The CDISC SDTM Exposure Domains (EX & EC) Demystified
How EC Helps You Produce a Better (more compliant) EX

Tom Guinter, Independent Consultant
Clinical Data Standards and eSubmission

CDISC SDS Team Member Since 2001
Acknowledged Principle Contributor to CDISC SDTM (thru v1.2)

Janet Reich, Sr. Manager, Amgen
CDISC Consultancy Group

CDISC SDS Team Member Since 2006, 2018 Team Lead
SDS Exposure Team Lead (team that developed EX/EC approach)

SDTM EC & EX

- Purpose
  - To help industry leverage the EC domain to make a better EX
- Outline
  - Past
    - SDTMIG v3.1.1 to SDTMIG v3.1.3
  - Present
    - SDTMIG v3.2 & Examples
  - Future
    - Known Issues
  - Summary

SDTM EC & EX – Past

SDTM v1.1
- --TRTV & --ADJ added to Section 2.1.1
- TS domain added to Section 3.5.1

SDTMIG v3.1.1
- **EX, permissible**

SDTM v1.3
- TS Null Flavor variables added to Section 3.5.1

SDTMIG v3.1.3
- **EX – minor label & role updates**

2005* | 2006 | 2008* | 2009 | 2012*

Regulatory review challenges with EX

* CDISC SDTMIG & SDTM published

SDTM v1.2
- --PRESP, --VAMT, --VAMTU added to Section 2.1.1
- TSGRPID added to Section 3.5.1

SDTMIG v3.1.2
- **EX, expected/required**
  - **most accurate/complete representation of subject exposure from the collected data**
- **DA added**

SDTM EC & EX – Present

2013*

Mood is an activity status (eg, planned, scheduled, performed)

SDTM v1.4 Variables Added to Section 2.1.1

- Pharmaceutical Strength and Unit (--PSTRG, --PSTRGU)
- Fasting Status (--FAST)
- Anatomical Location Qualifiers (--LAT, --DIR, --PORTOT)
- Mood (--MOOD)

SDTMIG v3.2

- **EX domain recognized in most cases as a derived dataset**
  - **EXDOSU should reflect the protocol-specified unit**
- **Exposure as Collected (EC) added**
  - **Represents study treatment data as collected**
  - **Supports traceability from collection to derived EX records**

* CDISC SDTMIG & SDTM published

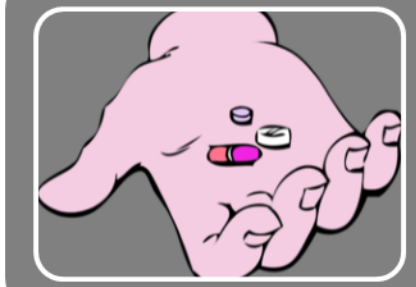
SDTM EC & EX – Matrix

Plan – Trial Level

- TS domain
- Study Treatment Parameters: TRT, DOSE, DOSFRQ, DOSU, ROUTE, TYPE, ADDON, CURTRT, BLIND, COMPTRT, etc.

Scheduled – Subject Level

- EC domain
- Investigator assessment; Scheduled study treatment
- When collected, ECMOOD = 'SCHEDULED'



Performed – Subject Level

- EC domain – collected intervals, dose form, missed doses
- EX domain – actual study treatment dose(s) in protocol-specified unit
- FA domain – study treatment dose(s) in alternative units

SDTM EC & EX – Hypothetical Example 1 (1)

- Open-label, single-dose study to evaluate the safety, tolerability, PK, and PD of study treatment Remedx
- Subjects will receive single oral dose of 0.25 mg/kg
  - Remedx is provided in 5 mg capsules

ts.xpt (abbreviated example due to space limits)

TSSEQ	TSGRPID	TSPARMCD	TSPARM	TSVAL
1	A	TRT	Interventional Therapy or Treatment	REMEDX
1	A	DOSE	Dose per Administration	0.25
1	A	DOSU	Dose Units	mg/kg
1	A	DOSFRQ	Dosing Frequency	ONCE
1	A	ROUTE	Route of Administration	ORAL

SDTM EC & EX – Hypothetical Example 1 (2)

CRF

Phase	TREATMENT
Study Treatment	REMEDX
Start Date	_ _ / _ _ _ / _ _ _ _
Start Time	_ _ : _ _
Dose	_ _ _
Unit	mg
Route	Oral

SDTM EC & EX – Hypothetical Example 1 (3)

ec.xpt (abbreviated example due to space limits)

USUBJID	ECLNKID	ECTRT	ECPRESP	ECOCCUR	ECDOSE	ECDOSU	ECDOSFRM
20160001	20160223	REMEDX	Y	Y	15	mg	CAPSULE

ECDOSFRQ	ECROUTE	ECPSTRG	ECPSTRGU	EPOCH	ECSTDTC	ECENDTC	ECSTDY	ECENDY
ONCE	ORAL	5	mg/capsule	TREATMENT	2016-02-23 T10:15	2016-02-23 T10:15	1	1

ex.xpt (abbreviated example due to space limits)

USUBJID	EXLNKID	EXTRT	EXDOSE	EXDOSU	EXDOSFRM	EXDOSFRQ
20160001	20160223	REMEDX	0.24	mg/kg	CAPSULE	ONCE

EXROUTE	EPOCH	EXSTDTC	EXENDTC	EXSTDY	EXENDY
ORAL	TREATMENT	2016-02-23T10:15	2016-02-23T10:15	1	1

- A one-to-one relationship between ECLNKID and EXLNKID should be defined in RELREC.
- EXDOSE Computational Method: Calculated using the dose administered (mg) and the most recent weight (kg) measured on or before the dose date.

SDTM EC & EX – Hypothetical Example 2 (1)

- Double-blind, Placebo-controlled study to evaluate the efficacy and safety of study treatment Ipsum
- Study treatment will be dosed monthly (QM) by subcutaneous (SC) injection (50 mg, 100 mg, placebo)
  - Ipsum is provided in a 1 mL pre-filled syringe containing 50 mg/mL

ts.xpt (abbreviated example due to space limits)

TSSEQ	TSGRPID	TSPARMCD	TSPARM	TSVAL
1		TCNTRL	Control Type	PLACEBO
1	A	TRT	Interventional Therapy or Treatment	IPSUM
1	A	DOSE	Dose per Administration	50
2	A	DOSE	Dose per Administration	100
1	A	DOSU	Dose Units	mg
1	A	DOSFRQ	Dosing Frequency	QM
1	A	ROUTE	Route of Administration	SUBCUTANEOUS

SDTM EC & EX – Hypothetical Example 2 (2)

CRF

Phase	TREATMENT
Treatment Name	Syringe 1
Start Date	_ _ / _ _ _ / _ _ _ _
Start Time	_ _ : _ _
Dose	_ _._
Unit	mL
Anatomical Location	○ Abdomen ○ Arm ○ Thigh
Reason Not Given or Missed	○ AE ○ Admin Error ○ Noncompliance
Treatment Name	Syringe 2
Start Date	_ _ / _ _ _ / _ _ _ _
Start Time	_ _ : _ _
Dose	_._
Unit	mL
Anatomical Location	○ Abdomen ○ Arm ○ Thigh
Reason not Given or Missed	○ AE ○ Admin Error ○ Noncompliance

SDTM EC & EX – Hypothetical Example 2 (3)

ec.xpt (abbreviated example due to space limits)

USUBJID	ECLNKID	ECTRT	ECPRESP	ECOCCUR	ECDOSE	ECDOSU	ECDOSFRM	ECDOSFRQ
20150205001	20160410	SYRINGE 1	Y	Y	1	mL	INJECTION	QM
20150205001	20160410	SYRINGE 2	Y	Y	1	mL	INJECTION	QM
20150205001	20160519	SYRINGE 1	Y	Y	1	mL	INJECTION	QM
20150205001	20160519	SYRINGE 2	Y	N			INJECTION	QM

ECROUTE	ECLOC	ECPSTRG	ECPSTRGU	EPOCH	ECSTDTC	ECENDTC	ECSTDY	ECENDY
SUBCUTANEOUS	ARM		mg/capsule	TREATMENT	2016-04-10 T08:00	2016-04-10 T08:00	1	1
SUBCUTANEOUS	ARM		mg/capsule	TREATMENT	2016-04-10 T08:03	2016-04-10 T08:03	1	1
SUBCUTANEOUS	THIGH		mg/capsule	TREATMENT	2016-05-19 T10:30	2016-05-19 T10:30	40	40
SUBCUTANEOUS	THIGH		mg/capsule	TREATMENT	2016-05-19	2016-05-19	40	40

suppec.xpt (abbreviated example due to space limits)

RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
EC	20150205001	ECSEQ	4	ECREASOC	Reason for Occur Value	AE

SDTM EC & EX – Hypothetical Example 2 (4)

ex.xpt (abbreviated example due to space limits)

USUBJID	EXLNKID	EXTRT	EXDOSE	EXDOSU	EXDOSFRM	EXDOSFRQ	EXROUTE
20150205001	20160410	IPSUM	100	mg	INJECTION	QM	SUBCUTANEOUS
20150205001	20160519	IPSUM	50	mg	INJECTION	QM	SUBCUTANEOUS

EXLOC	EPOCH	EXSTDTC	EXENDTC	EXSTDY	EXENDY
ARM	TREATMENT	2016-04-10T08:00	2016-04-10T08:03	1	1
THIGH	TREATMENT	2016-05-19T10:30	2016-05-19T10:30	40	40

relrec.xpt

STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
IPSUM20150205	EC		ECLNKID		MANY	EC-EX
IPSUM20150205	EX		EXLNKID		ONE	EC-EX

- EXDOSE Computational Method: Calculated using the sum of volumes administered (mL) across 2 syringes multiplied by syringe concentration (mg/mL).

SDTM EC & EX – Hypothetical Example 3 (1)

- Double-blind, placebo-controlled study to assess the Efficacy and Safety of study treatment Mirumed

- Dose levels will be assigned (every 4 weeks) based on lab test X results per the protocol titration algorithm
  - Once daily oral doses should be taken; the planned dose level will be assigned every 4 weeks.

ts.xpt (abbreviated example due to space limits)

TSSEQ	TSGRPID	TSPARMCD	TSPARM	TSVAL
1	A	TRT	Interventional Therapy or Treatment	MIRUMED
1	A	DOSE	Dose per Administration	5
2	A	DOSE	Dose per Administration	10
3	A	DOSE	Dose per Administration	20
1	A	DOSU	Dose Units	mg

SDTM EC & EX – Hypothetical Example 3 (2)

CRF

Visit	Day 1
Phase	TREATMENT
Treatment Name	MIRUMED/PLACEBO
Planned Daily Dose (mg)	_ _
Start Date	_ _ / _ _ _ / _ _ _ _
Stop Date	_ _ / _ _ _ / _ _ _ _
Tablets Taken Daily	_ _

Visit	Week 4
Phase	TREATMENT
Treatment Name	MIRUMED/PLACEBO
Planned Daily Dose (mg)	_ _
Start Date	_ _ / _ _ _ / _ _ _ _
Stop Date	_ _ / _ _ _ / _ _ _ _
Tablets Taken Daily	_ _

SDTM EC & EX – Hypothetical Example 3 (3)

ec.xpt (abbreviated example due to space limits)

USUBJID	ECLNKID	ECTRT	ECMOOD	ECPRESP	ECOCCUR	ECDOSE	ECDOSU
ABC123-101	D1	MIRUMED/PLACEBO	SCHEDULED			10	mg
ABC123-101	D1	MIRUMED/PLACEBO	PERFORMED	Y	Y	2	TABLET
ABC123-101	W4	MIRUMED/PLACEBO	SCHEDULED			20	mg
ABC123-101	W4	MIRUMED/PLACEBO	PERFORMED	Y	Y	4	TABLET

ECDOSFRM	ECDOSFRQ	EXROUTE	VISIT	EPOCH	ECSTDTC	ECENDTC
TABLET	QD	ORAL	DAY 1	TREATMENT		
TABLET	QD	ORAL		TREATMENT	2015-09-22	2015-10-22
TABLET	QD	ORAL	WEEK 4	TREATMENT		
TABLET	QD	ORAL		TREATMENT	2015-10-23	2015-11-23

SDTM EC & EX – Hypothetical Example 3 (4)

ex.xpt (abbreviated example due to space limits)

USUBJID	EXLNKID	EXTRT	EXDOSE	EXDOSU	EXDOSFRM	EXDOSFRQ
ABC123-101	D1	MIRUMED	10	mg	TABLET	QD
ABC123-101	W4	MIRUMED	20	mg	TABLET	QD

EXROUTE	EPOCH	EXSTDTC	EXENDTC	EXSTDY	EXENDY
ORAL	TREATMENT	2015-09-22	2015-10-22	1	31
ORAL	TREATMENT	2015-10-23	2015-11-23	32	63

- A many-to-one relationship should be defined in RELREC
  - where ECLNKID = EXLNKID
- EXDOSE Computational Method: Calculated using number of tablets taken daily multiplied by the pharmaceutical strength (mg/tablet).

SDTM EC & EX – Best Practices (1)

Do's	Don'ts
1. Populate TS with the protocol-planned IP administration details (eg, TSPARMCDs TRT, DOSE, DOSU, DOSFRQ, ROUTE). 2. Populate EC with collected IP administration data. 3. Populate DA with collected drug accountability data. 4. Populate FA with any findings about IP administration data. 5. Always create EX if IP administration occurs.	1. Populate EX with only protocol-planned IP administration details (unless no study treatment and/or drug accountability data were collected).

SDTM EC & EX – Best Practices (2)

Do's	Don'ts
5. Always create EX if IP administration occurs. a. Determine the most appropriate EX by understanding the protocol described dosing. b. Use all collected sources of IP admin to determine the most accurate/complete EX. c. Provide regulatory reviewers with the most accurate, complete, and review-friendly EX. d. Describe how EX records were derived and the level of uncertainty in the define.xml and SDRG.	1. Populate EX with only planned exposures from the protocol (unless no study treatment and/or drug accountability data were collected).

SDTM EC & EX – Common Questions

Q: Is EC Optional?

A: Yes, but…

- Remember, EC exists because of Regulators comments on EX
- EC should help create a more useful EX
- EC provides the audit-trail from collected to summarized dosing
- EC is the only place to represent missed doses
- EC allows representation of scheduled dosing (using ECMOOD)
- Unless EX would be an exact copy of EC, then EC should be considered required

Q: Is EC About Blinded Data?

A: No

- EC can represent blinded data, but that is not one of the primary objectives of EC
- Ask yourself this question: Would submitting blinded data help a reviewer?

SDTM EC & EX – Future

- **Representation of**
  - Combination products
  - Dermatologic and Opthalmic drugs
  - Level of certainty of collected or derived records
  - Unscheduled exposures
  - Unknown exposures
  - Dose within a specified interval of time (other than Total Daily Dose)

- **Enhancements supporting**
  - Dose adjustment details
    - Type (increase, decrease)
    - Reason (--ADJ) examples
  - Dose preparations
  - Additional CRF designs

- **Harmonization with CDASH**
  - Infusion Rate, Interruption Duration, Completed Treatment indicator

SDTM EC & EX – Summary

- Per the FDA Technical Conformance Guide,
  - The goal of standardizing data is to make the data more useful and to support semantically interoperable data exchange between sponsors, applicants, and the FDA such that it is commonly understood by all parties.

- EC & EX domains together make study treatment
  - Easier for sponsors to represent the collected data
  - More transparent from collected to derived data
  - Better for regulatory reviewers
    - EXDOSU clarified
    - Doses not taken, not given, missed standardized
    - Documentation expectations in the define.xml and SDRG clarified

Janet Reich, Sr. Manager, Amgen.
Co-author and presenter at the CDISC Interchange 2016.

Tom Guinter, Independent Consultant.
Co-author and presenter at PharmaSUG 2017.

www.pharmasug.org/proceedings/2017/DS/PharmaSUG-2017-DS08.pdf