

RECIST Temptation

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INTRODUCTION

With more and more focus in the pharmaceutical world on developing safe and effective drugs for the treatment of cancer, there has been a rise in the number of clinical trials in the therapeutic area of oncology. This paper is aimed at programmers of all levels and backgrounds who are keen to develop their understanding of Response Evaluation Criteria In Solid Tumours (RECIST).

This paper is designed to give the reader an insight into RECIST guidelines and handling RECIST data. We will discuss some of the main concepts of RECIST data, what we can expect from such data and how we can begin to think about programming from it. We will also look at interesting properties of this data that make programming with it a challenge, along with the different components that fit together to build up the evaluation. We will explore common issues that can occur when trying to summarize RECIST data and give ideas as to sensible approaches to minimize these issues.

WHAT IS RECIST?

Response Evaluation Criteria In Solid Tumours (RECIST) is a set of published international standards that are used to determine efficacy for oncology studies. These criteria provide a method of evaluating solid tumour response using X-ray, CT and MRI scans, and is recommended by the National Cancer Institute for sponsored trials, although it is not compulsory.

A patient's response to treatment is determined by combining the responses of 3 components.

- Target Lesions
- Non-Target Lesions
- New Lesions

Following these standards consistently can be challenging due to investigator interpretation, or how the lesions are measured.

COMPONENTS OF RECIST DATA

As mentioned, RECIST data is made up of 3 components:

1. Target Lesions:

Up to 5 measurable lesions per organ (up to 10 in total) are selected as target lesions based on size and suitability. These target lesions will be measured at each visit to assess sum of the longest diameter of all lesions.

2. Non-Target Lesions:

All other lesions that are not target lesions are recorded as non-target lesions (identified at baseline). These lesions are not measured, but are assessed by the investigator throughout the study.

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3. New Lesions

Any lesion post-baseline that has not been identified as a target or non-target lesion at baseline is defined as a new lesion. A presence or absence of any new lesions is recorded at each assessment.

ANALYSIS OF RECIST DATA

Each of the 3 components are assessed/analysed individually and the overall response at each visit can be determined from combining these outcomes.

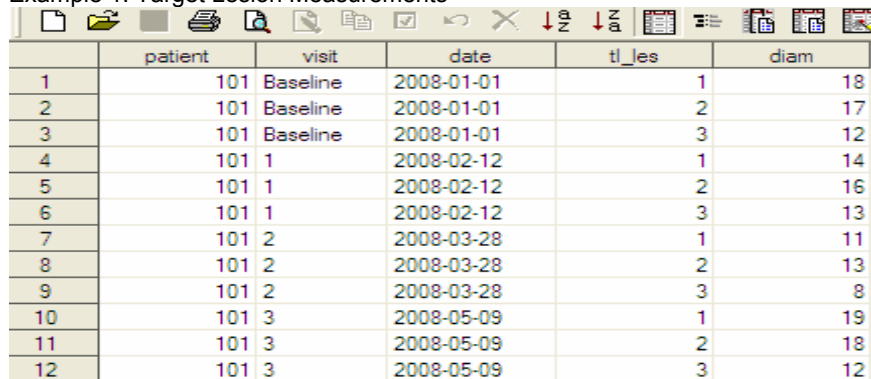
Assessment of Target Lesions (TL):

All target lesions should be measured at baseline and the sum of longest diameters recorded. The target lesion response at each visit can then be assigned using the following rules:

- CR (Complete Response), all lesions have disappeared – sum of longest diameters = 0
- PR (Partial Response), shrinkage >30% compared to baseline
- PD (Progressive Disease), >20% increase compared to any assessment
- SD (Stable Disease), an evaluable assessment that is neither CR, PR or PD
- NE (Non-Evaluable), generally study specific

A basic example for one patient who has 3 target lesions measured at each visit is given below:

Example 1: Target Lesion Measurements



	patient	visit	date	tl_jes	diam
1	101	Baseline	2008-01-01	1	18
2	101	Baseline	2008-01-01	2	17
3	101	Baseline	2008-01-01	3	12
4	101	1	2008-02-12	1	14
5	101	1	2008-02-12	2	16
6	101	1	2008-02-12	3	13
7	101	2	2008-03-28	1	11
8	101	2	2008-03-28	2	13
9	101	2	2008-03-28	3	8
10	101	3	2008-05-09	1	19
11	101	3	2008-05-09	2	18
12	101	3	2008-05-09	3	12

- Sum of target lesions at baseline is 18+17+12 = 47mm.
- Sum of target lesions at visit 1 is 14+16+13 = 43mm
- Sum of target lesions at visit 2 is 11+13+8 = 32mm
- Sum of target lesions at visit 3 is 19+18+12 = 49mm

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The table below shows how we would assign the target lesion visit response at each visit based on the RECIST criteria:

Table 1: Assigning RECIST Target Lesion (TL) Visit Response:

Visit	Baseline Sum of longest diameters	Visit Sum of longest diameters	Previous minimum sum of longest diameters	Have all lesions disappeared?	Is there a 30% shrinkage from baseline	Is there a 20% increase from any previous minimum assessment?	TL Visit Response
1	47mm	43mm	47mm	No	No	No	Stable Disease (SD)
2		32mm	43mm	No	Yes	No	Partial Response (PR)
3		49mm	32mm	No	No	Yes	Progressive Disease (PD)

Note: 49mm is not a 20% increase from the baseline, yet we still assign this as progressive disease as we evaluate the increase against any previous visit (previous minimum).

Also note that when comparing to the previous minimum assessment, this relates to the previous minimum observed throughout the entire study and is not specifically for the assessment at the visit prior to the current visit.

It is possible for the sum of target lesions at a visit to satisfy both the criteria >20% increase from a previous visit and also have a 30% shrinkage from baseline. Consider a sum at baseline of 30mm, a sum at visit 1 of 10mm and a sum at visit 2 of 20mm. At visit 2, the sum of target lesions is both <30% of baseline (PR) and >20% increase from visit 1 (PD). In this case a progressive disease would take precedence over any other response – hence it is important to note that the above definitions are not exclusive, and a study specific hierarchy should be established and documented.

A target lesion visit response can be assigned as Non-Evaluable due to missing target lesion measurements. Missing target lesions can be handled in different ways depending on the study (eg using last observation carried forward, scaling up techniques, or simply by not allowing any missing target lesion measurements to contribute to an evaluable visit response (unless still clear evidence of progressive disease)).

Assessment of Non-Target Lesions (NTL):

Investigator may enter a non-target lesion visit response based on the assessment of each NTL and overall. This can also be determined by the individual responses of non-target lesions using the following rules:

- CR (Complete Response, disappearance of all NTL's)
- Incomplete Response/Stable Disease, persistence of ≥ 1 NTL
- PD (Progressive Disease, unequivocal progression of existing NTL's)

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Overall Visit Response:

Overall visit response can be assessed using the following table as a guide:

Table 2: Assigning Overall Visit Response:

Target Lesions	Non-Target Lesions	New Lesions	Visit Response
Complete Response	Complete Response	No	Complete Response
Complete Response	Incomplete Response/ Stable Disease	No	Partial Response
Partial Response	Non – Progressive Disease	No	Partial Response
Stable Disease	Non – Progressive Disease	No	Stable Disease
Progressive Disease	Any	Yes or No	Progressive Disease
Any	Progressive Disease	Yes or No	Progressive Disease
Any	Any	Yes	Progressive Disease

These criteria now allows us to obtain an overall response at every visit for each patient in the study which can then be used to assess some of the study endpoints.

TYPICAL STUDY ENDPOINTS

Typical study endpoints when analysing RECIST data include:

- Progression Free Survival (PFS):
- Overall Survival (OS):
- Best Objective Tumour Response:
- Duration of Response

Endpoints will generally depend on the type and/or Phase of the study.

Progression Free Survival (PFS):

Progression free survival can be defined as the length of time during and after treatment in which a patient living with a disease does not get worse. More simply:

- Time up until patient progresses or dies (usually from when the patient was randomized, or started treatment)

The calculation of PFS can help you determine how well a new treatment is working.

An interesting property of this endpoint is that it can often be difficult to know exactly when a patient has disease progression. Typically a patient on a study will only have scans every 4-8 weeks, therefore the only time you can assess this progression is at these intervals. Obviously, this effect will be the same across all treatment/placebo groups, so any treatment effect should still be noticeable.

In Example 1 assuming the patient had no new lesions, or non-target lesions that progressed, then the PFS time for this patient would be calculated from randomization/start of treatment up until 09May2008. If we assume the patient was randomized and started treatment on the day of their baseline scan, then the

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progression free survival time would be calculated as the time between 01Jan2008 and 09May2008 = 129 days.

Overall Survival (OS):

OS can be defined as the percentage of patients in a study who have survived for a defined period of time. At a basic level, the overall survival is representative of cure rates.

Best Objective Response:

The best objective response is the best (confirmed) response the patient has had over the course of the study.

Patients can have a best response of:

- CR (CR recorded at a visit and confirmed at least xx days later)
- PR (PR recorded at a visit and confirmed at least xx days later)
- SD (SD recorded for at least yy weeks)
- PD (progressive disease without any response or SD > yy weeks)

xx and yy can vary from study to study. Most common values are xx = 28 days, yy = 8 weeks, which will be used in the 2 examples below:

Example 2.

	patient	visit	date	vis_resp	time
1	102	Baseline	2008-01-10	N/A	.
2	102	1	2008-03-17	SD	67
3	102	2	2008-05-14	PR	58
4	102	3	2008-07-19	PR	66
5	102	4	2008-09-19	PD	62

*time denotes the time in days since the last assessment. For simplicity we will assume that the patient was randomized and started treatment on the day of their baseline scan.

In this example the best objective response would be Partial Response (PR), since the Partial Response at visit 2 has been confirmed 66 days later at visit 3.

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Example 3.

	patient	visit	date	vis_resp	time
1	103	Baseline	2008-01-12	N/A	.
2	103	1	2008-03-09	SD	57
3	103	2	2008-05-06	PR	58
4	103	3	2008-06-01	PR	26
5	103	4	2008-08-27	SD	87

*time denotes the time in days since the last assessment. For simplicity we will assume that the patient was randomized and started treatment on the day of their baseline scan.

In this example the best objective response would be Stable Disease (SD). The Partial Response (PR) is not confirmed more than 28 days after the original partial response. Stable Disease (or better) is observed for at least 56 days.

Duration of Response:

Duration of response is only calculated for patients who have a confirmed response to treatment (i.e have a best objective response of CR or PR), and is defined as the time from when the response criteria was first met (the time of the first non-confirmed response (CR/PR) that later led to the confirmation of response) to when the patient progressed or died.

In Example 2 the duration of the response would be calculated from the first partial response at visit 2 up until progression at visit 4 = 66+62 = 128 days.

Whatever the chosen study endpoints, you should ensure that study protocols are well-defined with respect to the planned response evaluation. This may affect a patient's eligibility or may also cause unwelcome programming changes.

DATA COLLECTON

RECIST data can be very subjective and one of the main challenges is obtaining consistent data. The design of the CRF pages collecting this information is quite key in avoiding any mis-interpretations.

Common issues include investigators recording that a target lesion has disappeared, but then recording that it has come back at the next visit. In these cases we would not expect to see a target lesion reoccur and any lesion at a subsequent visit should be recorded as a new lesion. The reality of this may be that at the time the investigator believed that the target lesion had disappeared, but subsequently concluded that it had not disappeared but had just shrunk to a size too small to measure. The interpretation of this could lead to different assignments of overall response.

Identifying some of these types of issues can be quite challenging due to the amount of data collected for such a study, and often a review in the form of data listings is essential so that each patient can be examined individually for any irregularities or inconsistencies. Resolving such data issues can often involve people with all types of expertise, and agreement between statisticians, investigators and data management is usually necessary.

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Another area which could lead to inconsistencies in data collection is how to deal with a lesion that separates, or 2 lesions that fuse together. In order to minimise these inconsistencies we should aim to provide guidelines or training to all investigators at all sites on these areas and present detailed notes on the CRF pages to assist this process.

It is often a good idea to spend some time early on in the study thinking about what data issues/inconsistencies you are likely to come across and create some data-checking programs that will highlight reoccurrences of the same issues/inconsistencies on new data. It is likely that if something has previously been identified, then this may be something that could be present again at another site or entered by another investigator. Some ideas include:

- o Check that all sites/investigators are using the same units of measurements when entering the lesion diameter details, otherwise you could end up assigning a patient's visit response incorrectly.
- o Check that the number of target lesions measured at any particular visit does not exceed the number measured at baseline.

PROGRAMMING CHALLENGES

One of the main programming challenges when analysing RECIST data is that in many cases you may find exceptions to the rules. It is important to remember that RECIST guidelines are there to assist you in evaluating your data, but are by no means exhaustive criteria. In these cases it is important that you seek advice from appropriate project team members (e.g statisticians, clinicians) to identify the best method of interpreting the data. A seemingly minor update in the way you handle certain patient data can lead to quite complex programming changes or re-structures. A clearly defined protocol and/or statistical analysis plan should ensure that programming challenges of this type are avoided. It is common practice to review all patient data in the form of data listings, so that any unique occurrences can be highlighted.

RECIST data analysis is very subjective and can depend very much on the type and phase of study, and therefore it is often difficult and less efficient to use programs from previous studies.

Some of the derivations involved in RECIST programming can be quite complex. Be sure that these derivations are documented clearly in your dataset specifications to avoid misinterpretation.

If you have the opportunity to review the CRF prior to being finalised, this may help to avoid any potential programming issues that may later arise.

CONCLUSION

This paper has explored the properties of RECIST data and how we can program and analyze such data effectively. By now you should understand the components that form the evaluation criteria and some of the many rules that are attached to such evaluations. We have explored some of the main problems with handling RECIST data and have set in place some ideas to try to tackle these throughout the whole study design to analysis. We have learnt that although there are many rules for analyzing RECIST data, there will always be exceptions to these and hope that you have learnt enough to enable you to find sensible solutions in dealing with such issues.

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REFERENCES

1. National Cancer Institute - <http://imaging.cancer.gov/clinicaltrials/imaging/>
2. Measuring Response in Solid Tumors: Comparison of RECIST and WHO Response Criteria – Japanese Journal of Clinical Oncology 33:533-537 (2003)
3. Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference - <http://ctep.cancer.gov/forms/quickrcst.doc>

RECOMMENDED READING

New Guidelines to Evaluate the Response to Treatment in Solid Tumors – Patrick Therasse, Susan G. Arbuck, Elizabeth A. Eisenhauer, Jantien Wanders, Richard S. Kaplan, Larry Rubinstein, Jaap Verwij, Martine Van Glabbeke, Allan T. van Oosterom, Michael C. Christian, Steve G. Gwyther:
<http://ctep.cancer.gov/forms/TherasseRECIST.pdf>

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