6 Domain Models Based on the General Observation Classes

6.1 Interventions

Exposure Domains: EX and EC

Clinical trial study designs can range from open label (where subjects and investigators know which product each subject is receiving) to blinded (where the subject, investigator, or anyone assessing the outcome is unaware of the treatment assignment(s) to reduce potential for bias). To support standardization of various collection methods and details, as well as process differences between open-label and blinded studies, two SDTM domains based on the Interventions General Observation Class are available to represent details of subject exposure to protocol-specified study treatment(s).

The two domains are introduced below.

Exposure (EX)

EX – Description/Overview for the Exposure Domain Model

The Exposure domain model records the details of a subject's exposure to protocol-specified study treatment. 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.

EX – Specification for the Exposure Domain Model

ex.xpt, Exposure - Interventions, Version 3.2. One record per protocol-specified study treatment, constant-dosing interval, per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req
DOMAIN	Domain Abbreviation	Char	EX	Identifier	Two-character abbreviation for the domain.	Req
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req
EXSEQ	Sequence Number	Num		Identifier	Sequence Number given to ensure uniqueness of subject records within a domain. May be any valid number.	Req
EXGRPID	Group ID	Char		Identifier	Used to tie together a block of related records in a single domain for a	Perm

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core
					subject.	
EXREFID	Reference ID	Char		Identifier	Internal or external identifier (e.g., kit number, bottle label, vial identifier).	Perm
EXSPID	Sponsor-Defined Identifier	Char		Identifier	Sponsor-defined reference number. Perhaps pre-printed on the CRF as an explicit line identifier or defined in the sponsor's operational database. Example: Line number on a CRF Page.	Perm
EXLNKID	Link ID	Char		Identifier	Identifier used to link related records across domains.	Perm
EXLNKGRP	Link Group ID	Char		Identifier	Identifier used to link related, grouped records across domains.	Perm
EXTRT	Name of Treatment	Char	*	Topic	Name of the protocol-specified study treatment given during the dosing period for the observation.	Req
EXCAT	Category of Treatment	Char	*	Grouping Qualifier	Used to define a category of EXTRT values.	Perm
EXSCAT	Subcategory of Treatment	Char	*	Grouping Qualifier	A further categorization of EXCAT values.	Perm
EXDOSE	Dose	Num		Record Qualifier	Amount of EXTRT when numeric. Not populated when EXDOSTXT is populated.	Exp
EXDOSTXT	Dose Description	Char		Record Qualifier	Amount of EXTRT when non-numeric. Dosing amounts or a range of dosing information collected in text form. Example: 200-400. Not populated when EXDOSE is populated.	Perm
EXDOSU	Dose Units	Char	(UNIT)	Variable Qualifier	Units for EXDOSE, EXDOSTOT, or EXDOSTXT representing protocol-specified values. Examples: ng, mg, mg/kg, mg/m2.	Exp
EXDOSFRM	Dose Form	Char	(FRM)	Variable Qualifier	Dose form for EXTRT. Examples: TABLET, LOTION.	Exp
EXDOSFRQ	Dosing Frequency per Interval	Char	(FREQ)	Variable Qualifier	Usually expressed as the number of repeated administrations of EXDOSE within a specific time period. Examples: Q2H, QD, BID.	Perm
EXDOSRGM	Intended Dose Regimen	Char		Variable Qualifier	Text description of the intended schedule or regimen for the Intervention. Example: TWO WEEKS ON, TWO WEEKS OFF.	Perm
EXROUTE	Route of Administration	Char	(ROUTE)	Variable Qualifier	Route of administration for the intervention. Examples: ORAL, INTRAVENOUS.	Perm
EXLOT	Lot Number	Char		Record Qualifier	Lot Number of the intervention product.	Perm
EXLOC	Location of Dose Administration	Char	(LOC)	Record Qualifier	Specifies location of administration. Examples: ARM, LIP.	Perm
EXLAT	Laterality	Char	(LAT)	Variable Qualifier	Qualifier for anatomical location further detailing laterality of the intervention administration. Examples: LEFT, RIGHT.	Perm
EXDIR	Directionality	Char	(DIR)	Variable Qualifier	Qualifier for anatomical location further detailing directionality. Examples: ANTERIOR, LOWER, PROXIMAL, UPPER.	Perm
EXFAST	Fasting Status	Char	(NY)	Record Qualifier	Indicator used to identify fasting status. Examples: Y, N.	Perm

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core
EXADJ	Reason for Dose Adjustment	Char	*	Record Qualifier	Describes reason or explanation of why a dose is adjusted.	Perm
EPOCH	Epoch	Char	(EPOCH)	Timing	Trial Epoch of the Exposure record. Examples: RUN-IN, TREATMENT.	Perm
EXSTDTC	Start Date/Time of Treatment	Char	ISO 8601	Timing	The date/time when administration of the treatment indicated by EXTRT and EXDOSE began.	Exp
EXENDTC	End Date/Time of Treatment	Char	ISO 8601	Timing	The date/time when administration of the treatment indicated by EXTRT and EXDOSE ended. 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.	Exp
EXSTDY	Study Day of Start of Treatment	Num		Timing	Study day of EXSTDTC relative to DM.RFSTDTC.	Perm
EXENDY	Study Day of End of Treatment	Num		Timing	Study day of EXENDTC relative to DM.RFSTDTC.	Perm
EXDUR	Duration of Treatment	Char	ISO 8601	Timing	Collected duration of administration represented in ISO 8601 duration format. Used only if collected on the CRF and not derived from start and end date/times.	Perm
EXTPT	Planned Time Point Name	Char		Timing	1. Text Description of time when administration should occur. 2. This may be represented as an elapsed time relative to a fixed reference point, such as time of last dose. See EXTPTNUM and EXTPTREF.	Perm
EXTPTNUM	Planned Time Point Number	Num		Timing	Numerical version of EXTPT to aid in sorting.	Perm
EXELTM	Planned Elapsed Time from Time Point Ref	Char	ISO 8601	Timing	Planned elapsed time (in ISO 8601 format) relative to the planned fixed reference (EXTPTREF). This variable is useful where there are repetitive measures. Not a clock time. Represented in ISO 8601 duration format.	Perm
EXTPTREF	Time Point Reference	Char		Timing	Name of the fixed reference point referred to by EXELTM, EXTPTNUM, and EXTPT. Examples: PREVIOUS DOSE, PREVIOUS MEAL.	Perm
EXRFTDTC	Date/Time of Reference Time Point	Char	ISO 8601	Timing	Date/time for a fixed reference time point defined by EXTPTREF in ISO 8601 character format.	Perm

** Indicates variable may be subject to controlled terminology, (Parenthesis indicates CDISC/NCI code list code value)*

EX – Assumptions for the Exposure Domain Model

1 EX Definition

a. The Exposure domain model reflects details of a subject's exposure to protocol-specified study treatment(s), in protocol-specified unit(s). Study treatment may be an intervention that is prospectively defined as a test material within a study, and is typically but not always supplied to the subject. Examples include but are not limited to placebo, active comparators, and investigational products. Treatments that are not protocol-specified should be represented in the Concomitant Medication (CM) or another Interventions domain as appropriate.

b. The EX domain is recognized in most cases as a derived dataset where EXDOSU reflects the protocol-specified unit per study treatment. Collected data points (e.g., number of tablets, total volume infused) along with additional inputs (e.g., randomization file, concentration, dosage strength, drug accountability) are used to derive records in the EX domain.

c. The EX domain is required for all studies that include protocol-specified study treatment. Exposure records may be directly or indirectly determined; metadata should describe how the records were derived. Common methods for determining exposure (from most direct to least direct) include the following:

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

    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.

d. The EX domain should contain one record per constant-dosing interval per subject. "Constant-dosing interval" is sponsor defined, and may include any period of time that can be described in terms of a known treatment given at a consistent dose, frequency, infusion rate, etc. For example, for a study with once-a-week administration of a standard dose for 6 weeks, exposure may be represented as one of the following:

    1. If information about each dose is not collected, there would be a single record per subject, spanning the entire 6-week treatment phase.
    2. If the sponsor monitors each treatment administration, there could be up to six records (one for each weekly administration).

2 Exposure Treatment Description

a. EXTRT captures the name of the protocol-specified study treatment and is the topic variable. It is a Required variable and must have a value. EXTRT must only include the treatment name and must not include dosage, formulation or other qualifying information. For example, "ASPIRIN 100MG TABLET" is not a valid value for EXTRT. This example should be expressed as EXTRT = 'ASPIRIN', EXDOSE = 100, EXDOSU = 'mg', and EXDOSFRM = 'TABLET'.

b. Doses of placebo should be represented by EXTRT = 'PLACEBO' and EXDOSE = 0 (indicating 0 mg of active ingredient was taken or administered).

3 Categorization and Grouping

a. EXCAT and EXSCAT may be used when appropriate to categorize treatments into categories and subcategories. For example, if a study contains several active comparator medications, EXCAT may be set to 'ACTIVE COMPARATOR'. Such categorization may not be useful in all studies, so these variables are permissible.

4 Timing Variables
   a. The timing of exposure to study treatment is captured by the start/end date and start/end time of each constant-dosing interval. If the subject is only exposed to study medication within a clinical encounter (e.g., if an injection is administered at the clinic), VISITNUM may be added to the domain as an additional Timing variable. VISITDY and VISIT would then also be permissible Qualifiers. 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 in the EX domain. This is because 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. The SDTM does not have any provision for recording "start visit" and "end visit" of exposure.
   b. 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.

5 Collected exposure data points are to be represented in the EC domain (See Section 6.1.2.3). When the relationship between EC and EX records can be described in RELREC, then it should be defined. EX derivations must be described in the define.xml.

6 Additional Interventions Qualifiers
   a. The variables –PRESP, --OCCUR, --STAT, and --REASND from the Interventions General Observation Class would generally not be used in the EX domain. EX contains medications received; the inclusion of administrations not taken, not given or missed is under evaluation.
   b. --DOSTOT is under evaluation for potential deprecation and replacement with a mechanism to describe total dose over any interval of time (e.g., day, week, month). Sponsors considering use of EXDOSTOT may want to consider using other dose amount variables (EXDOSE or EXDOSTXT) in combination with frequency (EXDOSFRQ) and timing variables to represent the data.
   c. When the EC domain (See Section 6.1.2.3) is implemented in conjunction with the EX domain, EXVAMT and EXVAMTU should not be used in EX; collected values instead would be represented in ECDOSE and ECDOSU.
   d. Other additional Qualifiers from the SDTM Interventions General Observation Class may be added to this domain.