Paper DH04

Overcoming difficulties in implementing RECSIT criteria

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ABSTRACT

RECIST criteria (Response Evaluation Criteria in solid Tumors) are guidelines to evaluate the tumor progression or response to therapy. In most oncology studies the tumor burden is evaluated using the RECIST criteria.
The guidelines are easy to understand but implementing them is not. Tumors might split or merge, disappear and reappear, measurements might be missing, the investigator might have used another imaging method, a tumor might have shrunk below the limit for the measurement method. In some cases tumors are not easy to measure.
This paper discusses pitfalls we should be aware of and checks we can implement, how RECIST reacted with the revised version 1.1 and how it is implemented in the new CDISC tumor domains

INTRODUCTION

Tumor shrinkage (response) and time to progression are important endpoints in clinical trials. To get a widely accepted standardized set of guidelines an international working group was formed in 1990. The resulting RECIST criteria were published in 2000. They are based on an anatomical unidimensional measurement of the tumor burden. RECIST1.1 was published in January 2009 to address issues that arose during implementation of RECIST 1.0. With upcoming new technologies there are ongoing discussions regarding whether it is time to move to a volumetric or functional assessment.

OVERVIEW OF THE GUIDELINES

The guidelines discuss

- When is a measurable lesion regarded as target lesion and how many lesions can be defined as target lesion
- What is regarded as non-target lesion or as a new lesion
- Baseline documentation of lesions
- Assessment methods
- How progression or response will be calculated (target lesions non-target lesions new lesions overall)
- Frequency of tumor evaluation
- Confirmatory measurements

MOST IMPORTANT RULES

- Same imaging methods need to be used for a lesion during the whole study to ensure comparability between the measurements
- Lesions need to be followed during the whole study even if it disappears, splits or merge with other lesions. If a measurement of one lesion is missing the overall assessment is not assessable
- New lesions need to be defined as a new lesion. A split of a lesion is not regarded as new lesion. A lesion that disappeared and reappeared is not regarded as new lesion (according to RECIST 1.1)
- The sum of longest diameter (1 dimensional) is used to asses target lesions.

Overall Response is defined as:

Target lesions	Non-Target lesions	New lesions	Overall Response
CR	CR	No	CR
CR	NC	No	PR
PR	CR or NC	No	PR
SD	CR or NC	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = Complete response, PR = Partial response, SD = Stable disease, NC = No change and PD = Progressive disease

This paper is not regarded as training about RECIST. To learn about the complete guidelines please follow link to the guidelines in the references

COMMON ISSUES WHILE IMPLEMENTING RECIST

1) A Tumor might not have been measured with the same method or measurements might be missing
2) A Tumor might have split or merged.
3) The longest diameter can get very small. Progression is defined as 20% increase from the lowest preceding value (NADIR). If the value approaches 0 the increase of 20 % is not really measurable. This causes incorrect interpretation of the result.
4) A lesion might disappear and reappear.
5) Assessing affected lymphnodes needs some special attention as lymphnodes are also normal structures that can be measured.
6) Lesions might change the shape
7) Lesions might become inevaluable.

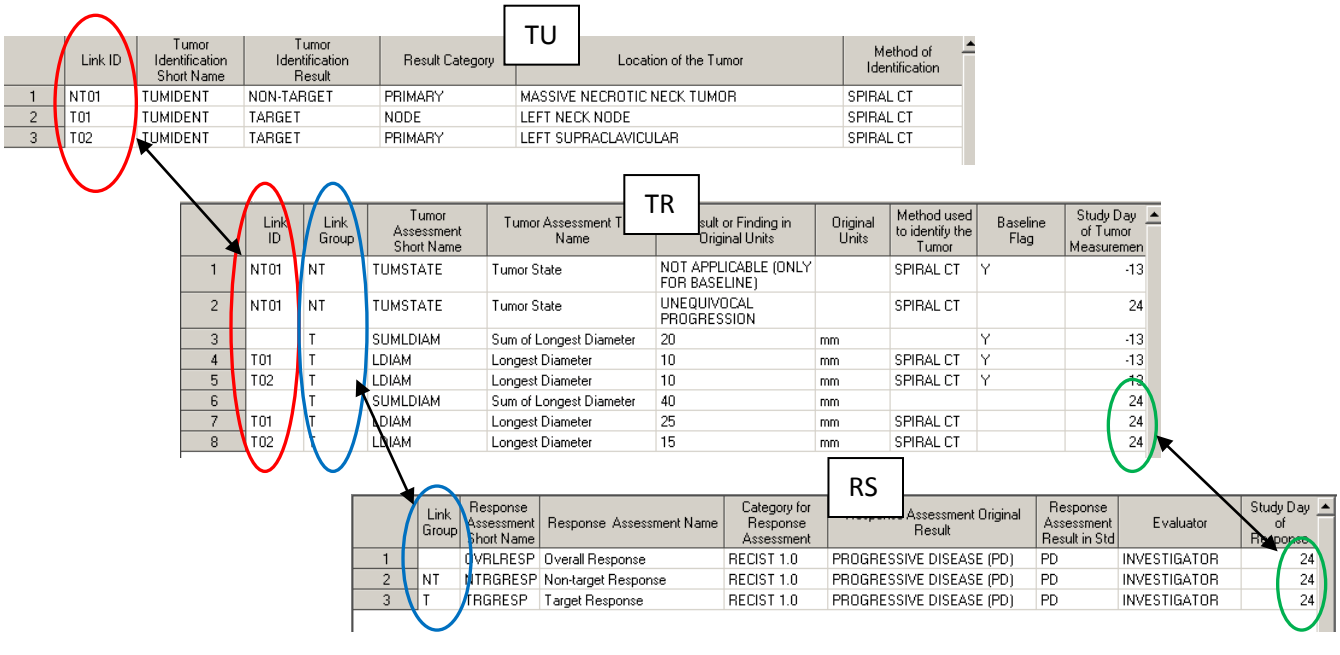
IMPLEMENTAION IN THE CDISC TUMOR DOMAINS

CDISC came up with 3 new SDTM tumor domains and most of the possible issues are addressed in these domains. All tumor domains are findings structure but with additional linking variables to link all tumor domains, acceptance and assessor variables that are needed in case of independent read and special anatomical variables.

- TU – Tumor identification: In this domain every lesion is captured once with a unique ID. Here all lesion specific details are described, such as description of the lesion, location of the lesion, imaging method to be used.
- TR – Tumor Results. Here all measurements of the lesions are captured by timepoint including the method that has been used in a visit. The longest diameter for target lesions, the assessment for non-target lesions, the sum of longest diameter for target lesions if it is captured in the CRF. It does not include derived parameter
- RS – Response. Here we find all response assessments: Target response, non-target response, overall response, best overall response, but also assessments that are not coming from the tumor domains like symptomatic deterioration or non-radiological progression

The domains are linked with RELREC

RDOMAIN	IDVAR	IDVARVAL	RELTYPE	RELID
RS	RSLNKGRP		ONE	RS-TR
TR	TRLNKGRP		MANY	RS-TR
TR	TRLNKID		MANY	TU-TR
TU	TULNKID		ONE	TU-TR



	Link ID	Tumor Identification Short Name	Tumor Identification Result	Result Category	Location of the Tumor	Method of Identification
1	NT01	TUMIDENT	NON-TARGET	PRIMARY	MASSIVE NECROTIC NECK TUMOR	SPIRAL CT
2	T01	TUMIDENT	TARGET	NODE	LEFT NECK NODE	SPIRAL CT
3	T02	TUMIDENT	TARGET	PRIMARY	LEFT SUPRACLAVICULAR	SPIRAL CT

	Link ID	Link Group	Tumor Assessment Short Name	Tumor Assessment T Name	sult or Finding in Original Units	Original Units	Method used to identify the Tumor	Baseline Flag	Study Day of Tumor Measuremen
1	NT01	NT	TUMSTATE	Tumor State	NOT APPLICABLE (ONLY FOR BASELINE)		SPIRAL CT	Y	-13
2	NT01	NT	TUMSTATE	Tumor State	UNEQUIVOCAL PROGRESSION		SPIRAL CT		24
3		T	SUMLDIAM	Sum of Longest Diameter	20	mm		Y	-13
4	T01	T	LDIAM	Longest Diameter	10	mm	SPIRAL CT	Y	-13
5	T02	T	LDIAM	Longest Diameter	10	mm	SPIRAL CT	Y	-13
6		T	SUMLDIAM	Sum of Longest Diameter	40	mm			24
7	T01	T	LDIAM	Longest Diameter	25	mm	SPIRAL CT		24
8	T02	T	LDIAM	Longest Diameter	15	mm	SPIRAL CT		24

	Link Group	Response Assessment Short Name	Response Assessment Name	Category for Response Assessment	Assessment Original Result	Response Assessment Result in Std	Evaluator	Study Day of
1		OVRLRESP	Overall Response	RECIST 1.0	PROGRESSIVE DISEASE (PD)	PD	INVESTIGATOR	24
2	NT	NTRGRESP	Non-target Response	RECIST 1.0	PROGRESSIVE DISEASE (PD)	PD	INVESTIGATOR	24
3	T	TRGRESP	Target Response	RECIST 1.0	PROGRESSIVE DISEASE (PD)	PD	INVESTIGATOR	24

HANDLING THE ISSUES

1) Check if all measurements are available and if the method has been used

Merge TU, TR and RS domains. Make sure that all lesions in TU are in every visit of TR and vice versa. Check that the RS entries are matching as well. Make sure that TUMETHOD = TRMETHOD
A measurement that has been measured with another method cannot be used, it is not comparable. If the measurement of one single lesion is not available the sum of longest diameter cannot be calculated

```
proc sql;
  create table tumortest as select
     coalesce(a.usubjid, b.usubjid,c.usubjid) as usubjid,
     tulnkid, trlnkid, trlnkgrp, rslnkgrp, tumethod, trmethod,
     tudy, trdy, rsdy, b.visitnum as trvisitnum, c.visitnum as rsvisitnum
  from sdtm.tu as   a
  full join sdtm.tr(where=(trtestcd ne "SUMLDIAM")) as b
    on a.usubjid = b.usubjid and
          tulnkid = trlnkid
  full join sdtm.rs(where=(rstestcd ne "OVRLRESP")) as c
    on a.usubjid = c.usubjid and
         trlnkgrp = rslnkgrp and
          b.visitnum = c.visitnum
 order by usubjid, tulnkid;
quit;
```

VIEWTABLE: Work.Tumortest

	TULNKID	TRLNKID	TRLNKGRP	RSLNKGRP	TUMETHOD	TRMETHOD	TUDY	TRDY	RSDY
647				NEW					45
648	NEW01				SPIRAL CT		45		
649	NEW02				SPIRAL CT		45		
650	NT01	NT01	NT		SPIRAL CT	SPIRAL CT	-27	-27	
651	NT01	NT01	NT	NT	SPIRAL CT	SPIRAL CT	-27	45	45
652	T01	T01	T		SPIRAL CT	SPIRAL CT	-27	-27	
653	T01	T01	T	T	SPIRAL CT	SPIRAL CT	-27	45	45
654	T02	T02	T		SPIRAL CT	SPIRAL CT	-27	-27	
655	T02	T02	T	T	SPIRAL CT	SPIRAL CT	-27	45	45

2) Splitted or merged lesions

In this example you can see how this is reflected in the TU domain. Lesion 04 split and lesions 02 and 03 merged. Make sure that the split of a tumor is not captured as a new lesion. A new lesion would be a progression. A split lesion will just be counted within the sum of longest diameter and might in fact be a shrinkage of the tumor.

TULINKID	TUTESTCD	TUTEST	TUORRES	VISIT
T01	TUMIDENT	Tumor Identification	TARGET	SCREEN
T02	TUMIDENT	Tumor Identification	TARGET	SCREEN
T03	TUMIDENT	Tumor Identification	TARGET	SCREEN
T04	TUMIDENT	Tumor Identification	TARGET	SCREEN
NT01	TUMIDENT	Tumor Identification	NON-TARGET	SCREEN
NT02	TUMIDENT	Tumor Identification	NON-TARGET	SCREEN
T04.1	TUSPLIT	Tumor Split	TARGET	WEEK 16
T04.2	TUSPLIT	Tumor Split	TARGET	WEEK 16
T02/T03	TUMERGE	Tumor Merged	TARGET	WEEK 24
NEW01	TUMIDENT	Tumor Identification	NEW	WEEK 32

3) Small values of the longest diameter:

According to RECIST 1.1 a value of 5 mm has to be used in these cases.

The SDTM tumor domain implementation guide gives following rule:

When a tumor is too small to measure per assessment criteria and a default value is expected to be recorded for that visit (e.g. in RECIST(v1.0) <5mm is considered too small and a value of 5mm should be recorded) the information should be represented on a single row of data showing the standardization between the original result, TRORRES, and the standard results, TRSTRESC/TRSTRESN, as follows:

TRLINKID	TRTESTCD	TRTEST	TRORRES	TRORRESU	TRSTRESC	TRSTRESN	TRSTRESU
T01	LDIAM	Longest Diameter	TOO SMALL TO MEASURE	mm	5	5	mm

4) Disappearing and reappearing lesions:

If a lesion disappears and reappears later it is not regarded as a new lesion. It should be handled as if it did not disappear and added to the sum of longest diameter. A value of 0 will be used for the disappeared lesion. -> Check if the new lesions are in fact not new lesions but reappearing lesions.

5) Lymphnodes should not be used as target lesions if there is another choice. In RECIST 1.1 lymphnodes are discussed separately. If lymphnodes are used as target lesion the short axis has to be taken for measurement. A Lymphnode < 1 cm is regarded as normal. -> Check all lesions that are classified as lymphnodes.

6) If the shape of a lesion changes still the longest diameter (or short axis in case of lymphnodes) has to be used. This is something we cannot check in the data. Therefore an independent read is favorable

7) If lesions become inevaluable the sum of longest diameter cannot be derived for that visit. There might be other visits with evaluable measurements otherwise it might be a solution to reassess the lesion as non target lesion and drop all measurements from the target lesions. -> Check the data for inevaluable measurements.

8) Other checks:

   a. Check the overall response for new lesions: Is it PD?

   b. Recalculate the percentage change from NADIR and from baseline for the sum of longest diameter. >20 % increase from NADIR is regarded as PD (if >=5 mm), 30 % decrease from baseline is regarded as partial response. (confirmation in a following visit is needed). Compare with the investigators assessment.

CONCLUSION

The assessment of tumor burden is challenging and there might be a lot of issues and patient specific special cases in the data. The new RECIST1.1 guidelines and the CDISC tumor domains help a lot regarding data handling and evaluation. But nothing replaces the special human attention to these special data.

REFERENCES

http://www.eortc.be/recist/documents/RECISTGuidelines.pdf
http://www.eortc.be/recist/RECIST_EORTC_NCI_AACR_OCtober_2008.pdf

http://www.cdisc.org/stuff/contentmgr/files/0/3fa5f30f40ce5ecc7b3f91e558b55f73/misc/tumor_domains_specifications.pdf

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