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Derivations of Response Status from SDTM Domains using RECIST 1.1

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ABSTRACT

The Response Evaluation Criteria in Solid Tumors (RECIST) provide standardized rules for solid tumor response assessments. RECIST defines categories of response, which include Complete Response (CR), Partial Response (PR), stable disease (SD), and progressive (worsening) disease (PD), after the start of treatment. Endpoints based on tumor response as determined by RECIST 1.1 can be the basis for regulatory approval by both the Food and Drug Administration (FDA) and European Medicines Agency (EMEA). This standardization of rules provides a framework for reproducible analysis of results in many oncology clinical trials.

This paper utilizes the CDISC SDTM oncology domains to illustrate by examples the use of SAS code to derive tumor response based on RECIST 1.1 to validate site and central response status. We will focus on defining baseline lesions types (target and non-target), and comparison with lesion assessments (target, non-target and new) from subsequent visits to derive an overall response for each time point. Best Overall Response (BOR) is not the focus of this paper but we will address briefly.

SAS®9, Windows, Intermediate Level
Key Words: CDISC, SDTM Domains, Oncology, RECIST 1.1

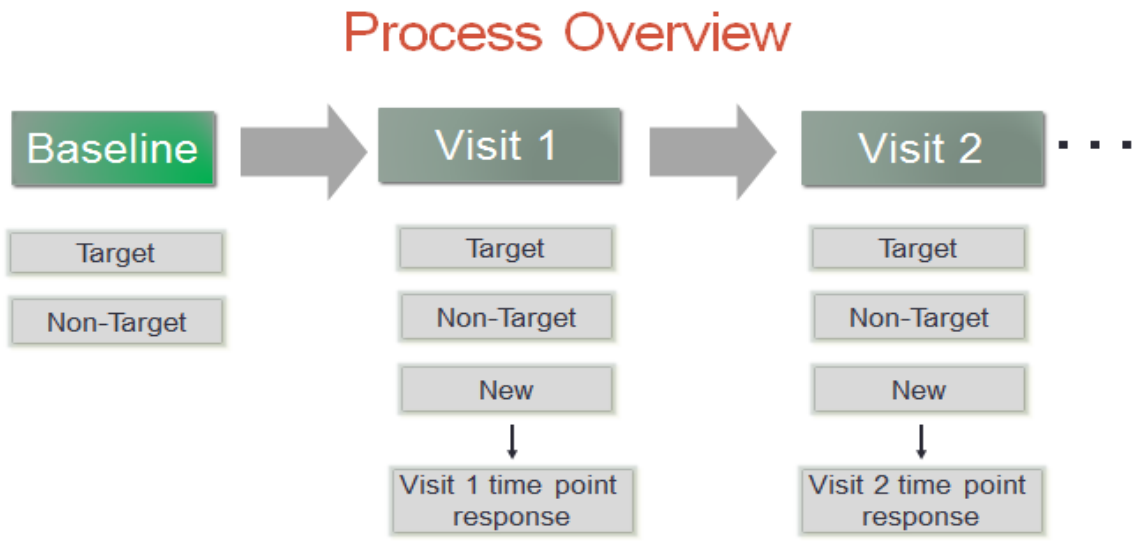
INTRODUCTION

RECIST is a widely accepted standardized approach to solid tumor measurement and definitions for assessment of change in tumor burden for use in cancer trials. To detect a favorable treatment result (the term commonly used is "objective response", which includes either partial or complete response) or progression, it is necessary to document the overall tumor burden at baseline and use it as comparator for subsequent measurements. Any modifications of the criteria made by the trial sponsor should be documented in the protocol and in supporting documentation (such as the imaging charter that describes the independent review process).

There are three types of lesion in the overall tumor response assessment by RECIST. Target lesions are defined as those followed quantitatively. Non-target lesion as defined as those followed qualitatively, as a whole. New lesions are evaluated in a qualitative and binary fashion in typical RECIST assessment, and the appearance of a new lesion is interpreted as progression. Site investigator assessments of the target, non-target, and new lesion status, along with an overall response assessment, are entered for each tumor assessment time-point. Variability is typically greater in site review than in central review, because site reviewers are a larger group with less consistent training in applying formal criteria than the reviewers at dedicated independent review

facilities. However, both Site and Central review should follow the same criteria in terms of definitions and methods.

The figure below depicts the high-level process flow for response assessment:



If objective response rate (ORR) – the proportion of subjects who achieve either partial or complete response – is the primary endpoint for the trial, only subjects with measurable disease at baseline (lesions eligible for selection as target lesions) should be included, because without target lesions it is not possible to detect a partial response.

RESPONSE CRITERIA

Lesion Types

Target lesions are measured at every visit, and their measurements are added to get the sum of diameters. Non-target lesions are evaluated as 'present', 'absent' or 'unequivocal progression'. A lesion identified post-baseline is consider a new lesion, which indicates disease progression.

The below charts summarize the definitions of categories for target and non-target lesion response.

Target Lesion (TL) Response Criteria

To derive target response, we need to have the following information:

- Identify Longest Diameter (LD) for non-nodal target lesions
- Identify Short Axis (SA) for target lymph nodes
- Add up sum of diameters (SOD) from LD and SA
- Calculate percentage change from nadir SOD
- Calculate percentage change from baseline SOD

Please note that the "nadir" is the smallest SOD prior to the current assessment. Follow below criteria to derive the target lesion time-point response. If an assessment met multiple criteria, PD overwrites all response result and NE overwrites any result other than PD.

Response	Definition
Complete Response (CR)	All non-nodal TLs disappeared; all lymph nodes short axis <10 mm
Partial Response (PR)	SOD decreased ≥ 30% from baseline
Progressive Disease (PD)	SOD increased ≥ 20% from nadir and the 20% has absolute increase ≥ 5 mm
Stable Disease (SD)	Not PR nor PD
Not Evaluable (NE)	Cannot determine target lesion response

Non-Target Lesion (NTL) Response Criteria

Please see further explanations for assessment of progression of non-target disease in section 4.3.3 and 4.4.4 of the RECIST guideline (see reference section). We will not provide programming examples in this paper.

Response	Definition
Complete Response (CR)	All NTLs disappeared All lymph nodes <10 mm
Non-CR/Non-PD	One or more NTLs still persist Lymph nodes ≥10 mm
Progressive Disease (PD)	Unequivocal progression NTL showing worsening collectively
Not Evaluable (NE)	Cannot evaluate non-target lesion response

AN EXAMPLE TO DERIVE TARGET LESION RESPONSE

TR (Tumor Results) Domain

TRTESTCD	TRTEST
LDIAM	Longest Diameter
LESNEVAL	Lesion Evaluable
LPERP	Longest Perpendicular
TUMSTATE	Tumor State

Programming logic:

Description	Logic	Variable
Sum of Diameter (Do for all visits)	total none lymph node (TRTESTCD='LDIAM') and all lymph node (TRTESTCD='LPERP')	SOD
Nadir (do for post baseline)	smallest SOD prior to current time point (does not include visits with NE)	NADIR

For every post baseline assessment, derive the response for each below criteria

Target Lesion Response	Logic	Variable
NE	TRTESTCD='LESNEVAL' and TRORRSC ne 'Y'	RESPNE
CR	total none lymph node =0 (TRTESTCD='LDIAM' tumor disappeared) and all lymph node (TRTESTCD='LPERP') <10 mm	RESPCR
PR	Calculate % change from baseline, if % change<=-30	RESPPR
PD	if change from nadir >=5 and % change from nadir >=20	RESPN
SD	Merge all conditions/response result and only pick worst case; if none of above conditions met (Not PR nor PD)	

Output scenarios for final target response TLRESP:

TLRESP	RESPCR	RESPPR	RESPN	RESPNE
CR	CR			
NE				NE
NE	CR			NE
PD			PD	NE
PD		PR	PD	NE
SD				

After TLRESP response derived for each time point, need to assign response PD for assessment result after visit that has CR. Target Lesions appear after CR is PD.

Output scenarios for nadir:

USUBJID	VISIT	SOD	BASE	ABLFL	CHG	PCHG	RESPPR	NADIR
1001	Screening	**22**	22	Y				
1001	Cycle 3	17	22		-5	-23		**22**
1001	Cycle 6	12	22		-10	-45	PR	17
1001	Cycle 9	10.2	22		-11.8	-54	PR	12
1001	Cycle 12	8.8	22		-13.2	-60	PR	10.2

TIME-POINT OVERALL RESPONSE

Table 1 and 2 of RECIST guideline (see appendix) provide time-point overall response derivations. The logic is very straightforward.

RS (Response) Domain

RSTESTCD	RSTEST
NEWLPROG	New Lesion Progression
NTRGRESP	Non-target Response
TRGRESP	Target Response
OVRLRESP	Overall Response

Sample code snippets: (Please note, study should confirm with sponsor data mapping specifications for case report forms and imaging charter, for final derivation logic)

```
*RECIST Table-1 (appendix), has Target Lesions;

 if  TRGRESP not  in ( '' 'NE') then do;  /* depending on sponsor crf */
      if TRGRESP='PD' or NTRGRESP='PD' or NEWLPROG='Y' then ORRESP='PD';
      if TRGRESP='CR' and NTRGRESP in ('CR' '') and
         NEWLPROG='N' then ORRESP ='CR';
      else if TRGRESP='CR' and NTRGRESP in ('Non-CR/Non-PD' 'NE'  ) and
            NEWLPROG='N' then ORRESP ='PR';
      if TRGRESP='PR' and (NTRGRESP not in ('PD' ) or NTRGRESP = 'NE') and
         NEWLPROG='N'   then ORRESP ='PR';
      if TRGRESP='SD' and (NTRGRESP not in ('PD' ) or NTRGRESP = 'NE') and
         NEWLPROG='N'   then ORRESP ='SD';
      if TRGRESP in ('NE' ') and NTRGRESP in ('Non-CR/Non-PD' 'NE' '' ' 'CR' ) and
         NEWLPROG='N'  then ORRESP ='NE';
end;
else  if NTRGRESP ne '' then  do;

*RECIST Table-2 (appendix),  if only has non-target Lesions and no target lesions;

     if NEWLPROG='Y' then ORRESP ='PD';
     else ORRESP =NTRGRESP;
end;
```

First, transpose data by time point so target lesion, non-target lesion, new lesion and overall response results are in one row. ORRESP is the derived overall response via programming. You can validate the result by comparing to the site/central provided overall response OVRLRESP. Above, we intentionally use all capital cases for variable names for clarity.

BEST OVERALL RESPONSE

Fundamentally, the best overall response (BOR) is simply the most favorable of the visit (overall) responses seen after the start of treatment. RECIST 1.1 states that PR and CR confirmation is required for non-randomized trials in which ORR is the primary endpoint, but some development programs require it for all trials. Table 3 of the RECIST guideline (See appendix) provides the best overall response derivations, for trials in which confirmation of PR and CR is required. The examples below illustrate data points for key analysis.

For those trials in which confirmation is required, PR and CR can only be considered the BOR if the initial PR or CR is confirmed by a scan that shows the same response or better (i.e. PR can be confirmed by PR or CR, and CR must be confirmed by another CR), at least 4 weeks after the initial response.

SD does not require confirmation. If SD is the best response ever seen (i.e. baseline, then SD, then PD), then to claim SD as the BOR it must last for some defined period of time since start of treatment (typically 6-8 weeks), since a BOR of SD is a claim that the treatment kept the disease in check for some clinically meaningful length of time.

Data Examples: BL is baseline V1 is visit 1 etc. and assuming duration requirements met.

First Confirmed Date (for CR or PR)
Best Overall Response (BOR)

BL	V1	V2
	CR	CR

BOR = CR

BL	V1	V2
	SD	PR

BOR = SD

BL	V1	V2
	PR	CR

BOR = PR

BL	V1	V2	V3	V4	V5
	PR	NE	PR	CR	CR

BOR = CR
First Confirmed Date V1

BL	V1	V2	V3	V4	V5	V6
	CR	NE	NE	**CR**	CR	SD

BOR = CR
First Confirmed Date V4

BL	V1	V2	V3	V4	V5
	PR	SD	CR	CR	PD

BOR = CR
First Confirmed Date V1

SITE vs. CENTRAL REVIEW

There are several advantages using assessments from central review, including reads performed by a small group of highly trained readers, a controlled read system, and complete blinding to treatment group and clinical condition. The RECIST derivations program can apply to both Site and Central Review data to confirm the quality of the response.

As mentioned earlier, certain level of discordance between site and central results is expected, and the degree of discordance is not systematically described in the scientific literature. The discordance could be summarized at different levels, e.g., for each target lesion/non-target lesion/new lesion response, overall response at each subject visit, or best overall response at subject level. These summary reports provide more information than the discordance report at study level. The summary reports can detect both the systematic errors in site imaging review and potential data issues due to other reasons. Data management and clinical operation need to understand the causes of discordance, and the report of site vs. central discordances can be an important source of information. If discordance was due to data entry or training issues, it could be resolved more efficiently by the data management. Other factors of discordance may also include how site radiologists select target lesions, define new lesions and use clinical data available to them.

There are challenges deriving the responses programmatically. We found not all lesions for a time point were assessed on the same date or same visit. Site may enter reading date instead of assessment date. We found missing lesions in subsequent visits after baseline. Data management should follow these types of issue to ensure accuracy. We exclude time points with partial data from the analyses of change (from baseline or nadir) for Site derivations.

SUMMARY

In summary, we encourage a thorough testing of sponsor-derived response to validate site and central review data. We share our programming steps and challenges to derive response result based on RECIST 1.1 criteria using raw data from SDTM domains. We expect some discordance between site and central review data, but the degree of discordance can be managed. Data management should monitor Sites with higher discordance rate relative to Central review data.

REFERENCE

New Response Evaluation Criteria in Solid Tumors: Revised RECIST Guideline (Version 1.1), European Journal of Cancer, 45:228-247
https://ctep.cancer.gov/protocoldevelopment/docs/recist_guideline.pdf

CDISC Study Tabulation Model Version 1.3
https://www.cdisc.org/system/files/members/standard/foundational/sdtm/SDTM%20v1.3.pdf

Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics
https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf

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APPENDIX

Revised RECIST Guideline (Version 1.1); Section 4 Table 1, p.235

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
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, PD = progressive disease, and NE = inevaluable.

Revised RECIST Guideline (Version 1.1); Section 4 Table 2, p.235

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Revised RECIST Guideline (Version 1.1); Section 4 Table 3, p.235

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.