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SDTM EX and EC: Considerations When Submitting Exposure Data

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ABSTRACT

Per the SDTMIG v3.2, the Exposure (EX) domain should contain only unblinded data for study treatment that was administered to subjects presented in protocol-specified units. Because of this, the Exposure as Collected (EC) domain can be used to collect blinded data during the study for all administrations given, not taken or missed. After the study is unblinded, the EX domain can be derived from EC. The SDTMIG recommends submitting both EX and EC if necessary, though including EC is not required. Sometimes it can be difficult to determine when both domains are needed to provide the full story of how subjects were exposed to treatment. This paper will focus on use cases where submitting EX is sufficient as well as instances when a reviewer would benefit from receiving both EX and EC.

INTRODUCTION

For studies involving an investigational product being given to subjects, the EX domain is “required” for submission and should include all protocol-specified treatments. In this context, for a placebo-controlled trial, even Placebo is considered a protocol-specified treatment and is represented in the SDTM EX domain. Reviewers count on sponsors to submit an EX dataset that tells the complete story of how trial subjects took study medication, However, even with this expectation, often sponsors don’t collect all the information they need or neglect to provide key pieces that they have collected. With the advent of SDTM 3.2, sponsors now have a mechanism for submitting both the “unblinded” representation of the data (in the EX dataset) as well as a “blinded” representation of the data (in the EC dataset) if they desire or if it is necessary to support the analysis. Many sponsors will collect data in the EC structure and then derive EX after applying the unblinded treatment codes. At that point, they will either choose to submit both datasets or just the unblinded EX dataset.

The EC domain also provides a way to submit details regarding “missed” doses that are collected on the case report form (CRF).

Our paper will discuss these different scenarios at length and provide relevant dataset examples.

CONSTANT DOSING INTERVAL

By way of review, it may help to explore the concept of a sponsor defined “constant dosing interval”. This concept is introduced in the Model and the SDTMIGs. A constant dosing interval can be loosely described as a subject taking the same “Intervention” at the same dose and at the same frequency over a period of time. Though how this constant dosing interval is defined for a given study and the granularity of the data collection is up to the sponsor. Consider the following EX record:

EXTRT	EXDOSE	EXDOSU	EXDOSFRQ	EXSTDTC	EXENDTC
DRUG A	200	mg	BID	2017-09-06	2017-10-18

Let’s contrast this single record across the 6-week dosing period (or constant dosing interval) with the following:

EXTRT	EXDOSE	EXDOSU	EXDOSFRQ	EXSTDTC	EXENDTC
DRUG A	200	mg	BID	2017-09-06	2017-09-12
DRUG A	200	mg	BID	2017-09-13	2017-09-20
DRUG A	200	mg	BID	2017-09-21	2017-09-27
DRUG A	200	mg	BID	2017-09-28	2017-10-04
DRUG A	200	mg	BID	2017-10-05	2017-10-11
DRUG A	200	mg	BID	2017-10-12	2017-10-18

The six records in the bottom table represents the same total exposure as the single record in the first table, however the constant dosing interval in the bottom table reflects “weekly” dosing. Both can be considered correct, however the bottom table has more information due to the increased granularity of the data collection. When it comes time to submit this data, the submitted records should never show a less granular representation than how the data was collected.

Consider the scenario where subjects take study medication daily for 2 weeks during which time subjects return to the clinic periodically where the investigator witnesses that day’s dose and the date and time of these “in-clinic” doses are collected on the CRF. The sponsor’s initial representation of EX (for a single subject) looked like this:

ex.xpt

Row	STUDYID	DOMAIN	USUBJID	EXSEQ	EXTRT
1	ABC0001	EX	0001-101	1	DRUG A
2	ABC0001	EX	0001-101	2	DRUG A
3	ABC0001	EX	0001-101	3	DRUG A

Row	EXCAT	EXDOSE	EXDOSFRQ	EXSTDTC	EXENDTC
Row 1 (Cont)	IN CLINIC	150	QD	2012-01-08T08:05	2012-01-08T08:05
Row 2 (Cont)	IN CLINIC	150	QD	2012-01-15T08:10	2012-01-15T08:10
Row 3 (Cont)	IN CLINIC	150	QD	2012-01-22T08:00	2012-01-22T08:00

Again, the subjects were taking drug every day for this 2-week period, however it appears from the data that subjects only received drug on 3 occasions. Obviously, these 3 records don’t tell the whole story as to how subjects were taking study medication. It’s perfectly acceptable for the CRF to collect the date and time of these “highlighted doses”, however there needs to be a record that establishes a “constant-dosing interval” for the subjects. It’s not enough to rely on the EXDOSFRQ of ‘QD’ to provide this context. This was a case where the CRF did collect all the information to be able to create this constant dosing interval record, which was ultimately included for each subject. It would look something like this:

ex.xpt

Row	STUDYID	DOMAIN	USUBJID	EXSEQ	EXTRT
4	ABC0001	EX	0001-101	4	DRUG A

Row	EXCAT	EXDOSE	EXDOSFRQ	EXSTDTC	EXENDTC
Row 4 (Cont)	DOSING PERIOD	150	QD	2012-01-08	2012-01-22

MISSED DOSES

Until the publication of SDTMIG 3.2, it has long been an issue as to how to represent "missed" doses that were identified on the CRF. Prior versions of the SDTMIG contained the "assumption" that "Interventions" class variables such as --STAT, --PRESP, and --OCCUR "would generally not be used in the EX domain" as the domain was designed to report only medications that the subject received. This left sponsors with very little choice but to violate this assumption if their CRF collected this level of detail.

This reporting issue was resolved in SDTMIG 3.2 with the publication of the EC domain. This domain does contain the paired variables of ECPRESP and ECOCCUR which are used to represent "blinded" doses that were administered along with possible doses that were missed. In the EC example table below, the subject missed his daily dose on 3-15 (ECOCCUR = 'N') and then resumed dosing on 3-16 (Note that ECDOSE is blank where ECOCCUR = 'N').

ec.xpt *(Blinded, as collected)*

Row	STUDYID	DOMAIN	USUBJID	ECSEQ	ECLNKID	ECTRT	ECPRESP	ECOCCUR
1	ABC0001	EC	001-101	1	101-01	BOT A	Y	Y
2	ABC0001	EC	001-101	2	101-02	BOT A	Y	N
3	ABC0001	EC	001-101	3	101-03	BOT A	Y	Y

Row	ECDOSE	ECDOSU	ECDOSFRQ	ECROUTE	ECSTDTC	ECENDTC
1 (Cont)	2	TABLET	QD	ORAL	2012-03-01	2012-03-14
2 (Cont)		TABLET	QD	ORAL	2012-03-15	2012-03-15
3 (Cont)	2	TABLET	QD	ORAL	2012-03-16	2012-03-28

The resulting EX domain would then look like this (Note the same values for --LNKID across the datasets**).**

ex.xpt *(Unblinded, actual)*

Row	STUDYID	DOMAIN	USUBJID	EXSEQ	EXLNKID	EXTRT	EXDOSE	EXDOSU
1	ABC0001	EX	001-101	1	101-01	DRUG A	50	mg
2	ABC0001	EX	001-101	2	101-03	DRUG A	50	mg

Row	EXDOSFRM	EXDOSFRQ	EXROUTE	EXSTDTC	EXENDTC
1 (Cont)	TABLET	QD	ORAL	2012-03-01	2012-03-14
2 (Cont)	TABLET	QD	ORAL	2012-03-16	2012-03-28

As the SDTMIG reminds us, where it's possible, a dataset-to-dataset RELREC relationship should be defined between EC and EX, based on the like value in the –LNKID identifier across the datasets.

STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
ABC0001	EC		ECLNKID		ONE	A
ABC0001	EX		EXLNKID		ONE	A

REPRESENTATION OF BLINDED AND UNBLINDED DATA

One of the basic aspects of SDTM is that the EX domain should "unblind" the reviewer to a subject's assigned dose level of study medication. A reviewer shouldn't have to merge the records in Exposure with DM, for example, to identify a subject's treatment group. Care should be taken not to populate EXDOSE and EXDOSU with protocol "constants". For example, consider the following example EX dataset:

ex.xpt

STUDYID	DOMAIN	USUBJID	EXSEQ	EXTRT	EXDOSE	EXDOSU	EXSTDTC	EXENDTC
ABC0001	EX	001-101	1	DRUG B	3	INJECTIONS	2012-03-01	2012-03-01
ABC0001	EX	001-102	1	DRUB B	3	INJECTIONS	2012-03-01	2012-03-01

In this trial, subjects were given a series of 3 injections at each Drug B dosing opportunity. This was defined in the protocol. However, within these 3 injections were different dose levels of Drug B according to the subject's randomized treatment group. At first, the sponsor thought that the above representation provided sufficient information as to what the subjects were receiving. They thought the reviewer would merge the EX dataset with the Arm Code in DM to arrive at the randomized dose level within these 3 injections. After consulting with the sponsor, they understood that simply verifying that the subject had received the proper number of injections as defined in the protocol wasn't enough information in EX. Again EX, by itself, needs to unblind a reviewer as to the amount the study medication that the subject was exposed to. This would be a perfect candidate for the use of the EC domain.

Similarly, depending on the granularity of the data collection, it's often not important to represent in EX what subjects take to "protect the blind". Again, if sponsors wish to submit the "data as collected", EC provides the mechanism for that. Consider the following datasets as an example of this representation:

ec.xpt

Row	STUDYID	DOMAIN	USUBJID	ECSEQ	ECTRT	ECDOSE	ECDOSU
1	DEF002	EC	002-101	1	BOTTLE A	1	TABLET
2	DEF002	EC	002-001	2	BOTTLE B	1	TABLET
3	DEF002	EC	002-002	1	BOTTLE A	1	TABLET
4	DEF002	EC	002-002	2	BOTTLE B	1	TABLET

Row	ECDOSFRQ	ECSTDTC	ECENDTC
1 (Cont)	QD	2012-02-01	2012-03-15
2 (Cont)	QD	2012-02-01	2012-03-15

3 (Cont)	QD	2012-01-15	2012-02-28
4 (Cont)	QD	2012-01-15	2012-02-28

ex.xpt

Row	STUDYID	DOMAIN	USUBJID	EXSEQ	EXTRT	EXDOSE	EXDOSU
1	DEF002	EX	002-001	1	CUREITALL	100	mg
2	DEF002	EX	002-002	1	CUREITALL	50	mg

Row	EXDOSFRQ	EXSTDTC	EXENDTC
1 (Cont)	QD	2012-02-01	2012-03-15
2 (Cont)	QD	2012-01-15	2012-02-28

In the above example, the unit strength of the “active” tablets is 50 mg, thus, upon study unblinding, subject 002-001 took 2 active tablets, while subject 002-002 took one active tablet and one placebo tablet to protect the blind. However, in EX, it is only necessary to show the amount (in mg) of active study medication that the subject received. In this scenario, including the EC domain in a submission is up to the sponsor.

It’s important to note that there may be times when including in EX the “Placebo” dose taken to protect the blind may be appropriate. Example 5 in the SDTMIG 3.2 highlights just such a case. In this example, subjects are randomized to one of three arms, Drug X at either 10 or 20 mg taken twice daily versus Placebo. The EC dataset will show subjects as having taken one tablet from Bottle A in the AM and one tablet from Bottle B in the PM. Upon applying the unblinded treatment codes, EX may look like this (for one subject from each of the treatment groups (EXLNKID being omitted to conserve space):

ex.xpt

Row	STUDYID	DOMAIN	USUBJID	EXSEQ	EXTRT	EXDOSE	EXDOSU
1	ABC	EX	ABC-001	1	DRUG X	10	mg
2	ABC	EX	ABC-001	2	DRUG X	10	mg
3	ABC	EX	ABC-002	1	DRUG X	10	mg
4	ABC	EX	ABC-002	2	PLACEBO	0	mg
5	ABC	EX	ABC-003	1	PLACEBO	0	mg
6	ABC	EX	ABC-003	2	PLACEBO	0	mg

Row	EXDOSFRQ	EXSTDTC	EXENDTC	EXTPT	EXTPTNUM
1 (Cont)	QD	2012-03-01	2012-03-08	AM	1
2 (Cont)	QD	2012-03-01	2012-03-08	PM	2
3 (Cont)	QD	2012-03-01	2012-03-08	AM	1
4 (Cont)	QD	2012-03-01	2012-03-08	PM	2
5 (Cont)	QD	2012-03-01	2012-03-08	AM	1
6 (Cont)	QD	2012-03-01	2012-03-08	PM	2

Subject ABC-002 was randomized to the 10 mg treatment group, thus they took one active tablet in the AM and then a Placebo tablet in the PM. Based on the granularity of the data collection, it's perfectly appropriate to show both the active dose in the AM and the Placebo dose in the PM.

It's also worth emphasizing Assumption 6 under the EC domain table in the IG that says "The degree of summarization of records between EC and EX is sponsor defined to support study purpose and analysis".

REPRESENTATION IN PROTOCOL SPECIFIED UNITS

In the EX/EC section of the SDTMIG 3.2, there are examples of how the intravenous administration of study medication in protocol specified units such as "mg/kg" might be represented. The EC domain allows for the ECMOOD variable which has been adapted from the BRIDG concept of "Mood". ECMOOD can identify "SCHEDULED" versus "PERFORMED" doses. For study medications such as chemotherapy drugs where dose adjustments may be likely, sponsors may wish to include an EC record that identifies the "planned" dose in protocol specified units. Consider the following EC table where a subject who weighs 55 kg receives a planned dose of 10 mg/kg of a 5.5 mg/ml solution:

ec.xpt

Row	STUDYID	DOMAIN	USUBJID	ECSEQ	ECTRT	ECMOOD	ECPRESP	ECOCCUR
1	DEF123	EC	123-001	1	DRUG Z	SCHEDULED		
2	DEF123	EC	123-001	2	DRUG Z	PERFORMED	Y	Y

Row	ECDOSE	ECDOSU	ECPSTRG	ECPSTRGU	VISITNUM	VISIT	ECSTDTC	ECENDTC
1 (Cont)	10	mg/kg			1	CYCLE 1 DY1	2013-03-01	2013-03-01
2 (Cont)	99	ml	5.5	mg/ml	1	CYCLE 1 DY1	2013-03-01T08:00	2013-03-01T08:50

In the above example, the first record shows the dosing that is "scheduled" to occur per protocol where the protocol specified unit is "mg/kg". The second record shows what actually occurred and was collected. We see that the subject received 99 ml of his "scheduled" dose. The resultant record in EX may look like this:

Row	STUDYID	DOMAIN	USUBJID	EXSEQ	EXTRT	EXDOSE	EXDOSU	EXDOSFRM
1	DEF123	EX	123-001	1	DRUG Z	9.9	mg/kg	SOLUTION

Row	VISITNUM	VISIT	EXSTDTC	EXENDTC
1 (Cont)	1	CYCLE 1 DY1	2013-03-01T08:00	2013-03-01T08:45

This EX record maintains the given dose in the protocol specified units of 'mg/kg'.

The SDTMIG 3.2 goes on to say that the dose of DRUG Z may be expressed in "alternative units" in the FA domain as the total number of 'mg' administered. With the 'mg/ml' already defined, this total would simply be the product of the number of "ml's" administered times the number of 'mg' per ml (the concentration of the solution).

While this is certainly a valid representation of the Exposure data in tandem with the "Exposure as Collected" information, it is apparent that after modeling many IV Administration CRFs, that sponsors are

more comfortable with presenting the "total amount administered" in EXDOSE, rather than the more cryptic representation of "protocol specified units". Again, with the exception of dose adjustments, presenting an EX domain where EXDOSE is largely a protocol defined "constant" doesn't provide much new information, or, indeed, enough information. Consider the following typical CRF and annotations for this same 55 kg subject, again, dosed at 10 mg/kg with a 5.5 mg/ml solution:

Date of Infusion _____ dd/MMM/yyyy **EC/EXSTDTC** **EC/EXENDTC**

Dose Level (mg/kg)_____ **ECDOSE/ECDOSU where ECMOOD = 'SCHEDULED'**

Dose Concentration (mg/ml) _____ **ECPSTRG/ECPSTRGU where ECMOOD = 'PERFORMED'**

Volume Infused_____ **ECDOSE/ECDOSU where ECMOOD = 'PERFORMED'**

Total Dose Administered (mg)_____ **EXDOSE** **EXDOSU**

Start Time of Infusion_____ (24 Hour clock time) **ECSTDTC/EXSTDTC**

End Time of Infusion_____(24 Hour clock time) **ECENDTC/EXENDTC**

ex.xpt

Row	STUDYID	DOMAIN	USUBJID	EXSEQ	EXTRT	EXDOSE	EXDOSU	EXDOSFRM
1	DEF123	EX	123-001	1	DRUG Z	544.5	mg	SOLUTION

Row	VISITNUM	VISIT	EXSTDTC	EXENDTC
1 (Cont)	1	CYCLE 1 DY1	2013-03-01T08:00	2013-03-01T08:45

Again, the submission of the EC domain is still up to the sponsor. If the sponsor doesn't submit EC, the "Dose Level", "Dose Concentration", and "Volume Infused" would be submitted in SUPPEX as non-standard variables. The above mapping would then preclude the need to use FA (or SUPPEX) to show the dose administered in "alternative units".

CONCLUSION

As with all clinical data, science and regulation determine what is collected. SDTM simply provides the mechanism for submitting the data to regulatory authorities and cannot make up for poor CRF design or poor clinical data management practices in general..

As challenging as Exposure can be, it's important for sponsors to make sure upfront that they are collecting and then submitting all the data necessary to tell the complete story of how subjects are exposed to study treatment. EC is there for sponsors to use if they require it, to either account for the collection of missed doses, or to submit exposure data in a "blinded" fashion if that is the sponsor's choice.

REFERENCES

SDTM Version 1.4 and SDTMIG Version 3.2

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