How to present exposure data nicely in the SDTM?

Manxi Chen, Everest Clinical Research

ABSTRACT

From 2005, the Exposure domain was considered permissible to represent study treatment administrations, many sponsors started to pay more attention to submit clear, tidy, and reviewer-friendly exposure data in the SDTM. Per the EC (Exposure as Collected) domain was introduced in the CDISC SDTMIG version 3.2 as a method to produce a more compliant and usable EX (Exposure) domain, there are many considerations and options to present exposure information on study treatment. This paper will focus on how to represent an accurate, complete, reviewer-friendly exposure data in the SDTM. It will introduce EX and EC domains in detail based on SDTMIG version 3.3. It will list specific points should be considered during mapping exposure domains, provide tips and tricks on the submission of EX and EC. It will also introduce some other domains related to exposure, especially two new added domains in SDTMIG version 3.3. In addition, under the COVID-19 pandemic, explanations of CDISC guides on ongoing studies disrupted by COVID-19 pandemic will be provide with examples.

INTRODUCTION

Clinical trial study designs can range from open label to blinded, and the collection methods of treatment information are diverse and hard to standardize. Two SDTM domains based on the Interventions General Observation Class are introduced to represent details of subject exposure to protocol specified study treatment(s). One is called Exposure (EX), which is an interventions domain that contains the details of a subject's exposure to protocol-specified study treatment; the other is called Exposure as Collected (EC), which is an interventions domain that contains information about protocol-specified study treatment administrations, as collect. Although these two domains' names and definitions look similar, they have different rules and purposes of use.

The EC domain was introduced in the CDISC SDTMIG v3.2 aiming to help sponsors produce a more compliant and accurate EX domain. The case report form (CRF) might have a different design of capturing treatment with treatment defined in protocol. The SDTMIG recommends submitting both EX and EC if necessary, although EC is not required. However, it might be hard to determine when EC join in the SDTM for presenting a nice and intact story of exposure to study treatment to reviewers. The following part will give the brief introduction of exposure domain, and considerations on when EC prefer to create. In addition, some tips and tricks which are easier to ignore in regular daily work of crating EX and EC will be provide.

EXPOSURE (EX)

In the SDTMIG, the EX domain is required for submission when studies involving an investigational product being given to subjects. EX is defined as an interventions domain contain subjects' information of exposure to protocol-specified study treatment over the sponsor-defined "constant dosing interval". Any discussion and operations of how exposure data should be represented in EX need to follow this definition. Study treatment may be any intervention that is prospectively defined as a test material within a study, and is typically but not always supplied to the subject. Like mentioned before, not all exposure records can be directly from data captured in the CRF. The SDTMIG provides 5 common methods for determining exposure listed in the following. The order of method is from most direct to least direct, which might be understood from most reliable to least reliable.

1. Derived from actual observation of the administration of drug by the investigator
2. Derived from automated dispensing device that records administrations
3. Derived from subject recall
4. Derived from drug accountability data
5. Derived from the protocol

EX derivations must be described in the Define-XML document.

CONSIDERATIONS WHEN ADDING THE EC DOMAIN

Although the EC domain has a lot advantages, like storing more exposure information, deriving the EX domain, it's not good to submit EC at any situations. The reason is not only consuming time on developing it, but also showing redundantly in your SDTM, when the entire EC dataset is an exact duplicate of the entire EX dataset. That will be difficult, especially for fresh statistical programmer, to determine whether the EC is added or not. The following will list general points on situations of recommended EC. It will be clear and easy to let you have an idea on whether adding EC with EX or not.

1. Blinded Study or not

One of the requirement in SDTM is that the EX domain should "unblind" the reviewer to a subject's assigned study treatment. Thus, the addition of the EC domain solves the problem encountered by many sponsors whose SOPs required, or data-management functions wanted to submit, blinded data. If a study is blinded, the EC domain can be used to store blinded data under blind process. When a study is still masked and protocol-specified study treatment doses cannot yet be reflected in the protocol-specified unit due to blinding requirements, then the EX domain is not expected to be populated. The EX domain can be created after blind process to have actual exposure information on study treatment.

2. Dose not Taken, not Given, or Missed or not

The EX domain couldn't represent information collected regarding doses not taken and --OCCUR variable is not recommended to use in the EX domain. However, in the EC domain, ECOCCUR value of "N" indicates a dose was not taken, not given, or missed. ECOCCUR would be used with ECPRESP, they are both showing either Y or N. The SDTMIG suggests that ECOCCUR is generally not applicable for Scheduled records. The reason of missed doses if have would be submitted in SUPPEC, with a QNAM of ECREASOC (QLABEL = Reason for Occur Value). Please see the below example for missed, not taken, or not given dose of Drug X on 2021-01-02 with reason of Adverse Event.

ec.xpt

ROW	USUBJID	ECSEQ	ECTRT	ECPRESP	ECOCCUR	ECDOSE	ECDOSEU	ECSTDTC
1	A001	1	Drug X	Y	Y	2	TABLET	2021-01-01
2	A001	2	Drug X	Y	N		TABLET	2021-01-02

ROW	USUBJID	ECENDTC
1 (cont.)	A001	2021-01-01
2 (cont.)	A001	2021-01-02

suppec.xpt

ROW	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL	QORIG	QEVAL
1	A001	ECSEQ	2	ECREASOC	Reason for Occur Value	Adverse Event	CRF	

3. Collected dose units are not protocol-specified units or not

If collected administrations units were different with protocol-specified units, the EC domain is recommended to use for derivation of the EX. For example, the dosing information could be collected as

a weight-adjusted volume of a dosing solution with a known concentration. The following is the example of it, for a protocol-specified dose of 5mg/kg, a subject weighted 80 kg would be dosed 10 mL of a 40 mg/mL solution. The volume dosed collected could be presented in the EC, while dose in mg/kg specified in protocol could be presented in the EX.

ec.xpt

ROW	DOMAIN	USUBJID	ECSEQ	ECTRT	ECDOSE	ECDOSEU
1	EC	A001	1	Drug X	10	mL

ex.xpt

ROW	DOMAIN	USUBJID	EXSEQ	EXTRT	EXDOSE	EXDOSEU
1	EX	A001	1	Drug X	5	mg/kg

4. Planned/Scheduled Exposure Information Needed or not

If the sponsor wants to present the planned treatment details, the EC domain is recommended to use. ECMOOD is the variable for providing a mechanism for representing planned and actual occurred exposure information. The --MOOD classifies observations as defined (in a global library), planned (in a protocol), scheduled (for a subject), and performed (for a subject). The use of –MOOD in SDTM-based domains is limited to the EC, with CDISC Controlled Terminology of SCHEDULED and PERFORMED. Qualifier variable should be populated with equal granularity across Scheduled and Performed records when known. For example, if ECDOSU and ECDOSFRQ are known at scheduling and administration, the they would be populated on both records. If ECLOC and ECLAT are determined at the time of administration, for example, left arm for the injection, then “Arm” and “Left” would be populated on the performed record only. Actual doses in protocol-specified unit would be submitted in the EX domain.

TIPS AND TRICKS ON THE SUBMISSION OF EX AND EC

1. The EX domain should contain one record per constant-dosing interval per subject.

2. The EX domain is recognized in most cases as a derived dataset where EXDOSU reflects the protocol specified unit per study treatment.

3. Don’t populate the EX domain with only planned exposures from protocol.

4. Don’t forget that SUPPEX and SUPPEC are good options for you to present information not fit in the EX and EC.

5. EXTRT must include only the treatment name and must not include dosage, formulation, or other qualifying information.

6. Doses of placebo should be represented by EXTRT = "PLACEBO" and EXDOSE = "0".

7. VISITNUM may be added to the EX and EC as additional Timing variable if the subject is only encounter. However, if the beginning and end of a constant-dosing interval is not confined within the time limits of a clinical encounter (e.g., if a subject takes pills at home), then it is not appropriate to include VISITNUM. The reason is that EX is designed to capture the timing of exposure to treatment, not the timing of dispensing treatment. Furthermore, VISITNUM should not be used to indicate that treatment began at a particular visit and continued for a period of time.

8. For administrations considered given at a point in time (e.g., oral tablet, pre-filled syringe injection), where only an administration date/time is collected, EXSTDTC should be copied to EXENDTC as the standard representation.

9. The following qualifiers would generally not be used in EX: --PRESP, --OCCUR, --STAT, and --REASND.

10. The following qualifiers would generally not be used in EC: --STAT, --REASND, --VAMT, and --VAMTU.

11. Drug accountability details (e.g., amount dispensed, amount returned) are represented in DA and not in EC.

12. If the entire EC dataset is an exact duplicate of the entire EX dataset, then EC is optional and at the sponsor's discretion.

13. ECTRT can be assigned the value of “MASKED” if the data are to be exchanged between sponsors, partners and/or regulatory agency(s) in a masked study the treatment is not known by a synonym.

14. ECMOOD is permissible, however, when implemented, it must be populated for all records.

15. ECOCCUR is generally not applicable for Scheduled records.

OTHER DOMAINS COLLECTED EXPOSURE DATA

Apart from the EX and EC domain, there are some other domains can collect exposure data in most cases. In the majority of studies, the information is not collected in the protocol-specified unit, and/or not collected correlate with the expectations for review. We perhaps need to map collected administrations to Drug Accountability (DA) and Findings About (FA). The following will state their relationship with exposure domains. In addition, there are two new domains added in SDTMIG v3.3, Procedure Agents (AG) and Meal Data (ML), which also can store some exposure information. The following will make a brief introduction of them.

DRUG ACCOUNTABILITY (DA)

DA is a findings domain that contains the accountability of study drug, such as information on the receipt, dispensing, return, and packaging. The DA domain is generally collected for use in the calculation of compliance. Sometimes, the exposure data was not collected based on the EX domain, for example, only dispensations and returns of study drug information were collected. The drug accountability data will be used to derive exposure records in EX. Although the SDTMIG indicates that it’s workable to use drug accountability for creating an EX dataset, it is generally not a good practice for the accurate and convenient representation of exposure. It should be paid more care while it is necessary to do so.

FINDINGS ABOUT (FA)

FA is a findings domain that contains the findings about an event or intervention that cannot be represented within an events or interventions domain record or as a supplemental qualifier. CDISC offers FA and Supplemental Qualifiers (SuppQual) to handle information that doesn’t fit into standard domains or standard variables. However, compared to SuppQual where data should be fit into the parent domain and relates to one parent record, FA has versatility beyond it and can cover almost all other situations, like data relates to multiple records, or two-way relationship is needed. Thus, additional information of study treatment which couldn’t be put in EC, SUPPEX, SUPPEC, or fitted in other domains, is suggested to put in FA, for example, treatment information with alternative unit may be put in FA.

PROCEDURE AGENTS (AG)

AG is a new provisional domain in SDTMIG v3.3 and is an interventions domain that contains the agents administered to the subject as part of a procedure or assessment, as opposed to drugs, medications and therapies administered with therapeutic intent. Such exposures have generally been difficult to characterize, since they are not really study treatments or concomitant medications. The Concomitant Medications (CM) domain seemed particularly inappropriate when the substance was never given as a medication. Even substances are medications, are not being used as such when they are given as part of a testing procedure. The EX domain also seemed inappropriate, since although the testing procedure might be part of study plan, these data would not be used or analyzed like study treatments.

In addition, despite Procedures (PR) domain can contain intervention procedure with diagnostic, preventive, therapeutic, or palliative effects, AG has its own advantages. AG allows recording of multiple substance administrations for a single testing procedure, and separates data about substance administration from data about procedure that do not involve substance administration. Information about the conduct of the procedure with which the procedure agent administration was associated, if collected, should be represented in the Procedures (PR) domain.

Examples so far of AG have included a short-acting bronchodilator administered as part of a reversibility assessment for asthma, glucose or meals administered as part of a tolerance test in subjects with diabetes, and contrast agents and radio-labeled substances used in imaging studies.

MEALS (ML)

ML is another new domain added in SDTMIG v3.3 and is an intervention domain that contains information regarding the subject's meal consumption, such as fluid intake, amounts, form (solid or liquid state), frequency, etc., typically used for pharmacokinetic analysis. The consumption of any food or nutritional item is represented in the ML domain when it would not be represented in EC/EX, Concomitant and Prior Medications (CM), AG, or Substance Use (SU), for example, investigational nutritional products represented in EC/EX, food or drink used to treat hypoglycemic events represented in CM, glucose given as part of a glucose tolerance test represented in AG, and caffeinated drinks represented in SU. The ML domain debuted in trials on Diabetes, and was used for the submission of meal data. The focus of ML domain is on details of meal consumed along with the timing and quantity of food intake by subject. Data about meal amounts and composition would need to be submitted in either TS (if the same for all subjects) or in a Findings About domain if unique to each subject. In addition, the nutritional information represented in ML may be prospectively defined within a protocol, collected retrospectively as potential precipitants of clinical events, and/or to describe nutritional intake.

COVID-19 PANDEMIC ON STUDY TREATMENT IN ONGOING STUDIES

Owing to the sudden onset and widespread impact of COVID-19, ongoing clinical studies are more or less influenced. There might be changes on administration of study treatments caused by the COVID-19 pandemic in variety of situations. In response to this global pandemic, CDISC provide some guides of changes in Exposure upon SDTMIG v3.3. –ADJ and –RSDISC, for reasons for dose adjustment and reasons for discontinuation, respectively might be used in EX or EC domains. A non-standard variable (NSV) to represent a reason for interruption, for example EXRSINT, might be added in the exposure domain. The following is detailed explanation with examples.

--ADJ IN EXPOSURE DOMAIN

--ADJ, reason for dose adjustment, is a permissible variable used in EX and EC domain, aiming to describes reason or explanation of why a dose is adjusted. However, the SDTMIG has no clear statement about whether –ADJ should be populated in the record before the adjustment or in the record after the adjustment. The following example assumes that the record is represented after the adjustment, that is, the record with the adjusted dose.

--RSDISC IN EXPOSURE DOMAIN

--RSDISC, reason the intervention was discontinued, is applicable only for the (chronologically) last record for the treatment, when dosing of a treatment is recorded over multiple successive records. Although it not showing in EX and EC domain in SDTMIG V3.3, you could see 'CMRSDISC' for reference. When the study treatment is stopped, it is hard to makes sure whether the treatment will be resumed or not. –RSDISC is used when the study treatment is permanently discontinued. If the study treatment is temporarily discontinued, NSV –RSINT can be used. The following will introduce some NSVs in EX and EC domains.

NSV IN EXPOSURE DOMAIN

For representing clear of dose adjustment or interruption information related to the pandemic, non-standard variables are introduced in EX and EC. The following tables show the NSV metadata in EX and EC related to COVID-19 pandemic. The following examples, use separate NSVs to indicate relationships to the pandemic for adjustments, interruptions, and discontinuations. The following examples just to show how NSVs use in the EX and EC domain. The sponsor can decide for a particular study whether NSVs are needed and which NSV included.

EX NSV Metadata

Variable	Label	Type	Codelist	Role	Origin
EXRSINT	Reason for interruption	text		Non-Standard Record Qualifier	CRF
EXEPADJI	Epi/Pandemic Related Adjustment Reas Ind	text	NY	Non-Standard Record Qualifier	CRF
EXEPINTI	Epi/Pandemic Related Interrupt Reas Ind	text	NY	Non-Standard Record Qualifier	CRF
EXEPDSCI	Epi/Pandemic Related Discontin Reas Ind	text	NY	Non-Standard Record Qualifier	CRF

EC NSV Metadata

Variable	Label	Type	Codelist	Role	Origin
ECREASOC	Reason for Occur Value	text		Non-Standard Record Qualifier	CRF
ECEPADJI	Epi/Pandemic Related Adjustment Reas Ind	text	NY	Non-Standard Record Qualifier	CRF
ECEPDSCI	Epi/Pandemic Related Discontin Reas Ind	text	NY	Non-Standard Record Qualifier	CRF

Example 1

Scenario: This was a blinded study and exposure was collected with treatment as “BLINDED PRODUCT” and study treatment is Drug X. The protocol included criteria for dose adjustments. It was allowed to reduce doses in subjects who contracted COVID-19. Additionally, the pandemic influence the supply of study treatment to some sites. The subject, ‘A001’, was affected on dosing and had withdrawn from study treatment (discontinuation information in the DS domain not shown).

ec.xpt

ROW	USUBJID	ECSEQ	ECTRT	ECPRESP	ECOCCUR	ECDOSE	ECDOSEU	ECADJ
1	A001	1	BLINDED PRODUCT	Y	Y	2	TABLET	
2	A001	2	BLINDED PRODUCT	Y	Y	1	TABLET	COVID-19 PROTOCOL AMENDMENT
3	A001	3	BLINDED PRODUCT	Y	N		TABLET	

4	A001	4	BLINDED PRODUCT	Y	Y	2	TABLET	

ROW	USUBJID	ECRSDISC	ECSTDTC	ECENDTC	ECREASOC	ECEPADJI	ECEPDSCI
1	A001		2021-01-01	2021-01-07			
2	A001		2021-01-08	2021-01-14		Y	
3	A001		2021-01-15	2021-01-21	Study Treatment Supply Disrupted		
4	A001	SUBJECT DID NOT WANT TO CONTINUE DUE TO COVID-19 CONCERNS	2021-01-21	2021-01-25			Y

Explanation:

Row 1: Shows the initial dosing period with normal dose level.

Row 2: Shows reduced dosing because of an amendment made due to the COVID-19 pandemic. Please see the change in ECDOSE, ECADJI, ECEPADJI.

Row 3: Shows the supply of study treatment was disrupted by the COVID-19 pandemic and the subject hadn't received treatment for 7 days. Please see the change in ECOCCUR, ECDOSE, ECREASOC.

Row 4: Shows that the subject resumed treatment, but decided to stop participation in the study due to COVID-19 concerns. Please see the change in ECDOSE, ECRSDISC, ECEPDSCI.

ex.xpt

ROW	USUBJID	EXSEQ	EXTRT	EXDOSE	EXDOSU	EXDOSFRM	EXADJ	EXRSDISC
1	A001	1	DRUG X	50	mg	TABLET		
2	A001	2	DRUG X	25	mg	TABLET	COVID-19 PROTOCOL AMENDMENT	
3	A001	4	DRUG X	50	mg	TABLET		SUBJECT DID NOT WANT TO CONTINUE DUE TO COVID-19 CONCERNS

ROW	USUBJID	EXSTDTC	EXENDTC	EXRSINT	EXEPADJI	EXEPINTI	EXEPDSCI
1	A001	2021-01-01	2021-01-07				

2	A001	2021-01-08	2021-01-14	Study Treatment Supply Disrupted	Y	Y	
3	A001	2021-01-21	2021-01-25				Y

Explanation:

When the EX dataset was derived from the Exposure as Collected (EC) dataset, the drug was unblinded, and the dose was converted from tablets to mg. The period of time during which the subject did not receive drug (row 3 in the preceding EC dataset) was represented as an interruption to the previous dosing, see EXEPINTI in row2.

Row 1: Shows the initial dosing period with normal dose level.

Row 2: Shows reduced dosing because of an amendment made due to the COVID-19 pandemic, and that dosing was later interrupted because the supply of study treatment was disrupted due to the COVID-19 pandemic. Please see the change in EXDOSE, EXADJ, EXRSINT, EXEPADJI, EXEPINTI.

Row 3: Shows that the subject resumed treatment, but decided to stop participation in the study due to COVID-19 concerns. Please see the change in ECDOSE, EXRSDISC, EXEPDSCI.

REFERENCES

CDISC Study Data Tabulation Model (SDTM) v1.7 and Study Data Tabulation Model Implementation Guide (SDTMIG) v3.3. https://www.cdisc.org/standards/foundational/sdtm

Jerry Salyers and Kristin Kelly. 2018. “SDTM EX and EC: Considerations When Submitting Exposure Data”. PharmaSUG2018 - Paper DS16

Tom Guinter. 2017. “The CDISC SDTM Exposure Domains (EX & EC) Demystified. How EC Helps You Produce a Better (more compliant) EX.”. PharmaSUG2017 - Paper DS08

Fred Wood, Jerry Salyers, Richard Lewis, and Kristin Kelly. 2014. “Considerations in the Submission of Exposure Data in SDTM-Based Datasets”. PharmaSUG2014 - Paper DS04

David C. Izard. 2010. “Help! The EX Domain is now an Analysis Dataset! What Do I Do?!?”. PharmaSUG 2010 - Paper CD05

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Manxi Chen
Everest Clinical Research
manxi.chen@ecrscorp.com