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Help! The EX Domain is now an Analysis Dataset! What Do I Do?!?

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ABSTRACT

The CDISC Study Data Tabulation Model (SDTM) [1] defines a standard structure for study data tabulations that are to be submitted as part of a product application to a regulatory authority such as the FDA. These data tabulations, delineated in the CDISC SDTM and augmented by the clarity offered by the corresponding CDISC SDTM Implementation Guide (IG) [2], are considered electronic listings of individual observations for a subject that comprise the essential data reported from a clinical trial. To quote the CDISC SDTM IG v3.1.2, Section 2.1, "The SDTM is built around the concept of observations collected about subjects who participated in a clinical study." The challenge is that a key section has been added to the CDISC SDTM IG v3.1.2, Section 6.1.2.1 which details assumptions for the Exposure domain model, in general stating that exposure may be directly or indirectly determined and, regardless of how it is known, must be represented using the Exposure domain. This paper will explore the implications for design and development of the Exposure domain under these revised rules in the context of preparing your submission package at the study level.

EVOLUTION OF THE EX DOMAIN WITHIN THE SDTM MODEL

Per the Study Data Specifications [3], articulated by the FDA as an appendix to the FDA's eCTD Guidance document [4], describe four presentations of study data in support of a regulatory submission: data tabulation datasets, data listing datasets, patient profiles and analysis datasets. By using the data tabulation datasets, defined in this appendix as SDTM domains per the CDSIC SDTM and articulated by the CDISC SDTM Implementation Guide, you "minimize the need to submit the same data in multiple formats." ([1], Section 1.1, 2nd paragraph). The agency as built or incorporated a number of tools into their medical, safety and statistical / efficacy review that utilize the SDTM domains to dynamically build patient profiles and data listing datasets. The focus, however, of the CDISC SDTM, CDISC SDTM IG and the Study Data Specifications, has been on the organization and presentation of collected data. Throughout the evolution of all of these documents has been the focus on presenting a standardized form of data obtained through investigator observation in the clinic. Until now.

The collection of exposure data in a clinical trial can be a daunting task. Cases range from the single dose of study medication administered in the clinical pharmacology research unit to the interventions administered in a critical care environment to the subject administered treatments in studies with infrequent clinical visits. The exposure (EX) domain has been designed to be flexible enough to effectively document each of these scenarios. The challenge is that, for clinical reasons, when the collection of exposure data puts the protocol at regulatory or financial risk due to the excessive costs associated with the monitoring and cleaning of truly accurate exposure data, a decision is made to limit or eliminate the collection of actual subject level exposure data on the case report form.

Historically, utilizing the now-retired '99 / traditional guidance as the method of organizing and submitting data to the FDA, exposure data could be obtained via any defensible means and placed into the set of data regardless of its source. With the introduction of the SDTM and SDTM IG, in versions up to and including SDTM v1.1 / SDTM IG v3.1.1, the requirement was that only collected data could be present in the SDTM domains. Section 6.1.2.1, Assumptions for the Exposure Domain Model, item #1, has always contained the following two sections of text, I have highlighted key phrases:

1. EX Definition
    a. 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. Examples include but are not limited to placebo, active comparators and investigational products. Treatments that are not protocol-specified should be recorded in the Concomitant Medication (CM) domain.
    b. This 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 and frequency. For example, for a study with a once-a-week administration of a standard dose for 6 weeks, exposure may be represented as one of the following:

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

Note that the focus is on a subject's specific exposure to protocol-specified study treatment. The onus is still on the sponsor to identify and articulate collected information related to a subject's study medication exposure. The following text was added to this same section with Version 3.1.2 of the SDTM IG:

c. The Exposure domain is required for all studies that include investigational product. Exposure information may be directly or indirectly determined. Regardless of how it is known, it must be represented using the Exposure domain, and the metadata should explain how it was populated. Common methods for determining exposure (from the most direct to least direct) include the following:

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

As you can see, a fundamental shift in focus and function for the EX domain has occurred with the introduction of SDTM IG v3.1.2. To step back a bit for a moment, we should look at the use of this data by medical and safety reviewers at the agency. They have built a number of tools to look at data in context, and a significant aspect of that context is the changes in observed subject data over time in relation to the presence / absence / change in investigational product. Without investigation product information it is impossible to put the remaining clinical trial data in context; this information must be present in order to make the trial data meaningful. The SDTM and SDTM IG, therefore, have now articulated a systematic way of documenting that information even if it is not a result of direct, specific subject observation.

To substantiate the claim that the EX domain is now an analysis dataset, take into consideration the language of item "c." above. "Exposure information may be directly or indirectly determined" – read: the source of EX domain content may not necessarily be a result of direct subject observation. Option 3 – "Subject recall (e.g., via diary)" – read: a non-monitorable source of subject data, a patient diary, can now be utilized to generate the EX domain. Option 4 – "Derived from drug accountability data (e.g., pill counts)" and Option 5 – "Derived from the protocol" – read: in the absence of any direct observation of study medication exposure, you now have license to record a subject's exposure to study medication based on what might have happened based on related data (drug accountability), or, even more liberally, on what should have happened based on the Study Schedule of Events and related sections of the clinical study protocol.

PLANNING AND PREPARING FOR EX DOMAIN IMPLEMENTATION UNDER SDTM V1.2 / SDTM IG V3.1.2

To put this effort in context, your ultimate goal is to represent the clinical trial accurately in the form of data as it is presented to the agency. You must create a data package that you can defend; it must stand up to a routine FDA audit, where an auditor will evaluate the data utilized in your clinical study report from collection through to presentation in the clinical study report or clinical database in the form of site level patient data listings. It must satisfy the medical/safety reviewer requirement for appropriate use of data in the assessment of safety and efficacy of the investigational product. Ultimately, you must preserve traceability – can you support the deployment and use of data in the context of a clinical trial from collection through to analysis. Great care must be taken to establish this traceability in the absence of actual subject level data that normally is available at the subject level in the source data.

The minimum set of variables that must (required) or should (expected) be present in an EX domain, aside from the subject, study identification and sequencing variables, are

- EXTRT – The name of the investigational product
- EXDOSE – Amount of EXTRT administered or given
- EXDOSU – Units for EXDOSE
- EXDOSFRM – Dose form for EXTRT

- EXSTDTC – The time when administration of the treatment indicated by EXTRT and EXDOSE began

I would suggest that, for the sake of meaningful and review and analysis of the data, you should strive to also populate the variable EXENDTC, as you generally need to know when an intervention started and stopped in order to analyze other related events in the appropriate context.

The first two cases, actual investigator observation of investigational product exposure and actual dispensing devices which record administration, are straightforward applications of the source data to the SDTM model in order to formulate your EX domain records. The use of subject diary data can be more of a challenge. Diary data cannot be monitored and subsequently changed after the fact as it is just that, a record made by the subject at a specific point in time. Any challenge to a subject's record in a diary is basically challenging the subject's judgment and perception at the time the diary entry was made. Therefore your challenge is to ensure you can effectively utilize the diary data to make a case for

The process for using drug accountability data and the exclusive use of the information available in the protocol in order to produce subject-level EX domain records are very similar. In both cases you get clues on information such as specific investigation product administered or taken, if there is more than one product being administered, from information sources such as randomization assignment. Using the protocol will allow you to build your

When actually constructing this domain from information other than subject level clinically observed data, you must take great care to clearly lay out the process used to make this happen. Some questions that you should ask as you build these records:

- Which clinical document best describes the intended study medication administration plan for the trial – the protocol, in places such as the Study Schedule of Events or Study Procedures section, the Statistical Analysis Plan, or perhaps the entry / completion guidelines available for the case report form?
- Which subjects should have records in the EX domain? Randomized subject? Members of the ITT population? Other criteria?
- Is ANY subject level study medication administration information available, such as a last dose date on a Study Disposition / Early Withdrawal CRF or information on the current dose of study medication at the time an AE occurred?
- If using the protocol to establish first and last administration dates, are there any other subject level sources of information that would influence changing the start and, more likely, the stop dates for study investigational product, such as information on an AE page for an AE that led to withdrawal?

When using any of this information, the key is to document clearly and unambiguously what was done to prepare these observations. The data definition table should clearly use the origin of "Protocol" and text should be added to the Supplemental Data Definitions section of the define.xml to define what steps were taken to assemble data at the subject level for the EX domain in the absence of subject level data being observed by the investigator and captured on the CRF.

CONCLUSION

The EX domain is the first domain to explicitly experience a transformation from a pure SDTM domain to an origin and format indicative of its value. For the EX domain, in the absence of this information, the review and interpretation of any other clinical trial results are difficult if not impossible. The consumers of SDTM – medical reviewers, statistical reviewers and FDA auditors – realized the value and necessity of having this information available at the time of submission as an SDTM domain regardless of the specific origin of this data. A question to ask is, are there other domains that are likely to undergo this transformation in the future? Will clarity be given to the pharmacokinetic parameters (PP) domain, as the contents of this domain are a number of calculated / derived values produced using statistical models based on the contents of trial-observed values of pharmacokinetic investigational product concentration data? Will we see a different direction for values such as indices, sub-scores and total scores derived as a result of questionnaire (QS) domain data analysis, on one hand a standardized calculation based on the collected data, but not a value that was observed in the clinic? This change in strategy for this SDTM domain opens the door for a number of other data elements traditionally captured within SDTM that should be evaluated and clarified in future versions of the model or implementation guides.

REFERENCES

[1] Study Data Tabulation Model, Version 1.2 Final. Published by CDISC November 12, 2008. Available for download at http://www.cdisc.org. Note: membership and/or registration required.

[2] Study Data Tabulation Model Implementation Guide: Human Clinical Trials. Published by CDISC November 12, 2008. Available for download at http://www.cdisc.org. Note: membership and/or registration required.

[3] Study Data Specification appendix to Reference #5 above, available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf, web location verified March 10, 2010.

[4] Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications. Revision 2, published July 2008. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf, web location verified March 10, 2010.

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RECOMMENDED READING

See “REFERENCES”…

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