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

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ABSTRACT

The EC (Exposure as Collected) domain was introduced in the CDISC SDTMIG (Study Data Tabulation Model Implementation Guide for Human Clinical Trials) version 3.2 as a means to help sponsors produce a more compliant and usable EX (Exposure) domain. It's a new concept in the SDTM as it establishes a new rule for related/paired domains, and/or breaks the established principle that a single intervention or event should have a single intervention or event record in the SDTM. The EC domain can loosely be considered part of the audit trail for the EX domain, which is recognized as at least a partially derived domain.

This paper reviews some of the rationale for the EC/EX combination of domains and provides recommendations on how sponsors should leverage the EC domain to produce a better, more usable EX domain.

HISTORY – PAST TO PRESENT

In 2005 the Exposure domain was considered permissible to represent study treatment administrations when explicitly collected. Many of us in industry thought if administrations weren't explicitly collected, perhaps only dispensations and returns were collected and mapped to the DA (Drug Accountability domain), then the EX domain wasn't necessary or appropriate to be created.

In 2006 regulatory review challenges with the Exposure domain were noted by agency representatives at industry conferences. Statements were made that the agency expected an EX domain, even when not explicitly collected as administrations. In response to the agency feedback, the Exposure domain became required in SDTMIG v3.1.2, recognized as at least a partially derived domain in some cases, and should reflect the most accurate and complete representation of subject exposure from the collected data.

In 2012, minor label and role updates were incorporated in SDTMIG v3.1.3. But there were more changes underway, expected to be incorporated into SDTMIG v3.2. Additional agency feedback, coupled with industry questions, suggested the EX domain was often not very helpful in reviews. It often either lacked complete information and/or didn't represent the information in the most user-friendly or consumable way.

In 2013:

- SDTM v1.4 was published which added several new variables to the Interventions general observation class. Pharmaceutical Strength, its Unit, Fasting Status, Anatomical Location Qualifiers, and the Mood variable which describes the status of an activity – whether it's scheduled or performed information.
- The SDTMIG v3.2 was published with the following Exposure updates:
    - The Exposure domain is recognized as a derived dataset in most cases
    - EX Dose Unit should reflect the protocol-specified unit
    - The EC (Exposure as Collected) domain was added to represent treatment as collected, and support traceability from collection to derived EX records

SO WHAT DOES THIS ALL MEAN TO US?

The bottom-line for us is we're expected to create an EX domain that represents the best information on subject exposure from all of the information we collected, and represents that information in the most usable/consumable way. If we collect individual administrations or regimens in the protocol-specified unit

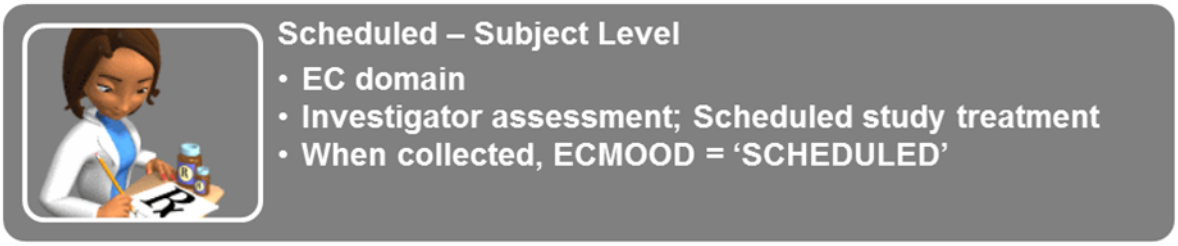
then we may not need EC. But in the majority of studies where we don't collect the information in the protocol-specified unit, and/or collected administration data doesn't correlate with the expectations for review, we should map our collected administrations to EC (and perhaps DA and/or FA), and then use that information to derive the EX records. We should think of EC (and DA/FA) as audit trail data supporting the EX records.

SDTM EC & EX - MATRIX

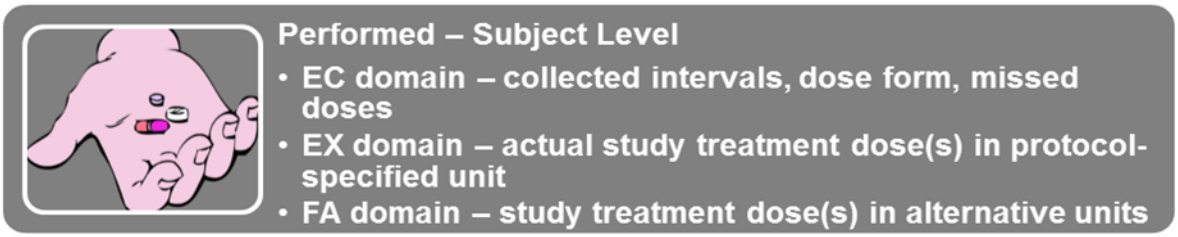
The study data exposure matrix includes 3 parts:

1. Planned information that is described at the trial level in the protocol. Planned exposure details are represented in the TS (Trial Summary) dataset.

2. Scheduled treatment information occurs at the subject level and when collected can be represented in EC. The Mood variable indicates when a record reflects scheduled information.



3. Performed treatments occur at the subject level. EC should reflect collected treatment details and missed dose information. EX should represent actual treatment administrations represented in the protocol-specified unit. And FA (Findings About) can represent study treatment doses in alternative units.



SDTM EC & EX EXAMPLES

Hypothetical Example 1:

In this hypothetical study, subjects will receive a single oral dose of 0.25 mg/kg and the treatment is provided in 5 mg capsules.

The protocol planned dose unit is mg/kg and is represented in TS.

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

Example CRF - The CRF collected dose unit is mg.

Phase	TREATMENT
Study Treatment	REMEDX
Start Date	__ / ___ / ____
Start Time	__ : __
Dose	___
Unit	mg
Route	Oral

In EC, 15 mg was the collected dose and the pharmaceutical strength was 5 with a unit of mg/capsule.

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	2016-02-23T10:15	2016-02-23T10:15	1	1

In EX, 0.24 mg/kg is the derived actual dose administered, represented in the protocol-specified unit of mg/kg.

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

The relationship between records in EC and EX should be represented in RELREC.

The Computational Method for EXDOSE should be in the define.xml.

Hypothetical Example 2:

In this second hypothetical study, subjects are to receive a monthly subcutaneous injection of either 50 mg, 100 mg, or placebo. The treatment is provided in a 1 mL pre-filled syringe containing 50 mg/mL or placebo.

The protocol planned dose unit is mg and is represented in TS.

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

Example CRF - The CRF collected dose unit is mL. To maintain the blind of 50 mg, 100 mg, or placebo dose levels, the treatment is administered using 2 syringes.

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

Two records are represented in EC for each treatment administration and ECDOSE represents the collected amount administered.

USUBJID	ECLNKID	ECTRT	ECPRESP	ECOCCUR	ECDOSE	ECDOSU	ECDOSFRM	ECDOSFRQ
20150001	20160410	SYRINGE 1	Y	Y	1	mL	INJECTION	QM
20150001	20160410	SYRINGE 2	Y	Y	1	mL	INJECTION	QM
20150001	20160519	SYRINGE 1	Y	Y	1	mL	INJECTION	QM
20150001	20160519	SYRINGE 2	Y	N			INJECTION	QM

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

On Day 1, both Syringe 1 and Syringe 2 administrations occurred.
On Day 40, only Syringe 1 was given and Syringe 2 did not occur, for the reason of AE (represented in the SUPPEC dataset).

RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
EC	20150001	ECSEQ	4	ECREASOC	Reason for Occur Value	AE

One record is represented in EX for each treatment administration.

USUBJID	EXLNKID	EXTRT	EXDOSE	EXDOSU	EXDOSFRM	EXDOSFRQ	EXROUTE
20150001	20160410	IPSUM	100	mg	INJECTION	QM	SUBCUTANEOUS
20150001	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

100 mg is the unblinded actual dose represented in the protocol-specified unit, mg, administered on Day 1 across Syringes 1 and 2. 50 mg is the actual dose received on Day 40 since only Syringe 1 was administered.

The relationship between records in EC and EX are represented in RELREC.

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

The Computational Method for EXDOSE should be represented in the define.xml.

Hypothetical Example 3:

This third hypothetical example is a double-blind, placebo-controlled study where a lab test is performed every 4 weeks and the dose level is assigned relative to it. The treatment is provided in tablets and taken once daily.

The protocol planned dose unit is mg and is represented in TS.

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

The CRF collected the Planned Daily Dose in mg and the actual number of tablets taken daily between Day 1 and Week 4.

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

The second CRF collected the Planned Daily Dose and actual number of tablets taken daily between Week 4 and Week 7.

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

In EC, the collected planned daily dose is represented as well as the reported number of daily tablets taken between Day 1 and Week 4. The Planned Daily Dose scheduled from Week 4 to Week 7 and the actual number of tablets taken in that interval is also represented. The Mood variable distinguishes the scheduled records from the performed records.

USUBJID	ECL NKID	ECTRT	ECMOOD	ECPRESP	ECOCCUR	ECDOSE	ECDOSU
ABC123101	D1	MIRUMED/ PLACEBO	SCHEDULED			10	mg
ABC123101	D1	MIRUMED/ PLACEBO	PERFORMED	Y	Y	2	TABLET
ABC123101	W4	MIRUMED/ PLACEBO	SCHEDULED			20	mg
ABC123101	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

EX represents the unblinded treatment and actual dose taken in the protocol-specified unit.

USUBJID	EXLNKID	EXTRT	EXDOSE	EXDOSU	EXDOSFRM	EXDOSFRQ
ABC123101	D1	MIRUMED	10	mg	TABLET	QD
ABC123101	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.

The Computational Method for EXDOSE should be represented in the define.xml.

SDTM EC & EX – BEST PRACTICES – DO'S/DON'TS

Do	Don't
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. 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).

THE FUTURE OF SDTM EXPOSURE DOMAIN(S)

Expansion of the SDTM Exposure domain to EC and EX with updated guidance to present the most accurate representation of subject exposure in EX in SDTMIG v3.2 is just the start. There are a number of additional issues to be address in future version of the SDTM and SDTMIG including, but not limited to:

- **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 (Clinical Data Acquisition Standards Harmonization)**
  - Infusion Rate, Interruption Duration, Completed Treatment indicator

SUMMARY

Per the FDA SDTCG (Study Data Technical Conformance Guide), the goal of standardizing data is to make the data more useful and to support semantically interoperable data exchange such that it is commonly understood by all parties.

The Exposure as Collected and Exposure domains together make study treatment:

- Easier for sponsors to represent the collected data
- More transparent from collected to derived data
- Better for regulatory reviewers
    - By clarifying Exposure Dose unit expectations
    - Providing a standard way to represent doses not taken / not given / missed

Hope you agree.

Thanks. 😊

REFERENCES

CDISC Study Data Tabulation Model (SDTM) v1.4 and Study Data Tabulation Model Implementation Guide (SDTMIG) v3.2. http://www.cdisc.org/sdtm

FDA STUDY DATA TECHNICAL CONFORMANCE GUIDE. Guidance for Industry Providing Regulatory Submissions in Electronic Format – Standardized Study Data. FDA CDER, CBER

SDTM Exposure Domains (EC & EX) Past, Present, Future. Presented at the CDISC Interchange 2016-09-28 by Janet Reich, content authors Thomas Guinter and Janet Reich.

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