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How to utilize the EC domain to handle complex exposure data

Varsha Korrapati and Johnny Maruthavanan, Seagen Inc., Bothell WA

ABSTRACT

Dose modifications including dose elimination, hold, delay, reduction, and mid-cycle adjustments due to treatment-related toxicities are common in oncology clinical trials. In certain studies, the design of CRFs that capture treatment administration involves a high degree of complexity to account for such unplanned dose modifications that occur within or between treatment cycles. Under those circumstances, the creation of an SDTM EC (Exposure as Collected) data set helps capture all dose modifications that may occur to a protocol-specified treatment administration. The EC data set in turn facilitates a seamless functional path to derive the subsequent EX (Exposure) data set that contains information on actual drug administered within each study cycle; this separation makes reviewing and consuming these data a lot easier.

This paper summarizes one approach of leveraging EC domain to capture dose modification scenarios, outlining the process flow and traceability of data from EC to EX with an example based on CDISC SDTMIG v3.3, and highlighting the benefits to reviewability and accessibility of constructing these SDTM data sets in this manner.

Keywords: exposure, dose modification, traceability, EC domain

INTRODUCTION

In Oncology clinical trials, treatment-related toxicities are common which necessitates dose modifications during the conduct of the trial. Several dose modifications such as dose elimination, hold, delay, increase or reduction, and mid-cycle adjustments are practiced to address those scenarios. This in turn requires the development of complex CRF designs, that capture such unplanned dose modifications which may occur within or between treatment cycles.

This paper explores how statistical programmers can utilize the SDTM domains 'Exposure as Collected' (EC) and 'Exposure' (EX) in capturing different dose modification data. Before implementing this approach, it is critical to understand the major difference between EC and EX. While the EC domain captures all protocol-specified study treatment administrations, as collected, the EX domain presents only the actual treatment administered.

The transformation of raw collected data into CDISC-compliant SDTM EC and EX data sets is explained here based on a few different dose modification scenarios.

STUDY DESIGN AND CASE REPORT FORM

In our first example study design, the treatment drug will be administered orally once daily for 4 weeks. Two subjects with three cycles each are considered for this illustration. On the first day of each cycle, the investigator will witness the administration of the oral dose by the subjects on site. Subsequently, the subjects will take the capsule at home on a daily basis until the cycle ends.

The model CRF form (Figure 1) illustrates all possible dose modification scenarios and should be recorded at each visit when a drug is dispensed. It captures the investigator's intended dose and mid-cycle adjusted dosing information. The intended start date should reflect the planned visit date. Multiple entries can be filled to capture investigator-directed dosing adjustments.

Cycle Eliminated	[1] Yes [2] No
Related Adverse Event	
If not AE, Specify Reason	
Intended Dose Level	
Dose Start Date	
Dose Reduced for entire Cycle?	
Reason for Dose Reduction	
Any Mid Cycle Dose Adjustments?	
Start Date of Dose Adjustment	
End Date of Dose Adjustment	
Adjustment	[1] Hold [2] Reduced [3] Increased
Adjusted Dose	

Figure 1: Model Case Report Form

SCENARIO 1: RAW DATA WITHOUT DOSE ADJUSTMENTS

Based on the CRF design, the raw data set includes variables for dosing visits, start and end dates, amount, modifications, and mid-cycle adjustments. In scenario 1, the raw data for each subject has 3 records for a total of 3 cycles since there is no dose modification or mid-cycle adjustment.

RAW DATA

SUBJECT	ENTRY	ELIMINATED	INTENDED DOSE LEVEL	DOSE START DATE	REDUCE	MID CYCLE ADJUSTMENT
SUB100	VISIT1	No	100	01JAN2022	No	No
SUB100	VISIT2	No	150	01FEB2022	No	No
SUB100	VISIT3	No	75	01MAR2022	No	No
SUB200	VISIT1	No	100	10JAN2022	No	No
SUB200	VISIT2	No	150	15FEB2022	No	No
SUB200	VISIT3	No	75	15MAR2022	No	No

SUBJECT	ENTRY	ADJ START DATE	ADJ END DATE	ADJUSTMENT	ADJUSTED DOSE
SUB100	VISIT1				
SUB100	VISIT2				
SUB100	VISIT3				
SUB200	VISIT1				
SUB200	VISIT2				
SUB200	VISIT3				

After standardizing the above raw data into EC and EX, it will be a one-to-one record mapping as the number of records would remain the same for both. The EC.ECDOSE will contain the raw intended daily dosing value of each cycle while EX.EXDOSE will have summarized values for the entire cycle; EX.EXENDTC will be derived by adding 27 days to EX.EXSTDTC based on the study design. EC.ECMOOD represents the status of the ECDOSE whether it is intended to happen or has happened. In the current scenario ECMOOD is set to 'PERFORMED' as there is no change in the planned dose.

SDTM EC MAPPING

ROW	USUBJID	ECSEQ	ECTRT	ECMOOD	ECOCCUR	ECDOSE	ECDOSU	ECSTDTC	ECENDTC	VISIT
1	SUB100	1	TREAT A	PERFORMED	Y	100	mg	01JAN2022	01JAN2022	VISIT1
2	SUB100	2	TREAT A	PERFORMED	Y	150	mg	01FEB2022	01FEB2022	VISIT2
3	SUB100	3	TREAT A	PERFORMED	Y	75	mg	01MAR2022	01MAR2022	VISIT3
4	SUB200	1	TREAT A	PERFORMED	Y	100	mg	10JAN2022	10JAN2022	VISIT1
5	SUB200	2	TREAT A	PERFORMED	Y	150	mg	15FEB2022	15FEB2022	VISIT2
6	SUB200	3	TREAT A	PERFORMED	Y	75	mg	15MAR2022	15MAR2022	VISIT3

SDTM EX MAPPING

ROW	USUBJID	EXSEQ	EXTRT	EXOCCUR	EXDOSE	EXDOSU	EXSTDTC	EXENDTC	VISIT
1	SUB100	1	TREAT A	Y	2800	mg	01JAN2022	28JAN2022	VISIT1
2	SUB100	2	TREAT A	Y	4200	mg	01FEB2022	28FEB2022	VISIT2
3	SUB100	3	TREAT A	Y	2100	mg	01MAR2022	28MAR2022	VISIT3
4	SUB200	1	TREAT A	Y	2800	mg	10JAN2022	06FEB2022	VISIT1
5	SUB200	2	TREAT A	Y	4200	mg	15FEB2022	14MAR2022	VISIT2
6	SUB200	3	TREAT A	Y	2100	mg	15MAR2022	11APR2022	VISIT3

SCENARIO 2: RAW DATA WITH DOSE ELIMINATION

In scenario 2, the raw data for each subject has 3 records for a total of 3 cycles with 1 instance of dose elimination for both subjects (VISIT2 for SUB100 and VISIT3 for SUB200) and no mid-cycle adjustment. 'Dose elimination' is defined as subject not receiving any dose during the entire dosing cycle.

RAW DATA

SUBJECT	ENTRY	ELIMINATED	INTENDED DOSE LEVEL	DOSE START DATE	REDUCE	MID CYCLE ADJUSTMENT
SUB100	VISIT1	No	100	01JAN2022	No	No
SUB100	VISIT2	Yes				
SUB100	VISIT3	No	75	01MAR2022	No	No
SUB200	VISIT1	No	100	10JAN2022	No	No
SUB200	VISIT2	No	150	15FEB2022	No	No
SUB200	VISIT3	Yes				

SUBJECT	ENTRY	ADJ START DATE	ADJ END DATE	ADJUSTMENT	ADJUSTED DOSE
SUB100	VISIT1				
SUB100	VISIT2				
SUB100	VISIT3				
SUB200	VISIT1				
SUB200	VISIT2				
SUB200	VISIT3				

Standardizing the above raw data results in one-to-one record mapping in EC as it captures all collected records to maintain transparency and traceability, whereas it will be fewer records in EX as it captures only the dose administered information (rows 2 and 6 in EC will be excluded in EX). In the current scenario EC.ECMOOD is set to 'SCHEDULED' for rows 2 and 6 as the intended dose did not occur.

SDTM EC MODEL

ROW	USUBJID	ECSEQ	ECTRT	ECMOOD	ECOCCUR	ECDOSE	ECDOSU	ECSTDTC	ECENDTC	VISIT
1	SUB100	1	TREAT A	PERFORMED	Y	100	mg	01JAN2022	01JAN2022	VISIT1
2	SUB100	2	TREAT A	SCHEDULED	N					
3	SUB100	3	TREAT A	PERFORMED	Y	75	mg	01MAR2022	01MAR2022	VISIT3
4	SUB200	1	TREAT A	PERFORMED	Y	100	mg	10JAN2022	10JAN2022	VISIT1
5	SUB200	2	TREAT A	PERFORMED	Y	150	mg	15FEB2022	15FEB2022	VISIT2
6	SUB200	3	TREAT A	SCHEDULED	N					

SDTM EX MODEL

ROW	USUBJID	EXSEQ	EXTRT	EXOCCUR	EXDOSE	EXDOSU	EXSTDTC	EXENDTC	VISIT
1	SUB100	1	TREAT A	Y	2800	mg	01JAN2022	28JAN2022	VISIT1
2	SUB100	2	TREAT A	Y	2100	mg	01MAR2022	28MAR2022	VISIT3
3	SUB200	1	TREAT A	Y	2800	mg	10JAN2022	06FEB2022	VISIT1
4	SUB200	2	TREAT A	Y	4200	mg	15FEB2022	14MAR2022	VISIT2

SCENARIO 3: RAW DATA WITH MID-CYCLE DOSE HOLD

In scenario 3, the raw data for each subject has 3 records for a total of 3 cycles with 1 instance of dose hold for both subjects (VISIT2 for SUB100 and SUB200). 'Dose hold' is defined as a period within the cycle where dose is withheld after receiving dose for certain number of days.

RAW DATA

SUBJECT	ENTRY	ELIMINATED	INTENDED DOSE LEVEL	DOSE START DATE	REDUCE	MID CYCLE ADJUSTMENT
SUB100	VISIT1	No	100	01JAN2022	No	No
SUB100	VISIT2	No	150	01FEB2022	No	Yes
SUB100	VISIT3	No	75	01MAR2022	No	No
SUB200	VISIT1	No	100	10JAN2022	No	No
SUB200	VISIT2	No	150	15FEB2022	No	Yes
SUB200	VISIT3	No	75	15MAR2022	No	No

SUBJECT	ENTRY	ADJ START DATE	ADJ END DATE	ADJUSTMENT	ADJUSTED DOSE
SUB100	VISIT1				
SUB100	VISIT2	15FEB2022	28FEB2022	Dose Hold	
SUB100	VISIT3				
SUB200	VISIT1				
SUB200	VISIT2	20FEB2022	14MAR2022	Dose Hold	
SUB200	VISIT3				

In a dose hold scenario, the one-to-one record mapping is not applicable for EC. EC has to accommodate additional records (rows 3 and 7 will be added) that account for the number of days the dose is being held. This will help to maintain continuity of the exposure activity within a study cycle and facilitate accurate review. EX will still maintain a unique record for each visit that will have summarized values of the entire dosing cycle (rows 2 and 3 for SUB100 in EC will be summarized in row 2 of EX; rows 6 and 7 for SUB200 in EC will be summarized in row 5 of EX).

SDTM EC MODEL

ROW	USUBJID	ECSEQ	ECTRT	ECMOOD	ECOCCUR	ECDOSE	ECDOSU	ECSTDTC	ECENDTC	VISIT
1	SUB100	1	TREAT A	PERFORMED	Y	100	mg	01JAN2022	01JAN2022	VISIT1
2	SUB100	2	TREAT A	PERFORMED	Y	150	mg	01FEB2022	14FEB2022	VISIT2
3	SUB100	3	TREAT A	SCHEDULED	N			15FEB2022	28FEB2022	VISIT2
4	SUB100	4	TREAT A	PERFORMED	Y	75	mg	01MAR2022	01MAR2022	VISIT3
5	SUB200	1	TREAT A	PERFORMED	Y	100	mg	10JAN2022	10JAN2022	VISIT1
6	SUB200	2	TREAT A	PERFORMED	Y	150	mg	15FEB2022	19FEB2022	VISIT2
7	SUB200	3	TREAT A	SCHEDULED	N			20FEB2022	14MAR2022	VISIT2
8	SUB200	4	TREAT A	PERFORMED	Y	75	mg	15MAR2022	15MAR2022	VISIT3

SDTM EX MODEL

ROW	USUBJID	EXSEQ	EXTRT	EXOCCUR	EXDOSE	EXDOSU	EXSTDTC	EXENDTC	VISIT
1	SUB100	1	TREAT A	Y	2800	mg	01JAN2022	28JAN2022	VISIT1
2	SUB100	2	TREAT A	Y	2100	mg	01FEB2022	28FEB2022	VISIT2
3	SUB100	3	TREAT A	Y	2100	mg	01MAR2022	28MAR2022	VISIT3
4	SUB200	1	TREAT A	Y	2800	mg	10JAN2022	06FEB2022	VISIT1
5	SUB200	2	TREAT A	Y	750	mg	15FEB2022	14MAR2022	VISIT2
6	SUB200	3	TREAT A	Y	2100	mg	15MAR2022	11APR2022	VISIT3

SCENARIO 4: RAW DATA WITH MID-CYCLE DOSE HOLD AND REDUCTION

In scenario 4, the raw data for each subject has 4 records for a total of 3 cycles with 1 instance each of 2 different mid-cycle adjustments (dose hold and reduction) for both subjects (VISIT2 for SUB100 and SUB200). 'Mid-cycle adjustment' is defined as a period where subject does not receive any dosing followed by a dose reduction or increment within a dosing cycle.

RAW DATA

SUBJECT	ENTRY	ELIMINATED	INTENDED DOSE LEVEL	DOSE START DATE	REDUCE	MID CYCLE ADJUSTMENT
SUB100	VISIT1	No	100	01JAN2022	No	No
SUB100	VISIT2	No	150	01FEB2022	No	Yes
SUB100	VISIT2	No	150	01FEB2022	No	Yes
SUB100	VISIT3	No	75	01MAR2022	No	No
SUB200	VISIT1	No	100	10JAN2022	No	No
SUB200	VISIT2	No	150	15FEB2022	No	Yes
SUB200	VISIT2	No	150	15FEB2022	No	Yes
SUB200	VISIT3	No	75	15MAR2022	No	No

SUBJECT	ENTRY	ADJ START DATE	ADJ END DATE	ADJUSTMENT	ADJUSTED DOSE
SUB100	VISIT1				
SUB100	VISIT2	15FEB2022	25FEB2022	Dose Hold	
SUB100	VISIT2	26FEB2022	28FEB2022	Dose Reduction	100
SUB100	VISIT3				
SUB200	VISIT1				
SUB200	VISIT2	20FEB2022	22FEB2022	Dose Hold	
SUB200	VISIT2	23FEB2022	14MAR2022	Dose Reduction	75
SUB200	VISIT3				

In this mid-cycle adjustment scenario, the one-to-one record mapping is not applicable for EC. EC has to accommodate additional records (row 3 for dose hold and row 4 for dose reduction forSUB100, and row 8 for dose hold and row 9 for dose reduction in SUB200 will be added to EC) that account for the number of days with dose hold and reduction. EX will still maintain a unique record for each visit that will have summarized values of the entire dosing cycle (rows 2, 3, and 4 for SUB100 in EC will be summarized in row 2 of EX; rows 7, 8, and 9 for SUB200 in EC will be summarized in row 5 of EX).

SDTM EC MODEL

ROW	USUBJID	ECSEQ	ECTRT	ECMOOD	ECOCCUR	ECDOSE	ECDOSU	ECSTDTC	ECENDTC	VISIT
1	SUB100	1	TREAT A	PERFORMED	Y	100	mg	01JAN2022	01JAN2022	VISIT1
2	SUB100	2	TREAT A	PERFORMED	Y	150	mg	01FEB2022	14FEB2022	VISIT2
3	SUB100	3	TREAT A	SCHEDULED	N			15FEB2022	25FEB2022	VISIT2
4	SUB100	4	TREAT A	PERFORMED	Y	100	mg	26FEB2022	28FEB2022	VISIT2
5	SUB100	5	TREAT A	PERFORMED	Y	75	mg	01MAR2022	01MAR2022	VISIT3
6	SUB200	1	TREAT A	PERFORMED	Y	100	mg	10JAN2022	10JAN2022	VISIT1
7	SUB200	2	TREAT A	PERFORMED	Y	150	mg	15FEB2022	19FEB2022	VISIT2
8	SUB200	3	TREAT A	SCHEDULED	N			20FEB2022	22FEB2022	VISIT2
9	SUB200	4	TREAT A	PERFORMED	Y	75	mg	23FEB2022	14MAR2022	VISIT2
10	SUB200	5	TREAT A	PERFORMED	Y	75	mg	15MAR2022	15MAR2022	VISIT3

SDTM EX MODEL

ROW	USUBJID	EXSEQ	EXTRT	EXOCCUR	EXDOSE	EXDOSU	EXSTDTC	EXENDTC	VISIT
1	SUB100	1	TREAT A	Y	2800	mg	01JAN2022	28JAN2022	VISIT1
2	SUB100	2	TREAT A	Y	2500	mg	01FEB2022	28FEB2022	VISIT2
3	SUB100	3	TREAT A	Y	2100	mg	01MAR2022	28MAR2022	VISIT3
4	SUB200	1	TREAT A	Y	2800	mg	10JAN2022	06FEB2022	VISIT1
5	SUB200	2	TREAT A	Y	2250	mg	15FEB2022	14MAR2022	VISIT2
6	SUB200	3	TREAT A	Y	2100	mg	15MAR2022	11APR2022	VISIT3

SUMMARY

This paper summarizes one way of leveraging the EC domain to capture and document all dose modifications in clinical trials. With different dose modification scenarios, we established and outlined the process flow and traceability of exposure data from EC to EX. Creating a well-structured EC data set that contains exposure data as collected including any dose modifications, and an EX data set that contains actual drug administered within each study cycle, makes review, traceability, accessibility and summarizing of data for analysis a lot easier.

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CONTACT INFORMATION

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

Varsha Korrapati
Seagen Inc.
21823- 30th Drive S.E.
Bothell, WA 98021
vkorrapati@seagen.com

Johnny Maruthavanan
Seagen Inc.
21823- 30th Drive S.E.
Bothell, WA 98021
jamaruthavanan@seagen.com