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SDTM Oncology Domains: From Patient to Data to Narrative

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ABSTRACT

The CDISC SDTM standard has been a stable model for several years with its focus on the core data domains that serve as the data backbone for the majority of regulatory submissions. As the industry has begun to implement and use these domains, it has become apparent that additional standard domains are also needed to consistently describe specific types of data in a standard way across the industry. In particular, Therapeutic Areas have standard methodology for the efficacy data in their area, and thus would benefit from standard SDTM domains for submission. The Oncology area is one such space.

In 2012, CDISC released its latest version of the SDTM Implementation Guide, 3.1.3[1], which included new standard Oncology domains that capture the assessment of both the change in tumor burden and the disease progression as the standard endpoints in cancer clinical trials.

From my standards experience on both sides of the pharmaceutical industry - pharmaceutical companies and contract research organizations - it is apparent that the industry is now starting to implement these new standard domains into their clinical data processes. It is my objective here to share that experience and insight into that implementation from a standards perspective, but also introduce a focus on the patient's perspective.

SDTM ONCOLOGY DOMAINS

In the clinical evaluation of cancer treatments, one of the most important factors is the assessment of the change in tumor burden. This includes both objective response (tumor shrinkage) and more subjective response (clinical assessment of disease progression). The data collected in Oncology clinical trials follows the methodology of tumors, lymph nodes, or other evidence of disease being identified and then repeatedly measured (assessed) at subsequent time points. The change across these time points is the basis for the evaluation of response.

Three of the most commonly used evaluation constructs in the Oncology therapeutic area are RECIST[2] for solid tumors, Cheson[3] for malignant lymphomas, and Hallek[4] for chronic lymphocytic leukemia. The CDISC SDTM Oncology domains are intended to support these assessment criteria in the representation of data collected. It is valuable to note that some response criteria may require additional collected data to support the assessment of response and that data should be mapping to the appropriate SDTM domain (e.g. LB for lab test results).

The three SDTM domains in the tumor package are based on the SDTM Findings Observation Class, and are each related to the others, albeit each with a separate purpose.

- TU (Tumor Identification): unique identification of tumors for that patient
  - One record for each unique tumor identified
  - The initial identification of a tumor is usually performed only at baseline, except where a new tumor emerges during a post-baseline record requiring identification of the new tumor
  - Splitting or merging of tumors requires additional post-baseline records to distinctly identify the new resultant tumor(s)
  - The TULNKID variable is the key unique identifier that provides a unique code for each identified tumor
  - As per Findings domains within the core SDTM safety domains, the TUTESTCD and TUTEST have controlled terminology applied to the content. Examples include: TUMIDENT, TUMERGE, TUSPLIT
- TR (Tumor Results): quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain, assessed during subsequent visits
  - The TRLNKID variable provides the link back to the TU domain
  - The TRLNKGRP variable provides a link between the records in TR that support a response assessment record in the RS domain. RELREC relationships should exist to support this relationship

    - As per Findings domains within the core SDTM safety domains, the TRTESTCD and TRTEST have controlled terminology applied to the content. Examples include: AREA, DIAMETER, VOLUME
- RS (Disease Response): clinical response evaluations determined from the TR data and other SDTM domains
    - The RSLNKID variable provides the link back to the TU domain
    - The RSLNKGRP variable provides a link between the records in TR that support a response assessment record in the RS domain. RELREC relationships should exist to support this relationship
    - As per Findings domains within the core SDTM safety domains, the RSTESTCD and RSTEST have controlled terminology applied to the content. Examples include: BESTRESP, OVRLRESP, TRGRESP
    - Any data that contributes to the response assessment should be linked to the RS record through RELREC even where the supportive data resides outside of the SDTM Oncology domains (e.g.: lab results in LB)

THE ONCOLOGY PATIENT

While the "subject vs patient" debate still rages within the clinical organizations of some sponsors, the Oncology Therapeutic Area has long been the flag-bearer for the view of a person being referred to as a "patient" in a clinical trial. This comes from the experience that a very high percentage of people that participate in Oncology clinical trials are in fact patients with cancer, not healthy volunteers.

PATIENT RECORDS

Considering the progressive nature of the disease, the cancer patient often enters the clinical trial with a substantial chronicle of medical information that has accumulated over an extended timeframe that could include multiple failed therapies, numerous hospitalization events, and the associated medications needed to address the symptoms of the disease. The hypothetical patient presented in this paper is typical for an Oncology patient entering a clinical trial.

This is a 57 year old female patient with Stage IIB colorectal carcinoma who has spent nearly 2 years battling the disease and the associated symptoms. She has already been through a myriad of doctor's visits, non-invasive and invasive procedures, and participation in other clinical trials with treatments that did not yield a positive response in arresting this proliferative disease. This treatment pathway leaves a trail of patient records that can be a real challenge for the clinical monitor to manage to ensure accurate capture of data into domains such as medical history, prior medications, prior procedures, and baseline disease characteristics, to name but a few.

TRANSLATION OF RECIST TO SDTM

The primary endpoint used in this hypothetical trial is the Response Evaluation Criteria In Solid Tumors, more commonly known as RECIST. This set of criteria has been widely accepted by regulatory authorities as an appropriate guideline for trials where the primary endpoints are objective response or progression. RECIST uses measurements of measurable targeted tumor lesions in addition to non-measurable disease, such as pleural effusion and ascites, to determine an objective assessment of response or future progression.

The SDTM Oncology domains provide a tool with which to effectively capture the necessary RECIST components and response. The SDTM variables listed below that collect the key assessment data can be found across the 3 Oncology domains (TU, TR, RS):

- --LNKID: Identifier used to link identified tumor(s) across the 3 domains
- TRORRES: Result of the Tumor measurement/assessment as originally collected
- RSORRES: Result of the Response assessment as originally collected

They are no different from other domains in that the ease at which the collected data can be mapped to SDTM is dependent on how the data is collected. CRFs that are designed without considering the SDTM Oncology domains will likely increase the difficulty in mapping to TU, TR, and RS, providing more opportunity for erroneous transformation to SDTM. Translation (or mapping) issues that have been observed with these new Oncology domains include:

- The collected domains are mostly mis-aligned with TU, TR, and RS in SDTM
- CRFs are not designed to identify the lesion once which requires collapsing lesion identifiers
- Inconsistent representation of the location of lesion across the duration of the trial

PATIENT NARRATIVES

As the Oncology patient proceeds through the clinical trial, he or she accumulates a set of experiences, which are sometimes described by the sponsor in the clinical study report at the end of the trial. The SDTM Oncology domains can be used to accurately supply the data needed for this summary.

Regulatory guidance documents call for the submission of subjects' study experience in brief narrative form for those subjects who meet specific criteria. These consist of descriptions of each death, each serious adverse event, and those with other significant adverse events that are judged to be of special interest because of clinical importance. While these narratives historically have been developed via a manual, labor-intensive process using subject line listings or individual case report form tabulations, the use of standardized SDTM data enables sponsors to construct the narratives in a more consistent and efficient manner.

Patient narratives include specific content that includes, but is not limited to:

- subject identifier
- subject age and sex
- general condition of the subject
- relevant prior / concomitant medical conditions
- relevant prior / concomitant medications
- disease / medical condition characteristics, including the duration of condition
- investigator and sponsor opinion on nature, causality, and intensity of the event
- clinical experience leading up to the event
- timing of study medication in relationship to event onset
- relevant laboratory measurements

For the purposes of this paper, only a portion of an example patient narrative will be displayed here:

> Subject 1001/1234 was a 57 year old Caucasian female who presented with Stage IIB colorectal carcinoma without spread into other nearby tissues or organs, lymph nodes or distant sites. Her medical history included headache (2007), dizziness (2007), back pain (2007), vomiting (2008), and diarrhea (2008). This subject entered the study on 14SEP2009 and was first exposed to Treatment ABC on 28SEP2009. Medications taken by the subject in the four weeks leading up to study entry include loperamide, bismuth subsalicylate, acetaminophen, ibuprofen, and codeine phosphate. The subject completed the trial on 22FEB2010 as per protocol due to a partial response, as determined by a 30% decrease in the sum of the longest diameters of all measurable lesions from baseline.
>
> On 04NOV2009, the subject experienced a hypotensive crisis involving a blood pressure reading of 51/35 with accompanying symptoms of nausea, fainting, and blurred vision. This was considered a serious adverse event (SAE). At the time of event the subject had taken 2 infusions of a 5-day cycle of Treatment ABC. The SAE occurred on Day 3 after beginning dosing for Cycle 2 with study medication. As a result of the event, trial medication had an action of dose reduced.
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> The investigator considered the SAE to be related to dehydration and a food allergy. The final outcome was reported as resolved on 05NOV2009.

CONCLUSION

The Oncology patient faces a difficult road in front of them in a clinical trial, particularly considering the progressive nature of the disease that afflicts them. Those of us that support clinical trial execution have a responsibility to ensure that the patient's hardship that they endure in the trial translates into successful use and analysis of that information that they generate. The Oncology SDTM domains uphold that goal.

REFERENCES

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