2021 EUROPE INTERCHANGE

With Standards – Science Will Prevail!

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Live Stream | 28-30 April

CDISC 360: What's in It for Me?

Peter Van Reusel

CDISC European Interchange

Session 7 - April 29, 2021

Meet the Speaker

Peter Van Reusel

Title: Chief Standards Officer
Organization: CDISC

Peter Van Reusel provides executive leadership to the development and implementation of clinical standards in line with CDISC's strategy and operational plans, working closely with the President and CEO, as well as CDISC staff and stakeholders. He has over 20 years' experience in senior roles in pharma and at CROs, providing standards expertise and carrying out other standards work in various organizational settings. A long-time, CDISC-authorized instructor, Peter has helped significantly in developing CDISC training courses.

He previously served as CDISC's European Liaison, shepherding relationships with key European regulatory, academic, and biopharma stakeholders. Peter is also an active PhUSE collaborator.

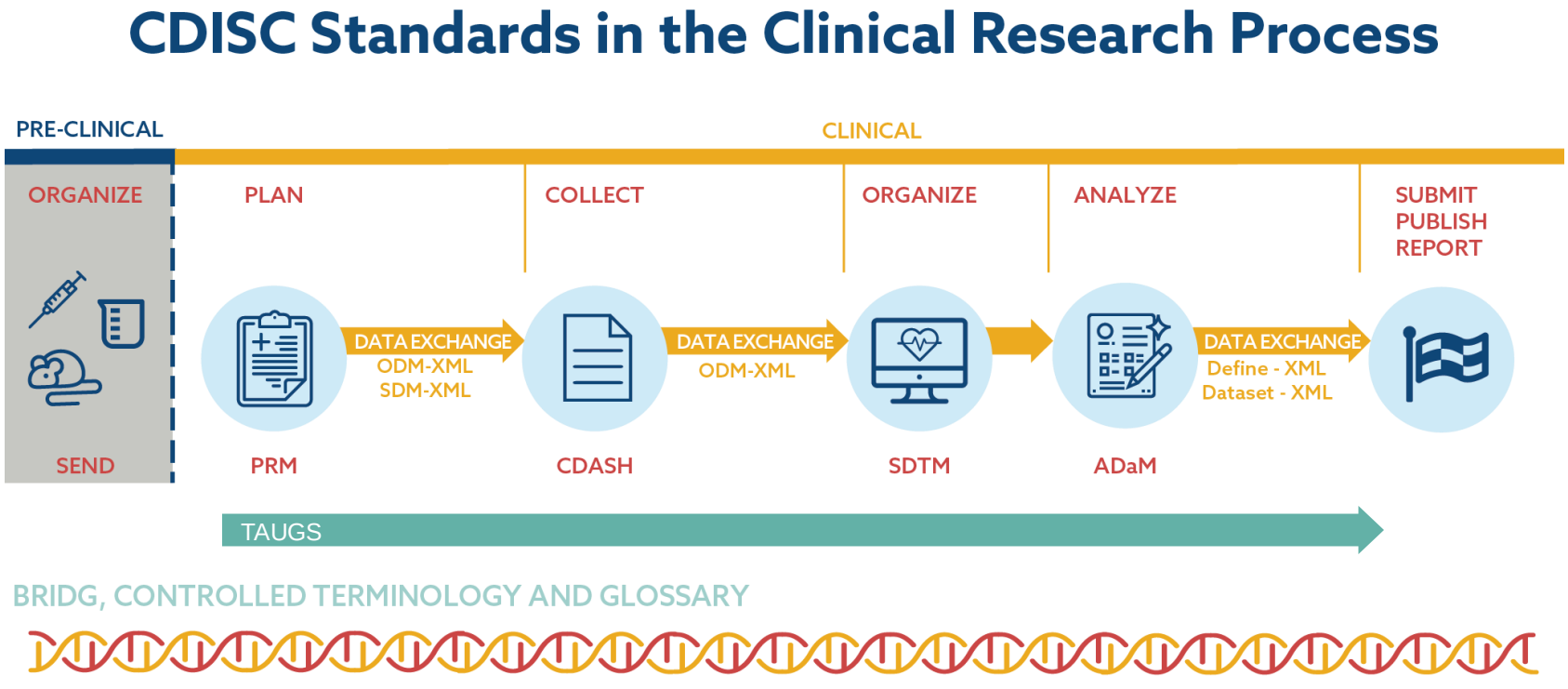
Agenda

1. Common Implementation Challenges Addressed by CDISC 360
2. Four Pillars of CDISC 360 Implementation
3. Summary of Projects

Common Implementation Challenges

What is CDISC 360 trying to address?

Today we are here



What is not in the standards?

- Lack comprehensive data meaning and relationships
- Do not describe the transformations and derivations
- Have flexibility that allows for inconsistencies, making automation difficult, allowing interpretation & unnecessary variability in using the standards
- Therapeut published as text instead of machine-readable content with machine executable transformation and derivation algorithms
- Therapeutic Area User Guides provide end-to-end knowledge standardization
  - From data collection to analysis
  - Analog documents, published as text

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

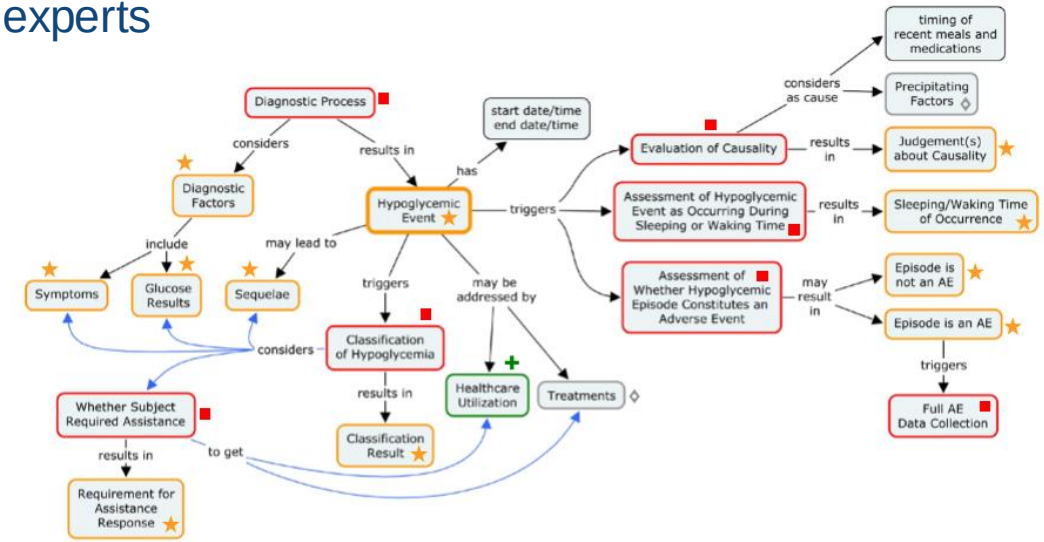
➔ *44 Therapeutic Area User Guides in 8 years*

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

Therapeutic Area Concept Maps

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

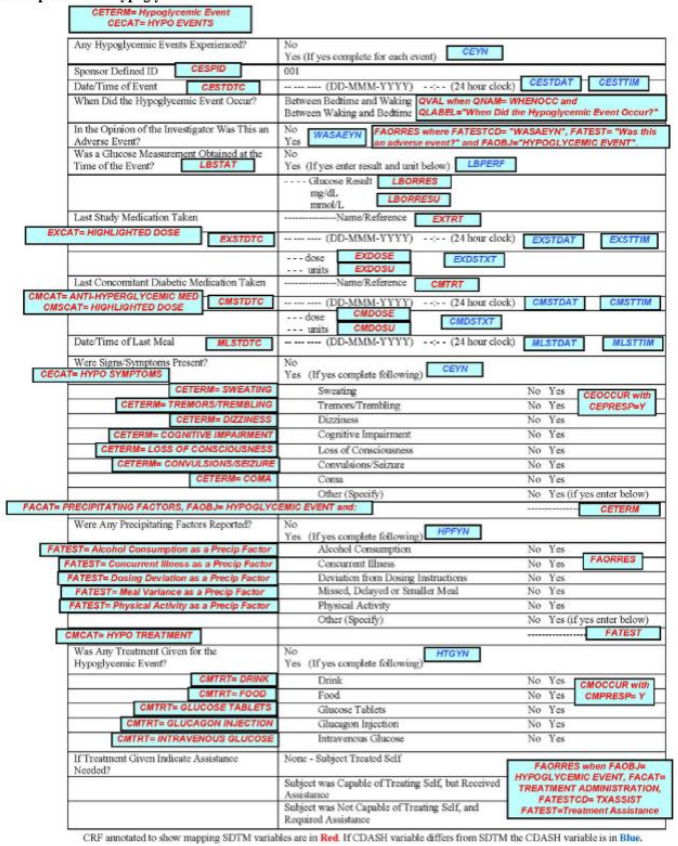
➔ *"This is a picture for humans, this knowledge does not exist for machines"*



Concept Map 7: Hypoglycemic Event

TAUG CRFs and Datasets

Example CRF 5: Hypoglycemia



Row	STUDYID	DOMAIN	USUBJID	CESEQ	CECAT	CETERM	CEDECOD	CEPRESP	CEOCCUR	CESTDTC	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	

➔ *Human readable only*

TAUG Analysis Datasets and Results

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	AVAL	TRTDURD	SEX	AGE	COUNTRY	TRTA
1	XYZ	000008	ASSYMP	Asymptomatic Hypoglycemia (frequency count)	Week 1	3	72	F	55	DZA	Drug B
2	XYZ	000008	ASSYMPC	Asymptomatic Hypoglycemia (cumulative frequency count)	Week 1	3	72	F	55	DZA	Drug B
3	XYZ	000008	ASSYMP	Asymptomatic Hypoglycemia (frequency count)	Week 2	1	72	F	55	DZA	Drug B
4	XYZ	000008	ASSYMPC	Asymptomatic Hypoglycemia (cumulative frequency count)	Week 2	4	72	F	55	DZA	Drug B
5	XYZ	000008	ASSYMP	Asymptomatic Hypoglycemia (frequency count)	Week 3	0	72	F	55	DZA	Drug B
6	XYZ	000008	ASSYMPC	Asymptomatic Hypoglycemia (cumulative frequency count)	Week 3	4	72	F	55	DZA	Drug B
7	XYZ	000008	ASSYMP	Asymptomatic Hypoglycemia (frequency count)	Week 4	1	72	F	55	DZA	Drug B
8	XYZ	000008	ASSYMPC	Asymptomatic Hypoglycemia (cumulative frequency count)	Week 4	5	72	F	55	DZA	Drug B
10	XYZ	000008	ASSYMPC	Asymptomatic Hypoglycemia (cumulative frequency count)	End of Treatment	7	72	F	55	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

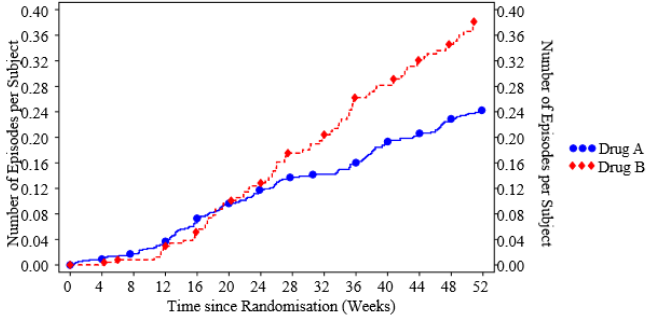
Hypoglycemic Episodes by Classification – Treatment Emergent – Summary – Safety Analysis Set

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



➔ *Only exists in PDF*

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Biomedical Concepts

The CDISC 360 Project: Adding a conceptual layer to standards

- Evolve from normative to informative standards
- Create and store standards as concepts which create meaning
- Electronically publish data standards as linked metadata
- Add computer executable process metadata which enables end to end automation
- Develop concept-based standard definitions, and test and demonstrate end-to-end automation of study specification, data processing, and analysis

➔ *Test and demonstrate, but* ***not building software***

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Four Pillars of CDISC 360 Implementation

Four Pillars of CDISC 360 Implementation

Four pillars of 360 implementation emerge from the 360 lessons learned:

1. **Complete** the E2E foundational standards where they are incomplete

2. **Enrich** the foundational standards with the additional metadata needed for full data meaning and relationships by creating a biomedical concept layer

3. **Extend** the CDISC Library model with implementation level metadata

4. **Collaborate** with industry to standup and curate biomedical concepts

Implementing 360: Projects

STANDARDS DEVELOPMENT

1. Complete E2E Foundational Standards

- **Project:** eCRF Portal
- **Project:** Analysis Results Standard
- **Project:** Safety User Guide

2. Enrich Foundational Standards

- **Project:** Mining Define.xml's

STANDARDS DELIVERY

3. Extend CDISC Library Model

- **Project:** Model concepts
- **Project:** Add QRS content

4. Collaborate with Industry

- **Project:** Use mining Define.xml project as prototype for collaborative curation process

Implementing 360: Completing E2E Foundational Standards

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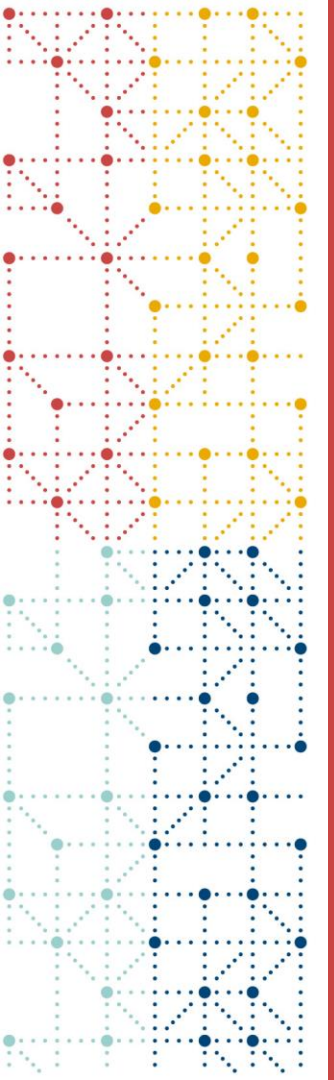

eCRF Portal Project

eCRF Portal Project

t form (CRF) layout

Form AE - Adverse Events			
1 AE - Adverse Events			
1.1	Were any adverse events experienced?	[N] No [Y] Yes	***AEYN***
1.2	What is the adverse event term?		***AETERM***
1.3	Start Date (DD-MMM-YYYY)		***AESTDAT***
1.4	Ongoing (as of [the study-specific time point or period])	[N] No [Y] Yes	
1.5	End Date (DD-MMM-YYYY)		
1.6	Severity	[MILD] M [MODERATE] [SEVERE]	

```
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<ItemGroupDef OID="CDASH_2-1_IG_8" Name="AE - Adverse Events" Repeating="No" Domain="AE">
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        </Description>
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        <ItemRef ItemOID="IT.AETERM" Mandatory="Yes" OrderNumber="2"/>
        <ItemRef ItemOID="IT.AESTDAT" Mandatory="Yes" OrderNumber="3"/>
        <ItemRef ItemOID="IT.AEONGO" Mandatory="No" OrderNumber="4"/>
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        <ItemRef ItemOID="IT.AESEV" Mandatory="No" OrderNumber="6"/>
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```

eCRF Portal – What's in it for Me?

- Helps complete the end-to-end CDISC vision
- ODM XML file can be used directly in compliant EDC systems
- Comes with underlying CDASH metadata
- CDASH annotation is included

➔ *Reduce unnecessary variability in data collection*

https://www.cdisc.org/kb/ecrf

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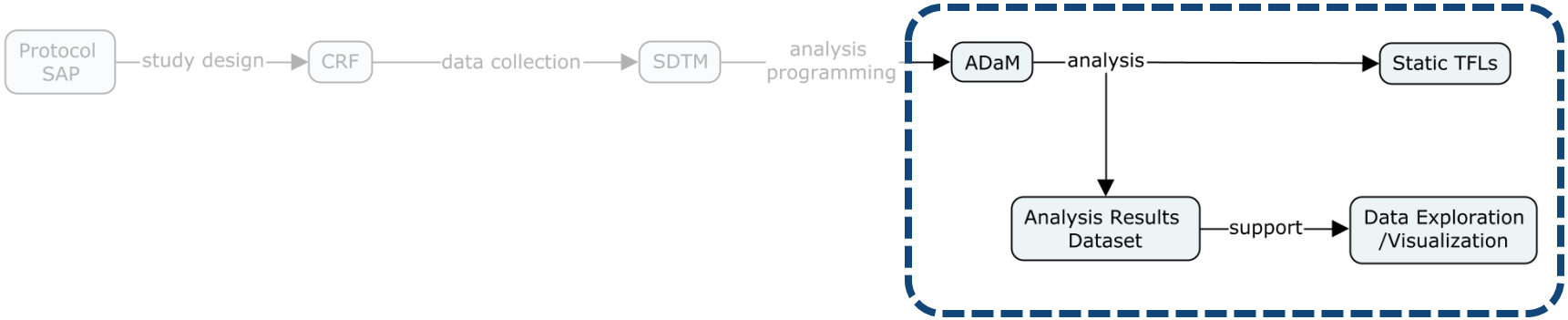
Analysis Results Standard Project

Analysis Results Standard

- ***Extend*** ARM to facilitate automated TFL generation
- ***Create*** a standardized structure for analysis results to support reuse and dynamic data display generation
- ***Tighten*** standardization around ADaM datasets for generally accepted analyses

Where Is Our Focus?



Standardized analysis results support dynamic data display generation

qb:Observation	qb:Table	dim.population	dim.treatment	dim.parameter	dim.sex	dim.agecat	dim.statistic	analysisResult
1001	dm.summary	enrolled	Treatment.A	param.subjects	sex.ALL	agecat.ALL	stat.freq	100
1002	dm.summary	enrolled	Treatment.A	param.subjects	sex.F	agecat.ALL	stat.freq	60
1003	dm.summary	enrolled	Treatment.A	param.subjects	sex.F	agecat.ALL	stat.percent	60
1004	dm.summary	enrolled	Treatment.A	param.subjects	sex.M	agecat.ALL	stat.freq	40
1005	dm.summary	enrolled	Treatment.A	param.subjects	sex.M	agecat.ALL	stat.percent	40
1006	dm.summary	enrolled	Treatment.B	param.subjects	sex.ALL	agecat.ALL	stat.freq	50
1007	dm.summary	enrolled	Treatment.B	param.subjects	sex.F	agecat.ALL	stat.freq	30
1008	dm.summary	enrolled	Treatment.B	param.subjects	sex.F	agecat.ALL	stat.percent	60
1009	dm.summary	enrolled	Treatment.B	param.subjects	sex.M	agecat.ALL	stat.freq	20
1010	dm.summary	enrolled	Treatment.B	param.subjects	sex.M	agecat.ALL	stat.percent	40
1011	dm.summary	enrolled	Treatment.ALL	param.subjects	sex.ALL	agecat.ALL	stat.freq	150
1012	dm.summary	enrolled	Treatment.ALL	param.subjects	sex.F	agecat.ALL	stat.freq	90
1013	dm.summary	enrolled	Treatment.ALL	param.subjects	sex.F	agecat.ALL	stat.percent	60
1014	dm.summary	enrolled	Treatment.ALL	param.subjects	sex.M	agecat.ALL	stat.freq	60
1015	dm.summary	enrolled	Treatment.ALL	param.subjects	sex.M	agecat.ALL	stat.percent	40
1016	dm.summary	itt	Treatment.A	param.age	sex.ALL	agecat.ALL	stat.freq	100
1017	dm.summary	itt	Treatment.A	param.age	sex.ALL	agecat.ALL	stat.mean	40.7
1018	dm.summary	itt	Treatment.A	param.age	sex.ALL	agecat.ALL	stat.stdev	10.7
1019	dm.summary	itt	Treatment.A	param.age	sex.ALL	agecat.ALL	stat.median	37.0
1020	dm.summary	itt	Treatment.A	param.age	sex.ALL	agecat.ALL	stat.min	21.0
1021	dm.summary	itt	Treatment.A	param.age	sex.ALL	agecat.ALL	stat.max	66.0
1022	dm.summary	itt	Treatment.B	param.age	sex.ALL	agecat.ALL	stat.freq	50
1023	dm.summary	itt	Treatment.B	param.age	sex.ALL	agecat.ALL	stat.mean	41.2
1024	dm.summary	itt	Treatment.B	param.age	sex.ALL	agecat.ALL	stat.stdev	10.3
1025	dm.summary	itt	Treatment.B	param.age	sex.ALL	agecat.ALL	stat.median	36.0
1026	dm.summary	itt	Treatment.B	param.age	sex.ALL	agecat.ALL	stat.min	23.0
1027	dm.summary	itt	Treatment.B	param.age	sex.ALL	agecat.ALL	stat.max	67.0
1028	dm.summary	itt	Treatment.ALL	param.age	sex.ALL	agecat.ALL	stat.freq	150
1029	dm.summary	itt	Treatment.ALL	param.age	sex.ALL	agecat.ALL	stat.mean	40.9
1030	dm.summary	itt	Treatment.ALL	param.age	sex.ALL	agecat.ALL	stat.stdev	10.4
1031	dm.summary	itt	Treatment.ALL	param.age	sex.ALL	agecat.ALL	stat.median	37.0
1032	dm.summary	itt	Treatment.ALL	param.age	sex.ALL	agecat.ALL	stat.min	21.0
1033	dm.summary	itt	Treatment.ALL	param.age	sex.ALL	agecat.ALL	stat.max	67.0

Table 4.2.1: HbA1c Longitudinal Repeated Measures Analysis - Table Shell

Protocol: XYZ — Page 1 of 2

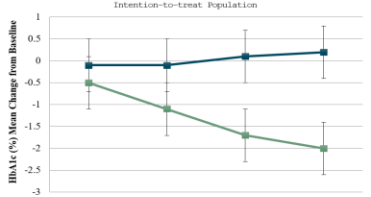
HbA1c (%) Longitudinal Repeated Measures Analysis
24-Week Short-term Double-blind Treatment Period
Intention-to-treat Population

		Drug A N=125	Drug B N=125
BASELINE	N#	125	125
	Mean (SD)	X.XX(X.XXX)	X.XX (X.XXX)
WEEK 4	N#	XXX	XXX
	Change from baseline: Mean (SD)	X.XX (X.XXX)	X.XX (X.XXX)
	Adjusted change from baseline: Mean (SD)	X.XX (X.XXX)	X.XX (X.XXX)
	95% Confidence interval for adjusted mean	(XX.XX, XX.X)	(XX.XX, XX.X)
	Difference vs. Drug B (SE)		XX.XX (X.XXXX)
	95% Confidence interval for difference		(XX.XX, XX.X)
	P-value vs. Drug B		X.XXXX
...			
WEEK 12	N#	X.XX(X.XXX)	X.XX (X.XXX)
	Change from baseline: Mean (SD)	XXX	XXX
	Adjusted change from baseline: Mean (SD)	X.XX (X.XXX)	X.XX (X.XXX)
	95% Confidence interval for adjusted mean	X.XX (X.XXX)	X.XX (X.XXX)
	Difference vs. Drug B (SE)	(XX.XX, XX.X)	(XX.XX, XX.X)
	95% Confidence interval for difference		XX.XX (X.XXXX)
	P-value vs. Drug B		(XX.XX, XX.X)
			X.XXXX

N: the number of subjects in the Intention-to-treat (ITT) Population.
N#: the number of subjects in the ITT population with non-missing baseline and non-missing Week t value.
Repeated measures model: change = baseline treatment visit visit*treatment
Program Source: xxxxxxxx\xxxx\xxxx\t-hbalc-repmeas.sas <date>:<time>

Protocol: XYZ — Page 2 of 2

Mean Change from Baseline in HbA1c (%) Over Time
24-Week Short-term Double-blind Treatment Period
Intention-to-treat Population



Repeated measures model: change = baseline treatment visit visit*base visit*treatment
Mean changes from baseline are based on adjusted changes from baseline from the repeated measure model.
Program Source: /xxxxx/xxxx/xxxx/t-hbalc-repmeas.sas <date>:<time>

Analysis Results Standard – What's in it for Me?

Add features that support automation of analysis results

Provide guidance on basic analysis structures towards analysis results generation

Provide greater traceability between analysis results and analysis data

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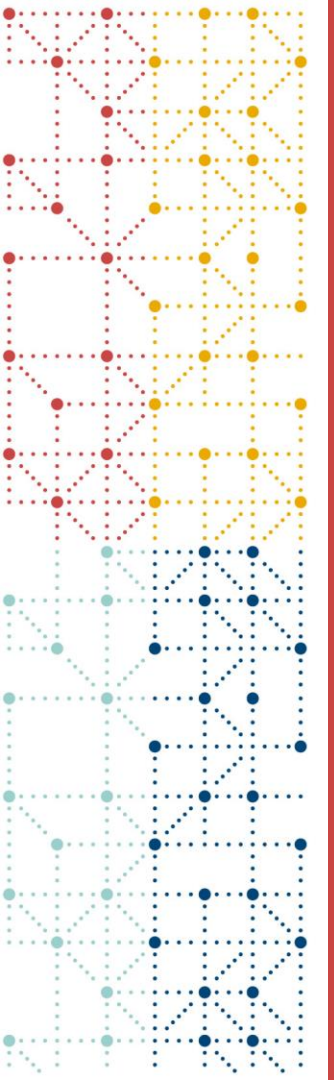


Safety User Guide Project

Why Create a Safety User Guide?

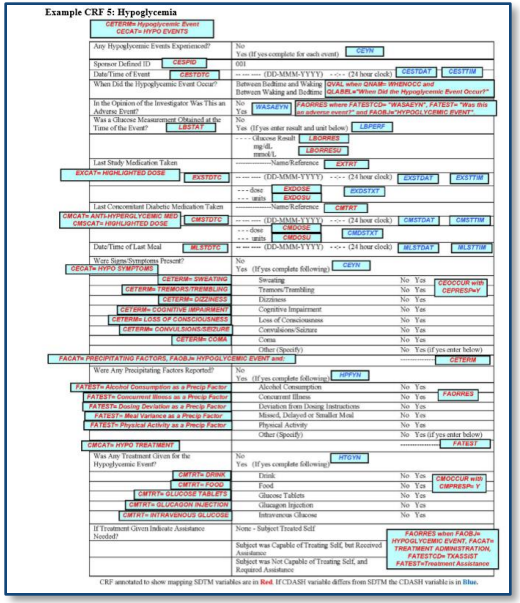
Currently there is lack of a unified CDISC Safety User Guide that spans from data collection through analysis results

Each CDISC Foundational Standard has information on Safety Data that is commonly collected across studies of a wide-variety of indications

The TAUGs also often collect disease-specific safety information and examples

Will identify the most commonly performed safety analyses

Scope: From Analysis Results to Collection



Data Collection

Row	STUDYID	DOMAIN	USUBJID	CESEQ	CECAT	CETERM	CEDECOD	CEPRESP	CEOCCUR	CESTDTC	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		
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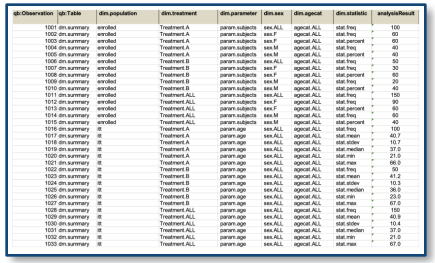
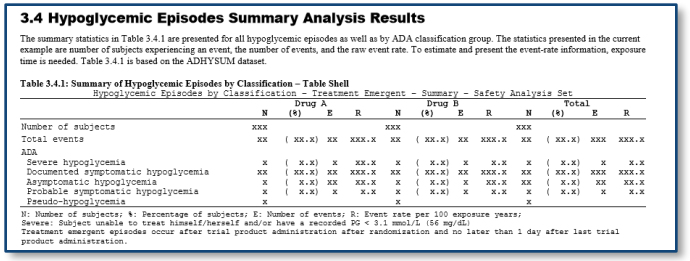
7 (cont)	DURING	HYPO 1	2013-09-01T11:00
8 (cont)	DURING	HYPO 1	2013-09-01T11:00
9 (cont)		HYPO 2	

Data Aggregation



Analysis



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

Hypoglycemic Episodes by Classification – Treatment Emergent – Summary – Safety Analysis Set

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

Analysis Results

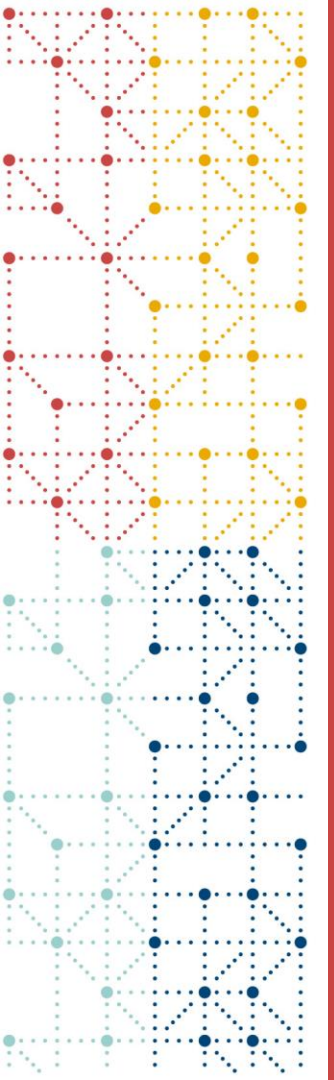
Safety User Guide – What's in it for Me?

- Standardize implementation of the most commonly performed Safety Analyses such as study drug exposure, adverse events, laboratory evaluations, vital signs, and others

- The Safety User Guide will provide:
  - Implementation guidance and examples using the new analysis results standards
  - Analysis datasets
  - Tabulation datasets
  - Data collection metadata
  - eCRFs in the eCRF portal

➡ *Provides common understanding of "how do we do safety"*

cdisc



Mining Biomedical Concepts from Define.xmls

Implementing 360: Standing Up Biomedical Concepts

STANDARDS DEVELOPMENT

1. Complete E2E Foundational Standards

- **Project:** eCRF Portal
- **Project:** Analysis Results Standard
- **Project:** Safety User Guide

2. Enrich Foundational Standards

- **Project:** Mining Define.xml's

STANDARDS DELIVERY

3. Extend CDISC Library Model

- **Project:** Model concepts
- **Project:** Add QRS content

4. Collaborate with Industry

- **Project:** Use mining Define.xml project as prototype for collaborative curation process

cdisc

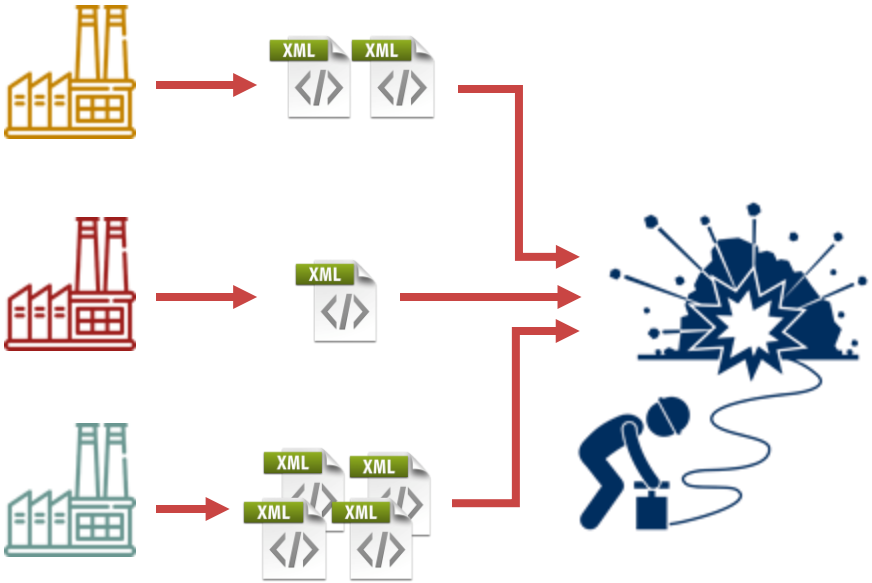
Mining Concepts from Define.xmls

- Retrieve metadata from Define.xmls to determine how standards are used in practice
- Curate the metadata (select best practice, standardize VLM) and stand up biomedical concepts
- Biomedical Concept modeling and load in CDISC Library

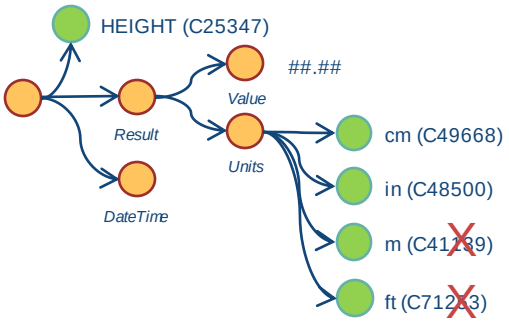
➔ *The first biomedical concepts will be available in the CDISC Library and can be retrieved as an SDTM specification and Define.xml*

cdisc

Select and Identify the Concepts



Mining concepts



Curating concepts

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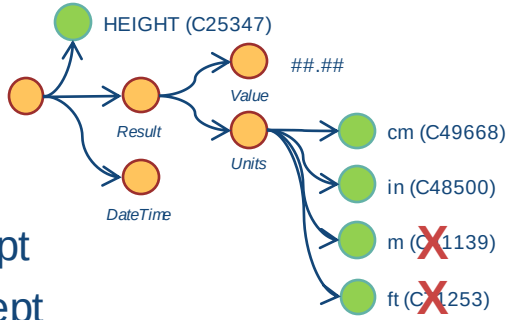
Curate the Concepts

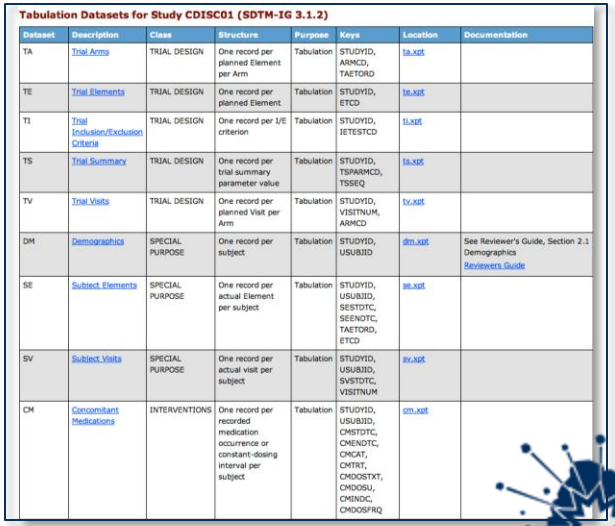


For the selected and identified concepts

- How are standards implemented in real studies?
- Determine the underlying SDTM structure for each concept
- Standardize the SDTM variable data types for each concept
  - e.g., Height STRESN is Float 4.1
- Standardize control terminology for each variable used in each concept
  - e.g., Height UNIT in CM or IN
- What do we consider?
  - Are there differences in how a concept is used across therapeutic areas?
  - Does this align with structure and business rules of the SDTMIG?
  - How do we compromise and reach consensus among different implementations?

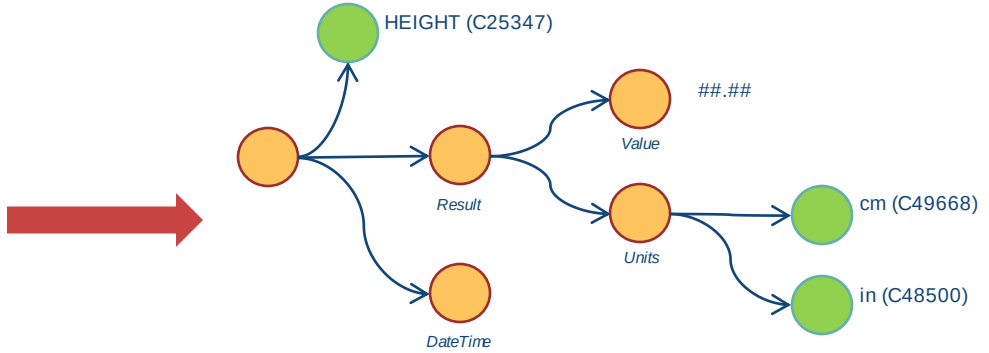
➡ *Choose the best practice implementation*

Load Concepts into CDISC Library



Tabulation Datasets for Study CDISC01 (SDTM-IG 3.1.2)

Dataset	Description	Class	Structure	Purpose	Keys	Location	Documentation
TA	Trial Arms	TRIAL DESIGN	One record per planned Element per Arm	Tabulation	STUDYID, ARMCD, TAETORD	ta.xpt	
TE	Trial Elements	TRIAL DESIGN	One record per planned Element	Tabulation	STUDYID, ETCD	te.xpt	
TI	Trial Inclusion/Exclusion Criteria	TRIAL DESIGN	One record per I/E criterion	Tabulation	STUDYID, IETESTCD	ti.xpt	
TS	Trial Summary	TRIAL DESIGN	One record per trial summary parameter value	Tabulation	STUDYID, TSPARMCD, TSSEQ	ts.xpt	
TV	Trial Visits	TRIAL DESIGN	One record per planned Visit per Arm	Tabulation	STUDYID, VISITNUM, ARMCD	tv.xpt	
DM	Demographics	SPECIAL PURPOSE	One record per subject	Tabulation	STUDYID, USUBJID	dm.xpt	See Reviewer's Guide, Section 2.1 Demographics Reviewers Guide
SE	Subject Elements	SPECIAL PURPOSE	One record per actual Element per subject	Tabulation	STUDYID, USUBJID, SESTDTC, SEENDTC, TAETORD, ETCD	se.xpt	
SV	Subject Visits	SPECIAL PURPOSE	One record per actual visit per subject	Tabulation	STUDYID, USUBJID, SVSTDTC, VISITNUM	sv.xpt	
CM	Concomitant Medications	INTERVENTIONS	One record per recorded medication occurrence or constant-dosing interval per subject	Tabulation	STUDYID, USUBJID, CMSTDTC, CMENDTC, CMCAT, CMTRT, CMDOSTXT, CMDOSU, CMINDC, CMDOSFRQ	cm.xpt	



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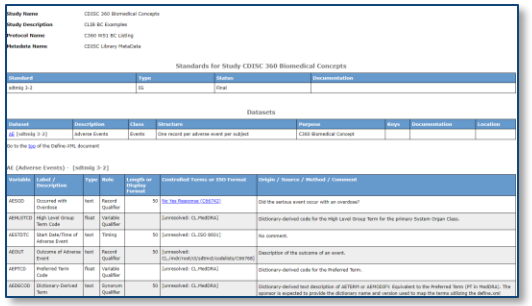
Retrieve Concept Metadata from CDISC Library

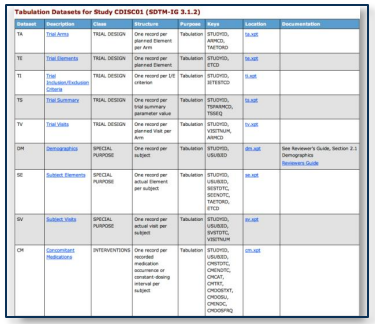
cdisc LIBRARY



Standards for Study CDISC 360 Biomedical Concepts

Datasets

SDTM Specifications



Tabulation Datasets for Study CDISC01 (SDTM-IG 3.1.2)

Define XML

“Mining Define.xmls” – What’s in it for Me?

- Standardizing Value Level Metadata to increase consistency across studies
- Standardizing Data Types and Controlled Terminology per concept
- Linking concepts to SDTM structure to enable automation
  - Ability to Generate Define XML and SDTM Specifications from CDISC Library

This is just the first step of an open path to:

- Link lab concepts to unique LOINC codes
- Link concepts to how they are collected
- How concepts are used in analysis

cdisc

Summary of Projects

Implementing 360: Projects' Summary

STANDARDS DEVELOPMENT

1. Complete E2E Foundational Standards

- **Project:** eCRF Portal
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- **Project:** Safety User Guide

2. Enrich Foundational Standards

- **Project:** Mining Define.xml's

STANDARDS DELIVERY

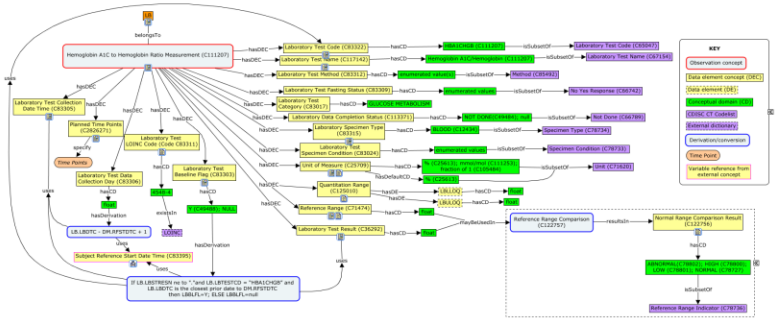
3. Extend CDISC Library Model

- **Project:** Model concepts
- **Project:** Add QRS content

4. Collaborate with Industry

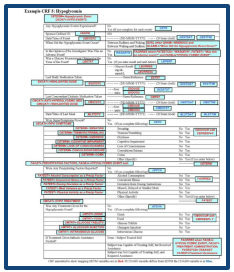
- **Project:** Use mining Define.xml project as prototype for collaborative curation process

Biomedical Concept Layer

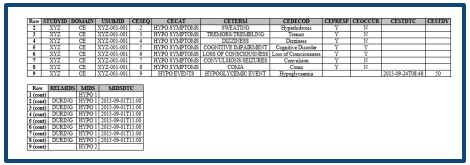


Biomedical Concept Layer

Presentation Layer



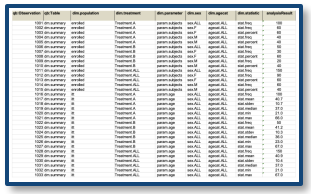
Data Collection



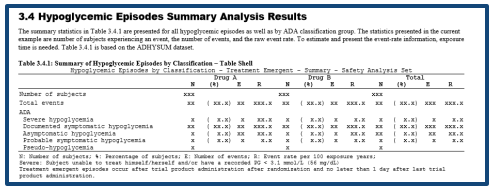
Row	STUDYID	DOMAIN	USUBJID	CESEQ	CECAT	CETERM	CEDECOD	CEPRESP	CEOCCUR	CESTDTC	CEENDTC
1	XYZ	CE	XYZ-001-001	1	HYPO HYPOGLYCEMIA	SWEATING	Hypohidrosis	Y	N		
2	XYZ	CE	XYZ-001-001	2	HYPO HYPOGLYCEMIA	TREMORS/TREMBLING	Tremor	Y	N		
3	XYZ	CE	XYZ-001-001	3	HYPO HYPOGLYCEMIA	HEADACHE	Headache	Y	N		
4	XYZ	CE	XYZ-001-001	4	HYPO HYPOGLYCEMIA	COGNITIVE IMPAIRMENT	Cognitive Disorder	Y	Y		
5	XYZ	CE	XYZ-001-001	5	HYPO HYPOGLYCEMIA	LOSS OF CONSCIOUSNESS	Loss of Consciousness	Y	Y		
6	XYZ	CE	XYZ-001-001	6	HYPO HYPOGLYCEMIA	CONVULSIONS/SEIZURES	Convulsion	Y	N		
7	XYZ	CE	XYZ-001-001	7	HYPO HYPOGLYCEMIA	COMA	Coma	Y	N		
8	XYZ	CE	XYZ-001-001	8	HYPO EVENTS	HYPOGLYCEMIC EVENT	Hypoglycemia			2021-08-24T08:48	30

Row	RELSUBS	MDS	MDSDTC
1 (cont)		HYPO 1	
2 (cont)	DCREVC	HYPO 1	2021-08-21T11:00
3 (cont)	DCREVC	HYPO 1	2021-08-21T11:00
4 (cont)	DCREVC	HYPO 1	2021-08-21T11:00
5 (cont)	DCREVC	HYPO 1	2021-08-21T11:00
6 (cont)	DCREVC	HYPO 1	2021-08-21T11:00
7 (cont)	DCREVC	HYPO 1	2021-08-21T11:00
8 (cont)	DCREVC	HYPO 1	2021-08-21T11:00
9 (cont)		HYPO 2	

Data Aggregation



Analysis



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 rate 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

Hypoglycemic Episodes by Classification – Treatment Emergent – Summary – Safety Analysis Set

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

Analysis Results

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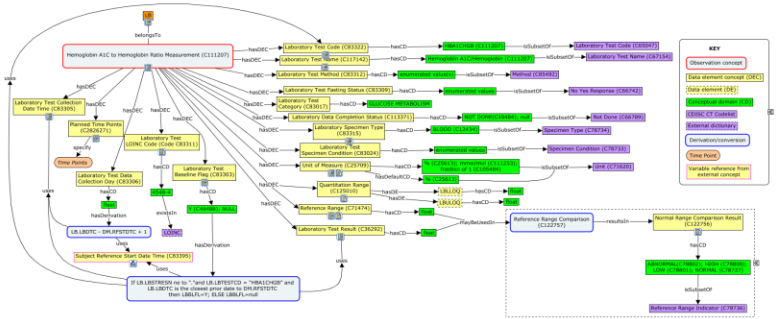
Data State

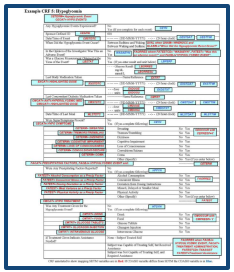
Data Flow

eCRF Portal project

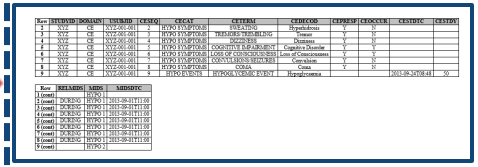


Biomedical Concept Layer

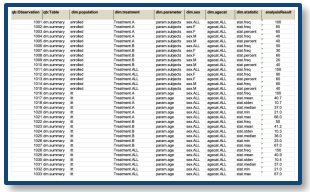
Presentation Layer



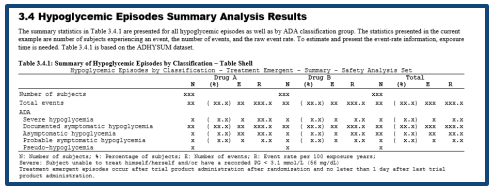
Data Collection



Data Aggregation



Analysis



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

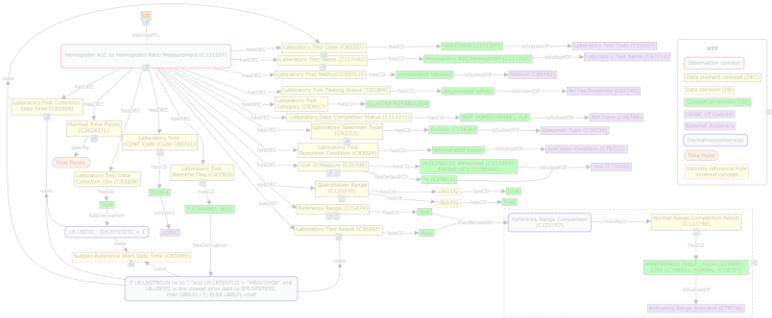
N: Number of subjects; %: Percentage of subjects; E: Number of events; R: Event rate per 100 exposure years;
Severe: Subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56 mg/dL)
Treatment emergent episodes occur after trial product administration after randomization and no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

Analysis Results

Data State

Data Flow

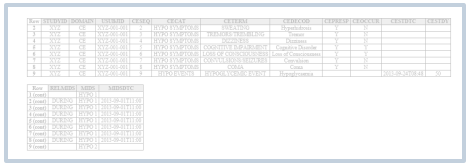
"Analysis Results Standard" Project



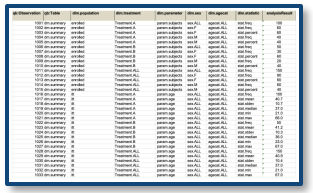
Biomedical Concept Layer

Presentation Layer

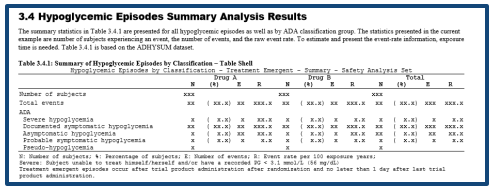
Data Collection



Data Aggregation



Analysis

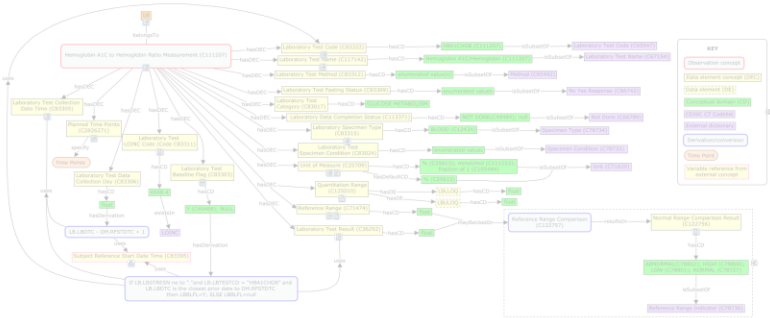


Analysis Results

Data State

Data Flow

"Safety User Guide" Project



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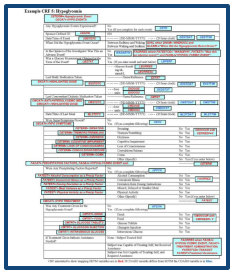
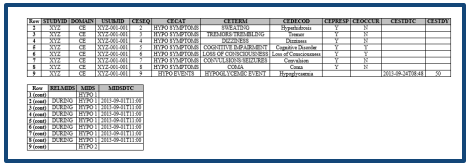
Presentation Layer



Data Collection



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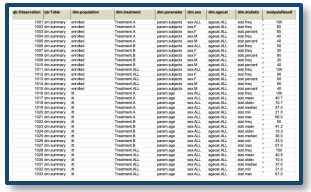
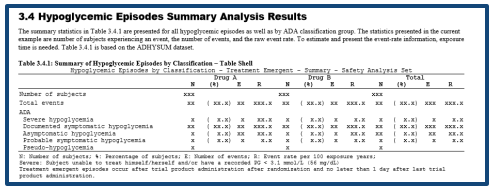


Analysis



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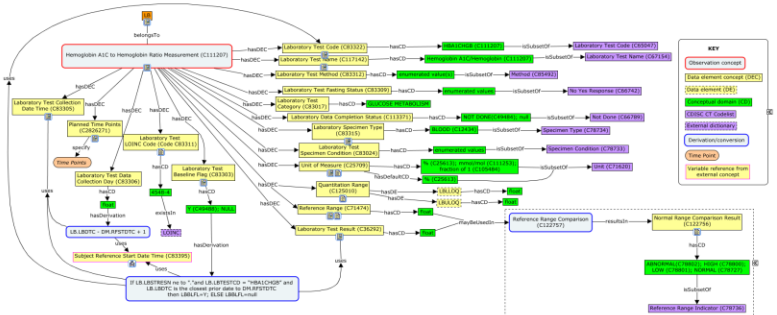
Total events	xx	(xx.x)	xx	xxx.x	xx	(xx.x)	xx	xxx.x	xx	(xx.x)	xxx	xxx.x
ADA												
Severe hypoglycemia	x	(x.x)	x	xx.x	x	(x.x)	x	x.x	x	(x.x)	x	x.x
Documented symptomatic hypoglycemia	xx	(xx.x)	xx	xxx.x	xx	(xx.x)	xx	xxx.x	xx	(xx.x)	xxx	xxx.x
Asymptomatic hypoglycemia	x	(x.x)	xx	xx.x	x	(x.x)	x	xx.x	x	(x.x)	xx	xx.x
Probable symptomatic hypoglycemia	x	(x.x)	x	x.x	x	(x.x)	x	x.x	x	(x.x)	x	x.x
Pseudo-hypoglycemia	x				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.

Data State

Data Flow

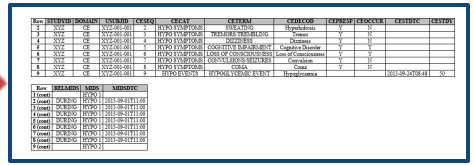
"Mining Define.xml" Project



Biomedical Concept Layer

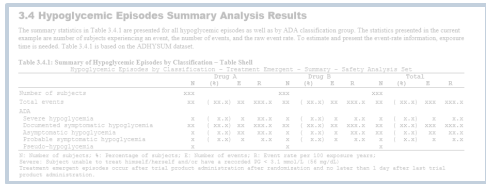
Presentation Layer

Data Collection



Data Aggregation

Analysis



Analysis Results

cdisc

Data State

Data Flow

We are on Our Way to

- Complete standards end-to-end (from analysis to collection)
- Content for standards implementation (e.g., value level metadata)
- Digitize therapeutic area user guides
- Extend the CDISC Library model to include biomedical concepts
- Set up a collaborative curation and governance process

Thank You!

Peter Van Reusel

pvanreusel@cdisc.org