CDISC Newcomer Webinar

Panelists

Kit Howard, Director of Education, CDISC

Shannon Labout, CCDM, Interim Chief Standards Officer; VP of Education, CDISC

Question & Answer

- ‘Panelist’: Question

OR

- ‘Presentation’: Question

Examples:

1) What should be supported by ADaM datasets?
2) Is there a limit to the number of variables that can be in ADSL?

Content Disclaimer

The purpose of CDISC webinars is to provide examples of implementation and should not be considered official recommendations by the standards development teams or CDISC unless otherwise stated in the presentation.

Webinars are not considered to be authorized CDISC courses, are not developed or delivered under COP-005, and should not replace a published IG or UG. Please refer to the latest published standards documents for the most authoritative implementation information.

What is CDISC?

Clinical Data Interchange Standards Consortium

- *Global Standards Development Organization (SDO)*
- *Founded in 1997 (all volunteers)*
- *Incorporated in 2000 as a non-profit organization*

***Mission**: To develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare*

CDISC Standards Development

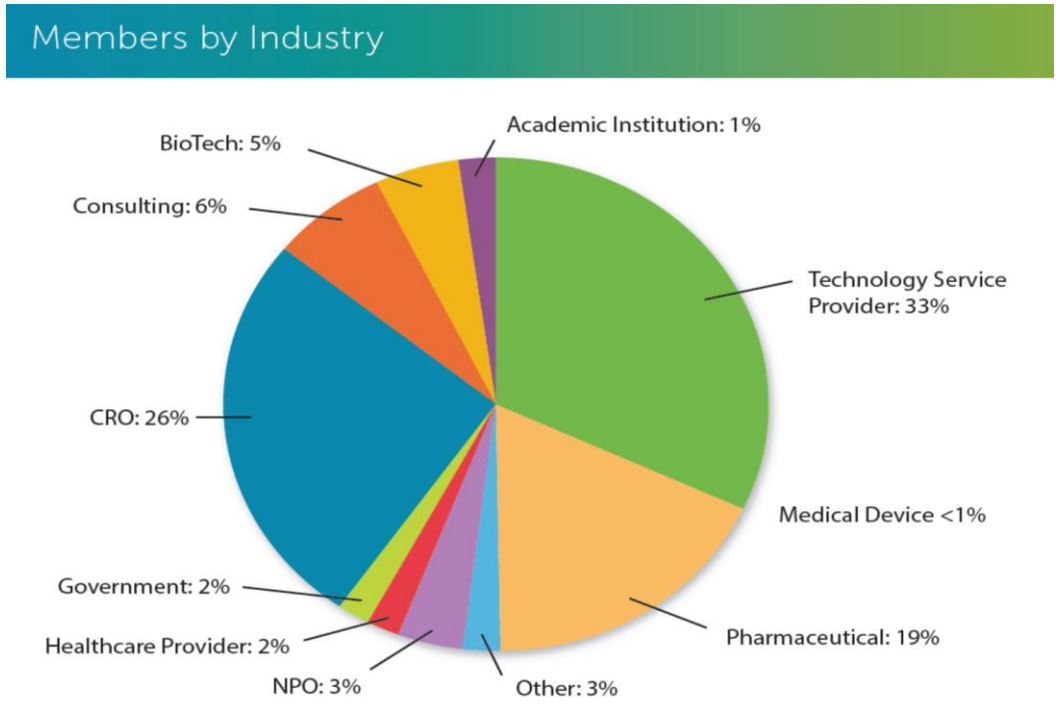
Drivers

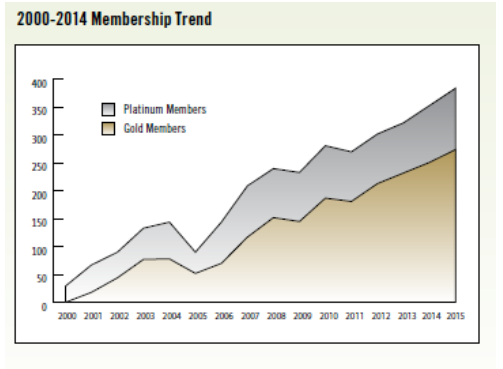
CDISC Team & Volunteers

SHARE Ecosystem

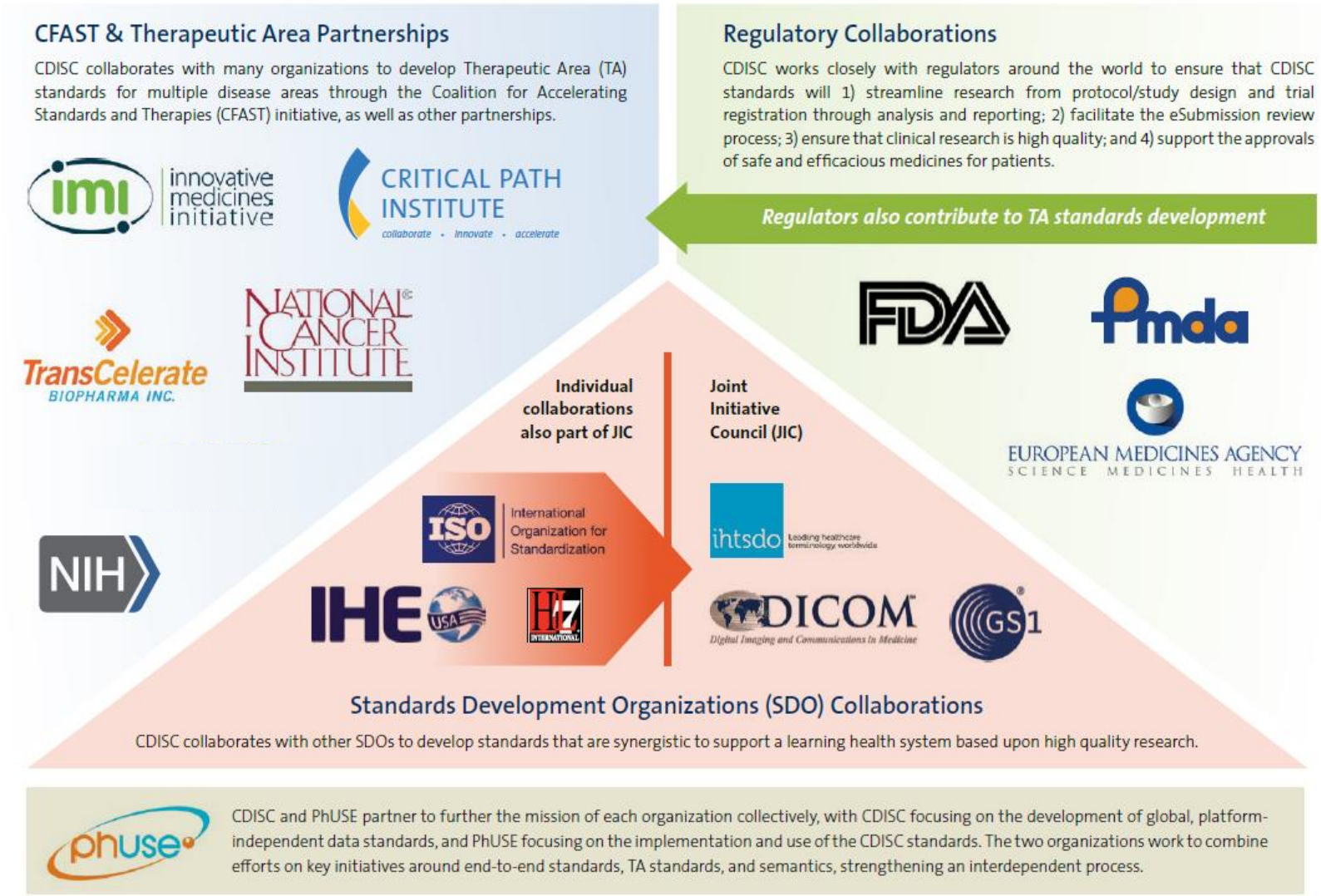
- *>440 organizational members*
- *Consensus based standards development*
- *Standards for clinical & translational research*
- *Standards are freely available at www.cdisc.org*
- *IP Policy ensures open standards*
- *Ongoing global research support in the Americas, Europe, Japan, China, India, Korea and other regions*
- *Standards downloaded in 90+ countries*

CDISC members

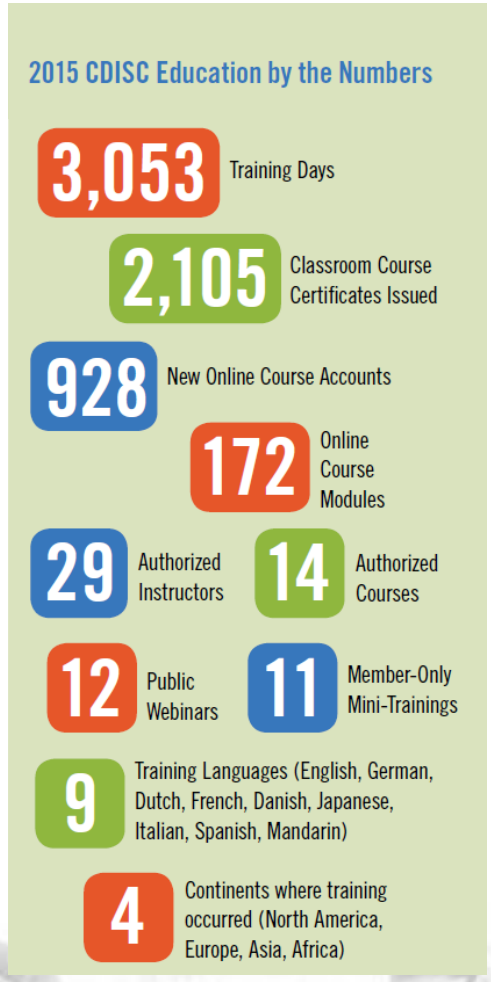




Alliances


CFAST & Therapeutic Area Partnerships
CDISC collaborates with many organizations to develop Therapeutic Area (TA) standards for multiple disease areas through the Coalition for Accelerating Standards and Therapies (CFAST) initiative, as well as other partnerships.
imi innovative medicines initiative
CRITICAL PATH INSTITUTE
collaborate • innovate • accelerate
TransCelerate BIOPHARMA INC.
NATIONAL CANCER INSTITUTE
NIH
Regulatory Collaborations
CDISC works closely with regulators around the world to ensure that CDISC standards will 1) streamline research from protocol/study design and trial registration through analysis and reporting; 2) facilitate the eSubmission review process; 3) ensure that clinical research is high quality; and 4) support the approvals of safe and efficacious medicines for patients.
Regulators also contribute to TA standards development
FDA
Pmda
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
Individual collaborations also part of JIC
Joint Initiative Council (JIC)
ISO International Organization for Standardization
IHE USA
HL7 INTERNATIONAL
ihtsdo
DICOM Digital Imaging and Communications in Medicine
GS1
Standards Development Organizations (SDO) Collaborations
CDISC collaborates with other SDOs to develop standards that are synergistic to support a learning health system based upon high quality research.
phuse
CDISC and PhUSE partner to further the mission of each organization collectively, with CDISC focusing on the development of global, platform-independent data standards, and PhUSE focusing on the implementation and use of the CDISC standards. The two organizations work to combine efforts on key initiatives around end-to-end standards, TA standards, and semantics, strengthening an interdependent process.

Education



- *Standards from the Start*
- *SDTM*
- *CDASH*
- *ADaM primer*
- *ADaM Theory and Application*
- *Define-XML*
- *Controlled Terminology*
- *SEND*
- *BRIDG*
- *Smarter Research Symposium*

Why Standards are needed

Why Standards are Needed

(the Pillars of Misunderstanding)

Homonyms

If you *misunderstand the meaning of clinical concepts* you can't merge or make any meaningful connections or conclusions.

Definitions

If you *have different definitions for clinical concepts* you can't merge or make meaningful connections or conclusions.

<< 5 companies oncol project ex.>>

Terminology

If you *can't agree on the naming conventions and where to use them*, you can't merge or make meaningful connections or conclusions.

SUBJ ID	SEX
0001	M
0002	F
0003	F
0004	M
0005	F

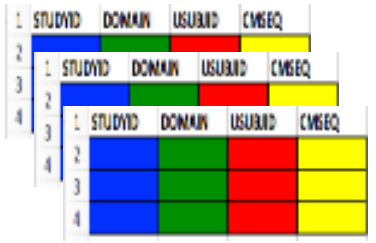
USUBID	SEX
0001	0
0002	1
0003	1
0004	0
0005	1

Relationships

If you *don't see the relationships* between and amongst you create variability in how standards implemented.

Organization

If you *can't find the data* you waste time and resource.



Data Sharing

You *can't share data* in a meaningful and efficient way without addressing each of the above aspects.

What are CDISC models and what are they used for?

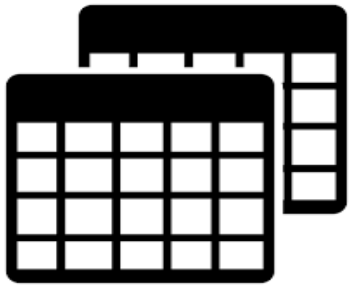
Published Standards

- Foundational Standards
  - Protocol - Data Collection - Aggregation - Analysis - Reporting
  - Operational Data Model
  - Controlled Terminology
- Therapeutic Area Standards
  - Examples of how to implement the foundational standards for particular disease or therapeutic area research

Support Common Functions for All Research

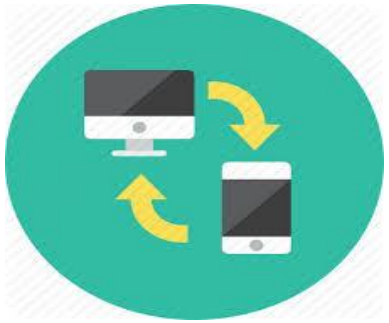
Providing Common Structure & Terminology for:

Data Collection



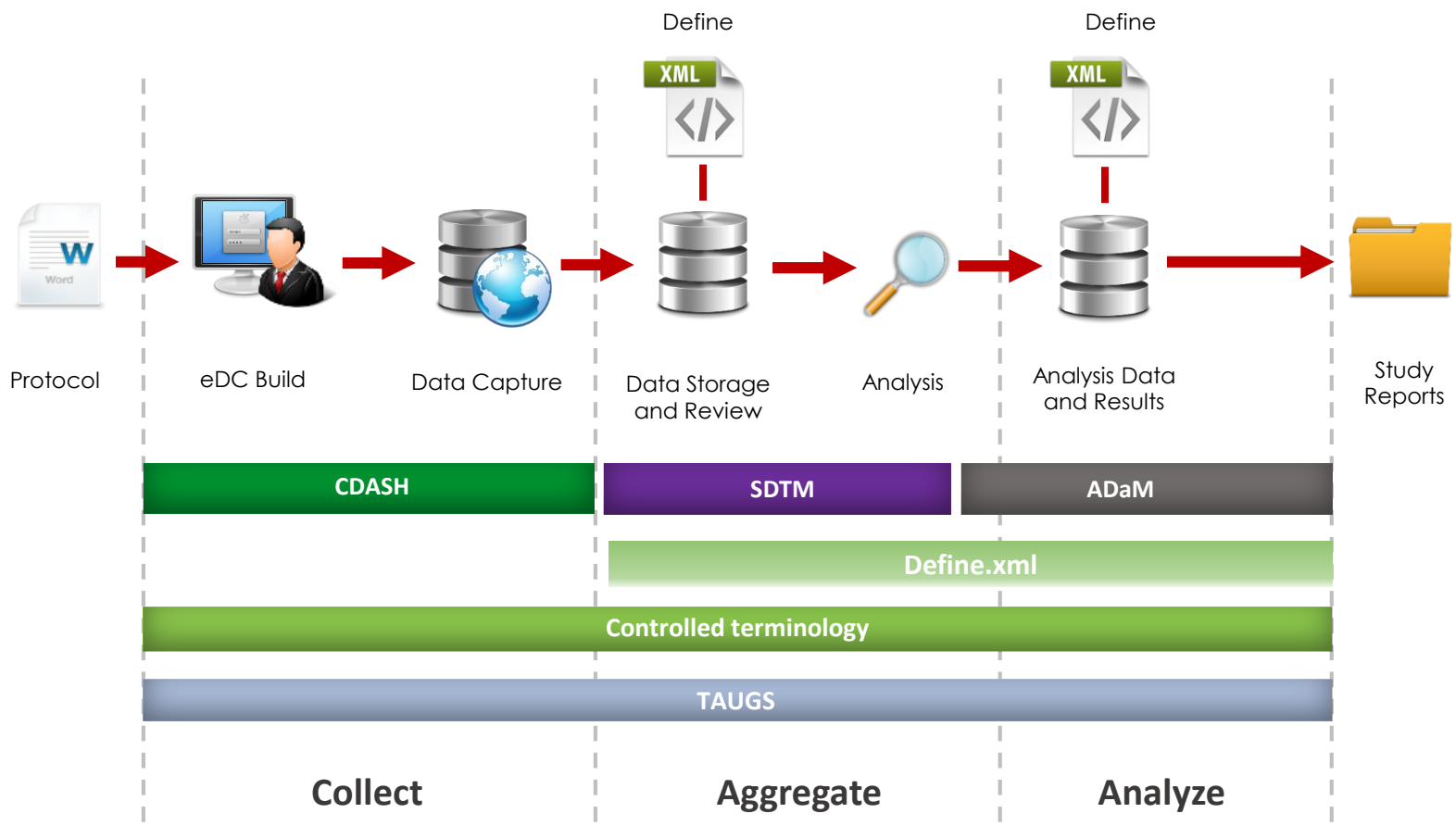
Data Aggregation (Tabulation)

Data Analysis



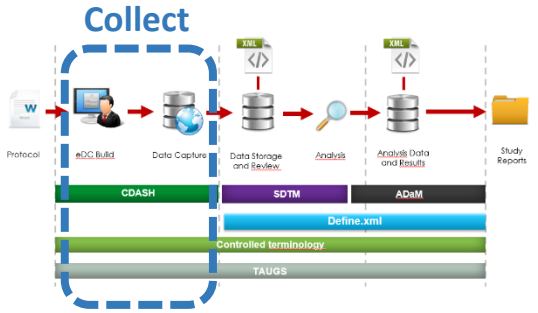
Data Transfer

Use of CDISC Standards in the Clinical Trial Process



CDASH

Clinical Data Acquisition Standards Harmonization



	Question Text	Prompt	SDTM or CDASH Variable Name	BRIDG	Definition	CRF Completion Instructions	Information for Sponsors	Core
1	Were vital signs collected?	Vital signs collected?	VSPERF	PerformedObservation Result.value	General prompt question regarding whether or not any VS were collected during the study. This provides verification that all other fields on the CRF were deliberately left blank. {NY} (See Section 2.2.)	Indicate if the vital signs were collected. If yes, include the appropriate details where indicated on the CRF.	The intent/purpose of collecting this field is to help with data cleaning and monitoring. See Best Practice Section 3.4, FAQ #6. **For the SDTM-based dataset**, SDTMIG variable VSSTAT is derived from a "No" value in VSPERF. This field does not map directly to an SDTM variable.	O
2	On what date were the measurements performed?	Date	VSDAT	PerformedActivity .dateRange*	Date of measurements.	Record date of measurements using this format (DD-MON-YYYY).	The date of measurement can be derived from a collected date of visit and in such cases a separate measurement date field is not required. **For the SDTM-based dataset,** the SDTM IG variable VSDTC is derived by concatenating CDASH Date (VSDAT) and Time (VSTIM) of Vital Sign Measurements (if time is collected) into VSDTC using the ISO 8601 format. For more detail see the Best Practice section. This field does not map directly to an SDTM variable. *See the BRIDG model for complete path.	R/C
3	At what time were the measurements performed?	Time	VSTIM	PerformedActivity .dateRange*	Time of measurements.	Record time of measurement (as complete as possible).	**For the SDTM-based dataset,** the SDTM IG variable VSDTC is derived by concatenating CDASH Date (VSDT) and Time (VSTIM) of Vital Sign Measurements (if time is collected) into VSDTC using the ISO 8601 format. For more detail see the Best Practice section. This field does not map directly to an SDTM variable. *See the BRIDG model for complete path.	R/C

- **Best Practices and Implementation Guides**
- **Standardized CRF questions**
- **Controlled Terminology**
- **Aligned with SDTM**

Example

VITAL SIGNS

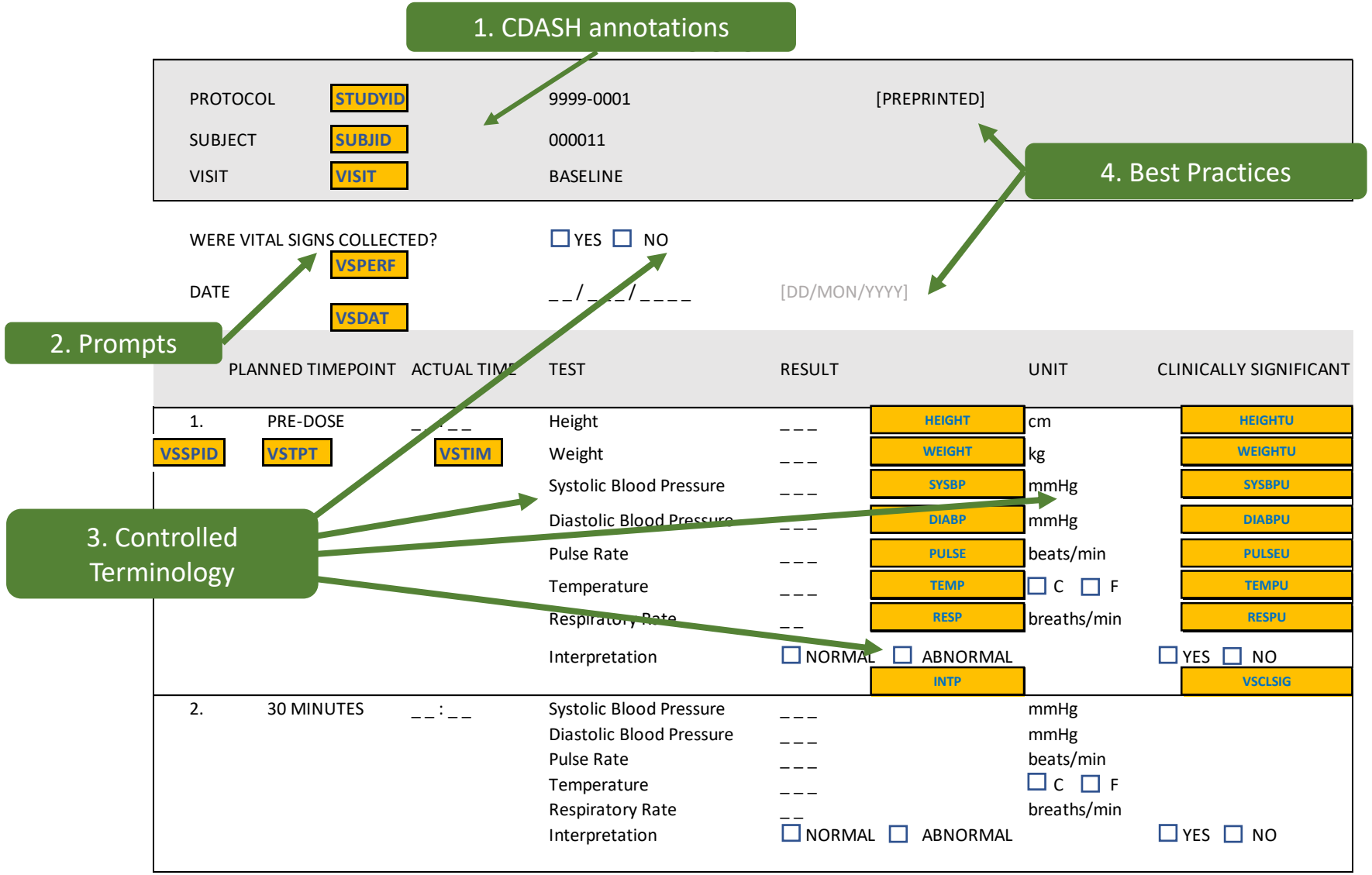
PROTOCOL	ABC-DIA-0012
SUBJECT	Z0001
VISIT	WEEK 4

WERE VITAL SIGNS COLLECTED? ☐ YES ☐ NO

DATE _ _ / _ _ _ / _ _ _ _ [DD/MON/YYYY]

	PLANNED TIMEPOINT	ACTUAL TIME	TEST	RESULT	UNIT	CLINICALLY SIGNIFICANT
1.	PRE-DOSE	_ _ : _ _	Height	_ _ _	cm	
			Weight	_ _ _	kg	
			Systolic Blood Pressure	_ _ _	mmHg	
			Diastolic Blood Pressure	_ _ _	mmHg	
			Pulse Rate	_ _ _	beats/min	
			Temperature	_ _ _	☐ C ☐ F	
			Respiratory Rate	_ _	breaths/min	
			Interpretation	☐ NORMAL ☐ ABNORMAL		☐ YES ☐ NO
2.	30 MINUTES	_ _ : _ _	Systolic Blood Pressure	_ _ _	mmHg	
			Diastolic Blood Pressure	_ _ _	mmHg	
			Pulse Rate	_ _ _	beats/min	
			Temperature	_ _ _	☐ C ☐ F	
			Respiratory Rate	_ _	breaths/min	
			Interpretation	☐ NORMAL ☐ ABNORMAL		☐ YES ☐ NO

Example – with CDASH metadata



CDASH – Data Collection

VITAL SIGNS

PROTOCOL	9999-0001
SUBJECT	000011
VISIT	BASELINE

WERE VITAL SIGNS COLLECTED? ☒ YES ☐ NO

DATE 14/JUN/2017 [DD/MON/YYYY]

	PLANNED TIMEPOINT	ACTUAL TIME	TEST	RESULT	UNIT	CLINICALLY SIGNIFICANT
1.	PRE-DOSE	08:55	Height	184	cm	
			Weight	100	kg	
			Systolic Blood Pressure	130	mmHg	
			Diastolic Blood Pressure	80	mmHg	
			Pulse Rate	62	beats/min	
			Temperature	36	☒ C ☐ F	
			Respiratory Rate	12	breaths/min	
			Interpretation	☒ NORMAL ☐ ABNORMAL		☐ YES ☐ NO
2.	30 MINUTES	09:31	Systolic Blood Pressure	150	mmHg	
			Diastolic Blood Pressure	100	mmHg	
			Pulse Rate	95	beats/min	
			Temperature	36	☒ C ☐ F	
			Respiratory Rate	30	breaths/min	
			Interpretation	☐ NORMAL ☒ ABNORMAL		☐ YES ☒ NO

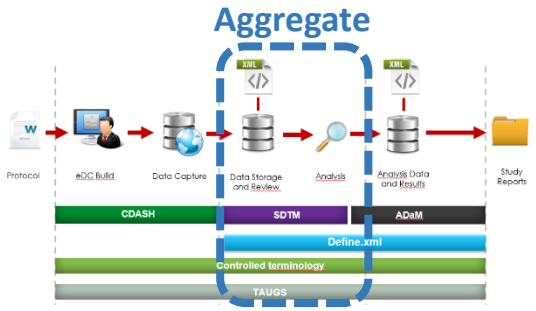
CDASH – EDC Data Extract

	STUDYID	SUBJID	VISIT	VSPERF	VSDAT	VSTIM	VSSPID	VSTPT	HEIGHT	HEIGHTU	WEIGHT	WEIGHTU
1	9999-0001	000011	BASE LINE	YES	14/06/2017	8:55	1	PRE_DOSE	184	cm	100	kg
2	9999-0001	000011	BASE LINE	YES	14/06/2017	9:31	2	30 MINUTES				

	SYSBP	SYSBPU	DIABP	DIABPU	PULSE	PULSEU	TEMP	TEMPU	RESP	RESPU	INT	VSCLSIG
1	130	mmHg	80	mmHg	62	BEATS/MIN	36	C	12	BREATHS/MIN	NORMAL	kg
2	150	mmHg	100	mmHg	95	BEATS/MIN	36	C	30	BREATHS/MIN	ABNORMAL	NO

SDTM

Study Data Tabulation Model



VS – Specification for Vital Signs Domain Model

vs.xpt, Vital Signs — Findings, Version 3.2. One record per vital sign measurement per time point per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req
DOMAIN	Domain Abbreviation	Char	VS	Identifier	Two-character abbreviation for the domain.	Req
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req
VSSEQ	Sequence Number	Num		Identifier	Sequence Number given to ensure uniqueness of subject records within a domain. May be any valid number.	Req
VSGRPID	Group ID	Char		Identifier	Used to tie together a block of related records in a single domain for a subject.	Perm
VSSPID	Sponsor-Defined Identifier	Char		Identifier	Sponsor-defined reference number. Perhaps pre-printed on the CRF as an explicit line identifier or defined in the sponsor's operational database.	Perm
VSTESTCD	Vital Signs Test Short Name	Char	(VSTESTCD)	Topic	Short name of the measurement, test, or examination described in VSTEST. It can be used as a column name when converting a dataset from a vertical to a horizontal format. The value in VSTESTCD cannot be longer than 8 characters, nor can it start with a number (e.g."1TEST"). VSTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: SYSBP, DIABP, BMI.	Req

- **Standard representation of collected data**
- **One model - multiple implementations**
  - Clinical (SDTMIG)
  - Non-clinical (SEND)
  - Medical Devices
  - Pharmaco-Genomics (PGx)

- SDTM is organized in classes
- SDTM is designed to aggregate data
- SDTM can handle all data!!

Example – with SDTM metadata

VITAL SIGNS

PROTOCOL	STUDYID	9999-0001	[PREPRINTED]
SUBJECT	SUBJID	000011	
VISIT	VISIT	BASELINE	

WERE VITAL SIGNS COLLECTED? ☐ YES ☐ NO [NOT SUBMITTED] If NO. VSSTAT = NOT DONE when VSTESTCD=VSALL = VSALL

DATE VSDTC __/___/____ [DD/MON/YYYY]

PLANNED TIMEPOINT		ACTUAL TIME	TEST		RESULT	UNIT	CLINICALLY SIGNIFICANT
			VSTESTCD	VSTEST	VSORRES	VSORRESU	VSCLIG in SUPPVS
1. VSSPID	PRE-DOSE VSTPT	__:__	HEIGHT	Height	___	cm	
			WEIGHT	Weight	___	kg	
			SYSBP	Systolic Blood Pressure	___	mmHg	
			DIABP	Diastolic Blood Pressure	___	mmHg	
			PULSE	Pulse Rate	___	beats/min	
			TEMP	Temperature	___	☐ C ☐ F	
			RESP	Respiratory Rate	__	breaths/min	
			INTP	Interpretation	☐ NORMAL ☐ ABNORMAL		☐ YES ☐ NO
2.	30 MINUTES	__:__		Systolic Blood Pressure	___	mmHg	
				Diastolic Blood Pressure	___	mmHg	
				Pulse Rate	___	beats/min	
				Temperature	___	☐ C ☐ F	
				Respiratory Rate	__	breaths/min	
				Interpretation	☐ NORMAL ☐ ABNORMAL		☐ YES ☐ NO

SDTM Data Storage and Review

	STUDYID	DOMAIN	USUBJID	VSSEQ	VSSPID	VSTESTCD	VSTEST	VSORRES	VSORRESU	VSSTRESC	VSSTRESN	VSBLFL	VSDRVFL	VISITNUM	VISIT	VISITDY	VSDTC	VSTPT
1	9999-0001	VS	9999-0001-000011	1	1	HEIGHT	HEIGHT	184	CM	184	184	Y		2	BASELINE	10	2017-06-14T08:55	PRE-DOSE
2	9999-0001	VS	9999-0001-000011	2	1	WEIGHT	WEIGHT	100	KG	100	100	Y		2	BASELINE	10	2017-06-14T08:55	PRE-DOSE
3	9999-0001	VS	9999-0001-000011	3		BMI	BODY MASS INDEX	29.54	KG/CM2			Y	Y	2	BASELINE	10	2017-06-14T08:55	PRE-DOSE
4	9999-0001	VS	9999-0001-000011	4	1	SYSBP	SYSTOLIC BLOOD PRESSURE	130	mmHG	130	130	Y		2	BASELINE	10	2017-06-14T08:55	PRE-DOSE
5	9999-0001	VS	9999-0001-000011	5	1	DIABP	DIASTOLIC BLOOD PRESSURE	80	mmHG	80	80	Y		2	BASELINE	10	2017-06-14T08:55	PRE-DOSE
6	9999-0001	VS	9999-0001-000011	6	1	PULSE	PULSE RATE	62	BEATS/MIN	62	62	Y		2	BASELINE	10	2017-06-14T08:55	PRE-DOSE
7	9999-0001	VS	9999-0001-000011	7	1	TEMP	TEMPERATURE	36	C	36	36	Y		2	BASELINE	10	2017-06-14T08:55	PRE-DOSE
8	9999-0001	VS	9999-0001-000011	8	1	RESP	RESPIRATORY RATE	12	BREATHS/MIN	12	12	Y		2	BASELINE	10	2017-06-14T08:55	PRE-DOSE
9	9999-0001	VS	9999-0001-000011	9	1	INTP	INTERPRETATION	NORMAL		NORMAL				2	BASELINE	10	2017-06-14T09:31	30 MINUTES
10	9999-0001	VS	9999-0001-000011	10	2	SYSBP	SYSTOLIC BLOOD PRESSURE	150	mmHG	150	150			2	BASELINE	10	2017-06-14T09:31	30 MINUTES
11	9999-0001	VS	9999-0001-000011	11	2	DIABP	DIASTOLIC BLOOD PRESSURE	100	mmHG	100	100			2	BASELINE	10	2017-06-14T09:31	30 MINUTES
12	9999-0001	VS	9999-0001-000011	12	2	PULSE	PULSE RATE	95	BEATS/MIN	95	95			2	BASELINE	10	2017-06-14T09:31	30 MINUTES
13	9999-0001	VS	9999-0001-000011	13	2	TEMP	TEMPERATURE	36	C	36	36			2	BASELINE	10	2017-06-14T09:31	30 MINUTES
14	9999-0001	VS	9999-0001-000011	14	2	RESP	RESPIRATORY RATE	30	BREATHS/MIN	30	30			2	BASELINE	10	2017-06-14T09:31	30 MINUTES
15	9999-0001	VS	9999-0001-000011	15	2	INTP	INTERPRETATION	ABNORMAL		ABNORMAL				2	BASELINE	10	2017-06-14T09:31	30 MINUTES

	STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL	QORIG	QEVAL
1	9999-0001	VS	9999-0001-000011	VSSEQ	15	VSCLSIG	CLINICALLY SIGNIFICANT	NO	CRF	

What is define.xml?

- **Single file per trial**
- **Documentation of the metadata, standards and versions used**
- **Machine Readable & Human Readable**
- **Components**
  - XML : Machine Readable code
  - XSL (stylesheet) : Transforms XML into HTML to make it human readable

```
      <!-- Dataset Definition (TA) -->
      <ItemGroupDef OID="IG.TA"
        Domain="TA"
        Name="TA"
        Repeating="No"
        IsReferenceData="Yes"
        SASDatasetName="TA"
        Purpose="Tabulation"
        def:Structure="One record per planned Element per Arm"
        def:Class="TRIAL DESIGN"
        def:ArchiveLocationID="LF.TA">
        <Description>
          <TranslatedText xml:lang="en">Trial
Arms</TranslatedText>
        </Description>
        <ItemRef ItemOID="IT.STUDYID" OrderNumber="1"
Mandatory="Yes" KeySequence="1"/>
        <ItemRef ItemOID="IT.TA.DOMAIN" OrderNumber="2"
Mandatory="Yes"/>
        <ItemRef ItemOID="IT.TA.ARMCD" OrderNumber="3"
Mandatory="Yes" KeySequence="2"/>
        <ItemRef ItemOID="IT.TA.ARM" OrderNumber="4"
Mandatory="Yes"/>
        <ItemRef ItemOID="IT.TA.TAETORD" OrderNumber="5"
Mandatory="Yes" KeySequence="3"/>
        <ItemRef ItemOID="IT.TA.ETCD" OrderNumber="6"
Mandatory="Yes"/>
        <ItemRef ItemOID="IT.TA.ELEMENT" OrderNumber="7"
Mandatory="No"/>
        <ItemRef ItemOID="IT.TA.TABRANCH" OrderNumber="8"
Mandatory="No"/>
        <ItemRef ItemOID="IT.TA.TATRANS" OrderNumber="9"
Mandatory="No"/>
        <ItemRef ItemOID="IT.TA.EPOCH" OrderNumber="10"
Mandatory="Yes"/>
        <def:leaf ID="LF.TA" xlink:href="ta.xpt">
          <def:title>ta.xpt</def:title>
        </def:leaf>
```

Trial Arms (TA) [Location: ta.xpt]

Variable	Label	Key	Type	Length	Controlled Terms or Format	Origin	Derivation/Comment
STUDYID	Study Identifier	1	text	7		Protocol	
DOMAIN	Domain Abbreviation		text	2	["TA" = "Trial Arms"] <Domain Abbreviation (TA)>	Assigned	
ARMCD	Planned Arm Code	2	text	8	["PLACEBO" = "Placebo", "SCRNFAIL" = "Screen Failure", "WONDER10" = "Miracle Drug 10 mg", "WONDER20" = "Miracle Drug 20 mg"] <Planned Arm Code>	Assigned	
ARM	Description of Planned Arm		text	20	["Miracle Drug 10 mg", "Miracle Drug 20 mg", "Placebo", "Screen Failure"] <Description of Planned Arm>	Protocol	
TAETORD	Order of Element within Arm	3	integer	1		Assigned	
ETCD	Element Code		text	8		Assigned	
ELEMENT	Description of Element		text	40		Protocol	
TABRANCH	Branch		text	35		Protocol	
TATRANS	Transition Rule		text	1		Protocol	
EPOCH	Epoch		text	30		Protocol	

Define.xml (SDTM Metadata)

Dataset	Description	Class	Structure	Purpose	Keys	Location	Documentation
VS	Vital Signs	FINDINGS	One record per vital sign measurement per visit per subject	Tabulation	STUDYID, USUBJID, VSTESTCD, VSDTC, VISITNUM, VSPOS	vs.xpt	
SUPPVS	Supplemental Qualifiers for VS	RELATIONSHIP	One record per IDVAR, IDVARVAL, and QNAM value per subject	Tabulation	STUDYID, RDOMAIN, USUBJID, IDVAR, IDVARVAL, QNAM	suppvs.xpt	

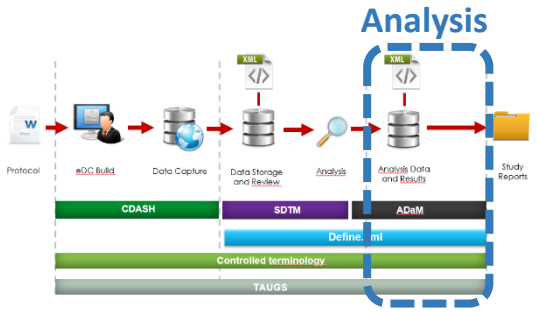
Vital Signs (VS) [Location: vs.xpt]

Variable	Label	Key	Type	Length	Controlled Terms or Format	Origin	Derivation/Comment
STUDYID	Study Identifier	1	text	7		Protocol	
DOMAIN	Domain Abbreviation		text	2	["VS" = "Vital Signs"] <Domain Abbreviation (VS)>	Assigned	
USUBJID	Unique Subject Identifier	2	text	14		Derived	Concatenation of STUDYID and SUBJID
VSSEQ	Sequence Number		integer	2		Derived	Sequential number identifying records within each USUBJID in the domain.
VSTESTCD	Vital Signs Test Short Name	3	text	20	Vital Signs Test Code	Assigned	
VSTEST	Vital Signs Test Name		text	24	Vital Signs Test Name	CRF Page 11	
VSPOS	Vital Signs Position of Subject	6	text	7		CRF Page 11	
VSORRES	Result or Finding in Original Units		text	30		CRF Page 11	
VSORRESU	Original Units		text	20		CRF Page 11	
VSSTRESC	Character Result/Finding in Std Format		text	30		Derived	Data collected in non-standard units (i.e. lbs, inches) is converted using standard conversion factors to standard units (kg, cm).
VSSTRESN	Numeric Result/Finding in Standard Units		float	5		Derived	VSSTRESN = numeric value of VSSTRESC, when VSSTRESC contains numeric data.
VSSTRESU	Standard Units		text	9	["BEATS/MIN" = "Beats per Minute", "cm" = "Centimeter", "kg" = "Kilogram", "mmHg" = "Millimeter of Mercury"] <Units for Vital Signs Results>	Assigned	Standard units consistent with CDISC controlled terminology
VSBLFL	Baseline Flag		text	1	["N" = "No", "U" = "Unknown", "Y" = "Yes"] <No Yes Response Subset>	Derived	Safety subjects only: VSBLFL = "Y" for last record with non Null VSORRES on or before the first dose date (RFSTDTC). Null otherwise.
VISITNUM	Visit Number	5	integer	2		Assigned	Assigned from the TV domain based on the VISIT
VISIT	Visit Name		text	8		Assigned	
VISITDY	Planned Study Day of Visit		integer	3		Protocol	
VSDTC	Date/Time of Measurements	4	date		ISO8601	CRF Page 11	
VSDY	Study Day of Vital Signs		integer	3		Derived	VSDY = VSDTC-RFSTDTC+1 if VSDTC is on or after RFSTDTC. VSDTC - RFSTDTC if VSDTC precedes RFSTDTC.
Related dataset: Supplemental Qualifiers for VS (SUPPVS)							

Go to the top of the define.xml

ADaM

Analysis Data Model



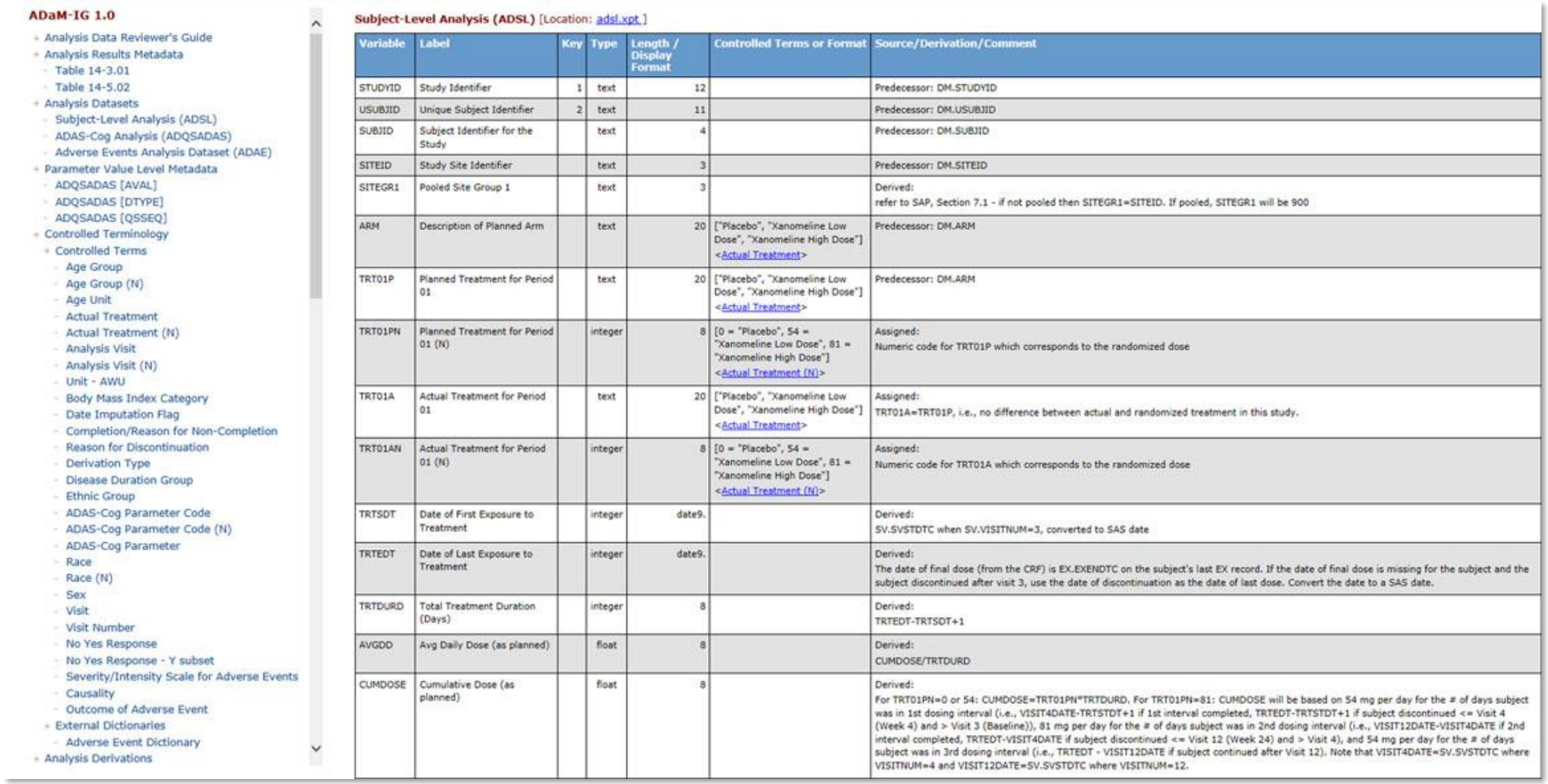
Variable Name	Variable Label	Type	Codelist/ Controlled Terms	Core	CDISC Notes
STUDYID	Study Identifier	Char		Req	DM.STUDYID
USUBJID	Unique Subject Identifier	Char		Req	DM.USUBJID
SUBJID	Subject Identifier for the Study	Char		Req	DM.SUBJID. SUBJID is required in ADSL, but permissible in other datasets.
SITEID	Study Site Identifier	Char		Req	DM.SITEID. SITEID is required in ADSL, but permissible in other datasets.
SITEGRy	Pooled Site Group y	Char		Perm	Character description of a grouping or pooling of clinical sites for analysis purposes. For example, SITEGR3 is the name of a variable containing site group (pooled site) names, where the grouping has been done according to the third site grouping algorithm, defined in variable metadata; SITEGR3 does not mean the third group of sites.
SITEGRyN	Pooled Site Group y (N)	Num		Perm	The numeric code for SITEGRy. One-to-one mapping to SITEGRy within a study.
REGIONy	Geographic Region y	Char		Perm	Character description of geographical region. For example, REGION1 might have values of 'Asia', 'Europe', 'North America', 'Rest of World'; REGION2 might have values of 'United States', 'Rest of World'.
REGIONyN	Geographic Region y (N)	Num		Perm	The numeric code for REGIONy. Orders REGIONy for analysis and reporting. One-to-one mapping to REGIONy within a study.

- ***Provides information about statistical parameters (plan) and how they are applied in the analysis (report)***
- ***Enables traceability back to aggregated data so reviewers understand the statistical method applied and how the conclusions were reached***
- ***Standard structure of analysis data***
- ***Supports the documentation of Tables, Listings, Figures (TFLs) in Clinical Study Report (CSR)***
  - One PROC away

Analysis Dataset

	STUDYID	USUBJID	SUBJID	BMI	BMIGR1	BMIGR1N	BMIGR2	BMIGR2N
2	9999-0001	9999-0001-000001	000001	27.777777778	<30 kg/m**2	1	25-<30 kg/m**2	2
3	9999-0001	9999-0001-000002	000002	25.503615702	<30 kg/m**2	1	25-<30 kg/m**2	2
4	9999-0001	9999-0001-000003	000003	26.175194521	<30 kg/m**2	1	25-<30 kg/m**2	2
5	9999-0001	9999-0001-000004	000004	35.15625	>=30 kg/m**2	2	>=30 kg/m**2	3
6	9999-0001	9999-0001-000005	000005	30.968858131	>=30 kg/m**2	2	>=30 kg/m**2	3
7	9999-0001	9999-0001-000006	000006	39.697163916	>=30 kg/m**2	2	>=30 kg/m**2	3
8	9999-0001	9999-0001-000007	000007	25.826446281	<30 kg/m**2	1	25-<30 kg/m**2	2
9	9999-0001	9999-0001-000008	000008	30.103806228	>=30 kg/m**2	2	>=30 kg/m**2	3
10	9999-0001	9999-0001-000009	000009	32.280962683	>=30 kg/m**2	2	>=30 kg/m**2	3
11	9999-0001	9999-0001-000010	000010	28.876133787	<30 kg/m**2	1	25-<30 kg/m**2	2
12	9999-0001	9999-0001-000011	000011	29.372397383	<30 kg/m**2	1	25-<30 kg/m**2	2
13	9999-0001	9999-0001-000012	000012	26.714852608	<30 kg/m**2	1	25-<30 kg/m**2	2
14	9999-0001	9999-0001-000013	000013	32.718619869	>=30 kg/m**2	2	>=30 kg/m**2	3
15	9999-0001	9999-0001-000014	000014	28.719723183	<30 kg/m**2	1	25-<30 kg/m**2	2
16	9999-0001	9999-0001-000015	000015	32.270420377	>=30 kg/m**2	2	>=30 kg/m**2	3

Define.xml (ADaM metadata)



ADaM-IG 1.0

- Analysis Data Reviewer's Guide
- Analysis Results Metadata
  - Table 14-3.01
  - Table 14-5.02
- Analysis Datasets
  - Subject-Level Analysis (ADSL)
  - ADAS-Cog Analysis (ADQSADAS)
  - Adverse Events Analysis Dataset (ADAE)
- Parameter Value Level Metadata
  - ADQSADAS [AVAL]
  - ADQSADAS [DTYPE]
  - ADQSADAS [QSSEQ]
- Controlled Terminology
  - Controlled Terms
    - Age Group
    - Age Group (N)
    - Age Unit
    - Actual Treatment
    - Actual Treatment (N)
    - Analysis Visit
    - Analysis Visit (N)
    - Unit - AWU
    - Body Mass Index Category
    - Date Imputation Flag
    - Completion/Reason for Non-Completion
    - Reason for Discontinuation
    - Derivation Type
    - Disease Duration Group
    - Ethnic Group
    - ADAS-Cog Parameter Code
    - ADAS-Cog Parameter Code (N)
    - ADAS-Cog Parameter
    - Race
    - Race (N)
    - Sex
    - Visit
    - Visit Number
    - No Yes Response
    - No Yes Response - Y subset
    - Severity/Intensity Scale for Adverse Events
    - Causality
    - Outcome of Adverse Event
  - External Dictionaries
    - Adverse Event Dictionary
- Analysis Derivations

Subject-Level Analysis (ADSL) [Location: adsl.xpt]

Variable	Label	Key	Type	Length / Display Format	Controlled Terms or Format	Source/Derivation/Comment
STUDYID	Study Identifier	1	text	12		Predecessor: DM.STUDYID
USUBJID	Unique Subject Identifier	2	text	11		Predecessor: DM.USUBJID
SUBJID	Subject Identifier for the Study		text	4		Predecessor: DM.SUBJID
SITEID	Study Site Identifier		text	3		Predecessor: DM.SITEID
SITEGR1	Pooled Site Group 1		text	3		Derived: refer to SAP, Section 7.1 - if not pooled then SITEGR1=SITEID. If pooled, SITEGR1 will be 900
ARM	Description of Planned Arm		text	20	["Placebo", "Xanomeline Low Dose", "Xanomeline High Dose"] <Actual Treatment>	Predecessor: DM.ARM
TRT01P	Planned Treatment for Period 01		text	20	["Placebo", "Xanomeline Low Dose", "Xanomeline High Dose"] <Actual Treatment>	Predecessor: DM.ARM
TRT01PN	Planned Treatment for Period 01 (N)		integer	8	[0 = "Placebo", 54 = "Xanomeline Low Dose", 81 = "Xanomeline High Dose"] <Actual Treatment (N)>	Assigned: Numeric code for TRT01P which corresponds to the randomized dose
TRT01A	Actual Treatment for Period 01		text	20	["Placebo", "Xanomeline Low Dose", "Xanomeline High Dose"] <Actual Treatment>	Assigned: TRT01A=TRT01P, i.e., no difference between actual and randomized treatment in this study.
TRT01AN	Actual Treatment for Period 01 (N)		integer	8	[0 = "Placebo", 54 = "Xanomeline Low Dose", 81 = "Xanomeline High Dose"] <Actual Treatment (N)>	Assigned: Numeric code for TRT01A which corresponds to the randomized dose
TRTSDT	Date of First Exposure to Treatment		integer	date9.		Derived: SV.SVSTDTC when SV.VISITNUM=3, converted to SAS date
TRTEDT	Date of Last Exposure to Treatment		integer	date9.		Derived: The date of final dose (from the CRF) is EX.EXENDTC on the subject's last EX record. If the date of final dose is missing for the subject and the subject discontinued after visit 3, use the date of discontinuation as the date of last dose. Convert the date to a SAS date.
TRTDURD	Total Treatment Duration (Days)		integer	8		Derived: TRTEDT-TRTSDT+1
AVGDD	Avg Daily Dose (as planned)		float	8		Derived: CUMDOSE/TRTDURD
CUMDOSE	Cumulative Dose (as planned)		float	8		Derived: For TRT01PN=0 or 54: CUMDOSE=TRT01PN*TRTDURD. For TRT01PN=81: CUMDOSE will be based on 54 mg per day for the # of days subject was in 1st dosing interval (i.e., VISIT4DATE-TRTSTDT+1 if 1st interval completed, TRTEDT-TRTSTDT+1 if subject discontinued <= Visit 4 (Week 4) and > Visit 3 (Baseline)), 81 mg per day for the # of days subject was in 2nd dosing interval (i.e., VISIT12DATE-VISIT4DATE if 2nd interval completed, TRTEDT-VISIT4DATE if subject discontinued <= Visit 12 (Week 24) and > Visit 4), and 54 mg per day for the # of days subject was in 3rd dosing interval (i.e., TRTEDT - VISIT12DATE if subject continued after Visit 12). Note that VISIT4DATE=SV.SVSTDTC where VISITNUM=4 and VISIT12DATE=SV.SVSTDTC where VISITNUM=12.

Analysis Results

Table 1 Demographic Data - Per-Protocol

	Treatment 1	Treatment 2
Baseline body mass index (BMI) [kg/m**2]		
N	167	167
Mean	29.08	29.04
SD	4.84	4.80
Min	20.3	16.0
Median	28.69	28.47
Max	40.1	41.2
Baseline BMI (categorical) [N (%)]		
<25 kg/m**2	41 (24.6%)	71 (21.1%)
25-<30 kg/m**2	60 (35.9%)	130 (38.7%)
>=30 kg/m**2	66 (39.5%)	135 (40.2%)

Define.xml (Analysis Results metadata)

ADaM-IG 1.0

- Analysis Data Reviewer's Guide
- Analysis Results Metadata
  - Table 14-3.01
  - Table 14-5.02
- Analysis Datasets
  - Subject-Level Analysis (ADSL)
  - ADAS-Cog Analysis (ADQSADAS)
  - Adverse Events Analysis Dataset (ADAE)
- Parameter Value Level Metadata
  - ADQSADAS [AVAL]
  - ADQSADAS [DTYPE]
  - ADQSADAS [QSSEQ]
- Controlled Terminology
  - Controlled Terms
    - Age Group
    - Age Group (N)
    - Age Unit
    - Actual Treatment
    - Actual Treatment (N)
    - Analysis Visit
    - Analysis Visit (N)
    - Unit - AWU
    - Body Mass Index Category
    - Date Imputation Flag
    - Completion/Reason for Non-Completion
    - Reason for Discontinuation
    - Derivation Type
    - Disease Duration Group
    - Ethnic Group
    - ADAS-Cog Parameter Code
    - ADAS-Cog Parameter Code (N)
    - ADAS-Cog Parameter
    - Race
    - Race (N)
    - Sex
    - Visit
    - Visit Number
    - No Yes Response
    - No Yes Response - Y subset

Analysis Results Metadata (Summary) for Study CDISC-Sample

Table 14-3.01 Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population) Dose response analysis for ADAS-Cog changes from baseline Pairwise comparisons to placebo for ADAS-Cog changes from baseline
Table 14-5.02 Incidence of Treatment Emergent Serious Adverse Events by Treatment Group Incidence of Treatment Emergent Serious Adverse Events by Treatment Group

Analysis Results Metadata (Detail) for Study CDISC-Sample

Table 14-3.01

Display	Table 14-3.01 Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
Analysis Result	**Dose response analysis for ADAS-Cog changes from baseline**
Analysis Parameter(s)	PARAMCD = "ACTOT" (Adas-Cog(11) Subscore)
Analysis Variable(s)	CHG (Change from Baseline)
Analysis Reason	SPECIFIED IN SAP
Analysis Purpose	PRIMARY OUTCOME MEASURE
Data References (incl. Selection Criteria)	ADQSADAS [PARAMCD = "ACTOT" and AVISIT = "Week 24" and EFFFL = "Y" and ANL01FL = "Y"]
Documentation	Linear model analysis of CHG for dose response; using randomized dose (0 for placebo; 54 for low dose; 81 for high dose) and site group in model. Used PROC GLM in SAS to produce p-value (from Type III SS for treatment dose). SAP Section 10.1.1

Programming Statements	[SAS version 9.2]
	`proc glm data = ADQSADAS;`
	`  where EFFFL='Y' and ANL01FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT";`
	`  class SITEGR1;`
	`  model CHG = TRTPN SITEGR1;`
	`run;`

Analysis Result	**Pairwise comparisons to placebo for ADAS-Cog changes from baseline**
Analysis Parameter(s)	PARAMCD = "ACTOT" (Adas-Cog(11) Subscore)
Analysis Variable(s)	CHG (Change from Baseline)
Analysis Reason	SPECIFIED IN SAP
Analysis Purpose	PRIMARY OUTCOME MEASURE

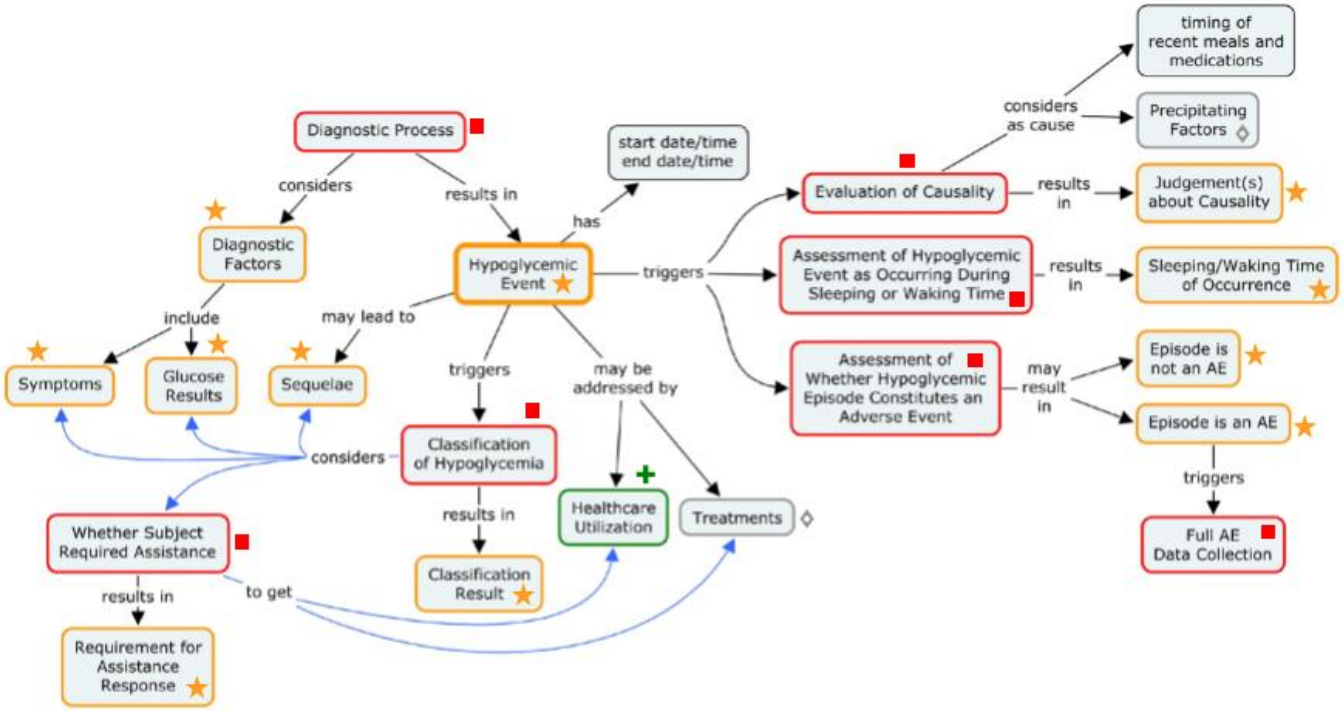
Therapeutic Area User Guides
- Based on Foundational Standards

Therapeutic Area User Guide overview

Oncology	Infectious Diseases	Mental & Behavioral Disorders	CV	Neurology	Chronic Respiratory Diseases	Auto-immune Diseases	Endocrinology	Other
Breast Cancer v1	Tuberculosis v1 Tuberculosis v2, *Gates*	Schizophrenia *FDA*	Dyslipidemia v1	Parkinson's Disease v1	Asthma v1	Rheumatoid Arthritis v1	Polycystic Disease v1 University of Rochester	Pain v1 *University of Rochester*
Prostate Cancer v1 **FDA**	Influenza v1	Alzheimer's v1, v2	CV Endpoints v1 *FDA*	Multiple Sclerosis v1 *MS Society*	COPD v1		Diabetes v1	*Solid Organ (Kidney Transplant) v1* FDA
Colorectal Cancer v1 FDA	Hepatitis C, v1 *FDA*	Parkinson's v1	CV Imaging v1	**Duchenne Muscular Dystrophy v1**			Diabetic Kidney Disease v1	
Lung Cancer v1 **FDA**	Virology v1, v2 *FDA*	Traumatic Brain Injury v1 *One Mind*	QT Studies v1	**Huntington's Disease v1**				
	Malaria v1 Gates / WWARN	Major Depressive Disorder v1 FDA		***Parkinson's v2***				
	Ebola v1	Post Traumatic Stress Disorder v1 Cohen Veterans Bioscience						
	Vaccines v1	Bi-Polar v1						
	HIV v1 **NIAID & FDA**	General Anxiety Disorder v1						
	CDAD **FDA**							
4	*9*	*8*	4	5	2	1	3	2

Bold - ongoing
Planned

Therapeutic Area- Concept Map (example)



Concept Map 7: Hypoglycemic Event

A hypoglycemic event triggers several assessments that help characterize and classify the event. Other collection points regarding diagnostic factors, treatment, and who administered treatment may also be included to describe the event. Classification of hypoglycemic events will usually be part of analysis, rather than data collection.

Data collected about a hypoglycemic event may include some or all of the following:

- The occurrence of each of several symptoms typical of hypoglycemia
- Blood glucose measurement(s) at the time of the event
- The subject's awareness of the event (e.g. presence of signs/symptoms)

Therapeutic Area- Annotated Case Report Forms and Datasets

Example CRF 5: Hypoglycemia

CETERM= Hypoglycemic Event
CECAT= HYPO EVENTS

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

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

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	

Therapeutic Area- 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	AVAL	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	ASSYMPC	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	ASSYMPC	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	ASSYMPC	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	ASSYMPC	Asymptomatic Hypoglycemia (cumulative frequency count)	Week 4	5	72	F	35	DZA	Drug B
10	XYZ	000008	ASSYMPC	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

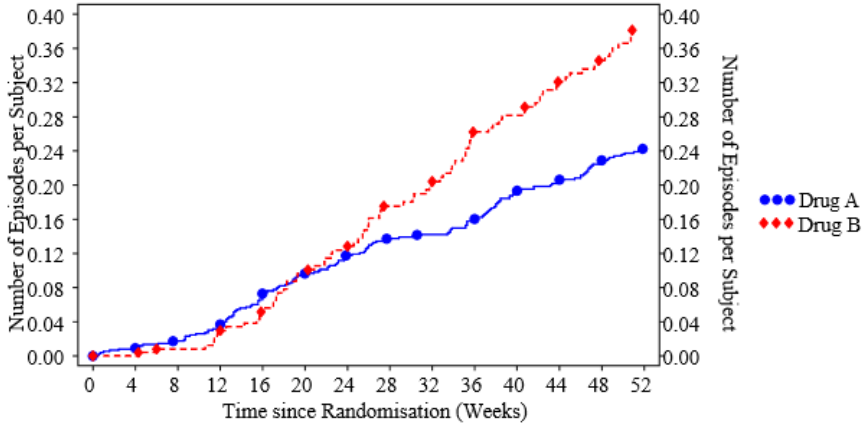
Hypoglycemic Episodes by Classification – Treatment Emergent – Summary – Safety Analysis Set

	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.

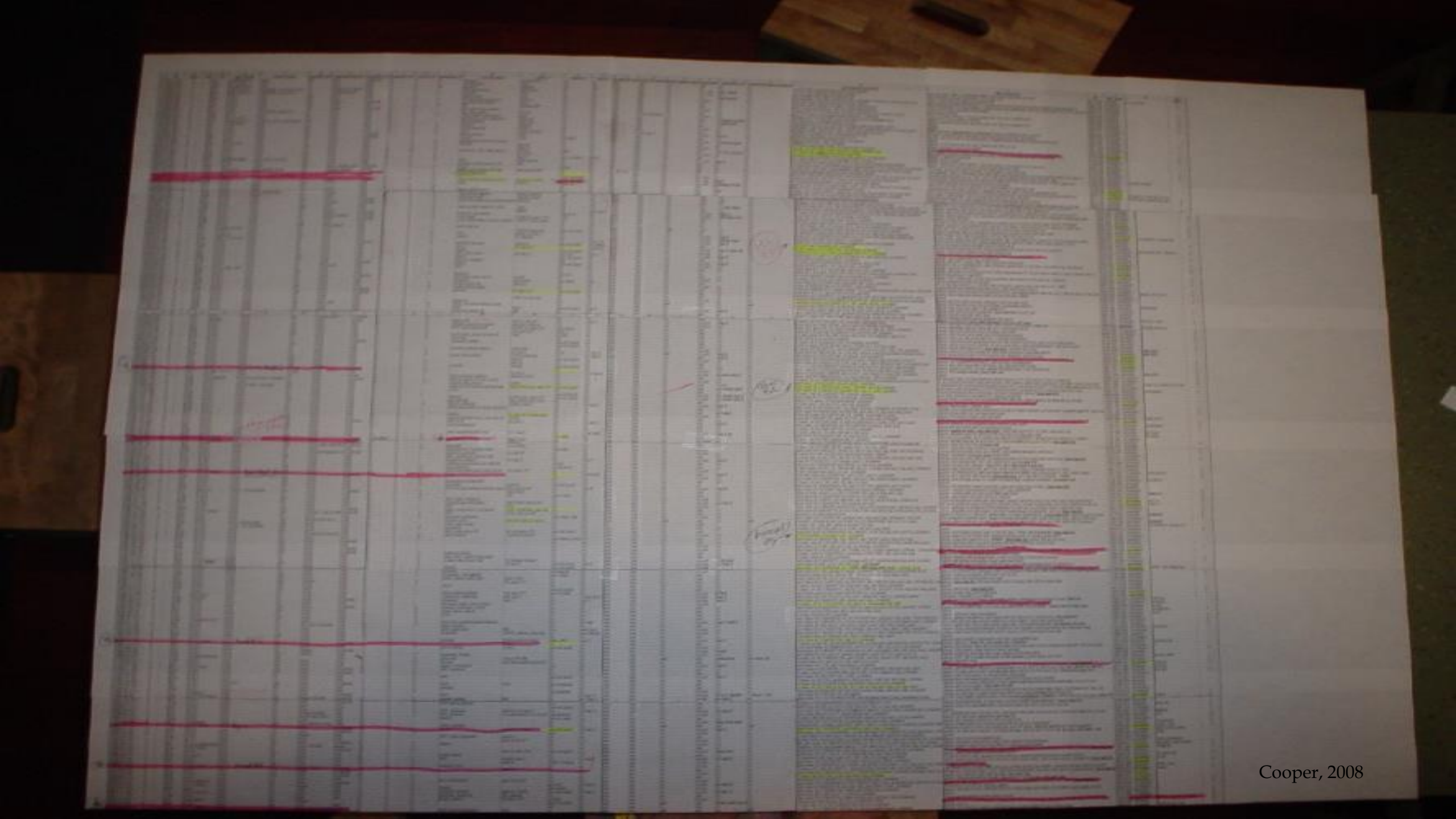
Figure 3.4.1: Mean Cumulative Function Plot of Documented and Severe Symptomatic Hypoglycemic Episodes

Documented and Severe Symptomatic Hypoglycemic Episodes – Treatment Emergent - Mean Cumulative Function - Safety Analysis Set



Industry Regulatory Requirements

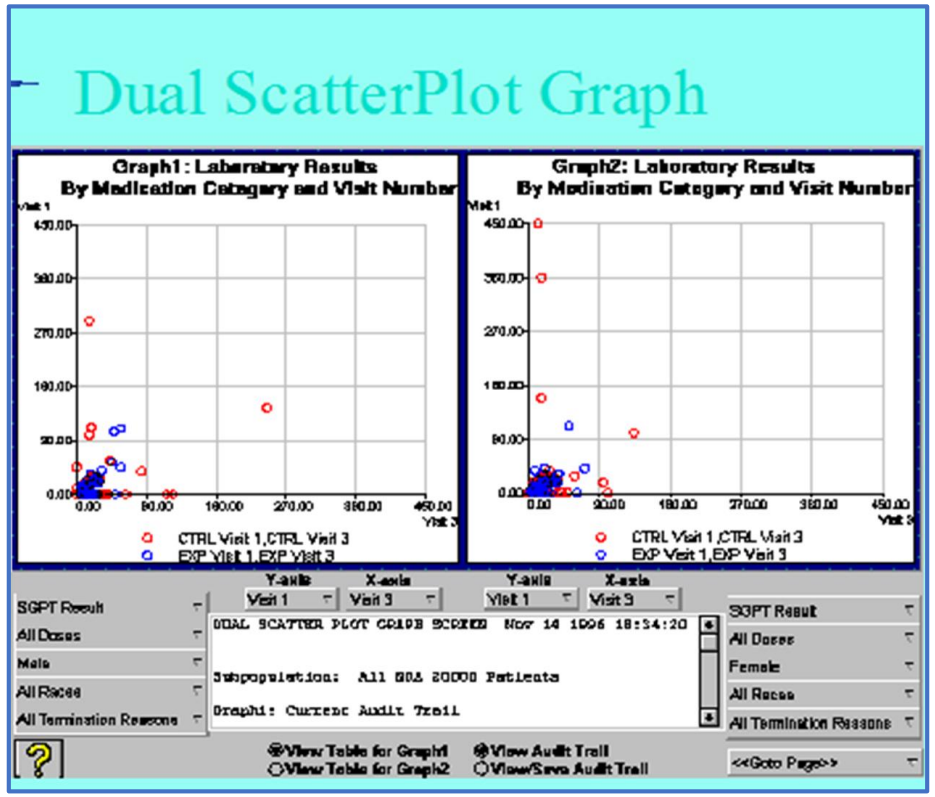
Last Century FDA Regulatory Review



Cooper, 2008

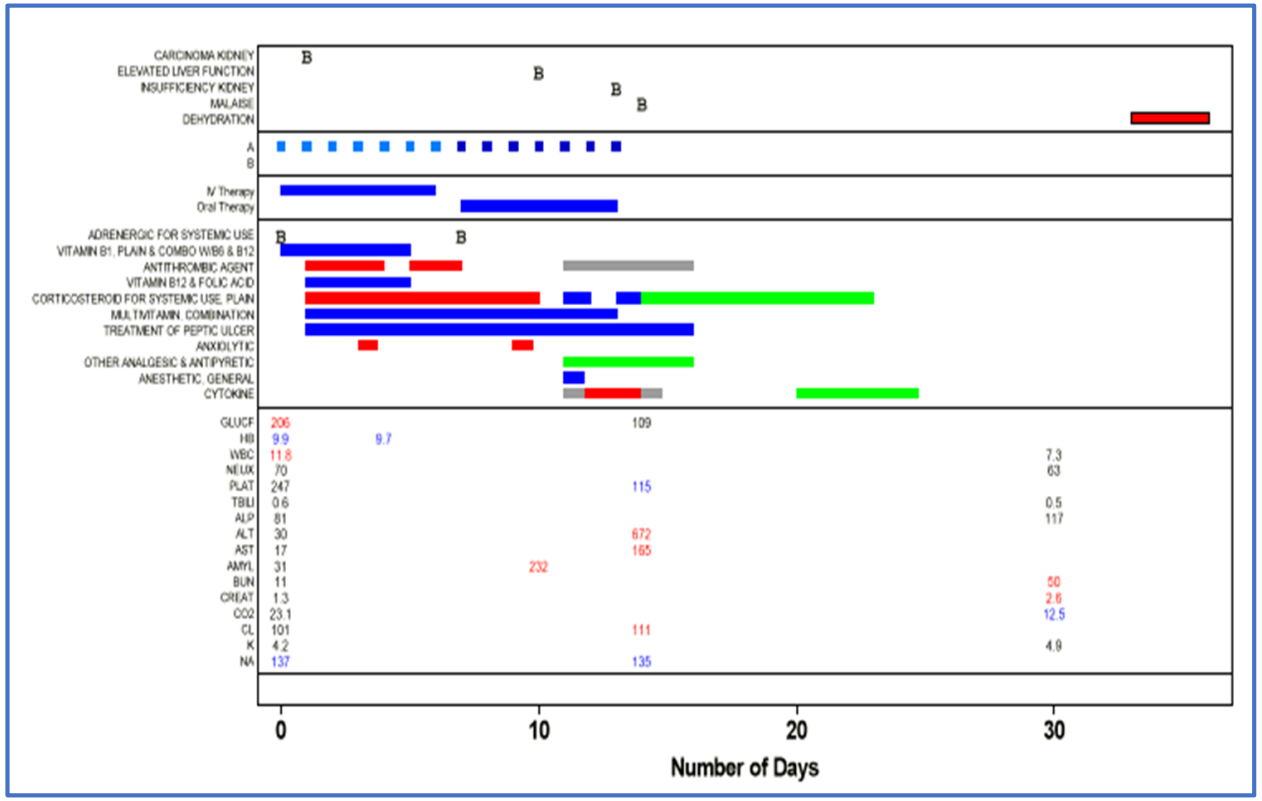
Regulatory Review Tools

CARS Project



Fendt

Patient Profile Viewer



Szarfman/Korvick

FDA & CDISC Data Standards

U.S. Food and Drug Administration

Department of Health and Human Services

FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA

FDA News

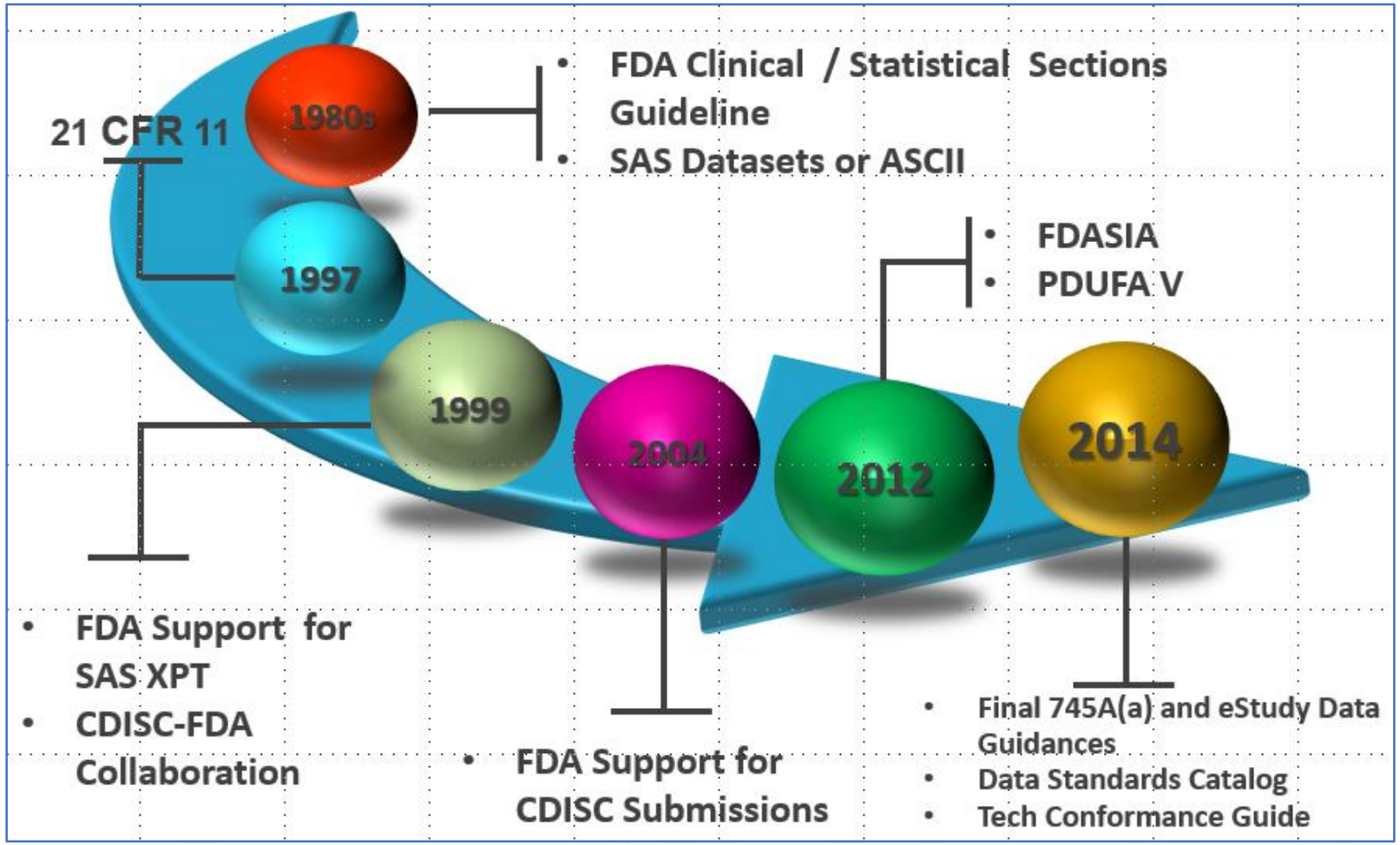
FOR IMMEDIATE RELEASE
P04-73
July 21, 2004

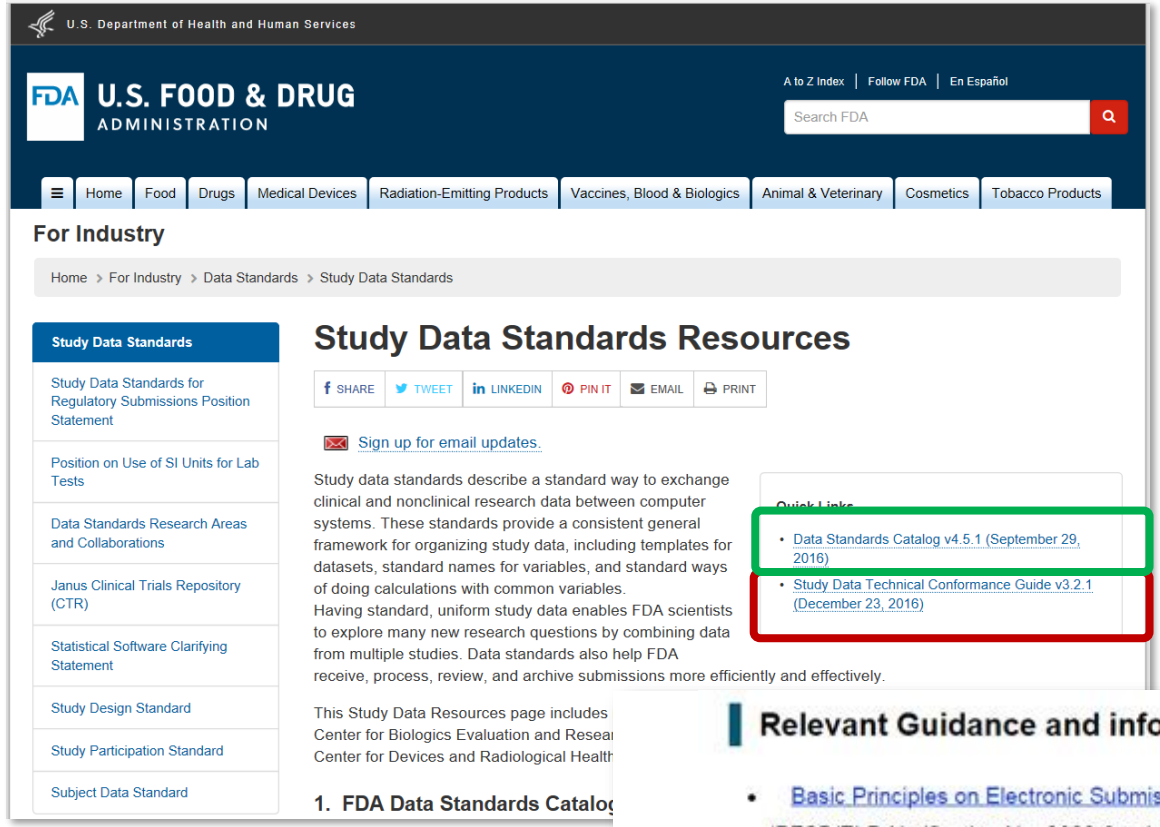
Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Announces Standard Format That Drug Sponsors Can Use to Submit Human Drug Clinical Trial Data

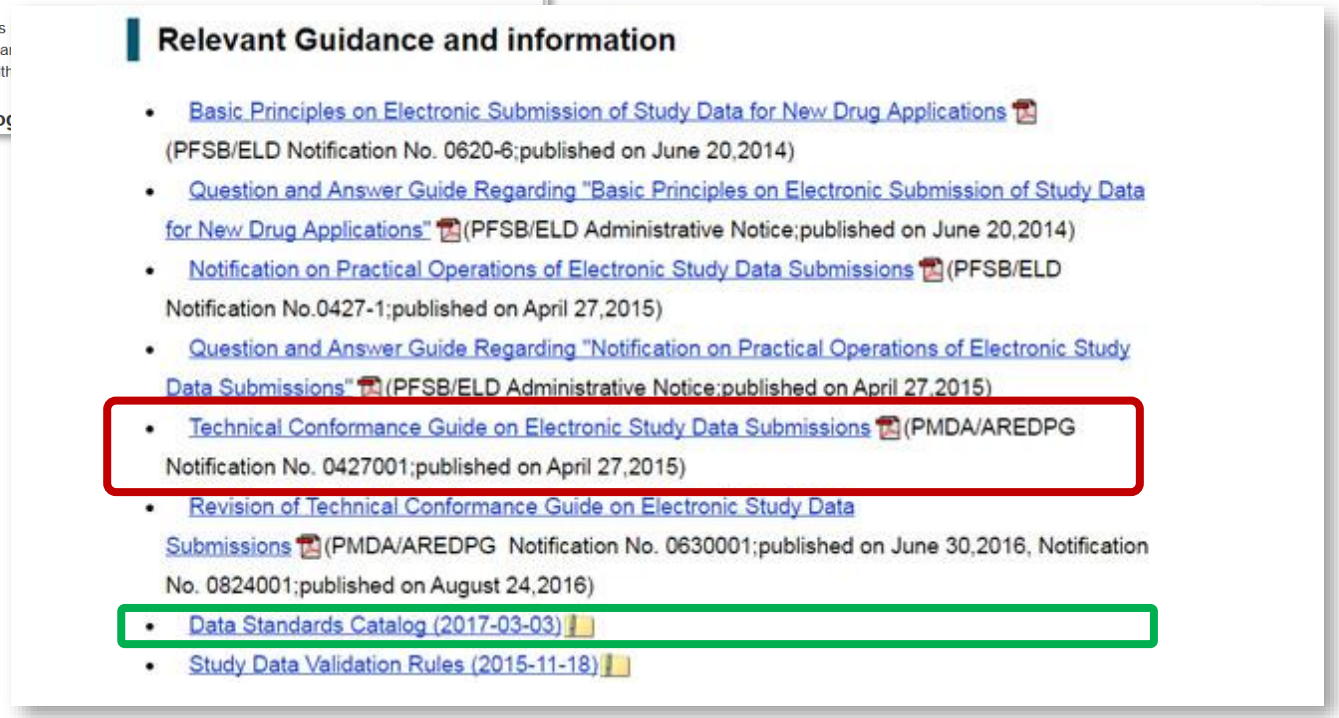
The Food and Drug Administration (FDA) today announced a standard format, called the Study Data Tabulation Model (SDTM) developed by the Clinical Data Interchange Standards Consortium (CDISC), that sponsors of human drug clinical trials can use to submit data to the agency. It is expected that this step will lead to greater efficiencies in clinical research and FDA reviews of New Drug Applications (NDAs).

The Journey


21 CFR 11
1980s
1997
1999
2004
2012
2014
• FDA Clinical / Statistical Sections Guideline
• SAS Datasets or ASCII
• FDASIA
• PDUFA V
• FDA Support for SAS XPT
• CDISC-FDA Collaboration
• FDA Support for CDISC Submissions
• Final 745A(a) and eStudy Data Guidances
• Data Standards Catalog
• Tech Conformance Guide



https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm



http://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0002.html

FDA Data Standards Catalog v4.5.1 (08-31-2016) - Supported and Required Standards

This table contains a listing of the data exchange, file formats and terminology standards supported at FDA. These standards have gone through all the steps necessary to make this part of the regulatory review process, including posting of regulatory guidance documents and associated implementation guidelines and technical specifications. The submission of standardized data using any standard not listed, or to an FDA Center not listed, should be discussed with the Agency in advance. This catalog is incorporated by reference in the guidance to industry, *Providing Regulatory Submissions in Electronic format-Standardized Study Data (http://www.fda.gov/downloads/Drugs/Guidances/UCM292334.pdf)*.

Use	Data Exchange Standard	Exchange Format	Standards Development Organization (SDO)	Supported Version	Implementation Guide Version	FDA Center(s)	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins (MM/DD/YYYY)	Date Requirement Ends	Regulatory Reference and Information Sources
Clinical study datasets	Study Data Tabulation Model (SDTM)	XPT	Clinical Data Interchange Standards Consortium (CDISC)	1,4	3,2	CDER, CBER	08/17/2015		03/15/2018 [1] 03/15/2019 [2]		CDISC.org - SDTM See Technical Conformance Guide
Clinical study datasets	SDTM	XPT	CDISC	1,3	3.1.3	CDER, CBER	12/01/2012		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1,2	Version 3.1.2 Amendment 1	CDER, CBER	08/07/2013		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1,2	3.1.2	CDER, CBER	30/10/2009		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1,1	3.1.1	CDER, CBER	Ongoing	01/28/2015			CDISC.org - SDTM
Clinical study datasets	Analysis Data Model (ADaM)	XPT	CDISC	2,1	1,0	CDER, CBER	Ongoing		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - ADaM

https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

PMDA Data Standards Catalog (2017-03-03) - Data Exchange Standards

Use	Data Exchange Standard	Supported Version(s)	Implementation Guide Version	Exchange Format	Date Support Begins (YYYY-MM-DD)	Date Support Ends (YYYY-MM-DD)	Notes
Clinical study datasets - Transport	SAS Transport (XPORT)	5	-	XPT	2016-10-01		
Clinical study datasets	SDTM	1,4	3,2	XPT	2016-10-01		
Clinical study datasets	SDTM	1,3	3.1.3	XPT	2016-10-01		
Clinical study datasets	SDTM	1,2	3.1.2 Amendment1	XPT	2016-10-01		
Clinical study datasets	SDTM	1,2	3.1.2	XPT	2016-10-01		
Clinical study datasets	ADaM	2,1	1.0	XPT	2016-10-01		
Clinical study data definition files	Define	2.0	-	XML	2016-10-01		
Clinical study data definition files	Define	1.0	-	XML	2016-10-01		
Documents	PDF	1.4-1.7	-	PDF	2016-10-01		In principle, eCTD PDF specification should be referenced for details.

http://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0002.html

STUDY DATA TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

This Document is incorporated by reference into the following Guidance Document(s):

Guidance for Industry *Providing Regulatory Submissions in Electronic Format – Standardized Study Data*

For questions regarding this technical specifications document, contact CDER at cder-edata@fda.hhs.gov or CBER at cber.cdisc@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm#guides

Contains Nonbinding Recommendations

Table of Contents

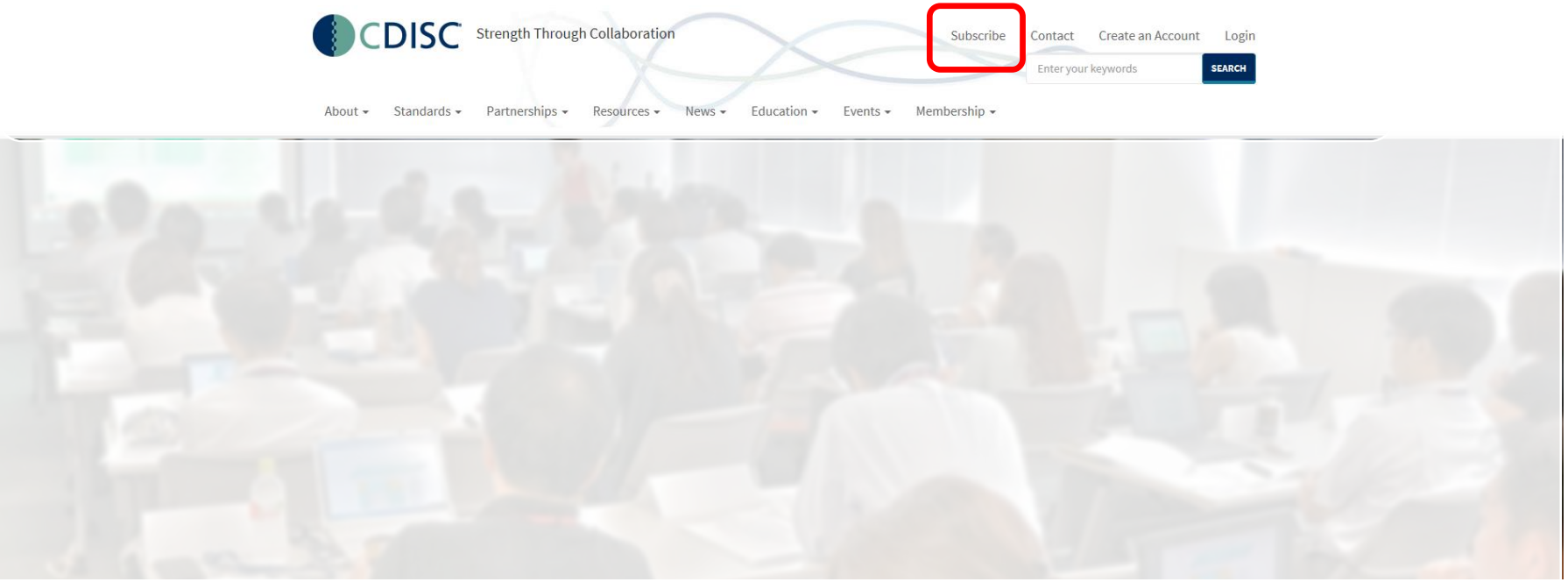
How does CDISC work?

As a CDISC newcomer, you may want to

- Subscribe to the newsletter
- Find information on the CDISC website
- Attend a CDISC training course or conference
- Become a member
- Participate in public review
- Volunteer on a standards development team

Announcements

- On the website
- E-mail “blasts” to our mailing list



ALL CURRENT PUBLIC REVIEWS

Huntington's Disease Therapeutic Area User Guide v1.0 Available for Public Review
Comments Due by: 10 Nov 2017

Post Traumatic Stress Disorder v1.0 Available for Public Review
Comments Due by: 13 Nov 2017

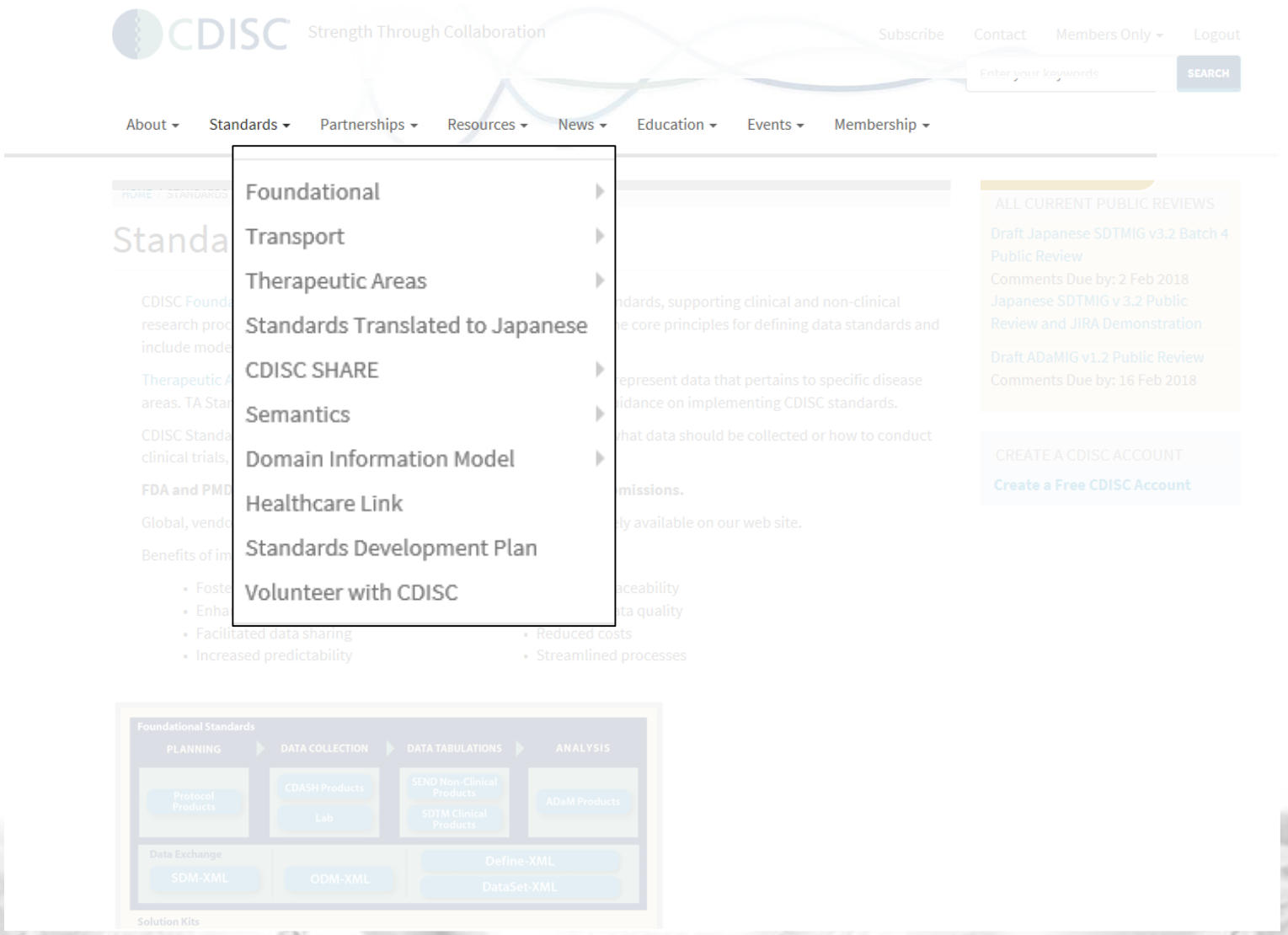
SDTM v1.7 Available for Public Review
Comments Due by: 13 Nov 2017

Draft Japanese SDTMIG v3.2 Batch 2 Public Review
Comments Due by: 24 Nov 2017

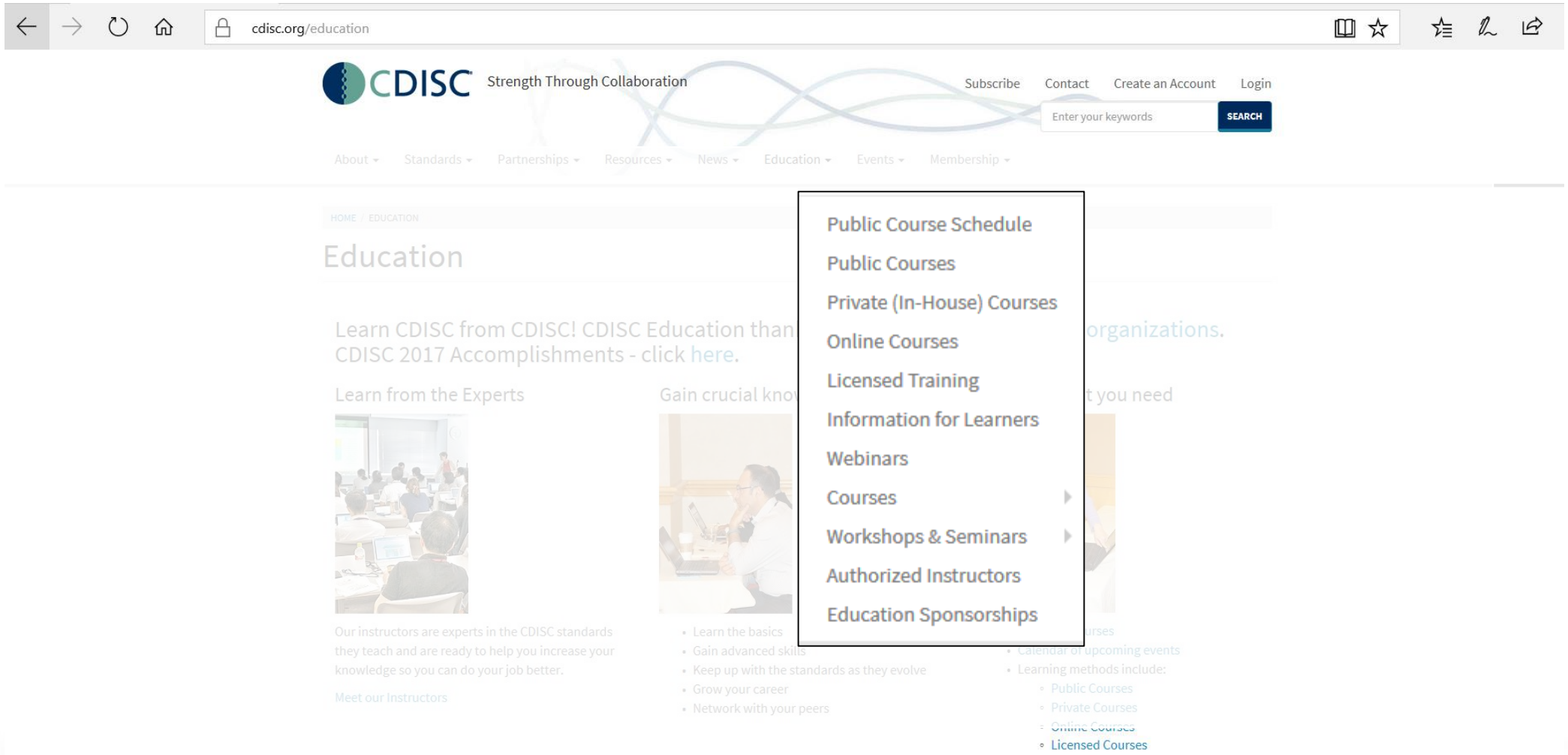
Japanese SDTMIG v 3.2 Public Review and JIRA Demonstration

CDISC SHARE API 2.0 Public Input
Comments Due by: 30 Nov 2017

Standards

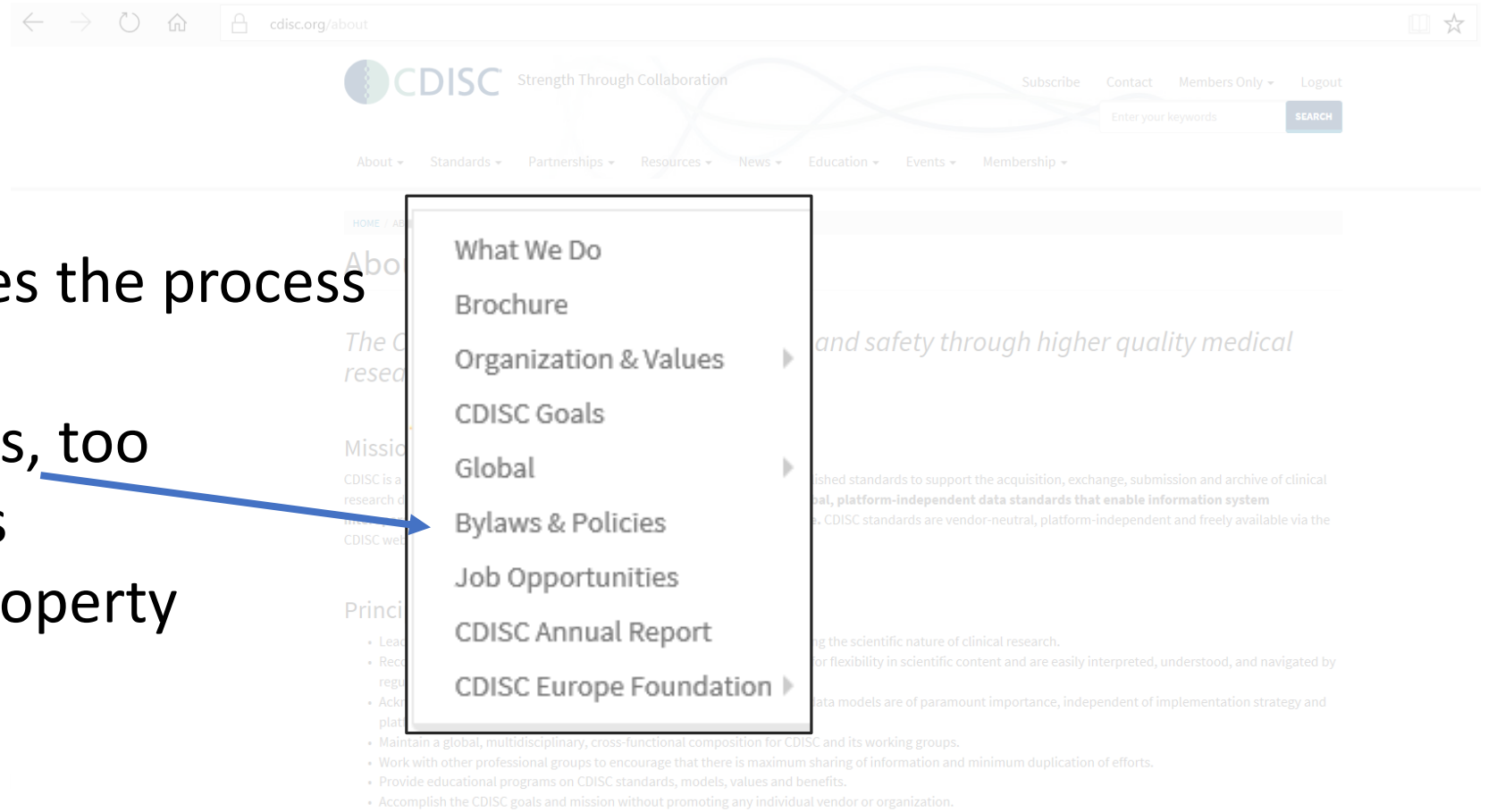

CDISC
Strength Through Collaboration
Subscribe
Contact
Members Only
Logout
SEARCH
About
Standards
Partnerships
Resources
News
Education
Events
Membership
Foundational
Transport
Therapeutic Areas
Standards Translated to Japanese
CDISC SHARE
Semantics
Domain Information Model
Healthcare Link
Standards Development Plan
Volunteer with CDISC
ALL CURRENT PUBLIC REVIEWS
Draft Japanese SDTMIG v3.2 Batch 4 Public Review
Comments Due by: 2 Feb 2018
Japanese SDTMIG v 3.2 Public Review and JIRA Demonstration
Draft ADaMIG v1.2 Public Review
Comments Due by: 16 Feb 2018
CREATE A CDISC ACCOUNT
Create a Free CDISC Account
Facilitated data sharing
Increased predictability
Reduced costs
Streamlined processes
Foundational Standards
PLANNING
DATA COLLECTION
DATA TABULATIONS
ANALYSIS
Protocol Products
CDASH Products
Lab
SEND Non-Clinical Products
SDTM Clinical Products
ADaM Products
Data Exchange
SDM-XML
ODM-XML
Define-XML
DataSet-XML
Solution Kits

Education


cdisc.org/education
CDISC
Strength Through Collaboration
Subscribe
Contact
Create an Account
Login
Enter your keywords
SEARCH
About
Standards
Partnerships
Resources
News
Education
Events
Membership
HOME / EDUCATION
Education
Public Course Schedule
Public Courses
Private (In-House) Courses
Online Courses
Licensed Training
Information for Learners
Webinars
Courses
Workshops & Seminars
Authorized Instructors
Education Sponsorships
Learn CDISC from CDISC! CDISC Education than
organizations.
CDISC 2017 Accomplishments - click here.
Learn from the Experts
Gain crucial kno
t you need
Our instructors are experts in the CDISC standards they teach and are ready to help you increase your knowledge so you can do your job better.
Meet our Instructors
Learn the basics
Gain advanced skills
Keep up with the standards as they evolve
Grow your career
Network with your peers
Calendar of upcoming events
Learning methods include:
Public Courses
Private Courses
Online Courses
Licensed Courses

Standards Development Process

- COP 001 describes the process
- Check out Policies, too
  - Code of Ethics
  - Intellectual Property



MEMBERSHIP

Join over 440 member organizations who collaborate through CDISC to foster *Smarter Research to Unlock Cures*
www.cdisc.org

Members section

Get Involved with CDISC

- Volunteer to:

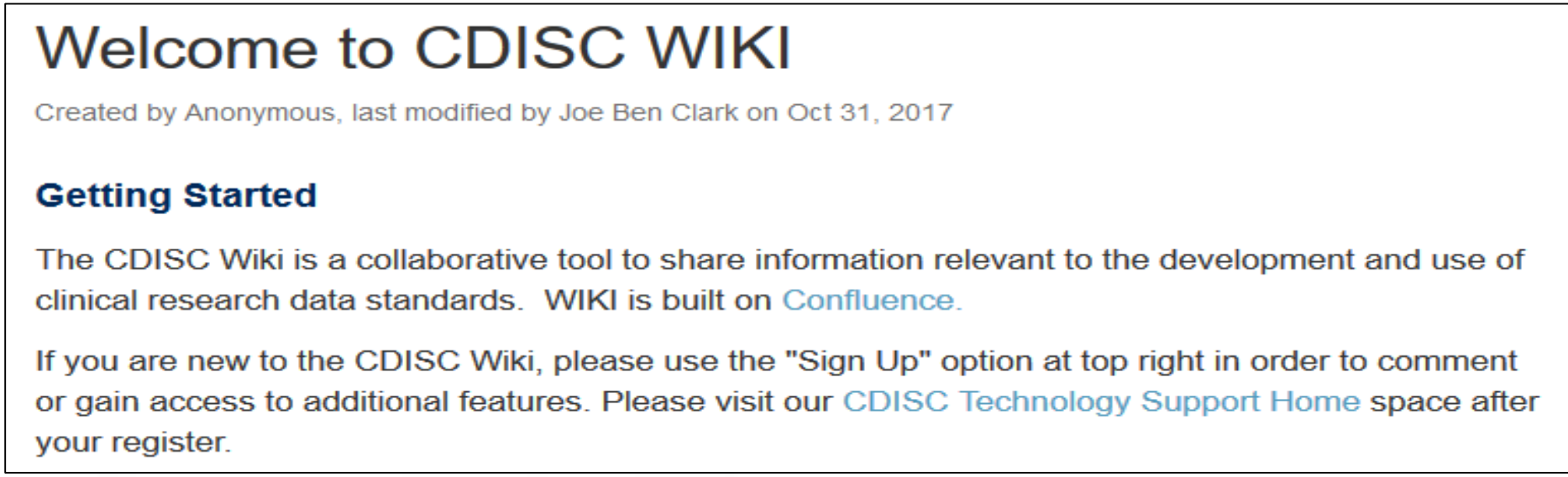
- Participate in public review of the standards
- Join a team and help us develop standards

What is out for review?

- On the website
- E-mail “blasts” to our mailing list

Wiki/JIRA Registration

- Separate from CDISC website registration
- Register from the wiki
- https://wiki.cdisc.org



- One userid/password for both wiki and JIRA
- https://jira.cdisc.org

Standards in the wiki

Study Data Tabulation Model v1.7

Created by Darcy Wold, last modified by Ann White on Oct 26, 2017

This is the landing page for the Study Data Tabulation Model v1.7 (SDTM).

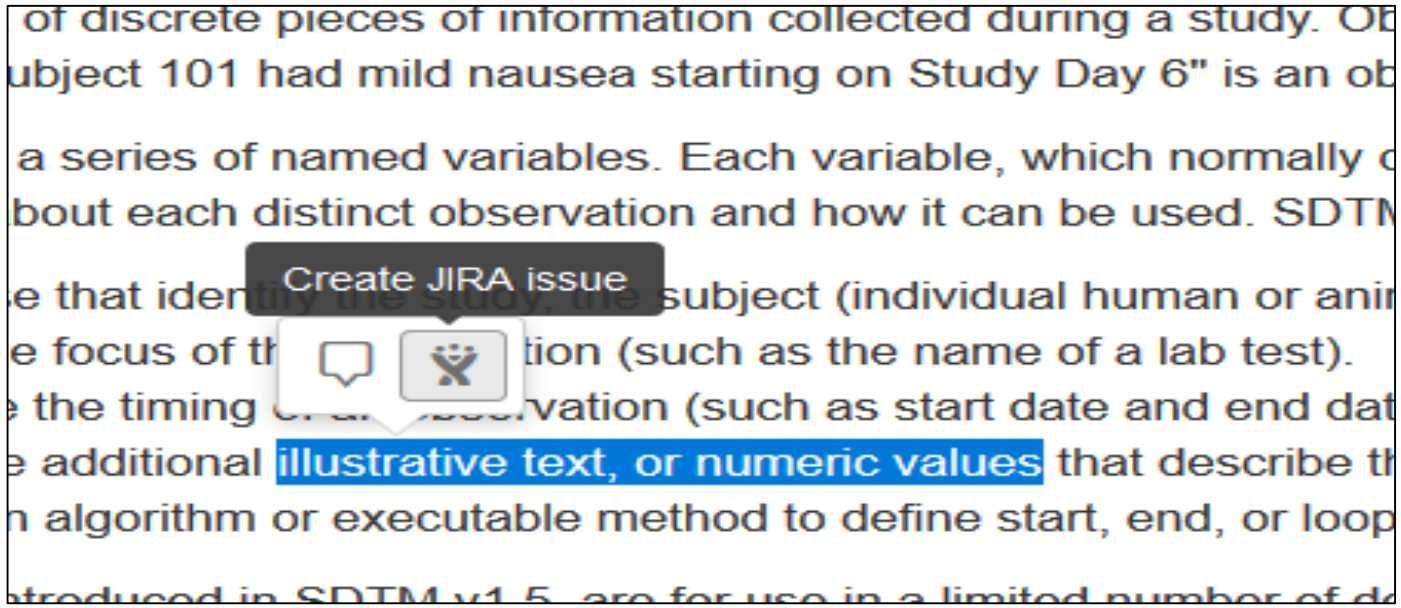
View the instructions: Instructions for Reviewers

What would you like to do?

- Read the entire document in one piece: SDTM compiled
- Read by section: SDTM sections
  - Jump to a specific section:
- View the tables: SDTM tables
  - Jump to a specific table:

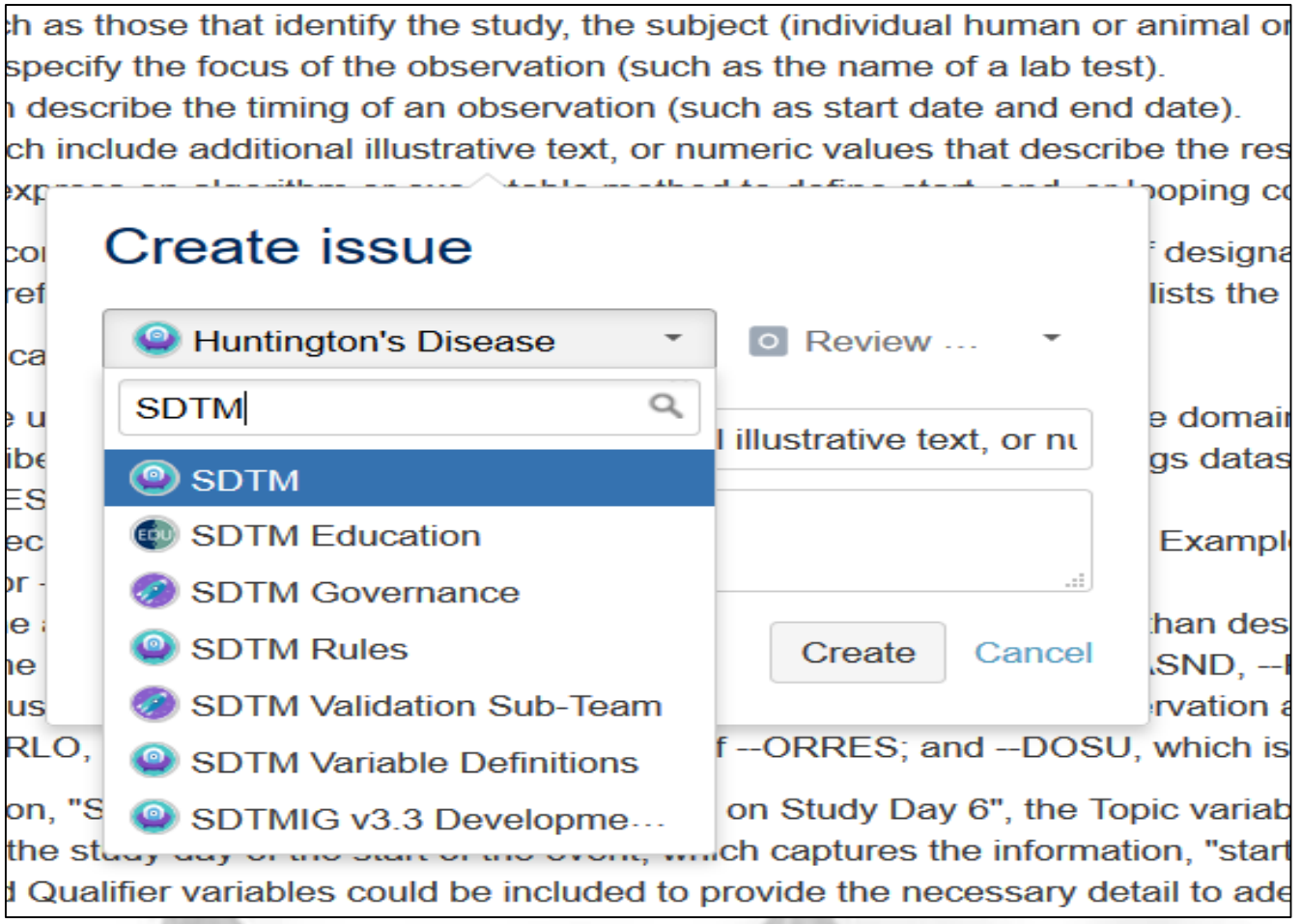
Creating a Comment

- From the wiki, highlight text, then click to create JIRA issue



Recording a Comment

- Choose the project
- Write comment in box
- Create

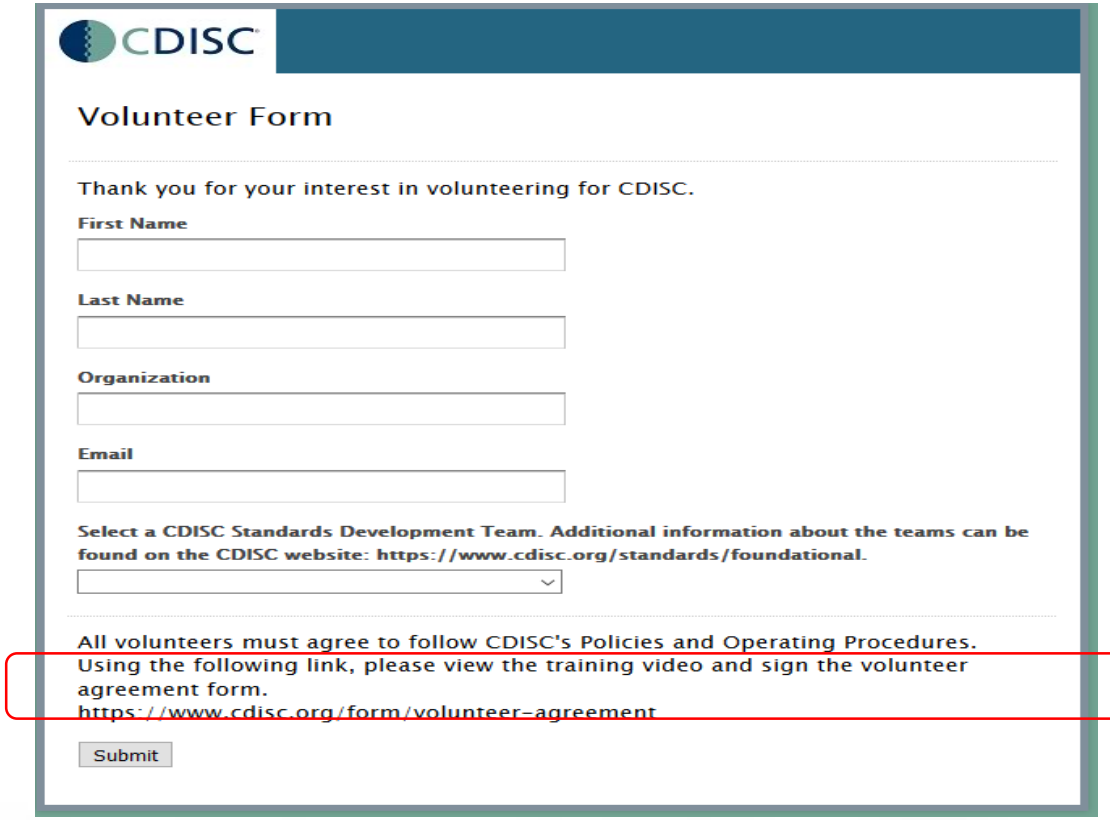


Joining a Standards Development Team

- Volunteer form
- Collaboration tools

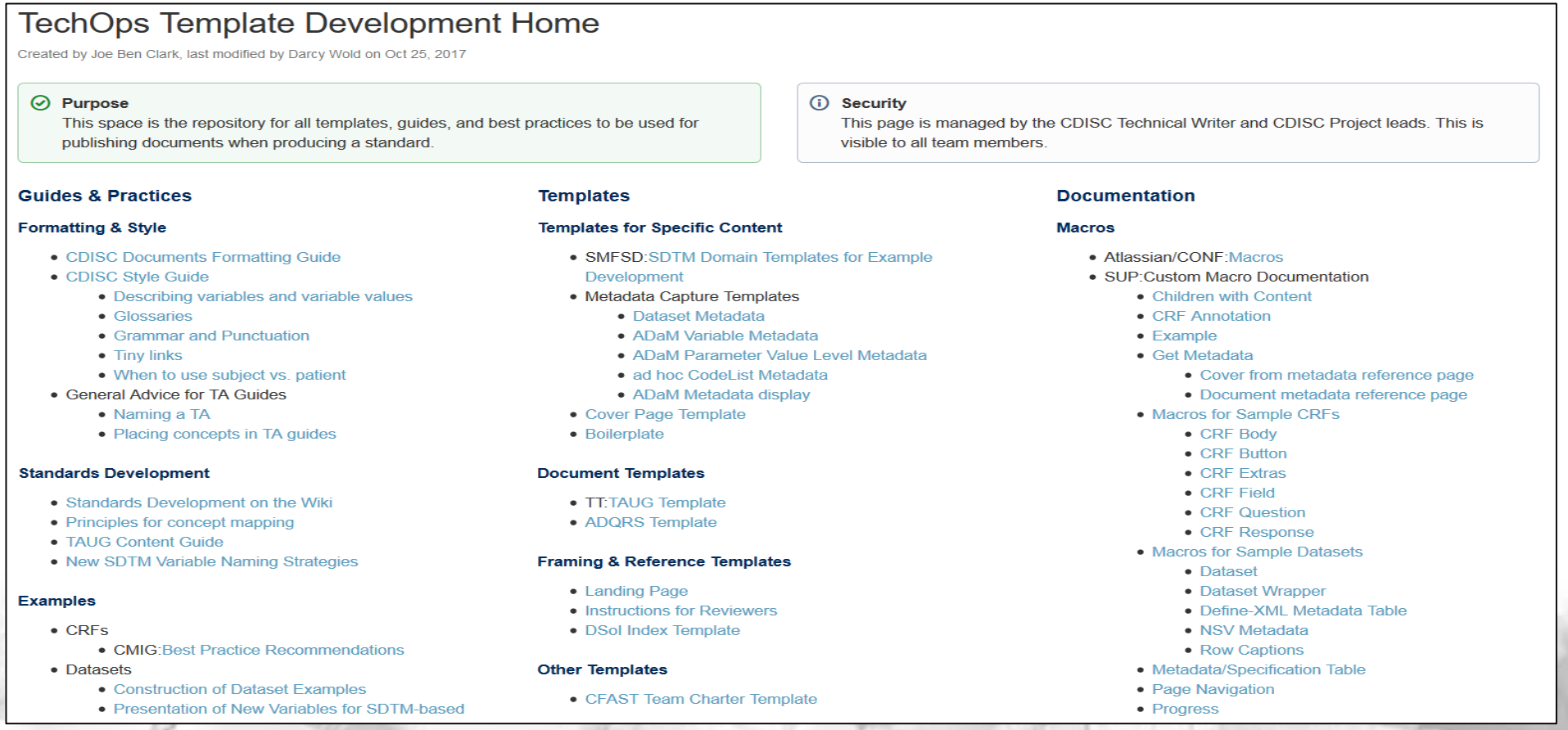
Volunteer form

home page



Collaboration Tools – CDISC wiki

- Standards are developed in the wiki
  - Lots of help at https://wiki.cdisc.org/display/TTD/TechOps+Template+Development+Home



TechOps Template Development Home

Created by Joe Ben Clark, last modified by Darcy Wold on Oct 25, 2017

Purpose
This space is the repository for all templates, guides, and best practices to be used for publishing documents when producing a standard.

Security
This page is managed by the CDISC Technical Writer and CDISC Project leads. This is visible to all team members.

Guides & Practices

Formatting & Style

- CDISC Documents Formatting Guide
- CDISC Style Guide
  - Describing variables and variable values
  - Glossaries
  - Grammar and Punctuation
  - Tiny links
  - When to use subject vs. patient
- General Advice for TA Guides
  - Naming a TA
  - Placing concepts in TA guides

Standards Development

- Standards Development on the Wiki
- Principles for concept mapping
- TAUG Content Guide
- New SDTM Variable Naming Strategies

Examples

- CRFs
  - CMIG:Best Practice Recommendations
- Datasets
  - Construction of Dataset Examples
  - Presentation of New Variables for SDTM-based

Templates

Templates for Specific Content

- SMFSD:SDTM Domain Templates for Example Development
- Metadata Capture Templates
  - Dataset Metadata
  - ADaM Variable Metadata
  - ADaM Parameter Value Level Metadata
  - ad hoc CodeList Metadata
  - ADaM Metadata display
- Cover Page Template
- Boilerplate

Document Templates

- TT:TAUG Template
- ADQRS Template

Framing & Reference Templates

- Landing Page
- Instructions for Reviewers
- DSoI Index Template

Other Templates

- CFAST Team Charter Template

Documentation

Macros

- Atlassian/CONF:Macros
- SUP:Custom Macro Documentation
  - Children with Content
  - CRF Annotation
  - Example
  - Get Metadata
    - Cover from metadata reference page
    - Document metadata reference page
  - Macros for Sample CRFs
    - CRF Body
    - CRF Button
    - CRF Extras
    - CRF Field
    - CRF Question
    - CRF Response
  - Macros for Sample Datasets
    - Dataset
    - Dataset Wrapper
    - Define-XML Metadata Table
    - NSV Metadata
    - Row Captions
  - Metadata/Specification Table
  - Page Navigation
  - Progress

Summary

- CDISC is a non-profit SDO, developing and maintaining data standards that support medical research
- CDISC standards are required for submissions to FDA and PMDA
- You can learn more about CDISC through our website, webinars, training courses and conferences
- You can get involved by becoming a member, reviewing standards, and joining a team

Q&A

Questions…

Upcoming CDISC Webinars

- **CDISC Standards Updates – CDAD TAUG v 1.0**
  - Version 1.0 of the Therapeutic Area User Guide for Clostridium Difficile Associated Diarrhea (TAUG-CDAD) is developed under the CFAST program and the CDISC Standards Development Process. TAUG-CDAD v1.0 describes the most common biomedical concepts relevant to CDAD, and the necessary metadata to represent such data consistently with CDISC standards.23 Jan 2018 – 10am CST
  - 8 Feb 2018, 10am CST/5p CET
  - For registration, visit our webinars page at www.cdisc.org/education/webinars

- **Members-Only TECH Webinar – Getting Started with SHARE API v1.0**

- Join the CDISC SHARE Team for a technology webinar introducing the CDISC SHARE Application Programming Interface (API), which is available free to CDISC Platinum Members as a 2018 Member benefit.
- The CDISC SHARE API, a RESTful web service, allows real-time access to standards in a variety of formats (XML, RDF and JSON) for programmatic use by developers to create CDISC metadata libraries within your metadata repositories, support CDISC standards in electronic case report forms, and use within clinical research and learning health systems. The API facilitates the implementation of CDISC standards to further automate clinical research processes.

  - 13 Feb2018 – 10am CST/5pm CET
  - For registration, visit our webinars page at www.cdisc.org/education/webinars