

SAS Macro for Derivation of Best Overall Response per RECIST 1.1

Bob Zhong, Jiangfan Li, Hong Xie, Peter De Porre, Kenneth Maahs, Kyoungwha Bae
Johnson & Johnson, Spring House, PA

ABSTRACT

Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) has been quickly adopted since its publication in 2009 as an efficacy assessment standard in oncology clinical trials in solid tumors. However, the rules for determining best overall response (BOR) need to take into considerations of practical situations and certain clarifications in details are needed to handle real-world data. We addressed some ambiguities in RECIST 1.1 and provided detailed handlings required to develop a SAS macro for an accurate derivation of BOR.

BOR is derived from time-point overall responses of CR, PR, SD, PD, NE, and Unknown. To derive BOR, responses that do not affect derivation of BOR are taken out first. After this step of data manipulation, only the first three remaining time-point overall responses are needed to derive BOR. Complicated cases such as PR-SD-PR and unconfirmed CR or PR are calculated in more detail. Our macro can be applied to clinical trials with/without requirement of CR/PR confirmation, and in both interim analyses (potential future data available) and final analysis (no future data).

This macro will allow for both accurate and timely determination of best overall responses via computer programming.

INTRODUCTION

RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 ([1]) provides good concept of best overall responses (BOR). However, the RECIST rules for determining BOR have ambiguities and inaccuracies. For example, the RECIST Table 3 ([1] 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.

Display 1. Best Overall Response when Confirmation of CR and PR Required

The table concludes that the best overall response for two consecutive CRs is CR. While this is correct most of times, there are cases when this is incorrect. When confirmation is involved, the second CR is required to be after certain period (defined in the protocol, usually 4 weeks) from the first CR to confirm the first CR. If the two CRs are too close, then the second CR cannot confirm the first CR, and the conclusion may not be CR. Another example is a CR followed by PR, the table gives SD, PD, or PR as possible BOR. However, it is not clear which one should be assigned. In this paper, we clarified these

ambiguities, extensively filled in details to bridge gaps in the original RECIST 1.1, set up rules for deriving BOR, and developed solid SAS macro tools for quick and accurate derivation of BOR. User-guide, sample programs, and the SAS macro tools (in SAS catalog for both Windows and Linux/Unix) will be provided upon request.

CR/PR CONFIRMATION

CR CONFIRMATION

To confirm a CR (the first CR), we look for another CR (the confirming CR) at least 4 weeks (study-dependent) after the first CR. It is required that there is no other overall response, except CR and NE, between the first CR and the confirming CR.

- If such confirming CR exists, then the subject BOR is *confirmed CR*.
- If such confirming CR is guaranteed non-existing (e.g. the first CR followed by PD or off-study), then the subject BOR can be NE or SD, if the requirement of SD is satisfied.
- If there is no confirming CR in the current data, but there is a chance for such confirming CR in the future data. Then the subject's BOR is an *unconfirmed CR* (uCR). This is only applicable to the interim analysis.

PR CONFIRMATION

To confirm a PR (the first PR), we look for another CR or PR (the confirming CR or PR) at least 4 weeks (study-dependent) after the first PR. It is required that there is no other overall response, except CR or PR or NE, between the first PR and the confirming CR or PR.

- If such confirming CR or PR exists, then the subject's BOR is *PR (confirmed)*.
- If such confirming CR or PR is guaranteed non-existing (e.g. the first PR followed by PD or off-study), then the subject BOR can be NE or SD, if the requirement of SD is satisfied .
- If there is no confirming CR or PR in the current data but there is a chance for such confirming CR or PR in the future data. Then the subject's BOR is an *unconfirmed PR* (uPR). This is only applicable to interim analysis.

WHY ENHANCE RECIST 1.1

In some cases, RECIST 1.1 is open to interpretation as it does not give every detail needed to properly assign BOR. For example, as one can see from Display 1:

- (CR - CR) In a study with CR confirmation of 4 weeks, for a patient with CR-CR-PD on Days 7, 21, 35, RECIST 1.1 concludes the BOR is CR. However, the BOR for this patient should be PD.
- (CR - PR) RECIST 1.1 offers multiple conclusions SD, PD or PR. However, in practice, we need a one-valued conclusion.
- (PR - CR) In a study with PR confirmation of 4 weeks, for a patient with PR-CR-PD on Days 7, 21, 35, RECIST 1.1 concludes the BOR is PR. However, the BOR for this patient should be PD.
- (PR - PR) RECIST 1.1 unconditionally concludes BOR is PR for two consecutive PRs. However, for a patient with PR-PR-PD on Days 7, 21, 35, the BOR should be PD, not PR.
- (PR - SD) RECIST 1.1 unconditionally concludes BOR is SD. However, for a patient with PR-SD-PD on Days 7, 21, 35, the BOR should be PD, not SD.

SAS MACROS FOR BEST OVERALL RESPONSE PER RECIST 1.1

We developed two SAS macro tools %BESTOVRS_FA (for final analysis) and %BESTOVRS_IA (for interim analysis) with the same syntax.

```
%bestovrs_fa( dsn    = ,  
              insl   = ,  
              inrs   = ,  
              sdwin  = ,  
              crwin  = ,  
              opt    = ,  
              cleanup = yes );
```

where

dsn

is the input/output dataset which should contain USUBJID (Unique Subject Identifier).

insl

is the subject level input dataset:

1. should include all patients in &dsn
2. one record per subject
3. sorted by USUBJID
4. contains the following variables:
USUBJID
RFSTDTC - Subject Reference Start Date/Time
For interim analysis, &insl should also contain
FINALFL - Final Status Flag (Y/N)

The value of FINALFL should be exact 'Y' or 'N', case sensitive. If FINALFL = 'Y', then the patient has no more disease assessment expected in the future. In the final analysis, everyone has FINALFL = 'Y', and so the flag FINALFL is not needed in %BESTOVRS_FA. For interim analysis, caller needs to derive FINALFL of which "Y" includes (but not limited to)

- lost-to-follow up
- withdrawal of consent
- ended the study
- died
- In some studies, a subsequent anti-cancer therapy also makes FINALFL = 'Y'.

FINALFL does not play the role if the patient has experienced a PD.

inrs

is the input overall response data, containing standard variables: USUBJID RSDTC RSSTRESC, and sorted by USUBJID. &inrs should contain all overall responses only. &inrs should contain neither target lesion assessment nor non-target lesion assessment. RSSTRESC should hold standard values

```
COMPLETE RESPONSE  
PARTIAL RESPONSE  
STABLE DISEASE  
PROGRESSIVE DISEASE  
NOT EVALUABLE
```

or their abbreviations CR/PR/SD/PD/NE. Non-standard values in RSSTRESC will be ignored.

sdwin

is the SD sustaining windows in days. sdwin = 0 or missing means no requirement on SD windows.

crwin

is the CR/PR confirmation windows in days. If missing or 0, then no CR/PR will be confirmed.

opt

is the output dataset option for convenience.

cleanup

is the yes/no option to clean up working data sets.

COMPUTATIONAL PRINCIPLES

The computation is trivial if the study does not require CR/PR confirmation. So here we only address the case when CR and PR need to be confirmed.

NOTATIONS

- X_1 - number of days from randomization/start of study treatment to 1st time point overall response evaluation
- X_2 - number of days from randomization/start of study treatment to 2nd time point of overall response evaluation
- X_3 - number of days from randomization/start of study treatment to 3rd time point of overall response evaluation
- XX - minimal number of days required for SD per protocol (i.e. $\&sdwin$). This is the timespan from RFSTDT to the day of SD.
- YY - minimal number of weeks required for CR/PR confirmation (i.e. $\&crwin$)

DATA PREPARATION

Each of the following steps does not affect one's best overall response. The purpose of data preparation is to enable the best overall response to be determined by one's first 3 time-point assessments.

- Step 1. Remove any NE if any other disease evaluation exists except NE.
- Step 2. Keep only the last NE from a queue of continuous NEs.
- Step 3. Remove any assessment after the first PD, (CR, PR), or (CR, SD).
- Step 4. Keep only the last SD from a queue of continuous SDs.
- Step 5. Keep only the first PR and the last PR from a queue of continuous PRs
- Step 6. Keep only the first CR and the last CR from a queue of continuous CRs.
- Step 7. Remove SD before PR or CR for a queue beginning with SD, followed by PR or CR. That is, (SD, PR, ...) or (SD, CR, ...).
- Step 8. Remove the second PR from data queue (PR, PR, CR)
- Step 9. Remove the first PR from any two consecutive PRs from a queue of (PR, PR, SD) if the time interval between the two PRs is less than YY.
- Step 10. Remove the first CR from any two consecutive CRs from a queue of (PR, CR, CR) if the time interval between the two CRs is less than YY.
- Step 11. Remove (PR, SD) from a queue beginning with (PR, SD), followed by PR or CR. That is (PR, SD, PR) or (PR, SD, CR).
- Step 12. Remove any assessments except CR if two consecutive CRs exist with the time interval between two CRs are $\geq YY$.

DERIVATION OF BEST OVERALL RESPONSE WITH CR/PR CONFIRMATION

After the above data preparation, we can derive the best overall response using only overall responses at the first three time-points.

Overall response at 1st time point (X_1)	Overall response at 2nd time point (X_2)	Overall response at 3rd time point (X_3)	Best overall Response	
CR	Unknown	Unknown	Final: SD if $X_1 \geq XX$ otherwise, NE Interim: If no additional disease assessments are expected* then SD if $X_1 \geq XX$ otherwise, NE else uCR	
	CR with $X_2 - X_1 \geq YY$	Any	CR	
	CR with $X_2 - X_1 < YY$	Unknown	Unknown	Final: SD if $X_2 \geq XX$ otherwise, NE Interim: If no additional disease assessments are expected* then SD if $X_2 \geq XX$ otherwise, NE else uCR
		PR	PR	Flag as a data issue with note: cannot be PR after CR. SD if $X_2 \geq XX$ otherwise, PD
		SD	SD	Flag as a data issue with note: cannot be SD after CR. SD if $X_2 \geq XX$ otherwise, PD
		PD	PD	SD if $X_2 \geq XX$ otherwise, PD
	PR	Any	Flag as a data issue with note: cannot be PR after CR. SD if $X_1 \geq XX$, otherwise PD	
	SD	Any	Flag as a data issue with note: cannot be SD after CR. SD if $X_1 \geq XX$, otherwise PD	
	PD	Any	SD if $X_1 \geq XX$, otherwise PD	
PR	CR	CR	if $X_3 - X_2 \geq YY$, CR; else it will be changed to leading (PR, CR) sequence due to data Step 10	
	Unknown	Unknown	Final: SD if $X_1 \geq XX$ otherwise, NE Interim: If no additional disease assessments are expected* then SD if $X_1 \geq XX$ otherwise, NE else uPR	
	CR with $X_2 - X_1 \geq YY$	PR, SD, PD, NE, Unknown	PR Flag as a data issue if PR or SD is the overall response at the 3rd time point.	
	CR with $X_2 - X_1 < YY$	Unknown	Unknown	Final: SD if $X_2 \geq XX$ otherwise, NE Interim: If no additional disease assessments are expected* then SD if $X_2 \geq XX$ otherwise, NE else uCR
		PR	PR	Flag as a data issue with note: cannot be PR after CR. SD if $X_2 \geq XX$, otherwise, PD
	SD	SD	Flag as a data issue with note:	

			Cannot be SD after CR. SD if $X_2 \geq XX$ otherwise, PD
		PD	SD if $X_2 \geq XX$ otherwise, PD
	PR with $X_2 - X_1 \geq YY$	Any	PR
	PR with $X_2 - X_1 < YY$	Unknown	Final: SD if $X_2 \geq XX$ otherwise, NE Interim: If no additional disease assessments are expected* then SD if $X_2 \geq XX$ otherwise, NE else uPR
		PD	SD if $X_2 \geq XX$, otherwise, PD
	SD	Unknown	SD if $X_2 \geq XX$ otherwise NE
		PD	SD if $X_2 \geq XX$ otherwise PD
	PD	Any	SD if $X_1 \geq XX$ otherwise PD
SD	Unknown	Unknown	SD if $X_1 \geq XX$ otherwise NE
	PD	Any	SD if $X_1 \geq XX$ otherwise PD
PD	Any	Any	PD
NE	Unknown	Unknown	NE

* Subjects are considered “no additional disease assessments are expected” with the following cases but not limited to

- lost-to-follow up
- withdrawal of consent
- ended the study
- died

Note that, after data preparation, the above listing exhausts all cases.

SPECIAL CASES

There are a few special cases that RECIST 1.1 offers multiple conclusions in the discussion. However, in reality, given data, we need to derive a single best overall response. By working with different groups in clinical trials, we set up the following derivation rules.

CR FOLLOWED BY PR (CR-PR)

In this case, the PR implicitly might be a PD. So if $X_1 \geq XX$, then the BOR is SD. Otherwise the BOR is PD.

CR FOLLOWED BY SD (CR-SD)

Similar as in the previous case, the SD implicitly might be a PD. So if $X_1 \geq XX$, then the BOR is SD. Otherwise the BOR is PD.

SD APPEARS BETWEEN TWO PRS (PR-SD-PR)

Different clinical studies may handle this situation differently. We pick up the most conservative way of handling this case, i.e. removing the leading PR-SD (step 11 in the data preparation).

It is noted that this choice here is a conservative one but may not be the best one. The SAS macro will be updated at the next version with different options so that users can choose the desired one.

SINGLE CR OR PR IN INTERIM ANALYSIS

If a subject (patient) is off the study, then the BOR of the subject follows the conclusion in the final analysis. That is, if $X_1 \geq XX$ then BOR = SD, otherwise BOR = NE.

If the subject is on the study, then BOR = uCR (unconfirmed CR), or uPR (unconfirmed PR) respectively.

SAMPLE PROGRAMS

CREATE SAMPLE DATA

```
data dat(drop=i);
  length USUBJID $1;
  do i=1 to 6;
    USUBJID = i;
    output;
  end;
  label USUBJID = Unique Subject Identifier;

%let DATES = 2019-06-16 2018-04-29 2017-07-07 2017-05-14 2016-10-27;
%let DATES = &DATES 2016-10-21 2016-11-01 2015-10-22 2015-02-10;
data insl(drop=i);
  length USUBJID $1 RFSTDTC $10 FINALFL $1;
  do i=1 to 9;
    usubjid = i;
    rfstdtc = scan("&DATES", i);
    finalfl = ifc(i<'3', 'Y', 'N');
    output;
  end;
  label USUBJID = Unique Subject Identifier
        RFSTDTC = Subject Reference Start Date/Time
        FINALFL = Final Status Flag;

data inrs;
  infile datalines;
  input USUBJID $1. RSSTRESC $21. RSDTC $10.;
  datalines;
1 COMPLETE RESPONSE      2019-07-02
1 COMPLETE RESPONSE      2019-09-01
2 PARTIAL RESPONSE       2018-05-10
2 STABLE DISEASE         2018-06-14
2 PARTIAL RESPONSE       2018-07-10
3 STABLE DISEASE         2017-08-07
3 STABLE DISEASE         2017-09-07
3 STABLE DISEASE         2017-10-07
3 PARTIAL RESPONSE       2017-11-07
3 PARTIAL RESPONSE       2017-12-07
4 STABLE DISEASE         2017-06-14
4 PROGRESSIVE DISEASE    2017-07-14
5 STABLE DISEASE         2016-11-27
5 UNKNOWN                2016-12-27
6 PARTIAL RESPONSE       2017-03-10
6 PARTIAL RESPONSE       2017-04-01
;
run;
```

BEST OVERALL RESPONSES IN FINAL ANALYSIS

```
libname _TOOLS_ "SAS-library to sasmacr.sas7bcac" access=readonly;
options mstored sasstore=_TOOLS_;

%bestovrs_fa(dsn      = dat,
             insl     = insl,
             inrs     = inrs,
```

```
sdwin = 84, %* 12 weeks;  
crwin = 28, %* 4 weeks;  
opt = drop=note);  
%* Now dat has two variables: USUBJID, BESTOVRs.;
```

BEST OVERALL RESPONSES IN INTERIM ANALYSIS

```
libname _TOOLS_ "SAS-library to sasmacro.sas7bcat" access=readonly;  
options mstored sasstore=_TOOLS_;  
  
%bestovrs_ia(dsn = dat,  
            insl = insl,  
            inrs = inrs,  
            sdwin = 84, %* 12 weeks;  
            crwin = 28, %* 4 weeks;  
            opt = drop=note);  
%* Now dat has two variables: USUBJID, BESTOVRs. In this example,  
output from %bestovrs_ia and %bestovrs_fa are different.;
```

CONCLUSION

We developed this macro tool on Windows SAS 9.2 as well as Linux SAS 9.4. All cases are examined thoroughly in order to make computation possible. We followed RECIST 1.1, filled in all gaps, covered all cases, and produced a one-valued macro tool. The macros enable the programming team to compute Best Overall Response quickly, easily, and reliably.

REFERENCES

- [1]. Eisenhauer, E.A., Therasse, P., Bogaerts, J., Schwartz, L.H., Sargent, D., Ford, R., Dancey, J., Arbuck, S., Gwyther, S., Mooney, M., Rubinstein, L., Shankar, L., Dodd, L., Kaplan, R., Lacombe, D., Verweij, J. 2009. "New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)." *European Journal of Cancer*, 45:228 – 247. Also available at https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Name: Bob Zhong
Email: bzhong@its.jnj.com

Name: Jiangfan Li (James)
Email: jli54@its.jnj.com

Name: Hong Xie
Email: hxie57@its.jnj.com

Name: Peter De Porre
Email: pdporre@its.jnj.com

Name: Kenneth Maahs
Email: kmaahs@its.jnj.com

Name: Kyoung-hwa Bae
Email: kbae6@its.jnj.com

<paper title>, continued

Janssen Research & Development, LLC.
Johnson & Johnson
1400 McKean Road
PO Box 776
Spring House, PA 19477