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Where Is the Link Broken – Another Look at SDTM Oncology Tumor Packages

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ABSTRACT

CDISC published three oncology tumor related domains – Tumor Identification (TU), Tumor Results (TR) and Disease Response (RS) in SDTM IG v3.2 (2013). A general guideline is provided for data regulation and standardization for oncology studies based on RECIST criteria and/or its modifications as well as other assessment criteria (Cheson or Hallek). Essentially three domains do not function independently; instead they have inherent connections and have been linked through –LNKIDs and –LNKGRPs. For example, TRLNKID/TULNKID is used to link assessment records in TR domain with corresponding identification records in TU domain. However, using RSLNKGRP and TRLNKGRP to connect RS and TR might not be sufficient; neither is it clear to group records within RS domain. As an illustration, solely using –LNKGRPs is feasible to connect all the measurements, including those for target/non-target/new lesion responses, in TR domain with respective overall assessment in RS domain at a measurement point. However, it is not straightforward to identify within RS domain which response records contribute to overall response especially when symptomatic deterioration is of interest; nor is it clear of the link of measurements for target/non-target/new lesions in TR domain with corresponding responses in RS domain at a particular visit. Being able to establish/clarify such link relations is not only crucial for keeping traceability within/between domains, but also important for future time-to-event analysis. In this paper, the authors propose a more efficient and accurate way to link TR and RS domain. Furthermore, a modification and extension of using this link logic will be presented as well for studies whose response criteria are not based on RECIST. Examples are provided for illustration purpose.

INTRODUCTION

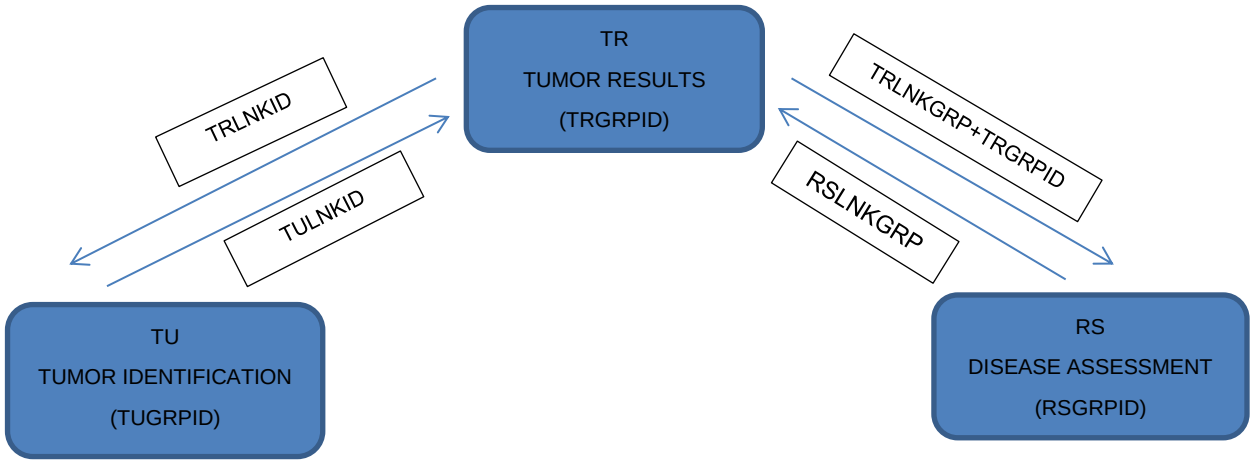
SDTM IG v3.2 (2013) first introduces three oncology related domains, which are mainly based on tumor measurement/RECIST criteria and fall into SDTM Findings Observation Class. These three domains are Tumor Identification (TU), which represents data that uniquely identify tumors; Tumor Results (TR), which records quantitative measurements and/or qualitative assessments of tumors that are identified in TU domain. Last but not least, Disease Response (RS) is the place where saves the response evaluation determined from measurements/assessments in TR. These three domains serve different purposes in terms of functionality whereas they do not exist independently. Instead, there are inherent and integral connections within and between domains. However, the current SDTM IG does not fully depict this special "within-and-between" relations and has its own known limitations, i.e., it is difficult to identify and group records for a given assessment time point in RS domain especially if symptomatic deterioration could be a concern and there is a lack of sufficient link between RS and TR, in particular when it comes to specific response records in RS and their corresponding measurements in TR domain either with or without potential unscheduled assessments.

In this paper, a different way of relating records within and between domains is proposed for current oncology domains, in particular TR and RS. Examples under different scenarios will be given. The discussion and illustrations will be mostly based on assessments guided by RECIST criteria. Last but not least, a novel idea is also presented, which is based on tumor package but applies it to hematological disease, taking Acute Myeloid Leukemia (AML) as an example.

OVERVIEW

This section provides a general overview about the proposed "within and between" link relations. Hypothetical examples are employed for illustration purposes.

Figure 1. Overview of "within-and-between" link relation among TU, TR and RS domains.



As mentioned before, current RS domain lacks sufficient "within-domain" categorization. In the new proposal, **RSGRPID** is used to group responses at a certain assessment time point, for example to classify target response, non-target response, new lesion assessment, symptomatic deterioration (if there are any) as well as the overall response at week 6 (Table 1). In this way, RSGRPID serves the same purpose of grouping related records as TRGRPID in TR domain and TUGRPID in TU domain. As a consequence, a harmonization across domains within tumor package has also been achieved.

Considering the link relationship across domains, RSLNKGRP in RS domain together with TRGRPID and TRLNKGRP in TR domain will be employed. **RSLNKGRP** will be populated with the same values (e. g. A2) for all the records at an assessment point (Table 1). Meanwhile, in TR domain for records from the same assessment point, TRLNKGRP will be populated with exactly the same value as RSLNKGRP (A2 in this case). In such way, a group of measurements for target/non-target/new lesions in TR at week 6 could be connected with a group of corresponding response records (target/non target responses/ new lesion) in RS domain at week 6 (Table 1 and 2). In this sense, -LNKGRP also fulfills its name as "linking group". Further, with the assistance of **TRGRPID**, using TRLNKGRP can also help to identify which measurements in TR domain contribute to the target/non-target responses respectively at a specific measurement. In the given example, it is feasible and clear to use TRGRPID (TARGET) together with TRLNKGRP (A2) from TR domain and RSLNKGRP (A2) in RS domain to pinpoint corresponding target response assessment (TRGRESP) at week 6 (Table 1 and 2).

Table 1 RS domain

RSGRPID	RSLNKGRP	RSTESTCD	RSTEST	RSORRES	VISIT
R1	A2	TRGRESP	Target Response	SD	WEEK 6
R1	A2	NTRGRESP	Non-target Response	CR	WEEK 6
R1	A2	NEWLPROG	New Lesion Progression	UNEQUIVOCAL	WEEK 6
R1	A2	OVRLRESP	Overall Response	PD	WEEK 6

Table 2: TR domain

TRGRPID	TRLNKGRP	TRLNKID	TRTESTCD	TRTEST	TRORRES	TRORRESU	VISIT
TARGET	A2	T01	LIDIAM	Longest Diameter	12	mm	WEEK 6
TARGET	A2	T02	LIDIAM	Longest Diameter	6	mm	WEEK 6
TARGET	A2		SUMLDIAM	Sum of Longest Diameters	18	mm	WEEK 6
NONTARGET	A2	NT01	TUMSTATE	Tumor State	ABSENT		WEEK 6
NEW	A2	NEW01	TUMSTATE	Tumor State	PRESENT		WEEK 6

CASE ILLUSTRATIONS

In this session, guided by the above proposal, examples of different scenarios from clinical trials will be presented.

CASE NO. 1: MEASUREMENTS/RESPONSES FROM INVESTIGATORS ONLY WITHOUT COLLECTING NON-RADIOLOGICAL PROGRESSION/SYMPTOMATIC PROGRESSION.

The illustration starts with a simple case, which has a set of measurements from investigators only. Sometimes, for certain trials, non-radiological progression/symptomatic deterioration might not be of special interest, nor has been collected. As a consequence, such information will not be reflected in below examples. Two assessments were done at week 6 and week 12 respectively (Case 1, table 3). RSGRPID was populated with “R01” and “R02” to group responses within each visit. In addition, RSLNKGRP was populated with the same values as TRLNKGRP in TR domain serving to link groups of records together.

Table 3: Case 1: assessments from investigator WITHOUT collecting non-radiological progressive disease – RS domain.

ROW	STUDYID	DOMAIN	USUBJID	RSSEQ	RSGRPID	RSLNKGRP	RSTESTCD	RSTEST	RSORRESU
1	ABC	RS	ABC123	1	R01	A02	TRGRESP	Target Response	SD
2	ABC	RS	ABC123	2	R01	A02	NTRGRESP	Non-Target Response	Non-CR/Non-PD
3	ABC	RS	ABC123	3	R01	A02	NEWLPROG	New Lesion Progression	EQUIVOCAL
4	ABC	RS	ABC123	4	R01	A02	OVRLRESP	Overall Response	SD
5	ABC	RS	ABC123	5	R02	A03	TRGRESP	Target Response	SD
6	ABC	RS	ABC123	6	R02	A03	NTRGRESP	Non-Target Response	Non-CR/Non-PD
7	ABC	RS	ABC123	7	R02	A03	NEWLPROG	New Lesion Progression	UNEQUIVOCAL
8	ABC	RS	ABC123	8	R02	A03	OVRLRESP	Overall Response	PD

CASE NO. 2: ASSESSMENTS FROM BOTH INVESTIGATORS AND INDEPENDENT REVIEWERS AND COLLECTING NON-RADIOLOGICAL PROGRESSION / SYMPTOMATIC PROGRESSION.

For the majority of trials especially later phase confirmatory trials, independent reviewers will get involved. Most of the time tumor images are the only packages that are sent for independent review. Therefore, information about non-radiological progression would only come from investigators/clinicians. This explains when independent reviewers get involved, symptomatic deterioration results are barely present from their ends. In below example at week 12 (Case 2.1, table 4), there is a clinical progression from investigator

(Table 4, row 12). However there are not such records for independent reviewers since this information is not available. On the other hand, whether non-radiological progression/symptomatic progression would really contribute to overall response assessment also varies among trials. If the overall response is purely based on tumor burden measurements according to RECIST v1.1, as is shown in below case, even though there is a clinical assessment of "Pleural Effusion" from investigators (Table 4, row 12), the overall response will be stable disease instead of progressive disease (Table 4, row 13). Correspondingly, the RSLNKGRP cell in row 12 is not populated since this information has not been considered while assessment is being made.

Table 4 Case 2.1: assessment from both investigators and independent reviewers and collecting non-radiological progression – RS domain.

ROW	STUDYID	DOMAIN	USUBJID	RSSEQ	RSGRPID	RSLNKGRP	RSCAT	RSTESTCD	RSTEST
1	ABC	RS	ABC123	1	R01	A02	RECIST 1.1	TRGRESP	Target Response
2	ABC	RS	ABC123	2	R01	A02	RECIST 1.1	NTRGRESP	Non-Target Response
3	ABC	RS	ABC123	3	R01	A02	RECIST 1.1	NEWLPROG	New Lesion Progression
4	ABC	RS	ABC123	4	R01	A02	RECIST 1.1	OVRLRESP	Overall Response
5	ABC	RS	ABC123	5	R01	R-A02	RECIST 1.1	TRGRESP	Target Response
6	ABC	RS	ABC123	6	R01	R-A02	RECIST 1.1	NTRGRESP	Non-Target Response
7	ABC	RS	ABC123	7	R01	R-A02	RECIST 1.1	NEWLPROG	New Lesion Progression
8	ABC	RS	ABC123	8	R01	R-A02	RECIST 1.1	OVRLRESP	Overall Response
9	ABC	RS	ABC123	9	R02	A03	RECIST 1.1	TRGRESP	Target Response
10	ABC	RS	ABC123	10	R02	A03	RECIST 1.1	NTRGRESP	Non-Target Response
11	ABC	RS	ABC123	11	R02	A03	RECIST 1.1	NEWLPROG	New Lesion Progression
12	ABC	RS	ABC123	12	R02		CLINICAL ASSESSMENT	NRADPROG	Non-Radiological Progression
13	ABC	RS	ABC123	13	R02	A03	RECIST 1.1	OVRLRESP	Overall Response
14	ABC	RS	ABC123	14	R02	R-A03	RECIST 1.1	TRGRESP	Target Response
15	ABC	RS	ABC123	15	R02	R-A03	RECIST 1.1	NTRGRESP	Non-Target Response
16	ABC	RS	ABC123	16	R02	R-A03	RECIST 1.1	NEWLPROG	New Lesion Progression
17	ABC	RS	ABC123	17	R02	R-A03	RECIST 1.1	OVRLRESP	Overall Response

(Cont'd)

ROW	RSORRES	RSSTRESC	RSEVAL	RSEVALID	EPOCH	VISIT	RSDTC	RSDY
1	SD	SD	INVESTIGATOR		TREATMENT	WEEK 6	2017/1/2	42
2	Non-CR/Non-PD	Non-CR/Non-PD	INVESTIGATOR		TREATMENT	WEEK 6	2017/1/2	42
3	EQUIVOCAL	EQUIVOCAL	INVESTIGATOR		TREATMENT	WEEK 6	2017/1/2	42
4	SD	SD	INVESTIGATOR		TREATMENT	WEEK 6	2017/1/2	42
5	SD	SD	INDEPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 6	2017/1/2	42
6	Non-CR/Non-PD	Non-CR/Non-PD	INDEPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 6	2017/1/2	42
7	EQUIVOCAL	EQUIVOCAL	INDEPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 6	2017/1/2	42
8	SD	SD	INDEPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 6	2017/1/2	42
9	SD	SD	INVESTIGATOR		TREATMENT	WEEK 12	2017/2/13	84
10	Non-CR/Non-PD	Non-CR/Non-PD	INVESTIGATOR		TREATMENT	WEEK 12	2017/2/13	84
11	EQUIVOCAL	EQUIVOCAL	INVESTIGATOR		TREATMENT	WEEK 12	2017/2/13	84
12	Pleural Effusion	PD	INVESTIGATOR		TREATMENT	WEEK 12	2017/2/13	84
13	SD	SD	INVESTIGATOR		TREATMENT	WEEK 12	2017/2/13	84
14	SD	SD	INDEPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 12	2017/2/13	84
15	Non-CR/Non-PD	Non-CR/Non-PD	INDEPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 12	2017/2/13	84
16	EQUIVOCAL	EQUIVOCAL	INDEPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 12	2017/2/13	84
17	SD	SD	INDEPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 12	2017/2/13	84

However, for a certain trial, in addition to tumor burdens, symptomatic deterioration/non radiological progression could also be a factor in determining a time point overall response, and the situation will be different. Taking below case as an example (Case 2.2, table 5),compared with previous case, in row 13 the RSCAT cell is populated with “RECIST 1.1/CLINICAL ASSESSMENT” and RSLNKGRP cell is populated with “A03” as well, because in this particular case “Pleural Effusion” from clinical assessment has contributed to the overall response “Progressive Disease”. Meanwhile, RSLNKGRP for row 12 is now filled with “A03” since the overall assessment “Progressive Disease” results from this non radiological progressive disease.

Table 5 Case 2.2: assessment from both investigators and independent reviewers and collecting non-radiological progression – RS domain.

ROW	STUDYID	DOMAIN	USUBJID	RSSEQ	RSGRPID	RSLNKGRP	RSCAT	RSTESTCD	RSTEST
1	ABC	RS	ABC123	1	R01	A02	RECIST 1.1	TRGRESP	Target Response
2	ABC	RS	ABC123	2	R01	A02	RECIST 1.1	NTRGRESP	Non-Target Response
3	ABC	RS	ABC123	3	R01	A02	RECIST 1.1	NEWLPROG	New Lesion Progression
4	ABC	RS	ABC123	4	R01	A02	RECIST 1.1	OVRLRESP	Overall Response
5	ABC	RS	ABC123	5	R01	R-A02	RECIST 1.1	TRGRESP	Target Response
6	ABC	RS	ABC123	6	R01	R-A02	RECIST 1.1	NTRGRESP	Non-Target Response
7	ABC	RS	ABC123	7	R01	R-A02	RECIST 1.1	NEWLPROG	New Lesion Progression
8	ABC	RS	ABC123	8	R01	R-A02	RECIST 1.1	OVRLRESP	Overall Response
9	ABC	RS	ABC123	9	R02	A03	RECIST 1.1	TRGRESP	Target Response
10	ABC	RS	ABC123	10	R02	A03	RECIST 1.1	NTRGRESP	Non-Target Response
11	ABC	RS	ABC123	11	R02	A03	RECIST 1.1	NEWLPROG	New Lesion Progression
12	ABC	RS	ABC123	12	R02	A03	CLINICAL ASSESSMENT	NRADPROG	Non-Radiological Progression
13	ABC	RS	ABC123	13	R02	A03	RECIST 1.1 /CLINICAL ASSESSMENT	OVRLRESP	Overall Response
14	ABC	RS	ABC123	14	R02	R-A03	RECIST 1.1	TRGRESP	Target Response
15	ABC	RS	ABC123	15	R02	R-A03	RECIST 1.1	NTRGRESP	Non-Target Response
16	ABC	RS	ABC123	16	R02	R-A03	RECIST 1.1	NEWLPROG	New Lesion Progression
17	ABC	RS	ABC123	17	R02	R-A03	RECIST 1.1	OVRLRESP	Overall Response

(Cont’d)

ROW	RSORRES	RSSTRESC	RSEVAL	RSEVALID	EPOCH	VISIT	RSDTC	RSDY
1	SD	SD	INVESTIGATOR		TREATMENT	WEEK 6	2017/1/2	42
2	Non-CR/Non-PD	Non-CR/Non-PD	INVESTIGATOR		TREATMENT	WEEK 6	2017/1/2	42
3	EQUIVOCAL	EQUIVOCAL	INVESTIGATOR		TREATMENT	WEEK 6	2017/1/2	42
4	SD	SD	INVESTIGATOR		TREATMENT	WEEK 6	2017/1/2	42
5	SD	SD	INDEPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 6	2017/1/2	42
6	Non-CR/Non-PD	Non-CR/Non-PD	INDEPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 6	2017/1/2	42
7	EQUIVOCAL	EQUIVOCAL	INDEPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 6	2017/1/2	42
8	SD	SD	INDEPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 6	2017/1/2	42
9	SD	SD	INVESTIGATOR		TREATMENT	WEEK 12	2017/2/13	84
10	Non-CR/Non-PD	Non-CR/Non-PD	INVESTIGATOR		TREATMENT	WEEK 12	2017/2/13	84
11	EQUIVOCAL	EQUIVOCAL	INVESTIGATOR		TREATMENT	WEEK 12	2017/2/13	84
12	Pleural Effusion	PD	INVESTIGATOR		TREATMENT	WEEK 12	2017/2/13	84
13	PD	PD	INVESTIGATOR		TREATMENT	WEEK 12	2017/2/13	84
14	SD	SD	INDEPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 12	2017/2/13	84
15	Non-CR/Non-PD	Non-CR/Non-PD	INDEPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 12	2017/2/13	84
16	EQUIVOCAL	EQUIVOCAL	INDEPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 12	2017/2/13	84
17	SD	SD	INDEPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 12	2017/2/13	84

CASE NO. 3: FOR MULTIPLE MEASUREMENTS (FROM EITHER INVESTIGATORS OR INDEPENDENT REVIEWERS) AT A CERTAIN ASSESSMENT TIME POINT, ONLY A SUBSET OF THOSE MEASUREMENTS HAS BEEN SELECTED FOR RESPONSES.

In real life, data are not always perfect and as what we expect. Sometimes, the measurement at a scheduled visit might not be considered valid to be used for diagnosis. Under such circumstances, unscheduled visits could happen and there come the repeated/multiple measurements for certain lesions. For cases like this, special attention needs to be paid while establishing between domain relationships. The measurement records in TR domain that do not contribute to response assessments will not have TRLNKGRP populated as is shown in row 2 of table 6. Instead, the measurement from the unscheduled visit (row 3) will be selected and TRLNKGRP is populated with "A02", meaning this record is used for diagnosis.

Table 6 Case 3: for multiple assessments from either investigators or independent reviewers only a subset of measurements has been used for diagnosis – TR domain.

ROW	STUDYID	DOMAIN	USUBJID	TRSEQ	TRGRPID	TRLNKID	TRLNKGRP	TRTESTCD	TRTEST
1	ABC	TR	ABC123	1	TARGET	T01	A02	LDIAM	Longest Diameter
2	ABC	TR	ABC123	2	TARGET	T02		LDIAM	Longest Diameter
3	ABC	TR	ABC123	3	TARGET	T02	A02	LDIAM	Longest Diameter
4	ABC	TR	ABC123	4	TARGET	T03	A02	LDIAM	Longest Diameter
5	ABC	TR	ABC123	5	TARGET	T03.1	A02	LDIAM	Longest Diameter
6	ABC	TR	ABC123	6	TARGET	T03.2	A02	LDIAM	Longest Diameter
7	ABC	TR	ABC123	7	TARGET		A02	SUMLDIAM	Sum of Longest Diameter
8	ABC	TR	ABC123	8	NON-TARGET	NT01	A02	TUMSTATE	Tumor State
9	ABC	TR	ABC123	9	NON-TARGET	NT02	A02	TUMSTATE	Tumor State
10	ABC	TR	ABC123	10	NEW	NEW01	A02	TUMSTATE	Tumor State
11	ABC	TR	ABC123	11	TARGET	R-T01	R-A02	LDIAM	Longest Diameter
12	ABC	TR	ABC123	12	TARGET	R-T02	R-A02	LDIAM	Longest Diameter
13	ABC	TR	ABC123	13	TARGET	R-T03	R-A02	LDIAM	Longest Diameter
14	ABC	TR	ABC123	14	TARGET	R-T03.1	R-A02	LDIAM	Longest Diameter
15	ABC	TR	ABC123	15	TARGET	R-T03.2	R-A02	LDIAM	Longest Diameter
16	ABC	TR	ABC123	16	TARGET		R-A02	SUMLDIAM	Sum of Longest Diameter
17	ABC	TR	ABC123	17	NON-TARGET	R-NT01	R-A02	TUMSTATE	Tumor State
18	ABC	TR	ABC123	18	NON-TARGET	R-NT02	R-A02	TUMSTATE	Tumor State
19	ABC	TR	ABC123	19	NEW	R-NEW01	R-A02	TUMSTATE	Tumor State

(Cont'd)

ROW	TRORRES	TRORRESU	TRSTRESC	TRSTRESN	TRSTRESU	TRMETHOD	TRSTAT	TRREASND
1	10	mm	10	10	mm	MRI		
2	8	mm	8	8	mm	MRI		
3	5	mm	5	5	mm	MRI		
4						MRI	NOT DONE	TUMOR SPLIT
5	2	mm	2	2	mm	MRI		
6	8	mm	8	8	mm	MRI		
7	25	mm	25	25	mm	MRI		
8	PRESENT		PRESENT			MRI		
9	PRESENT		PRESENT			MRI		
10	EQUIVOCAL		EQUIVOCAL			MRI		
11	9	mm	9	9	mm	MRI		
12	6	mm	6	6	mm	MRI		
13						MRI	NOT DONE	TUMOR SPLIT
14	2.5	mm	2.5	2.5	mm	MRI		
15	7.5	mm	7.5	7.5	mm	MRI		
16	25	mm	25	25	mm	MRI		
17	PRESENT		PRESENT			MRI		
18	PRESENT		PRESENT			MRI		
19	EQUIVOCAL		EQUIVOCAL			MRI		

(Cont'd)

ROW	TREVAL	TREVALID	EPOCH	VISIT	TRDTC	TRDY
1	INVESTIGATOR		TREATMENT	WEEK 6	2017/1/2	42
2	INVESTIGATOR		TREATMENT	WEEK 6	2017/1/2	42
3	INVESTIGATOR		TREATMENT	WEEK 6 UNSCHEDULE 01	2017/1/3	43
4	INVESTIGATOR		TREATMENT	WEEK 6	2017/1/2	42
5	INVESTIGATOR		TREATMENT	WEEK 6	2017/1/2	42
6	INVESTIGATOR		TREATMENT	WEEK 6	2017/1/2	42
7	INVESTIGATOR		TREATMENT	WEEK 6	2017/1/2	42
8	INVESTIGATOR		TREATMENT	WEEK 6	2017/1/2	42
9	INVESTIGATOR		TREATMENT	WEEK 6	2017/1/2	42
10	INVESTIGATOR		TREATMENT	WEEK 6	2017/1/2	42
11	INDPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 6	2017/1/2	42
12	INDPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 6	2017/1/2	42
13	INDPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 6	2017/1/2	42
14	INDPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 6	2017/1/2	42
15	INDPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 6	2017/1/2	42
16	INDPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 6	2017/1/2	42
17	INDPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 6	2017/1/2	42
18	INDPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 6	2017/1/2	42
19	INDPENDENT REVIEWER	RADIOLOGIST	TREATMENT	WEEK 6	2017/1/2	42

CASE NO. 4: DIFFERENT CRITERIA OTHER THAN RECIST V1.1 BUT USING SIMILAR SET OF MEASUREMENTS (IR-RECIST AS AN EXAMPLE)

With the rapid drug development in oncology, currently cancer immunotherapy gains more and more popularity. Accordingly, there are certain response criteria developed that use quite similar set of measurements, for example the modified immune related response criteria (Bohnsack, Hoops & Ludajic, 2014) shares similar sets of measurements as traditional RECIST to make a diagnosis. However, discrepancies exist as well. In terms of tumor burdens, the most significant difference between RECIST and irRECIST is how to handle newly appeared lesions. As is well known, based on RECIST (Eisenhauer, 2009), if a new lesion comes up and is considered unequivocal progressive, patients will be considered to have progressive disease and need to be removed from treatment. However, taking irRECIST for example, if there is a measureable new lesion, the patient might not necessarily be considered as developing progressive disease due to the special "immune-related" mechanism of action. Instead, the new measurable lesions will be measured and incorporated into total measurements of tumor burden (TMTB). Based on the new tumor burden which combines both target lesions and measureable new lesions, a response will be given accordingly. On the other hand if non measureable new lesions appear, according to irRECIST, the investigators or clinicians will make a judgment based on the size or number of the new lesions and decide whether the new lesions are massive enough to result in a progressive disease. With this novel idea in mind, TR and RS are updated accordingly to accommodate this new approach of handling newly appeared lesions. Unlike previously just presenting the tumor state of new lesions, if measurable, new lesions will be recorded quantitatively, as is shown below in TR domain row 8 (Case 4.1, table 8). Since the same sets of measurements have been used to get responses based on two criteria, in this case RSCAT is employed to distinguish which response is from RECIST and which is from irRECIST.

If a new measurable lesion shows up, as is shown in case 4.1(Table 7 and 8), the longest diameters will be measured and combined into the sum of diameters for target lesions. In this case at this time point assessment, after the measurable lesion has been counted into TMTB, the response for target lesion still qualifies for "irSD" and therefore the overall response is "irSD" as well given "irNN" for non-target lesion response (Table 7, row 5 to 7). Since the new measurable lesion has already been incorporated into total

measurements of tumor burden, there will not be additional records for new lesions progression in RS domain (Table 7). For this particular case, even based on the same set of measurements, overall responses are different while applying RECIST (PD) and irRECIST (irSD) due to different approaches of handling new lesions.

Table 7 Case 4.1: Similar measurements but based on different criteria (RECIST and irRECIST) with new measurable lesions – RS domain.

ROW	STUDYID	DOMAIN	USUBJID	RSSEQ	RSGRPID	RSLNKGRP	RSCAT	RSTESTCD	RSTEST
1	ABC	RS	ABC123	1	R01	A02	RECIST 1.1	TRGRESP	Target Response
2	ABC	RS	ABC123	2	R01	A02	RECIST 1.1	NTRGRESP	Non-Target Response
3	ABC	RS	ABC123	3	R01	A02	RECIST 1.1	NEWLPROG	New Lesion Progression
4	ABC	RS	ABC123	4	R01	A02	RECIST 1.1	OVRLRESP	Overall Response
5	ABC	RS	ABC123	5	R01	A02	irRECIST	TRGRESP	Target Response
6	ABC	RS	ABC123	6	R01	A02	irRECIST	NTRGRESP	Non-Target Response
7	ABC	RS	ABC123	7	R01	A02	irRECIST	OVRLRESP	Overall Response

(Cont'd)

ROW	RSSTRESC	EPOCH	VISIT	RSDTC	RSDY
1	SD	TREATMENT	WEEK 6	2017/1/2	42
2	Non-CR/Non-PD	TREATMENT	WEEK 6	2017/1/2	42
3	UNEQUIVOCAL	TREATMENT	WEEK 6	2017/1/2	42
4	PD	TREATMENT	WEEK 6	2017/1/2	42
5	irSD	TREATMENT	WEEK 6	2017/1/2	42
6	irNN	TREATMENT	WEEK 6	2017/1/2	42
7	irSD	TREATMENT	WEEK 6	2017/1/2	42

Table 8 Case 4.1: Similar measurements but based on different criteria (RECIST and irRECIST) with new measurable lesions – TR domain.

ROW	STUDYID	DOMAIN	USUBJID	TRSEQ	TRGRPID	TRLNKID	TRLNKGRP	TRTESTCD	TRTEST
1	ABC	TR	ABC123	1	TARGET	T01	A02	LDIAM	Longest Diameter
2	ABC	TR	ABC123	2	TARGET	T02	A02	LDIAM	Longest Diameter
3	ABC	TR	ABC123	3	TARGET	T03	A02	SAXIS	Short Axis
4	ABC	TR	ABC123	4	TARGET	T03.1	A02	SAXIS	Short Axis
5	ABC	TR	ABC123	5	TARGET	T03.2	A02	SAXIS	Short Axis
6	ABC	TR	ABC123	6	NON-TARGET	NT01	A02	TUMSTATE	Tumor State
7	ABC	TR	ABC123	7	NON-TARGET	NT02	A02	TUMSTATE	Tumor State
8	ABC	TR	ABC123	8	NEW	NEW01	A02	LDIAM	Longest Diameter

(Cont'd)

ROW	TRORRES	TRORRESU	TRSTRESC	TRSTRESN	TRSTRESU	TRMETHOD	TRSTAT	TRREASND
1	5	mm	5	5	mm	MRI		
2	5	mm	5	5	mm	MRI		
3						MRI	NOT DONE	TUMOR SPLIT
4	7	mm	7	7	mm	MRI		
5	8	mm	8	8	mm	MRI		
6	PRESENT		PRESENT			MRI		
7	PRESENT		PRESENT			MRI		
8	6	mm	6	6	mm	MRI		

Sometimes, newly appeared lesions might not be all measurable, take case 4.2 for example (Table 9 and 10). For situations like this, qualitative evaluation for tumor state is necessary (Table 10, row 8). In below example, two new lesions appear – one is measureable with longest diameter 6mm whereas the other one is not measureable and recorded as "PRESENT" qualitatively. As mentioned earlier, measureable new lesion has been counted into TMTB and contribute to target response "irSD". Meanwhile, investigators consider the non-measureable lesion is substantially progressive to be qualified as unequivocal progression (Table 9, row 7) and therefore leads to the overall response "irPD" at this assessment time point (Table 9, row 8). Compared with case 4.1, there is one more record for "New Lesion Progression" in RS domain, which comes from the assessment for non-measurable new lesion. As illustrated, two new lesions contribute to overall response in different way according to irRECIST (2014).

Table 9 Case 4.2: Similar measurements but based on different criteria with new non-measurable and measurable lesions – RS domain.

ROW	STUDYID	DOMAIN	USUBJID	RSSEQ	RSGRPID	RSLNKGRP	RSCAT	RSTESTCD	RSTEST
1	ABC	RS	ABC123	1	R01	A02	RECIST 1.1	TRGRESP	Target Response
2	ABC	RS	ABC123	2	R01	A02	RECIST 1.1	NTRGRESP	Non-Target Response
3	ABC	RS	ABC123	3	R01	A02	RECIST 1.1	NEWLPROG	New Lesion Progression
4	ABC	RS	ABC123	4	R01	A02	RECIST 1.1	OVRLRESP	Overall Response
5	ABC	RS	ABC123	5	R01	A02	irRECIST	TRGRESP	Target Response
6	ABC	RS	ABC123	6	R01	A02	irRECIST	NTRGRESP	Non-Target Response
7	ABC	RS	ABC123	7	R01	A02	irRECIST	NEWLPROG	New Lesion Progression
8	ABC	RS	ABC123	8	R01	A02	irRECIST	OVRLRESP	Overall Response

(Cont'd)

ROW	RSSTRESC	EPOCH	VISIT	RSDTC	RSDY
1	SD	TREATMENT	WEEK 6	2017/1/2	42
2	Non-CR/Non-PD	TREATMENT	WEEK 6	2017/1/2	42
3	UNEQUIVOCAL	TREATMENT	WEEK 6	2017/1/2	42
4	PD	TREATMENT	WEEK 6	2017/1/2	42
5	irSD	TREATMENT	WEEK 6	2017/1/2	42
6	irNN	TREATMENT	WEEK 6	2017/1/2	42
7	UNEQUIVOCAL	TREATMENT	WEEK 6	2017/1/2	42
8	irPD	TREATMENT	WEEK 6	2017/1/2	42

Table 10 Case 4.2: Similar measurements but based on different criteria (RECIST and irRECIST) with new non-measurable and measurable lesions – TR domain.

ROW	STUDYID	DOMAIN	USUBJID	TRSEQ	TRGRPID	TRLNKID	TRLNKGRP	TRTESTCD	TRTEST
1	ABC	TR	ABC123	1	TARGET	T01	A02	LDIAM	Longest Diameter
2	ABC	TR	ABC123	2	TARGET	T02	A02	LDIAM	Longest Diameter
3	ABC	TR	ABC123	3	TARGET	T03	A02	SAXIS	Short Axis
4	ABC	TR	ABC123	4	TARGET	T03.1	A02	SAXIS	Short Axis
5	ABC	TR	ABC123	5	TARGET	T03.2	A02	SAXIS	Short Axis
6	ABC	TR	ABC123	6	NON-TARGET	NT01	A02	TUMSTATE	Tumor State
7	ABC	TR	ABC123	7	NON-TARGET	NT02	A02	TUMSTATE	Tumor State
8	ABC	TR	ABC123	8	NEW	NEW01	A02	TUMSTATE	Tumor State
9	ABC	TR	ABC123	9	NEW	NEW02	A02	LDIAM	Longest Diameter

(Cont'd)

ROW	TRORRES	TRORRESU	TRSTRESC	TRSTRESN	TRSTRESU	TRMETHOD	TRSTAT	TRREASND
1	5	mm	5	5	mm	MRI		
2	5	mm	5	5	mm	MRI		
3						MRI	NOT DONE	TUMOR SPLIT
4	7	mm	7	7	mm	MRI		
5	8	mm	8	8	mm	MRI		
6	PRESENT		PRESENT			MRI		
7	PRESENT		PRESENT			MRI		
8	PRESENT		PRESENT			MRI		
9	6	mm	6	6	mm	MRI		

All cases presented in this section are based on irRECIST (2014). Aforementioned, there are quite a few other recommendations coming up about handling tumor burdens/responses in cancer immunotherapy by the time this paper is written, such as the newly published iRECIST (Seymour, 2017), which might require additional modification since instead of incorporating new measurable lesions into TMTB, a different approach of handling new lesions has been proposed and deserve additional attention.

CASE NO. 5: AN EXTENSION TO HEMATOLOGICAL DISEASE—AML AS AN EXAMPLE

There are some hematological diseases whose response criteria, such as Acute Myeloid Leukemia, are different from solid tumors. One of the distinctive features is there are no tumor burdens. Instead, percent of blasts, either in bone marrow or peripheral blood becomes a crucial factor in making a diagnosis. This being said, the tumor package provided by CIDSC SDTM IG might not be appropriate for some hematological diseases. In addition, for most hematological diseases, lab test results, such as neutrophil counts, platelet counts, etc., are integral elements while making a diagnosis. Such information is recorded in LB domain, which requires a RELREC relationship to be established. Therefore, in this session, a modification of the tumor packages is proposed and extended to diseases that do not have tumor burdens. Instead of TU and TR, a new domain BD, which shares the same data structures as other finding domains, comes to existence. Similar to what has been proposed for establishing within-and-between relationship in TU/TR/RS, -GRPID is used to categorize group of related records within domain, and -LNKGRP is used to link measurements in BD domain with response records in RS domain.

A few potential parameters to be included in BD domain are shown as below:

1. Bone marrow blasts from both central review and investigator at each measurement time point;
2. Peripheral blasts in blood from both central review and investigator at each measurement time point;
3. Auer rods status from both central review and investigator at each measurement time point;
4. Baseline extramedullary disease status;
5. Clinical judgment of progression from investigator at each measurement time point;
6. Appearance of new extramedullary disease from investigator;
7. Whether the patient has peripheral blood progression based on investigator's judgment.

Some parameters (such as Auer rods or peripheral blasts in blood) might also be mapped to LB domain. In the example below the authors prefer to keep them in BD domain since on one hand, they are crucial factors in deciding objective responses (complete remission or complete remission with incomplete blood cell recovery) and need to be highlighted; on the other hand, it is not efficient to put too much information into RELREC dataset, which might cause unexpected and unnecessary problems while establishing link relationship.

Table 11 Case 5: An extension to AML – BD domain.

ROW	STUDYID	DOMAIN	USUBJID	BDSEQ	BDGRPID	BDLNKGRP	BDTESTCD	BDTEST
1	ABC	BD	ABC123	1	BD01	INVRS25	AUERRODS	Auer Rods
2	ABC	BD	ABC123	2	BD01	INVRS25	BMBLAST	Bone Marrow Blast

3	ABC	BD	ABC123	3	BD01	INVRS25	PBBLAST	Peripheral Blast in Blood
4	ABC	BD	ABC123	4	BD01	INVRS25	BEXTREM	Baseline Extramedullary Disease
5	ABC	BD	ABC123	5	BD01	INVRS25	CLINPD	Clinical Assessment
6	ABC	BD	ABC123	6	BD01	INVRS25	NEWEXTRE	New Extramedullary Disease
7	ABC	BD	ABC123	7	BD01	INVRS25	PBPD	Peripheral Blood Progression
8	ABC	BD	ABC123	8	BD01	CRERS25	AUERRODS	Auer Rods
9	ABC	BD	ABC123	9	BD01	CRERS25	BMBLAST	Bone Marrow Blast
10	ABC	BD	ABC123	10	BD01	CRERS25	PBBLAST	Peripheral Blast in Blood

(Cont'd)

ROW	BDORRES	BDORRESU	BDSTRESC	BDSTRESN	BDSTRESU	BDNAM	BDEVAL
1	ABSENT		ABSENT				INVESTIGATOR
2	4	%	4	4	%		INVESTIGATOR
3	0	%	0	0	%		INVESTIGATOR
4	ABSENT		ABSENT				INVESTIGATOR
5	N		N				INVESTIGATOR
6	N		N				INVESTIGATOR
7	N		N				INVESTIGATOR
8	ABSENT		ABSENT			QUEST	INDEPENDENT REVIEWER
9	4	%	4	4	%	QUEST	INDEPENDENT REVIEWER
10	0	%	0	0	%	QUEST	INDEPENDENT REVIEWER

RS domain in this case is similar to what has been presented in tumor package. RSGRPID groups responses from both investigator and central review at Cycle 2 Visit 5 together within RS domain. RSLNKGRP and BDLNKGRP serve to link groups of measurements in BD domain with responses in RS domain for investigators and central reviewers respectively. Another noticing fact is about RSCAT. The diagnosis criteria published in BLOOD by international working group in 2010 is the criterion that is used for evaluating response assessments for this particular example.

Table 12 Case 5: an extension to AML – RS domain.

ROW	STUDYID	DOMAIN	USUBJID	RSSEQ	RSGRPID	RSLNKGRP	RSTESTCD	RSTEST	RSCAT
1	ABC	RS	ABC123	1	R01	INVRS25	RESPINV	Response from Investigator	IWG2010
2	ABC	RS	ABC123	2	R01	CRERS25	RESPCREV	Response from Central Review	IWG2010

(Cont'd)

ROW	RSORRES	RSSTRESC	RSEVAL	VISITNUM	VISIT	EPOCH	RSDTC	VISITDY
1	CRi	CRi	INVESTIGATOR	25	Cycle 2 Visit 5	TREATMENT	2013-05-21	47
2	CRi	CRi	INDEPENDENT REVIEWER	25	Cycle 2 Visit 5	TREATMENT	2013-05-21	47

In addition to measurements recorded in BD domain, additional information from other domains, such lab tests results from LB domain, blood transfusion from CM domain, all contributed to response evaluation. Below is a simple example of the RELREC relations at cycle 2 visit 5.

Table 13 Case 5: an extension to AML – RELREC.

STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
ABC	RS	ABC123	RSSEQ	1		1
ABC	LB	ABC123	LBSEQ	11		1
ABC	LB	ABC123	LBSEQ	12		1
ABC	RS	ABC123	RSLNKGRP		ONE	2
ABC	BD	ABC123	BDLNKGRP		MANY	2

ABC	RS	ABC123	RSSEQ	1		3
ABC	CM	ABC123	CMSEQ	5		3
ABC	RS	ABC123	RSSEQ	2		4
ABC	LB	ABC123	LBSEQ	11		4
ABC	LB	ABC123	LBSEQ	12		4
ABC	RS	ABC123	RSLNKGRP		ONE	5
ABC	BD	ABC123	BDLNKGRP		MANY	5
ABC	RS	ABC123	RSSEQ	2		6
ABC	CM	ABC123	CMSEQ	5		6

CONCLUSION

In this paper, the authors present a different way of relating in-and-between domains for current oncology domains, in particular TR and RS. Examples under different scenarios have been presented not only based on RECIST but also its modification irRECIST. Last but not least, the authors also presented a novel idea, which is based on tumor package but extends it to hematological disease, taking Acute Myeloid Leukemia (AML) as an example.

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CDISC Study Data Tabulation Model Implementation Guideline (SDTMIG V 3.2) available at www.cdisc.org

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