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Considerations in the Submission of Exposure Data in an SDTM-Compliant Format

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ABSTRACT

The submission of data regarding a subject's exposure to a study treatment is critical in making decisions regarding its safety and efficacy. While many sponsors are concerned about getting their data into an SDTM-compliant format, our experience in legacy-data conversion has revealed that many studies don't collect sufficient data to get a reliable assessment of actual exposure. It is also clear that many sponsors are unsure how to properly represent the exposure data they do collect. This paper will discuss the pros and cons of various methods of collecting and representing exposure, as well as some of the challenges sponsors may face in converting data to be consistent with the SDTMIG Exposure (EX) domain.

INTRODUCTION

As the SDTMIG stipulates, the EX domain is required for any study where subjects are "exposed" to investigational product. The SDTMIG (CDISC.org) indicates that this domain is for "protocol-specified study treatments." This could include the drug entity under study, any comparator medication, other medications supplied by the sponsor, and/or any placebo dosing.

In EX, exposure is represented over the sponsor-defined "constant dosing interval". Any discussion of how exposure data should be captured and represented in EX begins with this definition. The SDTMIG defines it as "any period of time that can be described in terms of a known treatment given at a consistent dose and frequency". The protocol and case report form (CRF) may further define the granularity at which study drug doses are captured across this constant dosing interval. For example: will each dose be captured on the CRF, will doses be captured within or across protocol "visits", or will a single record with the start and end date across the subject's study participation suffice?

The goal of EX is to present to a reviewer the complete and accurate picture of a subject's exposure to study medication as outlined in the protocol and captured on the CRF. The SDTMIG presents five methods that can be used as the basis for the collection and ultimate submission of exposure data, listed as most to least reliable:

1. Actual observation of the administration of drug by the investigator
2. Automated dispensing device which records administrations
3. Subject recall (e.g., via diary)
4. Derived from drug accountability data (e.g., pill counts)
5. Derived from the protocol

The metadata should describe the method by which the exposure data was determined. Our experiences in legacy-data conversion have provided ample evidence that many of these methods have drawbacks and that in all cases, good data collection and sound data management processes are needed to overcome them.

CHALLENGES TO THE ACCURATE REPRESENTATION OF EXPOSURE DATA

In the sections below, we will provide examples in which we have had sponsors fail to recognize limitations of the data they intended to submit, and recommendations we have made to remedy some of these. In order to conserve space, the data examples show only the columns relevant to the point being made. There may be other Expected and Permissible variables for which data were collected that would be included in a sponsor's submission dataset.

The Collection of Dosing Information

We have seen many studies in our legacy-data conversion work for which no dosing information has been collected. For these studies, dosing information (e.g., dose levels and frequency) must be derived from the protocol (SDTMIG Method 5). The start and end dates must also be derived, usually from dates of protocol-specified events such as a specific visit at which medication was dispensed. The SDTMIG recognizes that this is the least reliable method for determining exposure; however, the EX dataset is required, and the derived data at least gives the reviewers some approximation of the subjects' exposure in a standard format, and doesn't require a search of the protocol.

Representing the Complete Dosing Period

The limitation to SDTMIG Method 1 is that the investigator must be present for each dose given to get the complete dosing information. This is rarely the case, however, in larger, later-phase trials. We have seen a number of cases where some dosing information has been collected, but from which a complete dosing picture cannot be obtained. One of these involves studies that collect only in-clinic doses. The data in the table below resulted from a CRF that collected the date/time of dosing at three visits to the site.

STUDYID	DOMAIN	USUBJID	EXSEQ	EXTRT	EXCAT	EXDOSE	EXDOSFRQ	EXSTDTC	EXENDTC
ABC0001	EX	0001-101	1	DRUG A	AT SITE	150	QD	2012-01-08	
ABC0001	EX	0001-101	2	DRUG A	AT SITE	150	QD	2012-01-15	
ABC0001	EX	0001-101	3	DRUG A	AT SITE	150	QD	2012-01-22	
ABC0001	EX	0001-102	1	DRUG A	AT SITE	150	QD	2012-01-08	
ABC0001	EX	0001-102	2	DRUG A	AT SITE	150	QD	2012-01-15	
ABC0001	EX	0001-102	3	DRUG A	AT SITE	150	QD	2012-01-22	

If these were the only records submitted, the data would lead a reviewer to conclude that the two subjects in this treatment Arm received three doses of "Drug A" over the course of the study. The protocol, however, specified that the subjects were to take the study drug on a daily basis for two weeks. The sponsor felt that by populating EXDOSFRQ with QD, it would be clear that the dosing was daily; however the absence of a date in EXENDTC does not allow for the establishment of a constant-dosing interval.

While SDTM datasets are expected to represent the raw collected data, this is a case where using only the collected data does not provide an accurate representation of the true exposure. Adding an additional record for each subject that reflects the entire span of dosing (e.g., a "constant dosing interval" record), is one solution to this problem, as shown in the table below. To clarify that there are two types of dosing records, EXCAT was populated with the value of "AT SITE" for the discrete in-clinic doses and left blank for the "blanket" dosing record.

STUDYID	DOMAIN	USUBJID	EXSEQ	EXTRT	EXCAT	EXDOSE	EXDOSFRQ	EXSTDTC	EXENDTC
ABC0001	EX	0001-101	4	DRUG A		150	QD	2012-01-08	2012-01-22
ABC0001	EX	0001-102	4	DRUG A		150	QD	2012-01-08	2012-01-22

Two other common scenarios are the following:

- the CRF captures only the dates of missed doses (the EX subteam is currently discussing the best method for submitting missed-dose information in EX)
- the CRF captures only the dates of dose adjustments (each dose adjustment record signals the start of a new constant dosing interval)

In both cases, records that "fill in the blanks" between these collected dates must be derived. To avoid this problem, at minimum, the first dose date/time and last dose date/time should be recorded on the CRF. If dosing changes are expected, then an additional CRF page to record these changes would be beneficial.

The Use of Drug Accountability Data

Drug accountability data, which is submitted in the SDTMIG Drug Accountability (DA) domain, is generally collected for use in the calculation of compliance. Although the SDTMIG Method 4 indicates that drug accountability can be used as a source for creating an EX dataset, our experience indicates this is generally not a good practice for the accurate representation of exposure. If, however, it is necessary to do so, it should be done with great care.

It may be practical to use the dates dispensed and returned as "anchors" from which to create a "constant dosing interval." Using drug accountability data for much more than this (e.g., dosing amounts on specific dates, dosing frequencies over the dosing period) could lead to some very misleading information. Consider the case where a subject was given 28 tablets for QD (daily) dosing, and returns 14 of them at the end of the four-week period. The actual exposure could have been one of many scenarios including, but not limited to the following:

- one tablet QOD (every other day)
- one tablet QD for the first two weeks
- one tablet QD for the last two weeks
- one tablet QD every other week

Without the collection of additional information from the subject, it would be impossible to know what their dosing pattern was, and why they didn't take 14 tablets. The evaluation of the safety of the drug is going to vary considerably under these scenarios if an adverse event occurs two weeks into the dosing period.

Doses Based upon Subject-Specific Factors

There are times, particularly in oncology studies, where subjects are administered doses of study drug based on body surface area rather than as fixed doses. An example would be a trial in which subjects were to receive doses of 150, 300, or 400 mg/m^2. Sponsors should consider whether it would be more convenient and efficient for the reviewer to

have the protocol-specified dose or the actual dose received (based upon body-surface area) in EXDOSE. What is not represented in EXDOSE could be submitted in SUPPEX. The decision on which option to use may depend upon previous acceptable methodologies and/or the plan for analyzing the data.

The Representation of Unblinded Data

For studies that were blinded during study execution, the submitted EX dataset should show the subject's "unblinded" treatment. In the study whose data are shown below, the treatment was administered as a series of injections. There were four dose levels plus placebo, and the number of injections and total volume injected were constant for all of them. In initial conversations with the sponsor concerning data migration, they indicated they wished to submit EXDOSE as being the number of injections, with EXTRT identifying the treatment as placebo or the active drug. Below are sample EX records for a subject when migrated according to the sponsor's wishes:

STUDYID	DOMAIN	USUBJID	EXSEQ	EXTRT	EXDOSE	EXDOSU	VISIT	EXSTDTC
DEF0001	EX	0001-101	1	DRUG B	8	INJECTIONS	VISIT 1	2012-01-15T08:30
DEF0001	EX	0001-102	1	DRUG B	8	INJECTIONS	VISIT 1	2012-01-17T10:30
DEF0001	EX	0001-103	1	PLACEBO	8	INJECTIONS	VISIT 1	2012-01-21T13:00

Although Subjects 0001-101 and 0001-102 received different dose levels, these records provide no information regarding the level of active drug. The sponsor suggested that merging ARMCD from DM would address this problem, but the EX dataset should not be dependent upon data from another dataset. EX is intended to provide a more granular representation of the treatments within the Elements of an Arm, and this was not considered to be a valid approach. The number of injections could have been submitted in SUPPEX if desired, but sponsors should be cautious in submitting superfluous data in SUPP- datasets.

This situation is analogous to instances where the number of "tablets taken" per dosing opportunity is shown in EXDOSE. Again, after study unblinding, the number of tablets taken becomes less important, and should be replaced by the subjects' actual randomized dosing information. This is especially important in cases where additional tablets were taken to protect the study blind, and in which the additional placebo tablets would be of little interest to the reviewer in understanding the true exposure. An example of this would be as follows: a study has four Arms consisting of placebo, and 5 mg, 10 mg, and 15 mg of study drug. Subjects may take 3 tablets at each dosing opportunity where all of them may be placebo or active depending on the combination needed to provide each subject's randomized dose. Any additional tablets taken beyond the active would not be accounted for in the final unblinded EX domain. Only the active (shown as the number of mg) would be migrated to EXDOSE.

To address the need that some sponsors may have to submit blinded dosing data, and to make it clear to sponsors that EX should contain unblinded data, the CDISC SDS Exposure subteam has been discussing the creation of a domain model that could be used for the submission of blinded dosing information.

Misuse of EX Variables

A number of EX variables are sometimes misused. Some of the most common misuses we have seen are as follows:

- In general, it is expected that doses of study drug can be represented in a numeric format, unlike concomitant medications for which dose values such as "200-400" might be collected. Therefore, EXDOSTXT is generally not present in EX datasets. It should not contain a duplication of the value in EXDOSE.
- EXTRT should contain the name of the treatment, and not additional information that can be represented in other variables (e.g., dose units and dose frequency).
- EXDOSTOT should be used only when the total daily dose has been collected. It should not be used for total doses collected over other periods, such as total dose for a week or a dosing period. This information should be submitted in SUPPEX.
- EXDOSRGM is often confused with EXDOSFRQ. The latter is generally considered to be at a more granular level, and has CDISC Controlled Terminology. EXDOSRGM may be used to represent higher level dosing patterns such as one week on, one week off.
- EXCAT values are intended to be used to identify categories of treatment. Populating EXCAT with a constant value such as "Study Medication" would have added no value, as it is redundant to information implied in the domain name itself.

Most Recent Dose Taken

Some studies collect "trough" PK samples at protocol-specified times. The CRF pages for these will collect the most recent dose taken prior to the PK sample collection so that the time between the dose and the blood measurement is known. This study-drug exposure may be the only dose information collected in some studies, or may supplement other exposure data collected for constant dosing intervals. We recommend these most recent dose dates and times be represented in EX with an appropriate value in EXCAT.

THE IMPORTANCE OF EXPOSURE DATES IN THE DETERMINATION OF SUBJECT ELEMENTS

Trial Element start rules (TESTRL) for any treatment Element are based upon the first date of exposure for that Element. When reviewing trial design specifications for sponsors, we have seen numerous instances where the TESTRL for a planned treatment element references a dose date that is not found or has been represented incorrectly in the EX dataset. The net result is that the Element will be missing the start date in the Subject Elements dataset. The absence of an Element start date will present challenges to reviewers in trying to assess the relationship of other observations, particularly adverse events, to treatment. It is therefore imperative that the design of the CRFs take this into account, and ensure that the appropriate dose dates are collected.

CONCLUSIONS

We have presented a number of pitfalls that could prevent a reviewer from obtaining an accurate representation of a subject's exposure to study medication. During the course of legacy-data conversion and the review of SDTM datasets, we are constantly reminded how important it is to decide up front, in the protocol and in the process of CRF creation, how best to ensure that the entire picture of exposure can be determined from data collection through submission.

Sponsors are reminded that science and regulation determine the data needed for a submission. The SDTM is simply a standard format for submitting the data that was collected. It will not, in and of itself, remedy deficiencies in data collection and data management. Despite its importance in understanding a drug's safety, our experience indicates that drug exposure data is one of the most vulnerable to poor and incomplete data collection and representation.

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