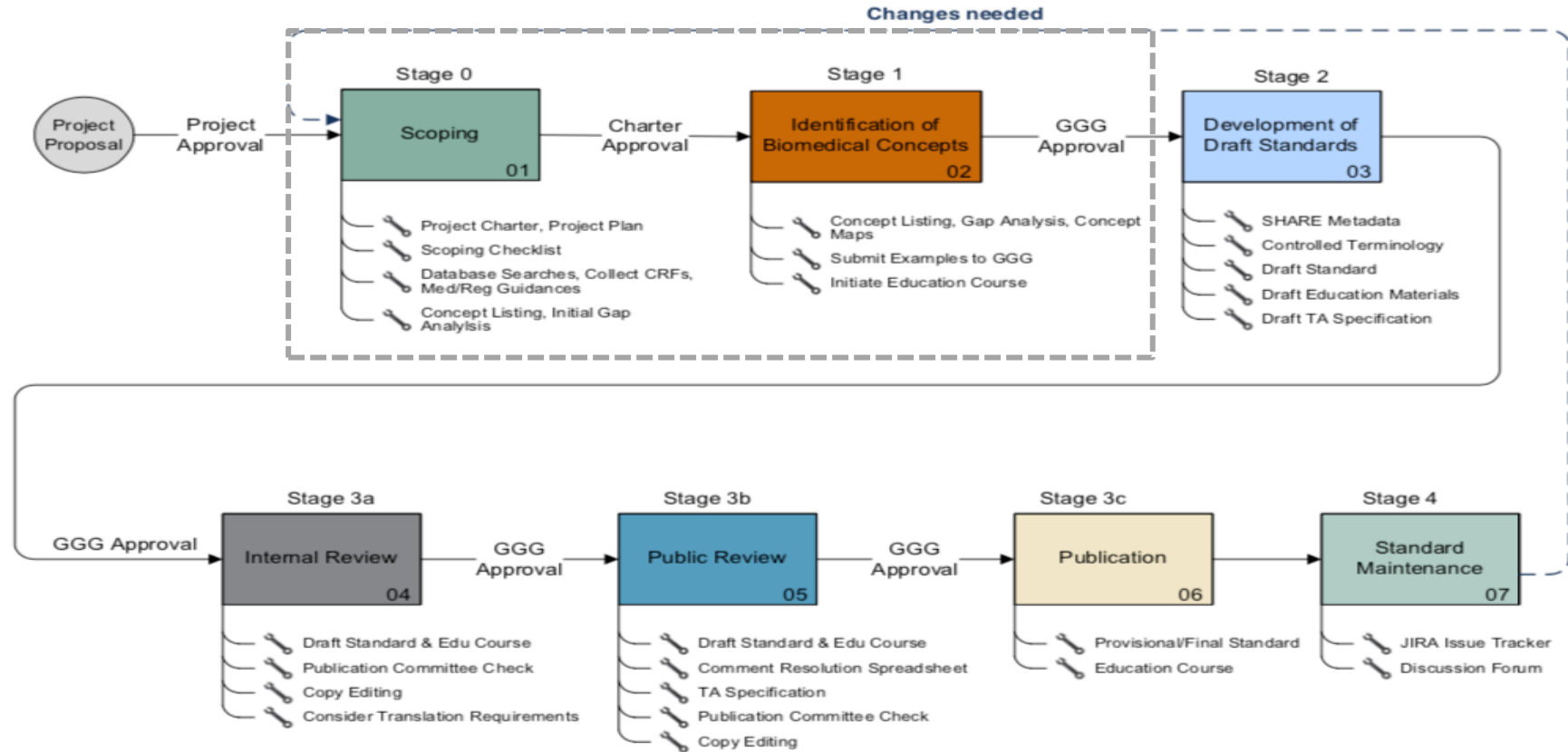
## Treatments

Pain

Vaccines

<https://www.cdisc.org/standards/therapeutic-areas/disease-area>

# CDISC Standards Development Process

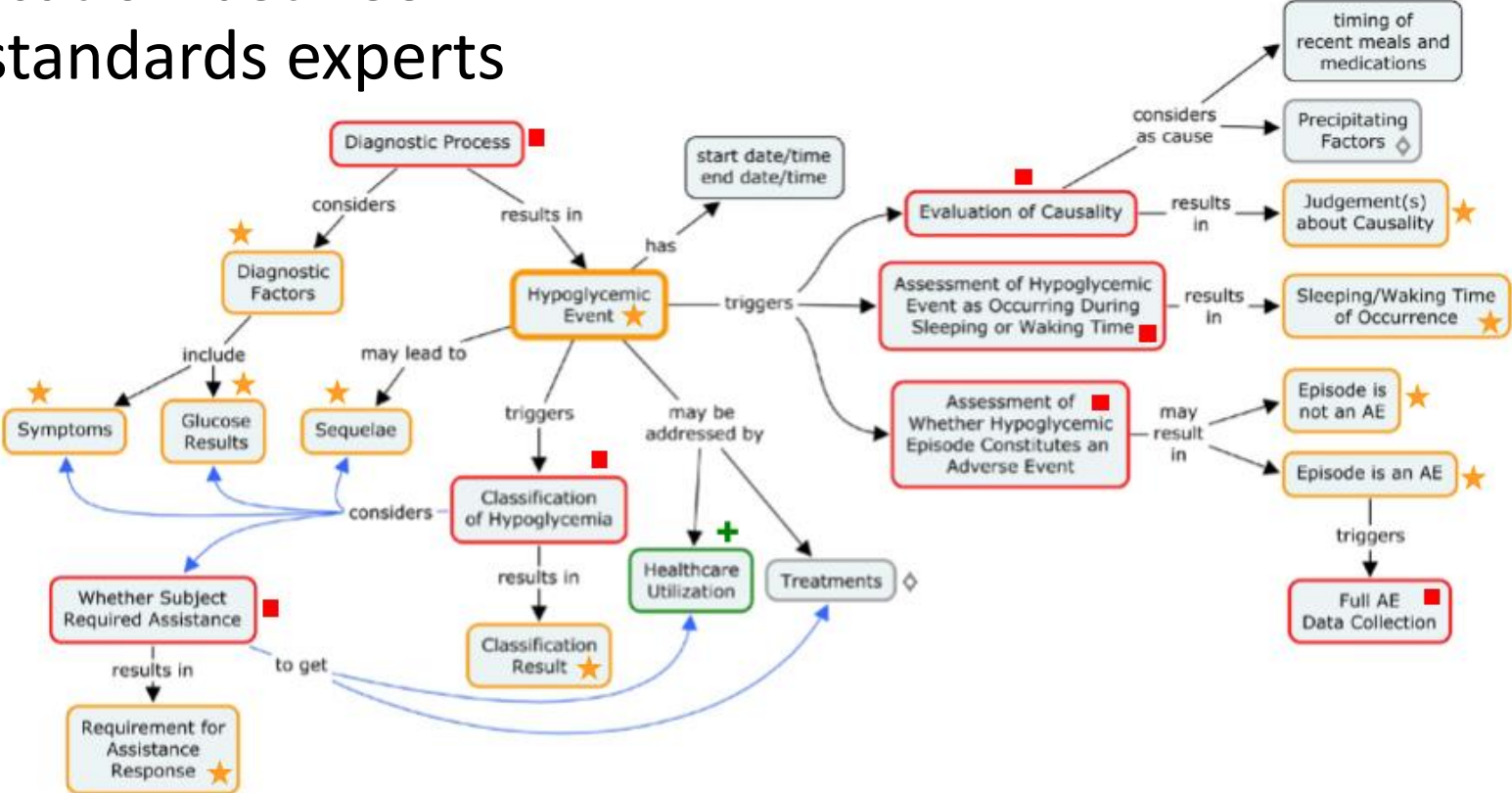


This task map is to be used in conjunction with the Standards Development Process Guideline.

GGG = Global Governance Group

# Concept Map (scoping)

- Provides scope and extent of TA User Guide
- Facilitates communication between scientists and data standards experts



Concept Map 7: Hypoglycemic Event

# Annotated Case Report Forms and Datasets

Example CRF 5: Hypoglycemia

<b>CETERM= Hypoglycemic Event</b> <b>CECAT= HYPO EVENTS</b>	
Any Hypoglycemic Events Experienced?	No Yes (If yes complete for each event) <b>CEYN</b>
Sponsor Defined ID	<b>CESPID</b> 001
Date/Time of Event	--- ---- (DD-MMM-YYYY) ---:-- (24 hour clock) <b>CESTDAT</b> <b>CESTTIM</b>
When Did the Hypoglycemic Event Occur?	Between Bedtime and Waking Between Waking and Bedtime <b>QVAL when QNAM= WHENOCC and QLABL="When Did the Hypoglycemic Event Occur?"</b>
In the Opinion of the Investigator Was This an Adverse Event?	No Yes <b>WASAEYN</b> <b>FAORRES where FATESTCD= "WASAEYN", FATEST= "Was this an adverse event?" and FAOBJ="HYPOGLYCEMIC EVENT"</b>
Was a Glucose Measurement Obtained at the Time of the Event?	No Yes (If yes enter result and unit below) <b>LBPERF</b>
	---- Glucose Result <b>LBORRES</b> mg/dL mmol/L <b>LBORRESU</b>
Last Study Medication Taken	-----Name/Reference <b>EXTRT</b>
<b>EXCAT= HIGHLIGHTED DOSE</b>	<b>EXSTDTC</b> --- ---- (DD-MMM-YYYY) ---:-- (24 hour clock) <b>EXSDAT</b> <b>EXSTTIM</b>
	--- dose <b>EXDOSE</b> --- units <b>EXDOSU</b> <b>EXDSTXT</b>
Last Concomitant Diabetic Medication Taken	-----Name/Reference <b>CMTRT</b>
<b>CMCAT= ANTI-HYPERGLYCEMIC MED</b> <b>CMSCAT= HIGHLIGHTED DOSE</b>	<b>CMSTDTC</b> --- ---- (DD-MMM-YYYY) ---:-- (24 hour clock) <b>CMSDAT</b> <b>CMSTTIM</b>
	--- dose <b>CMDOSE</b> --- units <b>CMDOSU</b> <b>CMDSTXT</b>
Date/Time of Last Meal	<b>MLSTDTC</b> --- ---- (DD-MMM-YYYY) ---:-- (24 hour clock) <b>MLSDAT</b> <b>MLSTTIM</b>
Were Signs/Symptoms Present?	No Yes (If yes complete following) <b>CEYN</b>
<b>CECAT= HYPO SYMPTOMS</b>	
<b>CETERM= SWEATING</b>	Sweating No Yes <b>CEOCCUR with</b>
<b>CETERM= TREMORS/TREMBLING</b>	Tremors/Trembling No Yes <b>CEPRES=P</b>
<b>CETERM= DIZZINESS</b>	Dizziness No Yes
<b>CETERM= COGNITIVE IMPAIRMENT</b>	Cognitive Impairment No Yes
<b>CETERM= LOSS OF CONSCIOUSNESS</b>	Loss of Consciousness No Yes
<b>CETERM= CONVULSIONS/SEIZURE</b>	Convulsions/Seizure No Yes
<b>CETERM= COMA</b>	Coma No Yes
	Other (Specify) No Yes (if yes enter below)
<b>FACAT= PRECIPITATING FACTORS, FAOBJ= HYPOGLYCEMIC EVENT and:</b>	----- <b>CETERM</b>
Were Any Precipitating Factors Reported?	No Yes (If yes complete following) <b>HPFYN</b>
<b>FATEST= Alcohol Consumption as a Precip Factor</b>	Alcohol Consumption No Yes
<b>FATEST= Concurrent Illness as a Precip Factor</b>	Concurrent Illness No Yes <b>FAORRES</b>
<b>FATEST= Dosing Deviation as a Precip Factor</b>	Deviation from Dosing Instructions No Yes
<b>FATEST= Meal Variance as a Precip Factor</b>	Missed, Delayed or Smaller Meal No Yes
<b>FATEST= Physical Activity as a Precip Factor</b>	Physical Activity No Yes
	Other (Specify) No Yes (if yes enter below)
<b>CMCAT= HYPO TREATMENT</b>	----- <b>FATEST</b>
Was Any Treatment Given for the Hypoglycemic Event?	No Yes (If yes complete following) <b>HTGYN</b>
	<b>CMTRT= DRINK</b> Drink No Yes <b>CMOCCUR with</b>
	<b>CMTRT= FOOD</b> Food No Yes <b>CMPRES= Y</b>
	<b>CMTRT= GLUCOSE TABLETS</b> Glucose Tablets No Yes
	<b>CMTRT= GLUCAGON INJECTION</b> Glucagon Injection No Yes
	<b>CMTRT= INTRAVENOUS GLUCOSE</b> Intravenous Glucose No Yes
If Treatment Given Indicate Assistance Needed?	None - Subject Treated Self Subject was Capable of Treating Self, but Received Assistance Subject was Not Capable of Treating Self, and Required Assistance
	<b>FAORRES when FAOBJ= HYPOGLYCEMIC EVENT, FACAT= TREATMENT ADMINISTRATION, FATESTCD= TXASSIST, FATEST=Treatment Assistance</b>



Row	STUDYID	DOMAIN	USUBJID	CESEQ	CECAT	CETERM	CEDECOD	CEPRES	CEOCCUR	CESTDT	CESTDY
2	XYZ	CE	XYZ-001-001	2	HYPO SYMPTOMS	SWEATING	Hyperhidrosis	Y	N		
3	XYZ	CE	XYZ-001-001	3	HYPO SYMPTOMS	TREMORS/TREMBLING	Tremor	Y	N		
4	XYZ	CE	XYZ-001-001	4	HYPO SYMPTOMS	DIZZINESS	Dizziness	Y	N		
5	XYZ	CE	XYZ-001-001	5	HYPO SYMPTOMS	COGNITIVE IMPAIRMENT	Cognitive Disorder	Y	Y		
6	XYZ	CE	XYZ-001-001	6	HYPO SYMPTOMS	LOSS OF CONSCIOUSNESS	Loss of Consciousness	Y	Y		
7	XYZ	CE	XYZ-001-001	7	HYPO SYMPTOMS	CONVULSIONS/SEIZURES	Convulsion	Y	N		
8	XYZ	CE	XYZ-001-001	8	HYPO SYMPTOMS	COMA	Coma	Y	N		
9	XYZ	CE	XYZ-001-001	9	HYPO EVENTS	HYPOGLYCEMIC EVENT	Hypoglycaemia			2013-09-24T08:48	50

Row	RELMIDS	MIDS	MIDSDTC
1 (cont)		HYPO 1	
2 (cont)	DURING	HYPO 1	2013-09-01T11:00
3 (cont)	DURING	HYPO 1	2013-09-01T11:00
4 (cont)	DURING	HYPO 1	2013-09-01T11:00
5 (cont)	DURING	HYPO 1	2013-09-01T11:00
6 (cont)	DURING	HYPO 1	2013-09-01T11:00
7 (cont)	DURING	HYPO 1	2013-09-01T11:00
8 (cont)	DURING	HYPO 1	2013-09-01T11:00
9 (cont)		HYPO 2	

CRF annotated to show mapping SDTM variables are in Red. If CDASH variable differs from SDTM the CDASH variable is in Blue.

# Analysis Datasets and Results (example)

## 3.3 Hypoglycemic Episodes Summary Dataset

The analysis dataset ADHYSUM is built from an ADHYPO data set and supports both the statistical analysis of the hypoglycemic events and the tabular summary of frequencies of hypoglycemic episodes (see Table 3.3.1). The dataset includes one observation per combination of subject, analysis parameter, time window and indicator (e.g., treatment emergent flag). Each record is a summary of the type of hypoglycemic episode described by the parameter, per subject. For each combination of parameter and the timing variable, AVISIT, records are created even if no hypoglycemic episodes occurred. The statistical model presented below is based on the actual treatment received (TRTA) and adjusted for subject-level values of country and sex. Therefore, these variables are included in ADHYSUM from ADSL to support analysis readiness. The duration of exposure (TRTDURD) is added to the dataset in order to facilitate exposure adjusted incidence rates. For overall summaries the records which have "cumulative frequency count" within the text of PARAM and AVISIT = "End of treatment" can be selected. In this example, parameters for each of the five ADA classification values are defined, along with a derived parameter that represents a grouping of two of the classification values (documented symptomatic or severe hypoglycemia). Mock data for this summary dataset is provided below in Table 3.3.1, yet this mock data shows only a subset of the possible values of analysis parameters. The examples below do not attempt to show all the data needed fully visualize the traceability between ADHYPO and ADHYSUM for a given subject since the volume of required mock data would be large. In practice, however, the counts derived in ADHYSUM for a given subject would be completely traceable to the counts of individual rows for that subject found in the source ADHYPO dataset.

Table 3.3.1: ADHYSUM Analysis Dataset

Row	STUDYID	USUBJID	PARAMCD	PARAM	AVISIT	AVAIL	TRTDURD	SEX	AGE	COUNTRY	TRTA
1	XYZ	000008	ASSYMP	Asymptomatic Hypoglycemia (frequency count)	Week 1	3	72	F	35	DZA	Drug B
2	XYZ	000008	ASSYMP	Asymptomatic Hypoglycemia (cumulative frequency count)	Week 1	3	72	F	35	DZA	Drug B
3	XYZ	000008	ASSYMP	Asymptomatic Hypoglycemia (frequency count)	Week 2	1	72	F	35	DZA	Drug B
4	XYZ	000008	ASSYMP	Asymptomatic Hypoglycemia (cumulative frequency count)	Week 2	4	72	F	35	DZA	Drug B
5	XYZ	000008	ASSYMP	Asymptomatic Hypoglycemia (frequency count)	Week 3	0	72	F	35	DZA	Drug B
6	XYZ	000008	ASSYMP	Asymptomatic Hypoglycemia (cumulative frequency count)	Week 3	4	72	F	35	DZA	Drug B
7	XYZ	000008	ASSYMP	Asymptomatic Hypoglycemia (frequency count)	Week 4	1	72	F	35	DZA	Drug B
8	XYZ	000008	ASSYMP	Asymptomatic Hypoglycemia (cumulative frequency count)	Week 4	5	72	F	35	DZA	Drug B
10	XYZ	000008	ASSYMP	Asymptomatic Hypoglycemia (cumulative frequency count)	End of Treatment	7	72	F	35	DZA	Drug B

## 3.4 Hypoglycemic Episodes Summary Analysis Results

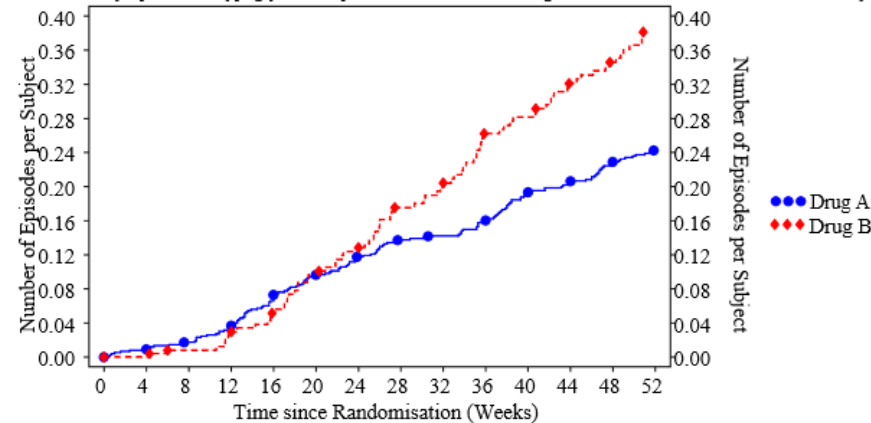
The summary statistics in Table 3.4.1 are presented for all hypoglycemic episodes as well as by ADA classification group. The statistics presented in the current example are number of subjects experiencing an event, the number of events, and the raw event rate. To estimate and present the event-rate information, exposure time is needed. Table 3.4.1 is based on the ADHYSUM dataset.

Table 3.4.1: Summary of Hypoglycemic Episodes by Classification - Table Shell

	Drug A		Drug B		Total			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	xxx				xxx			
Total events	xx	( xx.x)	xx	xxx.x	xx	( xx.x)	xxx	xxx.x
ADA								
Severe hypoglycemia	x	( x.x)	x	xx.x	x	( x.x)	x	x.x
Documented symptomatic hypoglycemia	xx	( xx.x)	xx	xxx.x	xx	( xx.x)	xxx	xxx.x
Asymptomatic hypoglycemia	x	( x.x)	xx	xx.x	x	( x.x)	xx	xx.x
Probable symptomatic hypoglycemia	x	( x.x)	x	x.x	x	( x.x)	x	x.x
Pseudo-hypoglycemia	x				x			

N: Number of subjects; %: Percentage of subjects; E: Number of events; R: Event rate per 100 exposure years;  
 Severe: Subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56 mg/dL)  
 Treatment emergent episodes occur after trial product administration after randomization and no later than 1 day after last trial product administration.

Figure 3.4.1: Mean Cumulative Function Plot of Documented and Severe Symptomatic Hypoglycemic Episodes  
 Documented and Severe Symptomatic Hypoglycemic Episodes - Treatment Emergent - Mean Cumulative Function - Safety Analysis Set





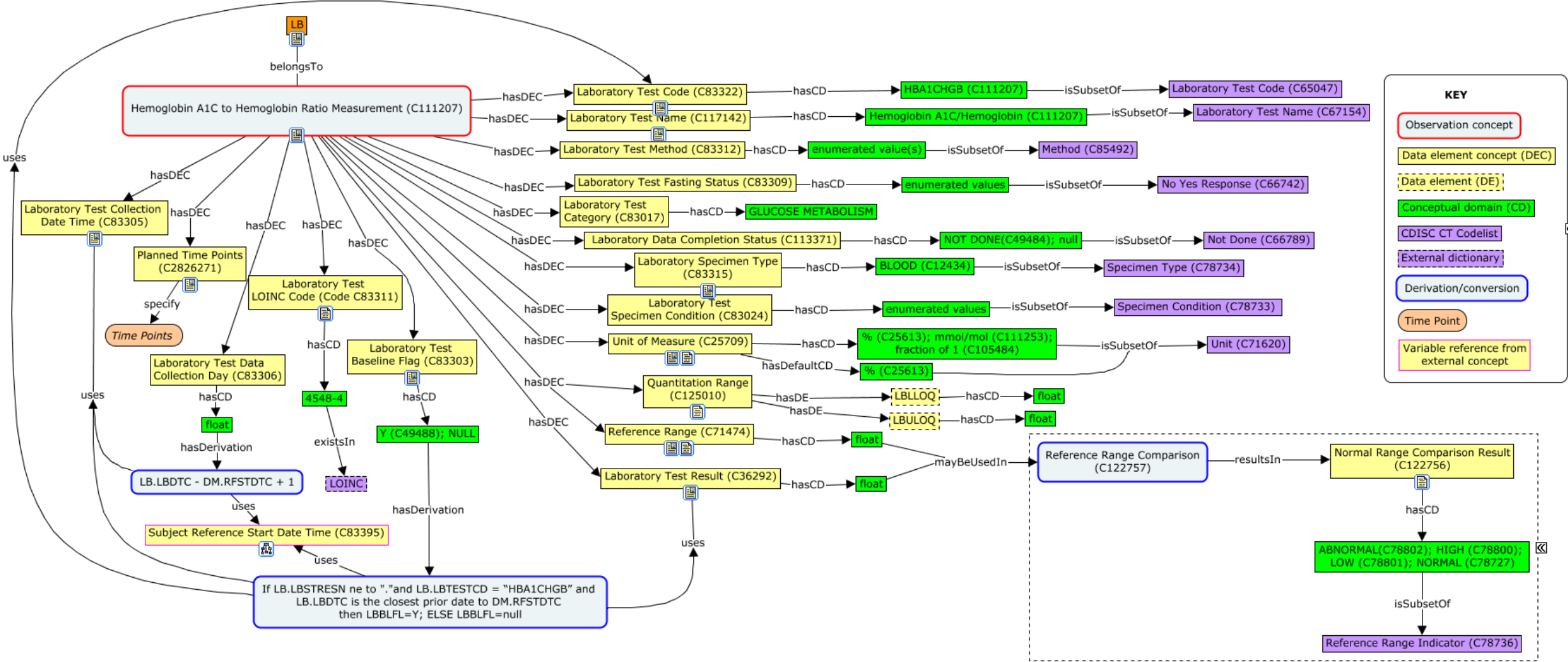
# Biomedical Concepts

The CDISC 360 Project: Adding a conceptual layer to standards

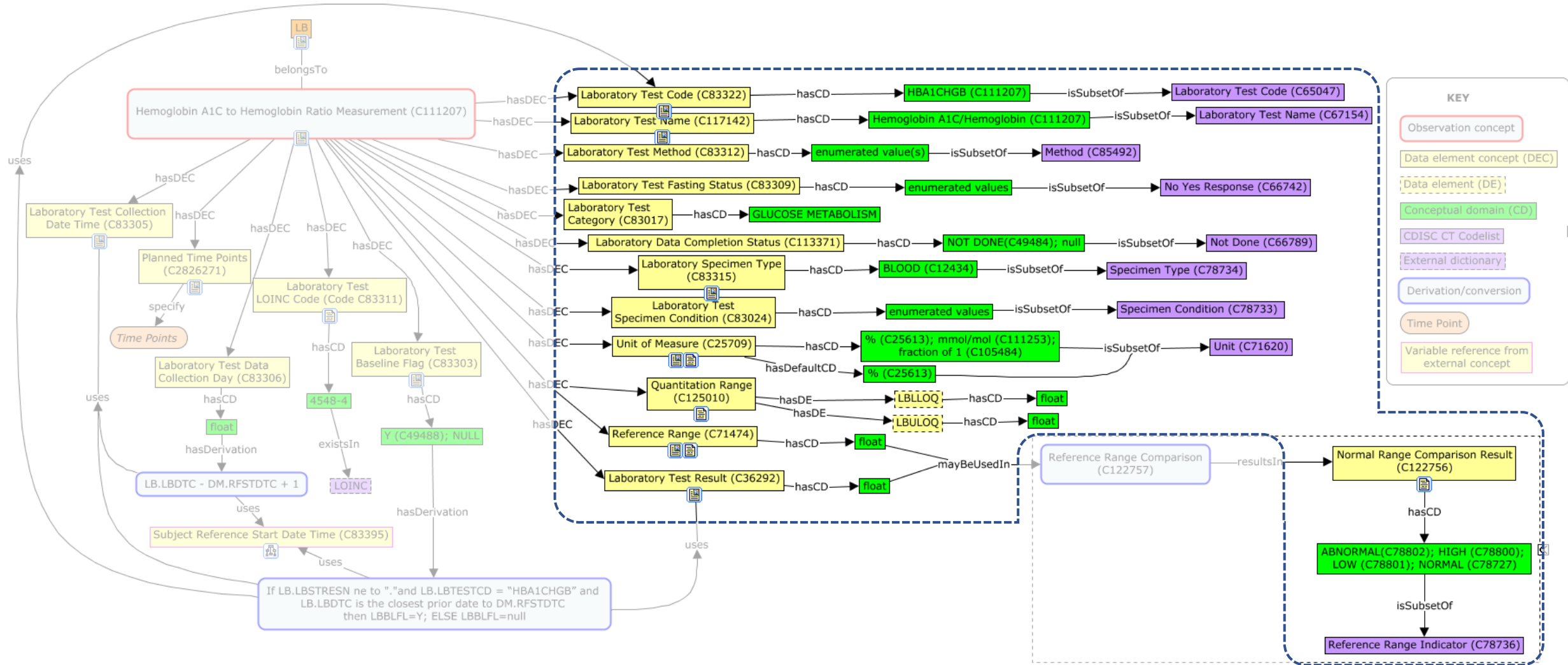
- Create and store standards as concepts which create meaning between data
- Electronically publish data standards as linked metadata
- Add derivation and transformation metadata to avoid unnecessary variability

*→ CDISC 360 will develop concept-based standard definitions, and test and demonstrate end-to-end automation of study specification, data processing, and analysis*

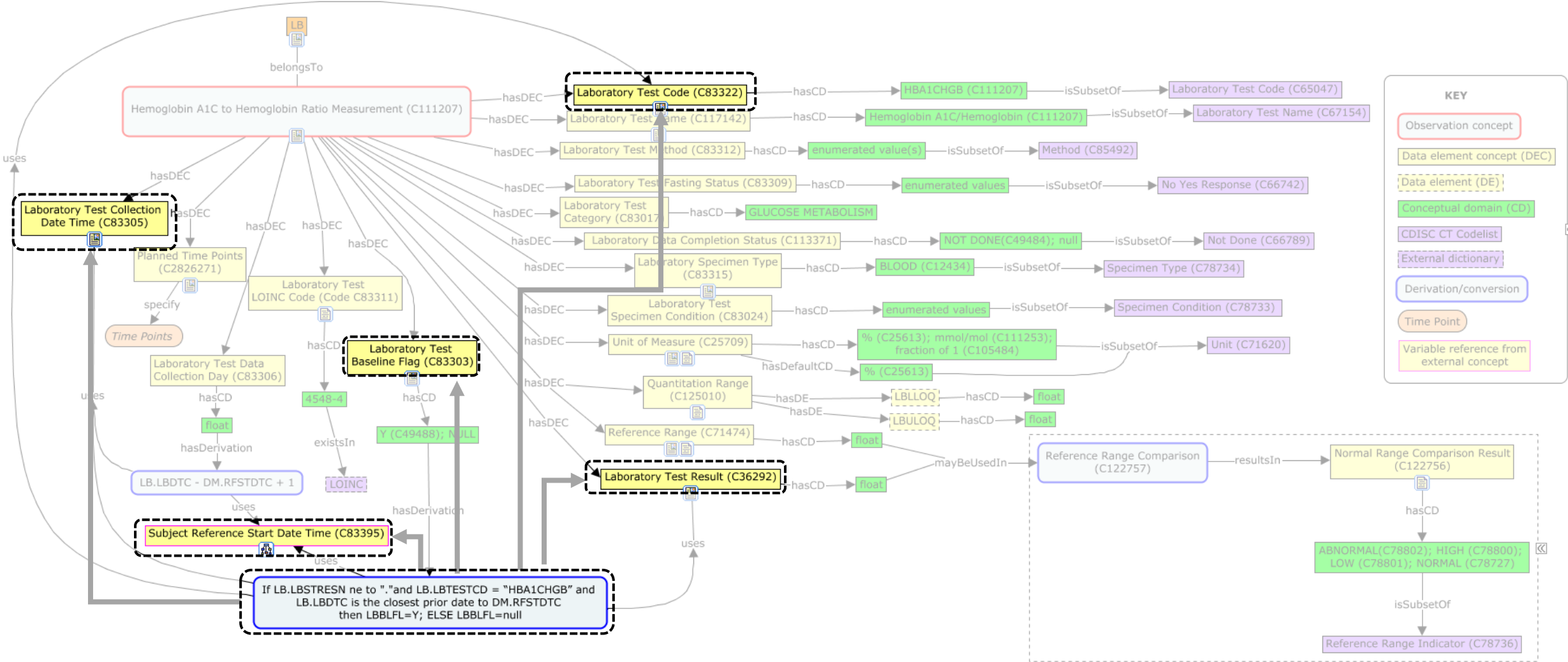
# Biomedical Concept



# Standardize implementation



# Linked derivations & transformations



# What Follows?

- **Create biomedical and analysis concepts**
  - Establish semantic link between end to end implementation
  - Standardize derivation and transformation metadata
- **Evolve Therapeutic Area standards**
  - Analog documents to electronic metadata
  - End to End: from collection through analysis
- **CDASH eCRF Library**
  - Will cover Therapeutic Area content
- **Analysis Results Metadata**
  - Standardize most common analysis

