Introduction of Programming and Submission Consideration for Diabetes and Women's Health Studies

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Outline

- Diabetes Studies
  - Endpoints
  - Data (SDTM, ADaM)
  - Analysis Reporting
- Women Health Studies
  - Endpoints
- Submission Consideration

Diabetes Studies

A Few Background

- Diabetes Mellitus (DM) Classification
  - Type 1 DM
  - Type 2 DM
  - Gestational DM
  - Other Special DM
- Treatment Solution/Therapies
  - Insulin supplements and insulin based therapies
  - Non-Insulin Therapies
    - GLP-1 Agonists (VICTOZA® Novo Nordisk)
    - DPP4 Inhibitors (JANUVIA®/JANUMET® MSD)
    - SGLT2 Inhibitors (INVOKANA®/INVOKAMET® J&J)
    - New Combination

Clinical Endpoints

- Efficacy
  - HbA1C
  - 2-hr PMG (Post Meal Glucose)
  - FPG (Fasting Plasma Glucose)
  - MTT (Meal Tolerance Test) Glucose/Insulin (0, 30, 60, 120 mins)
  - MTT Glucose/Insulin AUC
  - Lipid Panel (TG, HDL, LDL)
  - Insulin Dose
- Safety
  - Hypoglycemia
  - Rescue Medication
  - Exposure-adjusted AE
  - Cardiovascular Events
  - Body Weight

General Data Standard

- Foundational
  - SDTM (or SDTM like)
    - LB, CF, FA, AE, RELRSC
  - ADaM (or Analysis Datasets)
    - ADGLU/ADMTT (Lab Tests Continuous Measurements)
    - ADHA (Hypoglycemia Events)
    - ADADJ (Adjudication CV Events)
- Therapeutic Areas
  - Therapeutic Area Data Standards User Guide for Diabetes (CFAST Diabetes Team)
  - ADaM Supplement to the TAUG-Diabetes (CFAST Diabetes ADaM Sub-Team)

Diabetes

Diabetes Therapeutic Area User Guide v1 - Supplement for ADaM

1.0 Release Date: 2015-12-18

The Analysis Data Model (ADaM) Supplement to version 1.0 of TAUG-Diabetes, released 2015-12-18, is available for provisional use. The illustrates using ADaM to create datasets that support analyzing statistical endpoints common to diabetes clinical trials.
Downloads:

File	Size
Diabetes Therapeutic Area Data Standard User Guide v1 - Supplement for ADaM	792.87 KB
CDISC Diabetes ADaM Supplement Public Review Comments	31.9 KB

Diabetes Therapeutic Area Data Standard User Guide v1

1.0 Release Date: 2014-09-11

Version 1.0 Provisional of the Diabetes Therapeutic Area User Guide (TAUG-Diabetes), released 2014-09-11, provides guidance on the implementing the Study Data Tabulation Model (SDTM) to represent diabetes data in regulatory submissions. TAUG-Diabetes describes the most common biomedical concepts relevant to diabetes studies, and the necessary metadata to represent such data consistently with CDISC standards.
Downloads:

File	Size
Diabetes Therapeutic Area Data Standard User Guide v1	7.55 MB
CDISC Diabetes v1 Public Review Comments	78.32 KB

General ADaM Specification

- ADSL –
  - [DIABDURY] - Duration of Diabetes (years)
  - [STRATyNM] [STRATy] [STRATyN] - Stratification Variables
    - Baseline HbA1c (>7-<9%, ≥9%)
    - Background use of basal medication
- ADGLU, ADMTT (DS)
  - Continuous measures at pre-defined time points or longitudinally.
  - Calculate change or percent Change from baseline
  - Categorical measures such as a binary response based on achieving a pre-defined criterion (e.g. HbA1c < 7.0% at week X).
- ADHA (OCCDS)
  - Hypoglycemic events lends itself to creation of statistical endpoints that relate to events, such as incidence, prevalence, or event severity.
- ADADJ
  - Cardiovascular Adjurations Adverse Events

Tests in SDTM.LB to ADaM

Assessment	LBTESTCD	LBTEST	LBTPT	ADaM
Glycosylated Hemoglobin A1c	HBA1C	Hemoglobin A1C		ADGLU
2-hour Post Meal Glucose (PMG)	GLUC	Glucose	120 min	
Fasting Plasma Glucose (FPG)	GLUC	Glucose		
Fasting Serum Insulin	INSULN	Insulin	Pre-dose	
Fasting Serum C-peptide	CPEPTIDE	C-Peptide	Pre-dose	
Lipid Panel	HDL	HDL Cholesterol		
	LDL	LDL Cholesterol		
	TRIG	Triglycerides		
Other Related Markers	ANHYGL15	1,5-anhydroglucitol		
	HOMA-β (Derived)			
Meal Tolerance Test (MTT)	GLUC	Glucose	0 min	ADMTT
	GLUC	Glucose	30 min	
	GLUC	Glucose	60 min	
	GLUC	Glucose	120 min	
	INSULN	Insulin	0 min	
	INSULN	Insulin	30 min	
	INSULN	Insulin	60 min	
	INSULN	Insulin	120 min	
	CPEPTIDE	C-Peptide	0 min	
	CPEPTIDE	C-Peptide	30 min	
	CPEPTIDE	C-Peptide	60 min	
	CPEPTIDE	C-Peptide	120 min	
	Incremental AUC, Total AUC, Insulinogenic Index (Derived)			

ADGLU

STUDYID	USUBJID	FASPFL	TRT01P	VISIT	AVISIT	ADY	PARAM	PARAMCD	PARAMN	AVAL	BASE	ABLFL	CHG	DTYPE	ANL01FL
0001-001	0001-001_001100001	Y	Drug A	Visit 1	Week -10	-61	Fasting Plasma Glucose (mg/dL)	GLUC	100	145	188				Y
0001-001	0001-001_001100001	Y	Drug A	Visit 3	Week -2	-14	Fasting Plasma Glucose (mg/dL)	GLUC	100	199	188				Y
0001-001	0001-001_001100001	Y	Drug A	Visit 4	Week 0	1	Fasting Plasma Glucose (mg/dL)	GLUC	100	188	188	Y			Y
0001-001	0001-001_001100001	Y	Drug A	Visit 5	Week 4	29	Fasting Plasma Glucose (mg/dL)	GLUC	100	209	188		21		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 6	Week 8	57	Fasting Plasma Glucose (mg/dL)	GLUC	100	188	188		0		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 7	Week 12	85	Fasting Plasma Glucose (mg/dL)	GLUC	100	180	188		-8		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 8	Week 16	113	Fasting Plasma Glucose (mg/dL)	GLUC	100	207	188		19		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 9	Week 20	141	Fasting Plasma Glucose (mg/dL)	GLUC	100	207	188		19	LOCF	Y
0001-001	0001-001_001100001	Y	Drug A	Visit 10	Week 24	169	Fasting Plasma Glucose (mg/dL)	GLUC	100	205	188		17		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 1	Week -10	-61	HbA1c (%)	HBA1C	250	6.8	8.2				Y
0001-001	0001-001_001100001	Y	Drug A	Visit 3	Week -2	-14	HbA1c (%)	HBA1C	250	7.9	8.2				Y
0001-001	0001-001_001100001	Y	Drug A	Visit 4	Week 0	1	HbA1c (%)	HBA1C	250	8.2	8.2	Y			Y
0001-001	0001-001_001100001	Y	Drug A	Visit 5	Week 4	29	HbA1c (%)	HBA1C	250	8.6	8.2		0.4		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 6	Week 8	57	HbA1c (%)	HBA1C	250	8.8	8.2		0.6		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 7	Week 12	85	HbA1c (%)	HBA1C	250	9.1	8.2		0.9		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 8	Week 16	113	HbA1c (%)	HBA1C	250	9.1	8.2		0.9		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 9	Week 20	141	HbA1c (%)	HBA1C	250	9.1	8.2		0.9	LOCF	Y
0001-001	0001-001_001100001	Y	Drug A	Visit 10	Week 24	169	HbA1c (%)	HBA1C	250	9.2	8.2		1		Y

ADMTT

STUDYID	USUBJID	FASPFL	TRT01P	VISIT	AVISIT	ADY	PARAM	PARAMCD	PARAMN	AVAL	BASE	ABLFL	CHG	DTYPE	ANL01FL
0001-001	0001-001_001100001	Y	Drug A	Visit 4	Week 0	1	Plasma Glucose (0 minute) (mg/dL)	GLU-0M	110	191	191	Y			Y
0001-001	0001-001_001100001	Y	Drug A	Visit 10	Week 24	169	Plasma Glucose (0 minute) (mg/dL)	GLU-0M	110	149	191		-42		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 4	Week 0	1	Plasma Glucose (30 minutes) (mg/dL)	GLU-30M	113	244	244	Y			Y
0001-001	0001-001_001100001	Y	Drug A	Visit 10	Week 24	169	Plasma Glucose (30 minutes) (mg/dL)	GLU-30M	113	212	244		-32		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 4	Week 0	1	Plasma Glucose (60 minutes) (mg/dL)	GLU-60M	120	258	258	Y			Y
0001-001	0001-001_001100001	Y	Drug A	Visit 10	Week 24	169	Plasma Glucose (60 minutes) (mg/dL)	GLU-60M	120	235	258		-23		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 4	Week 0	1	2-Hour Post-Meal Glucose (mg/dL)	GLU-120M	130	237	237	Y			Y
0001-001	0001-001_001100001	Y	Drug A	Visit 10	Week 24	169	2-Hour Post-Meal Glucose (mg/dL)	GLU-120M	130	205	237		-32		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 4	Week 0	1	Serum Insulin (0 minute) (microIU/mL)	INS-0M	160	7.89	7.89	Y			Y
0001-001	0001-001_001100001	Y	Drug A	Visit 10	Week 24	169	Serum Insulin (0 minute) (microIU/mL)	INS-0M	160	11.5	7.89		3.61		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 4	Week 0	1	Serum Insulin (30 minutes) (microIU/mL)	INS-30M	163	16.6	16.6	Y			Y
0001-001	0001-001_001100001	Y	Drug A	Visit 10	Week 24	169	Serum Insulin (30 minutes) (microIU/mL)	INS-30M	163	34.2	16.6		17.6		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 4	Week 0	1	Serum Insulin (60 minutes) (microIU/mL)	INS-60M	170	35.6	35.6	Y			Y
0001-001	0001-001_001100001	Y	Drug A	Visit 10	Week 24	169	Serum Insulin (60 minutes) (microIU/mL)	INS-60M	170	24.5	35.6		-11.1		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 4	Week 0	1	2-Hour Post-Meal Insulin (microIU/mL)	INS-120M	180	40.8	40.8	Y			Y
0001-001	0001-001_001100001	Y	Drug A	Visit 10	Week 24	169	2-Hour Post-Meal Insulin (microIU/mL)	INS-120M	180	50.5	40.8		9.7		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 4	Week 0	1	Glucose Incremental AUC (mg.hr/dL)	GLUICAUC	291	99.75	99.75	Y			Y
0001-001	0001-001_001100001	Y	Drug A	Visit 10	Week 24	169	Glucose Incremental AUC (mg.hr/dL)	GLUICAUC	291	124	99.75		24.25		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 4	Week 0	1	Glucose Total AUC (mg.hr/dL)	GLUTTAUC	292	481.75	481.75	Y			Y
0001-001	0001-001_001100001	Y	Drug A	Visit 10	Week 24	169	Glucose Total AUC (mg.hr/dL)	GLUTTAUC	292	422	481.75		-59.75		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 4	Week 0	1	Insulin Incremental AUC (microIU.hr/mL)	INSICAUC	293	41.5925	41.5925	Y			Y
0001-001	0001-001_001100001	Y	Drug A	Visit 10	Week 24	169	Insulin Incremental AUC (microIU.hr/mL)	INSICAUC	293	40.6	41.5925		-0.9925		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 4	Week 0	1	Insulin Total AUC (microIU.hr/mL)	INSTTAUC	294	57.3725	57.3725	Y			Y
0001-001	0001-001_001100001	Y	Drug A	Visit 10	Week 24	169	Insulin Total AUC (microIU.hr/mL)	INSTTAUC	294	63.6	57.3725		6.2275		Y
0001-001	0001-001_001100001	Y	Drug A	Visit 4	Week 0	1	Insulinogenic Index (microIU/mL per mg/dL)	INSIDX	319	0.16434	0.16434	Y			Y
0001-001	0001-001_001100001	Y	Drug A	Visit 10	Week 24	169	Insulinogenic Index (microIU/mL per mg/dL)	INSIDX	319	0.360317	0.16434		0.195978		Y

Analysis Methods

Endpoint	Primary vs. Sensitivity	Statistical method	population	Missing data approach
Primary				
Change from baseline in *HbA1c* at Week X	P	cLDA	FAS	Model-based
	S	cLDA	FAS	Tipping Point (Pattern Mixture Model)
	S	Longitudinal ANCOVA	PP	Subjects with missing Week X measurements are not in the PP population
Secondary				
Change from baseline in *2-hr PMG/ FPG/MTT/etc.* at Week X	P	cLDA	FAS	Model-based
	S	Longitudinal ANCOVA	PP	Subjects with missing Week X measurements are not in the PP population
Percentage of subjects achieving HbA1c <7.0% at Week X (Goal Setting)	P	Logistic Regression	FAS	Multiple imputation

cLDA (constrained Longitudinal Data Analysis)

Constrained Longitudinal Data Analysis of Change from Baseline in HbA1c (%) at Week X (FAS)

Treatment	N	Baseline		Week X		Change from Baseline at Week X			
		mean	(SD)	mean	(SD)	mean	(SD)	LS Mean	(95% CI†)
TRT1	x	x	(x.x)	x	(x.x)	x	(x.x)	x	(x.x, x.x)
TRT2	x	x	(x.x)	x	(x.x)	x	(x.x)	x	(x.x, x.x)
Pairwise Comparison						Difference in LS Means (95% CI)†		p-Value	
TRT1 vs. TRT2						x.x (x, x)		x.xxx	

N = Number of subjects in the population.

LS Mean = Least Squares Mean.

Missing data approach is model-based.

Clinical Endpoints

- Efficacy
  - HbA1C
  - 2-hr PMG (Post Meal Glucose)
  - FPG (Fasting Plasma Glucose)
  - MTT (Meal Tolerance Test) Glucose/Insulin (0, 30, 60, 120 mins)
  - MTT Glucose/Insulin AUC
  - Lipid Panel (TG, HDL, LDL)
  - Insulin Dose
- Safety
  - Hypoglycemia
  - Rescue Medication
  - Exposure-adjusted AE
  - Cardiovascular Events
  - Body Weight

Hypoglycemia (Low Blood Glucose) Analysis

- Occurs when the level of blood glucose drops below normal (e.g. <=70 mg/dL)
- Symptoms
  - Mild to Moderate
    - Hungry, Sweaty, etc.
  - Severe
    - Unable to eat or drink, Unconscious, etc.
- Some times people won't have any symptoms.

HA (Hypoglycemia Assessment) eCRF

- If glucose measurements <= 70 mg/dL, or have symptoms related to hypoglycemia according to investigator, the patient would be asked to complete a HA form in eCRF.

Report from Subject		Investigator's Judgment		Enter into eCRF		
Subjective Symptom	SMBG	Hypoglycemic Episode	Adverse Event	HA	FSG	AE
With	>70 mg/dL or No data	Yes	Yes	X	X [1]	"hypoglycaemia"
		No	Yes			Relevant AE term
			No			
	≤70 mg/dL	-	Yes	X	X	"hypoglycaemia"
			No	X	X	
Without	≤70 mg/dL	-	Yes	X	X	"asymptomatic hypoglycaemia"
			No	X	X	

FSG : Fingerstick Glucose
SMBG: Self-monitoring blood glucose

HA (Hypoglycemia Assessment) eCRF

- Would include questions below
  - Date/ time of occurrence, while sleeping or not
  - Symptoms
  - Glucose measurement
  - Medication (study treatment and concomitant treatment)
  - Factors precipitated the hypoglycemic Episode
  - Action taken in response to the event
  - …

HA in CF/FA

- HA would be mapped to CF domain in and before version 3.1.2, and in the later version, would be mapped to CE and FA domain.

DOMAIN	CEGRPID	SUBJID	CESPID	CETERM	CESTDTC	CEENDTC
CE	HA	10001	1	HYPOGLYCEMIA	2016-07-31T11:40	

DOMAIN	CFGRP	SUBJID	CFOBJ	CFTEST	CFORRES	CFSTDTC	CFENDTC
CF	HA	10001		Symptoms of Hypoglycemia	NO SYMPTOMS	2016-07-31T11:40	
CF	HA	10001	HYPOGLYCEMIC EPISODE	Glucose Measurement	FINGERSTICK GLUCOSE	2016-07-31T11:40	
CF	HA	10001	HYPOGLYCEMIC EPISODE	Occurrence	N	2016-07-31T11:40	
CF	HA	10001	HYPOGLYCEMIA	Require Assistance of Another Individual	NO ASSISTANCE	2016-07-31T11:40	
CF	HA	10001	HYPOGLYCEMIA	Intervention to Treat Episode	T11:55	2016-07-31T11:40	
CF	HA	10001	HYPOGLYCEMIA	Factors for Hypoglycemic Episode	SKIPPED, DELAYED, OR SMALLER MEAL/SNACK	2016-07-31T11:40	

- AE and LB would also include part of HA related information.

ADHA

- Link CE/CF/FA with AE, LB, RELREC domains depending on analysis purpose.
- One hypoglycemia episode one row.
- Classification variables would be developed.
  - AE/Non-AE
  - Symptomatic/Asymptomatic
  - Glucose Level Category
  - Severe/Non-Severe
  - Precipitating Factor

Hypoglycemia Analysis Sample 1

Summary of Subjects with Hypoglycemia Adverse Events
(ASaT)

	TRT1 n (%)	TRT2 n (%)	Total n (%)
Subjects in population	x	x	x
With one or more:			
Adverse events of hypoglycemia (symptomatic or asymptomatic)	x (x.x)	x (x.x)	x (x.x)
Symptomatic	x (x.x)	x (x.x)	x (x.x)
Severe	x (x.x)	x (x.x)	x (x.x)
Requiring non-medical assistance	x (x.x)	x (x.x)	x (x.x)
Requiring medical assistance	x (x.x)	x (x.x)	x (x.x)
Asymptomatic	x (x.x)	x (x.x)	x (x.x)

Hypoglycemia Analysis Sample 2

Summary of Subjects with Hypoglycemia Adverse Events by Lowest Glucose Category (ASaT)

	TRT1 n (%)	TRT2 n (%)	Total n (%)
Subjects in population	x	x	x
With one or more:			
Adverse events of hypoglycemia (symptomatic or asymptomatic)	x (x.x)	x (x.x)	x (x.x)
≤70 mg/dL	x (x.x)	x (x.x)	x (x.x)
<50 mg/dL	x (x.x)	x (x.x)	x (x.x)
>70 mg/dL	x (x.x)	x (x.x)	x (x.x)
Unknown	x (x.x)	x (x.x)	x (x.x)
Asymptomatic	x (x.x)	x (x.x)	x (x.x)
≤70 mg/dL	x (x.x)	x (x.x)	x (x.x)
<50 mg/dL	x (x.x)	x (x.x)	x (x.x)
>70 mg/dL	x (x.x)	x (x.x)	x (x.x)
Unknown	x (x.x)	x (x.x)	x (x.x)
Symptomatic	x (x.x)	x (x.x)	x (x.x)
≤70 mg/dL	x (x.x)	x (x.x)	x (x.x)
<50 mg/dL	x (x.x)	x (x.x)	x (x.x)
>70 mg/dL	x (x.x)	x (x.x)	x (x.x)
Unknown	x (x.x)	x (x.x)	x (x.x)

Hypoglycemia Analysis Sample 3

Distribution of the Number of Episodes of Hypoglycemia Adverse Events per Subject (ASaT)

	TRT1 n (%)	TRT2 n (%)	Total n (%)
Subjects in population	X	X	X
Adverse events of hypoglycemia (symptomatic or asymptomatic)			
Total episodes n (%) by number of episodes per subject	x (x.x)	x (x.x)	x (x.x)
0 episode	x (x.x)	x (x.x)	x (x.x)
1 episode	x (x.x)	x (x.x)	x (x.x)
2 episodes	x (x.x)	x (x.x)	x (x.x)
≥3 episodes and ≤10 episodes	x (x.x)	x (x.x)	x (x.x)
>10 episodes	x (x.x)	x (x.x)	x (x.x)
Symptomatic			
Total episodes n (%) by number of episodes per subject	x (x.x)	x (x.x)	x (x.x)
0 episode	x (x.x)	x (x.x)	x (x.x)
1 episode	x (x.x)	x (x.x)	x (x.x)
2 episodes	x (x.x)	x (x.x)	x (x.x)
≥3 episodes and ≤10 episodes	x (x.x)	x (x.x)	x (x.x)
>10 episodes	x (x.x)	x (x.x)	x (x.x)
Severe			
Total episodes n (%) by number of episodes per subject	x (x.x)	x (x.x)	x (x.x)
0 episode	x (x.x)	x (x.x)	x (x.x)
1 episode	x (x.x)	x (x.x)	x (x.x)
2 episodes	x (x.x)	x (x.x)	x (x.x)
≥3 episodes and ≤10 episodes	x (x.x)	x (x.x)	x (x.x)
>10 episodes	x (x.x)	x (x.x)	x (x.x)

Cardiovascular Adverse Events

- Regulatory requirement specific to Diabetes studies is to demonstrate CV safety.
- ADADJ
  - Map adjudicated events from VCAS (Virtual Clinical Adjudication System) to SDTM CF domain CFCAT="ADJUDICATION"
  - Assigned adjudication event onset date rather CF date
  - Link adjudication records in CF and AE using RESREC domain

Cardiovascular AE Analysis Sample

Analysis of Patients With Confirmed, Adjudicated Cardiovascular Serious Adverse Events

	TRT1 n (%)	TRT2 n (%)	TRT 1 vs. TRT2 Estimate (95% CI) †
Patients in population	xx	xx	
Cardiovascular death or sudden death	x (x.x)	x (x.x)	x.x
Cardiovascular death	x (x.x)	x (x.x)	x.x
Sudden death	x (x.x)	x (x.x)	x.x
Cardiac events, excluding heart failure	x (x.x)	x (x.x)	x.x
Acute myocardial infarction	x (x.x)	x (x.x)	x.x
Resuscitated cardiac arrest	x (x.x)	x (x.x)	x.x
Unstable angina pectoris	x (x.x)	x (x.x)	x.x
Cerebrovascular events	x (x.x)	x (x.x)	x.x
Hemorrhagic stroke or hemorrhagic change	x (x.x)	x (x.x)	x.x
Ischemic stroke	x (x.x)	x (x.x)	x.x
Ocular vascular event	x (x.x)	x (x.x)	x.x

Rescue Medication

- Consider the medical risk of inadequate control, the subject who meets the rescue criteria should initiate rescue therapy (e.g. Metformin).
- Rescue medication will be collected in CM domain with [CMCAT] (Category for Medication)='RESCUE'
- Phasing (e.g EPOCH) in SDTM will be determined with the compare of CM.CMSTDTC and EX.EXSTDTC
- Safety:
  - Primary approach (Excluding Rescue)
  - Secondary approach (Including Rescue)
- Efficacy: Data after the initiation of rescue therapy will be censored (i.e., treated as missing) to avoid the confounding influence of rescue therapy.

Exposure-adjusted AE

- Consider individual subject's exposure time to access toleration and acceptable safety profile.
- Exposure-adjusted incidence rate = # of subjects or events/subject-year*100 = $\frac{n}{T} \times 100 = \frac{n}{\sum t_i} \times 100$

Exposure-adjusted Incidence Rate (Number of Subjects)

	TRT1			TRT2		
	n	m	(SY)†	n	m	(SY)†
Subjects in population	X			X		
With one or more specific adverse events below	X	X	(X.X)	X	X	(X.X)
Specific AE1	X	X	(X.X)	X	X	(X.X)
Specific AE2	X	X	(X.X)	X	X	(X.X)
Specific AE3	X	X	(X.X)	X	X	(X.X)

n = Number of subjects, m = Number of events

† (SY) = # of subjects/subject-year*100.

Exposure-adjusted Incidence Rate (Number of Events)

	Treatment			Placebo		
	n	m	(SY)†	n	m	(SY)†
Subjects in population	X			X		
With one or more specific adverse events below	X	X	(X.X)	X	X	(X.X)
Specific AE1	X	X	(X.X)	X	X	(X.X)
Specific AE2	X	X	(X.X)	X	X	(X.X)
Specific AE3	X	X	(X.X)	X	X	(X.X)

n = Number of subjects, m = Number of events

† (SY) = # of events/subject-year*100.

Programing Flow

1. Identifying specific events from AE dataset.
2. Capture the first incidence of each unique event term.
3. Get the first treatment start/end date from ADSL and then create a dummy dataset by subject ID and event term.
4. Merge event data and dummy data in order to assign event for each patient.
5. For number of subjects table, count exposure duration up to the first corresponding events or total exposure duration if no any events. For number of events table, count the total exposure duration.
6. Count the total number of subjects/events and sum of the exposure durations.
7. Get final exposure adjusted incidence rates.

Women Health Studies

A Few Background

- Women have unique health issues: pregnancy, menopause and conditions of the female organs. Some of the health issues that affect both men and women can affect women differently.
- Briefly introduce indication on:
  - Contraception
  - Dysmenorrhea
  - Assisted Reproductive Technology

Contraception

- Endpoint
  - Pearl Index (PI) = n/E
    - n=Number of in-treatment pregnancies
    - E=Exposure in 100 woman-years. Typically 1 woman-year is 13 menstrual cycles of 28 days.
    - 100 women can contracept for 1 year (13 menstrual cycles). If 3 pregnancies occur during this period in this group, the Pearl index will be 3.
- Population
  - rFAS (Primary): “at risk” cycle
  - FAS: (Supporting): All cycles (“at risk” or not)
- Cycle and “at risk” Cycle
  - “At risk” treatment cycles are those in which vaginal intercourse was affirmed and no contraceptive method other than trial medication was used.

Dysmenorrhea

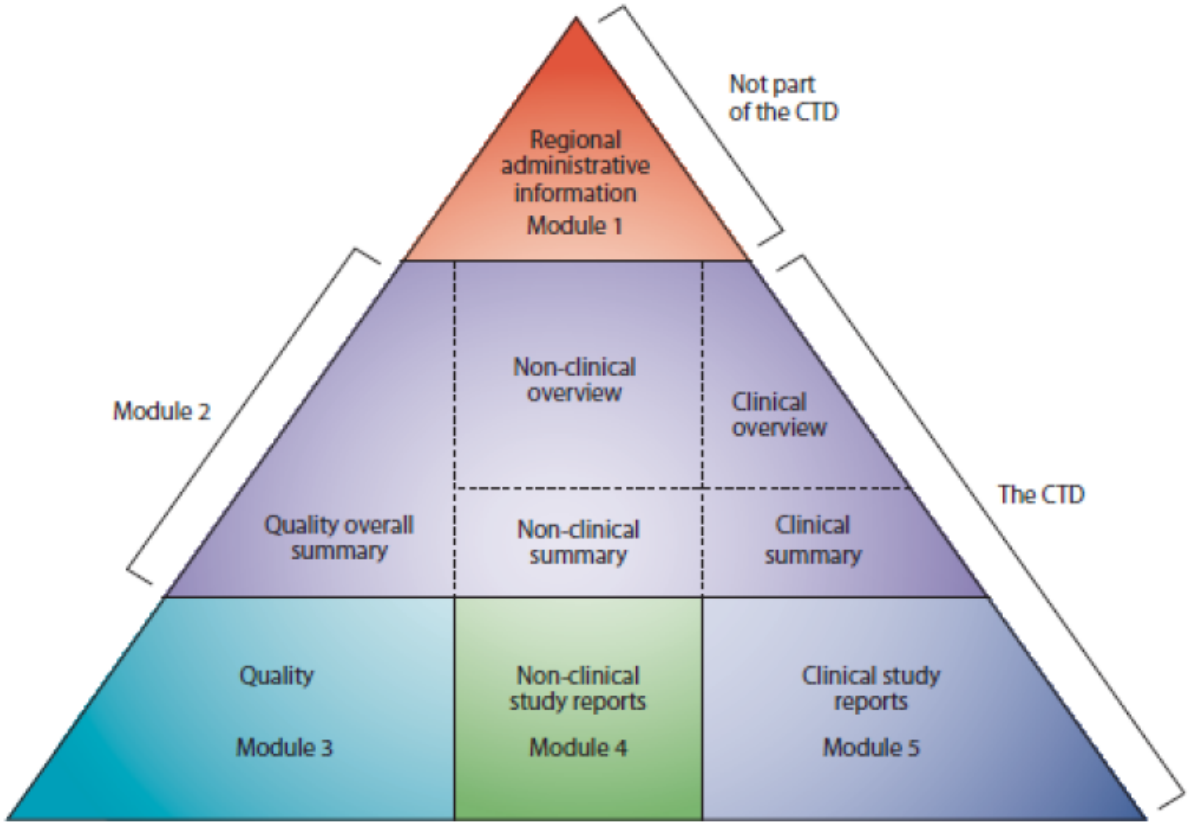
- Endpoint:
  - Change from baseline on reduction in peak pelvic pain score and no increase in number of ibuprofen tablets taken.
- Diary
  - Dysmenorrhea Daily Diary
  - Menstrual Distress Questionnaire, Cycle Version (MDQ-C)
  - Medical Outcomes Trust Short-Form 36

Assisted Reproductive Technology

- Efficacy
  - Number of oocytes retrieved
- Safety
  - Rates of congenital malformations in infants
  - Vital pregnancy rate
  - Rates of pregnancy outcomes

About Submission

Worldwide Marketing Application (WMA)

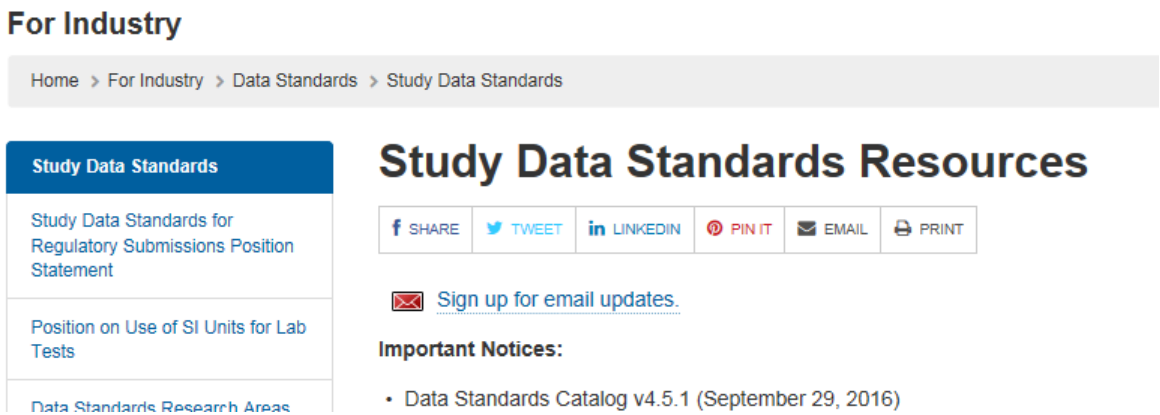


The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

Why Submission Delivery More and More Complicate and Critical?

- FDA required Study Data Standard in eCTD
  - December 17, 2016 is Coming
  - FDA Technical Rejection Process
  - …
- Submission requirement and process is keep changing
  - Traceability
  - Hyperlinking and Source
  - …
- Improve the value and speed of care delivered to patients
  - Competition on approval and market
  - The sooner the better
  - …

What is Study Data Standards ?



For Industry

Home › For Industry › Data Standards › Study Data Standards

Study Data Standards

- Study Data Standards for Regulatory Submissions Position Statement
- Position on Use of SI Units for Lab Tests
- Data Standards Research Areas

Study Data Standards Resources

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

Sign up for email updates.

Important Notices:

- Data Standards Catalog v4.5.1 (September 29, 2016)

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	10/30/2009		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
Animal study datasets	Standard for Exchange of Nonclinical Data (SEND)	XPT	CDISC	1.2	3.0	CDER	06/13/2011		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SEND
Study data definition	Define	XML	CDISC	1.0	N/A	CDER, CBER, CDRH	Ongoing	03/15/2018	12/17/2016 [1] 12/17/2017 [2]		CDISC.org - Define-XML
Study data definition	Define	XML	CDISC	2.0	N/A	CDER, CBER, CDRH	08/07/2013		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - Define-XML

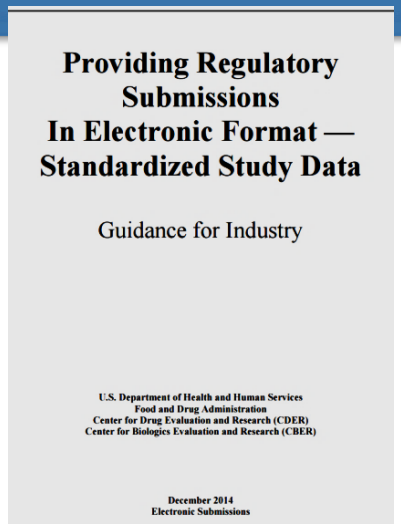
When and How Study Data Standards be Required?

December 17, 2014

FDA has determined that study data contained in the electronic submissions must be in a format that the Agency can process, review, and archive.

The Agency may Refuse To File (RTF) an electronic submission that does not have study data in conformance to the required standards specified in the Catalog.

Request a waiver.



Providing Regulatory Submissions In Electronic Format — Standardized Study Data

Guidance for Industry

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

December 2014
Electronic Submissions

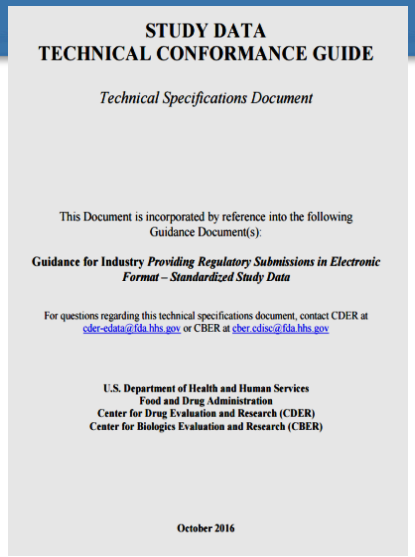
24 Months

December 17, 2016

After date must use the standards in the FDA Data Catalog (NDAs, ANDAs, BLAs).

Study Data Technical Conformance Guide v3.2 (October 31, 2016)

Recommendations for preparing a Study Data Standardization Plan



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.edisc@fda.hhs.gov

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

October 2016

Submission Package

- Study Data Standardization Plan
  - Planned data standards, formats, and terminologies and versions
  - Justification of studies that may not conform to the currently supported standard
- SDTM CRT (Case Report Tabulations) Package
  - SDTM datasets
  - Define
  - Annotated CRF
  - SDRG (Study Data Reviewer's Guide)
- Analysis Package
  - Analysis datasets
  - Define
  - Analysis Programs
  - ADRG (Analysis Data Reviewer's Guide)
- OSI (Office of Scientific Investigation)
  - Datasets
  - Define
  - Site Listings
- ISS/ISE

eCTD File Directory Structure

Figure 1: Folder Structure for Study Datasets

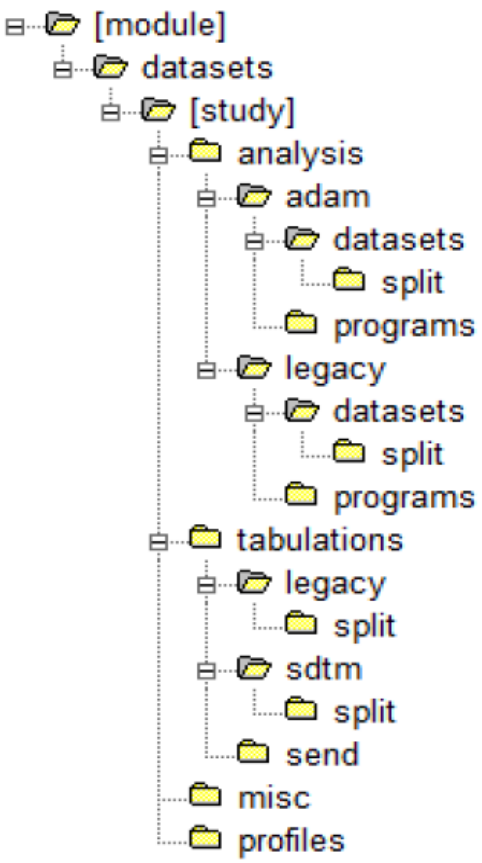


Table 2: Study Dataset and File Folder Structure and Description

Folder Name	Folder Level	Description/Contents
[module]	1	Refers to the eCTD module in which study data is being submitted. Name this folder m4 for nonclinical data and m5 for clinical data. Do not place files at this level.
datasets	2	Resides within the module folder as the top-level folder for study data (nonclinical or clinical) being submitted for the specified module (m4 or m5). Do not place files at this level.
[study]	3	Name this folder with the study identifier or analysis type performed (e.g., study123, iss, ise). Do not place files at this level.
analysis	4	Contains folders for analysis datasets and software programs; arrange in designated level 6 subfolders. Do not place files at this level.
adam	5	Contains subfolders for ADaM datasets and corresponding software programs. Do not place files at this level.
datasets	6	Place ADaM datasets in this subfolder.
split	7	Place any split ADaM datasets in this subfolder.
programs	6	Place software programs for ADaM datasets, tables and figures in this subfolder.
legacy	5	Contains legacy formatted analysis datasets and corresponding software programs. Do not place files at this level.
datasets	6	Place legacy analysis datasets in this subfolder.
split	7	Place split legacy analysis datasets in this subfolder.
programs	6	Place software programs for legacy analysis datasets, tables and figures in this subfolder.
misc	4	Place miscellaneous datasets that don't qualify as analysis, profile, or tabulation datasets in this subfolder. This subfolder was formerly named "listings".
profiles	4	Place patient profiles in this subfolder.
tabulations	4	Contains subfolders for tabulation datasets. Do not place files at this level.
legacy	5	Place legacy (non-standardized) tabulation datasets in this folder.
split	6	Place any split legacy tabulations datasets in this subfolder.
sdtm	5	Place SDTM tabulation datasets in this subfolder. Should only be used in m5 for clinical data.
split	6	Place any split SDTM files in this subfolder.
send	5	Place SEND tabulation datasets in this subfolder. Should only be used in m4 for animal data.

Submission Consideration

- Make the plan as early as possible.
- Enhance the CDISC understanding.
- Be compliant with the applicable data standards endorsed by FDA.
- Be proactive to the changing submission requirements.
- Review Guides (SDRG and ADRG) is very critically important.
  - Support reviewer (who has never seen your data before) to understand the data and be able to work with it.
- Let FDA love the submission package.

Thank You