

Considerations and Conventions in the Submission of the SDTM Tumor and Response Domains

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ABSTRACT

The SDTMIG tumor domains (TU, TR, and RS) were first published in conjunction with the release of SDTMIG v3.1.3. The original intended use of these domains was largely confined to oncology. The TU domain contains tumor identification data and the TR domain contains subsequent tumor measurements over the course of a clinical trial. The measurements of target lesions and the continued evaluation of non-target lesions are used to support response assessment criteria such as outlined in RECIST (Response Evaluation Criteria in Solid Tumors) and represented in the RS domain.

With the development of Therapeutic Area User Guides (TAUGs), most notably the CV TAUG, the use of the TU and TR domains has been broadened to allow for the identification and assessment of other types of “lesions”, not just those associated with cancer and its treatment. This paper will examine how these two domains are now used across the spectrum of clinical studies and indications.

Along with this expansion in the use of the “tumor domains”, is the similar broadening of the Response (RS) domain. In the oncology setting, RS is used to represent the subject’s response to treatment, either specifically pertaining to target or non-target lesions or their overall response. Starting with SDTMIG v3.3 (targeted for release in early 2017), RS will also be used to submit Clinical Classifications. Examples of this use would include the Child-Pugh hepatic assessment, the NYHA assessment of congestive heart failure, and the ECOG (Eastern Oncology Cooperative Group).

INTRODUCTION

The Tumor Domains, as detailed in the SDTMIG v3.2, were created to provide a mechanism for the collection and reporting of identified tumors as well as for their measurement and assessment at protocol defined junctures throughout a subject’s participation in a clinical trial. Along with the identification and measurement domains, a “Response” domain was developed to evaluate a subject’s “response” to treatment according to the criteria outlined in the study protocol, such as RECIST (**R**esponse **C**riteria in **S**olid **T**umors) or other standard response criteria for cancers such as lymphoma or chronic lymphocytic leukemia.

The TU domain (Findings Observation Class) is used to identify target and non-target tumors or lesions. For tumors or lesions identified at the Screening or Baseline visit, there would be a single record per tumor for the entirety of the trial. During the course of the trial (Post Baseline), any “New” tumors identified or “Merged” tumors would also have a record in TU. Other qualifiers such as “Location” or “Method of Identification” are also often collected, along with the “Evaluator”, be it the investigator or an independent assessor. If more than one independent assessor is used in the identification of target and non-target lesions, TU also provides for an “Accepted Record Flag” (TUACPTFL) to identify which of the independent assessors (e.g., Radiologist 1, Radiologist 2) is deemed to provide the “accepted” record for analysis.

The TR domain is used to collect the actual measurements of each target lesion at defined time points, including at the Screening or Baseline visit. For non-target lesions, TR is used to verify the continued presence of the lesion from Screening or Baseline through each time point or to validate its “absence” as the lesion responds to treatment. Just as with TU, any “New”, “Merged”, or “Split” tumor is also assessed from the time it was first identified. Just as with TU, TR also employs the standard Findings domain qualifiers including TREVAL and TREVALID.

The RS domain was created to capture a subject’s categorical response to treatment at whatever granularity is called for by the analysis and at whatever time points are defined in the protocol. This

response assessment may be at the individual lesion or tumor level, at the target and non-target lesion levels, and at an “overall” level. The protocol will detail the objective criteria to be used in this response assessment according to the standard scale used for the study indication.

For each of the three domains, extensive controlled terminology has been developed for --TESTCD, --TEST, and in the case of the RS domain, for the assessment itself as recorded in --ORRES.

TUMOR IDENTIFIERS

In conjunction with the initial release of the tumor domains, additional Identifiers were included in Table 2.2.4 of the SDTM v1.3. Anticipating that identifiers such as –GRPID, --REFID, and –SPID might already have been used for any given record, two new Identifiers were created, --LNKID and –LNKGRP.

In the TU dataset, each identified tumor or lesion, target or non-target, is assigned a unique TULNKID that follows that tumor or lesion through its multiple assessments recorded in TR. The TR dataset employs both TRLNKID and TRLNKGRP (in that order) that presents the measurements and assessments for each tumor or lesion identified in TU. The assigning of LNKID should be unique per tumor and “Evaluator” (if somebody in addition to the investigator is assessing the lesion).

The Identifier TRLNKGRP allows for the “linking” of multiple records according to the granularity of evaluation outlined in the protocol. This could be at the “Target” on “Non-Target” level or, most often, simply at the scheduled assessment time point across both target and non-target lesions.

This identification of --LNKID (if required) and –LNKGRP flows into the Response dataset as the investigator (or Independent Assessor) determines the subject’s response to treatment at whatever granularity is required by the protocol.

As will be addressed in the following sections, the use of --LNKID (in particular) has been expanded to other applications than just oncology. It bears emphasizing that, as an identifier, it may be useful in “linking” other records across SDTM domains. Though it originated as an oncology-specific identifier, its utility is recognized far beyond the oncology application. In SDTMIG v3.2, --LNKID and –LNKGRP are found in the EX and EC domains as a means of linking Exposure as Collected records in EC with Exposure records in EX.

These identifiers are often used to establish a RELREC dataset-to-dataset relationship, first between TU and TR, and then subsequently, between TR and RS.

ONCOLOGY EXAMPLES

This TU example shows three “Target” tumors having been identified by both the investigator and an independent assessor. Note the unique TULNKID for those records attributed to the independent assessor (Note: It bears mentioning that the TUDTC is the date of the “Spiral CT” from which the identifications were made):

Row	STUDYID	DOMAIN	USUBJID	TUSEQ	TULNKID	TUTESTCD	TUTEST	TUORRES
1	0606/ABC	TU	013-2486	1	TL01	TUMIDENT	Tumor Identification	TARGET
2	0606/ABC	TU	013-2486	2	TL02	TUMIDENT	Tumor Identification	TARGET
3	0606/ABC	TU	013-2486	3	NTL01	TUMIDENT	Tumor Identification	NON-TARGET
4	0606/ABC	TU	013-2486	4	R-TL01	TUMIDENT	Tumor Identification	TARGET
5	0606/ABC	TU	013-2486	5	R-TL02	TUMIDENT	Tumor Identification	TARGET
6	0606/ABC	TU	013-2486	6	R-NTL01	TUMIDENT	Tumor identification	NON-TARGET
7	0606/ABC	TU	013-2486	7	NEW01	TUMIDENT	Tumor identification	NEW
8	0606/ABC	TU	013-2486	8	R-NEW01	TUMIDENT	Tumor Identification	NEW

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Row	TULOC	TUMETHOD	TUEVAL	VISITNUM	VISIT	TUDTC
1 (Cont)	LIVER	SPIRAL CT	INVESTIGATOR	1	BASELINE	2014-11-01
2 (Cont)	LUNG	SPIRAL CT	INVESTIGATOR	1	BASELINE	2014-11-01
3 (Cont)	BREAST	SPIRAL CT	INVESTIGATOR	1	BASELINE	2014-11-01
4 (Cont)	LIVER	SPIRAL CT	INDEPENDENT ASSESSOR	1	BASELINE	2014-11-01
5 (Cont)	LUNG	SPIRAL CT	INDEPENDENT ASSESSOR	1	BASELINE	2014-11-01
6 (Cont)	BREAST	SPIRAL CT	INDEPENDENT ASSESSOR	1	BASELINE	2014-11-01
7 (Cont)	COLON	SPIRAL CT	INVESTIGATOR	4	CYCLE 2 DAY 28	2014-12-28
8 (Cont)	COLON	SPIRAL CT	INDEPENDENT ASSESSOR	4	CYCLE 2 DAY 28	2014-12-28

Following these same lesions through to TR while also employing TRLNKGRP at the "Visit" level for both the Investigator and Independent Assessor (TRTEST omitted to conserve space):

Row	STUDYID	DOMAIN	USUBJID	TRSEQ	TRLNKID	TRLNKGRP	TRTESTCD	TORRES
1	0606/ABC	TR	013-2486	1	TL01	V1	LDIAM	6.2
2	0606/ABC	TR	013-2486	2	TL02	V1	LDIAM	6.4
3	0606/ABC	TR	013-2486	3	NTL01	V1	TUMSTATE	PRESENT
4	0606/ABC	TR	013-2486	4	R-TL01	R-V1	LDIAM	6.0
5	0606/ABC	TR	013-2486	5	R-TL02	R-V1	LDIAM	6.2
6	0606/ABC	TR	013-2486	6	R-NTL01	R-V1	TUMSTATE	PRESENT
7	0606/ABC	TR	013-2486	7	TL01	V2	LDIAM	5.8
8	0606/ABC	TR	013-2486	8	TL02	V2	LDIAM	6.0
9	0606/ABC	TR	013-2486	9	NTL01	V2	TUMSTATE	PRESENT
10	0606/ABC	TR	013-2486	10	R-TL01	R-V2	LDIAM	5.8
11	0606/ABC	TR	013-2486	11	R-TL02	R-V2	LDIAM	6.0
12	0606/ABC	TR	013-2486	12	R-NTL01	R-V2	TUMSTATE	PRESENT
13	0606/ABC	TR	013-2486	13	NEW01	R-V2	LDIAM	5.2
14	0606/ABC	TR	013-2486	14	R-NEW01	R-V2	LDIAM	5.4

Row	TRORRESU	TRMETHOD	TREVAL	VISITNUM	VISIT	TRDTC
1 (Cont)	mm	SPIRAL CT	INVESTIGATOR	1	BASELINE	2014-11-01
2 (Cont)	mm	SPIRAL CT	INVESTIGATOR	1	BASELINE	2014-11-01
3 (Cont)		SPIRAL CT	INVESTIGATOR	1	BASELINE	2014-11-01
4 (Cont)	mm	SPIRAL CT	INDEPENDENT ASSESSOR	1	BASELINE	2014-11-01
5 (Cont)	mm	SPIRAL CT	INDEPENDENT ASSESSOR	1	BASELINE	2014-11-01
6 (Cont)		SPIRAL CT	INDEPENDENT ASSESSOR	1	BASELINE	2014-11-01
7 (Cont)	mm	SPIRAL CT	INVESTIGATOR	4	CYCLE 2 DAY 28	2014-12-28
8 (Cont)	mm	SPIRAL CT	INVESTIGATOR	4	CYCLE 2 DAY 28	2014-12-28

9 (Cont)		SPIRAL CT	INVESTIGATOR	4	CYCLE 2 DAY 28	2014-12-28
10 (Cont)	mm	SPIRAL CT	INDEPENDENT ASSESSOR	4	CYCLE 2 DAY 28	2014-12-28
11 (Cont)	mm	SPIRAL CT	INDEPENDENT ASSESSOR	4	CYCLE 2 DAY 28	2014-12-28
12 (Cont)		SPIRAL CT	INDEPENDENT ASSESSOR	4	CYCLE 2 DAY 28	2014-12-28
13 (Cont)	mm	SPIRAL CT	INVESTIGATOR	4	CYCLE 2 DAY 28	2014-12-28
14 (Cont)	mm	SPIRAL CT	INDEPENDENT ASSESSOR	4	CYCLE 2 DAY 28	2014-12-28

And then following this data to RS (Notice in our example that --LNKID drops out as the tumor responses are based on Target Lesions as a whole, Non-Target Lesions, and overall response. RSTEST has been omitted to conserve space):

Row	STUDYID	DOMAIN	USUBJID	RSSEQ	RSLNKGRP	RSTESTCD	RSCAT
1	0606/ABC	RS	013-2486	1		TRGRES	RECIST 1.1
2	0606/ABC	RS	013-2486	2		NTRGRES	RECIST 1.1
3	0606/ABC	RS	013-2486	3	V2	OVRLRES	RECIST 1.1
4	0606/ABC	RS	013-2486	4		TRGRES	RECIST 1.1
5	0606/ABC	RS	013-2486	5		NTRGRES	RECIST 1.1
6	0606/ABC	RS	013-2486	6	R-V2	OVRLRES	RECIST 1.1

Row	RSORRES	RSEVAL	VISITNUM	VISIT	RSDTC
1 (Cont)	SD	INVESTIGATOR	4	CYCLE 2 DAY 28	2014-12-28
2 (Cont)	SD	INVESTIGATOR	4	CYCLE 2 DAY 28	2014-12-28
3 (Cont)	SD	INVESTIGATOR	4	CYCLE 2 DAY 28	2014-12-28
4 (Cont)	SD	INDEPENDENT ASSESSOR	4	CYCLE 2 DAY 28	2014-12-28
5 (Cont)	SD	INDEPENDENT ASSESSOR	4	CYCLE 2 DAY 28	2014-12-28
6 (Cont)	SD	INDEPENDENT ASSESSOR	4	CYCLE 2 DAY 28	2014-12-28

RELREC would look like this (dataset to dataset)

STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
0606/ABC	TU		TULNKID		ONE	TUTR
0606/ABC	TR		TRLNKID		MANY	TUTR
0606/ABC	RS		RSLNKGRP		ONE	TRRS
0606/ABC	TR		TRLNKGRP		MANY	TRRS

NON-ONCOLOGY EXAMPLES

As work has proceeded on the Therapeutic Area User Guides, it has become evident that the scope of the "Tumor Domains" needs to be expanded to include other types of lesions than just those in oncology. This will be made clear when SDTMIG v3.3 is published. The current "User Guide for Cardiovascular

Studies” has already made use of this broadened scope. The following text is from the published CV TAUG:

“A lesion can be almost any abnormal change involving any tissue or organ, usually due to disease or injury. The requirements for identifying lesions other than tumors, such as the arterial lesions involved in CV endpoints, were found to be similar to those for tumors. The CDISC SDS Leadership Team decided to expand the scope of the existing TU and TR domains to include non-tumor lesions, rather than to create new domains for non-oncology data. The TU and TR domain names will be revised in the next version of the SDTMIG to Tumor/Lesion Identification (TU) and Tumor/Lesion Results (TR).”

The following is an example from the CV TAUG where Target Lesions have been identified as well as the vessel that the lesion is located in. TR just requires a single record to show the “Lesion Success Indicator (TUTEST and TRTEST have been omitted to conserve space):

Row	STUDYID	DOMAIN	USUBJID	TUSEQ	TULNKID	TUTESTCD	TUORRES	TUSTRESC
1	0606/ABC	TU	013-2486	1	L01	LESIDENT	TARGET	TARGET
2	0606/ABC	TU	013-2486	2	L01-1	VESIDENT	TARGET	TARGET

Row	TULOC	TUMETHOD	VISITNUM	VISIT	TUDTC
1 (Cont)	RIGHT CORONARY ARTERY OSTIUM	CORONARY ANGIOGRAPHY	1.1	UNSCHEDULED	2014-11-01T11:45
2 (Cont)	RIGHT CORONARY ARTERY	CORONARY ANGIOGRAPHY	1.1	UNSCHEDULED	2014-11-01T11:45

Row	STUDYID	DOMAIN	USUBJID	TRSEQ	TRLNKID	TRTESTCD	TRORRES	TRDTC
1	0606/ABC	TR	013-2486	1	L01	LESSCIND	Y	2014-11-01T11:45

Along with this broadening of the usage of TU and TR to include other types of lesions, the RS domain is also due to take on additional meaning by including "Clinical Classifications". As part of SDTMIG v3.3 Batch 3 that is currently in a public review period, "Assumption 2" has this to say regarding clinical classifications:

"Clinical classifications are named measures whose output is an ordinal or categorical score that serves as a surrogate for, or ranking of, disease status, symptoms, or other physiological or biological status. Clinical classifications may be based solely on objective data from clinical records, or they may involve a clinical judgement or interpretation of the directly observable signs, behaviors, or other physical manifestations related to a condition or subject status. These physical manifestations may be findings that are typically represented in other SDTM domains such as labs, vital signs, or clinical events."

As it is now allowable for there to be multiple codelists for a single variable, plans are for there to be multiple clinical classifications codelists, similar to those for Questionnaires. The oncology codelists ONCRTSCD (Response Assessment Test Code) and ONCRSR (Response Assessment Results) will remain oncology specific even as RS takes on this additional scope.

CONCLUSIONS

The tumor domains TU, TR, and RS have been instrumental in providing sponsors with a model for submitting data that identifies and measures target and non-target tumors in the oncology setting. Identifiers such as --LNKID and --LNKGRP that were initially oncology specific are being used as "linking" variables across other domains as needed.

With the advent of the Therapeutic Area User Guides, most notably the Cardiovascular User Guide, the utility of the tumor domains is being expanded to include "lesions" of different types.

The RS domain represents "disease response evaluations" that are based on collected data as well as multiple standard treatment response scales. Plans are under way to also expand the use of RS to include clinical classifications.

Extensive controlled terminology is available for test codes, test names, and results across all three domains.

RESOURCES

- Study Data Tabulation Model. Clinical Data Interchange Standards Consortium (CDISC) Submission Data Standards (SDS) Team, Version 1.4, December 2013.
- Study Data Tabulation Model Implementation Guide: Human Clinical Trials. Clinical Data Interchange Standards Consortium (CDISC) Submission Data Standards (SDS) Team, Version 3.2, December 2013
- The Cardiovascular Therapeutic Area User Guide.
- Controlled Terminology as published by NCI-EVS

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