

Ir-RECIST-ible

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ABSTRACT

The majority of oncology trials involving solid tumors follow RECIST (Response Evaluation Criteria in Solid Tumors) guidelines for tumor evaluation in order to assess intervention efficacy. RECIST provides a standard method for determining whether patients improve, remain stable, or worsen in response to therapy.

RECIST requires collecting and tracking a fairly large number of attributes about each of several tumors in every patient. Unfortunately, even small errors or inconsistencies in clinical procedure or data collection, both of which are common in a clinical trial setting, can make data unusable for RECIST response determination.

This paper discusses key problems that can negatively impact the use of data for RECIST response determination and describes integrity checks that can help identify and correct these problems. These integrity checks can be used in data cleaning to ensure that the maximum pool of data is available for determining response to treatment.

INTRODUCTION

RECIST is an acronym for Response Evaluation Criteria in Solid Tumors. The objective of RECIST is to provide a standard of measurement for response evaluation of solid tumors. These criteria are based on uni-dimensional measurement of tumor size and counts of the number of observable tumors. The evaluable response categories vary from Complete Remission to Progressive Disease with each category having a pre-defined derivation based on the RECIST guidelines. The data collected for RECIST consists of lesions which are measurable at baseline categorized as target lesions and lesions which are not measurable at baseline categorized as non-target lesions. Both target and non-target lesion data factor into determining the overall response of subjects to intervention.

DATA CAPTURE AND STRUCTURE OF RAW DATASETS

The data for tumor response is often collected on different CRF pages: data capturing target lesion measurements on one CRF page and data capturing non-target lesion measurements on a separate page. Baseline measurements for each lesion are made by using various pre-approved techniques like Spiral CT scans, conventional CT scans, chest X-rays, and MRIs. Other techniques like endoscopy, ultrasound, PET scan could potentially be used although they are generally disallowed. At Baseline, the target lesions are measured along their longest diameter and each lesion is given a lesion number. Other information captured about lesions at each assessment include: the lesion location, measurement method and assessment sequence number within a visit cycle. In most cases there is only one assessment per visit cycle, but there could be more than one which would have to be considered in the analysis. The non-target lesions are only measured as present or absent; information about location and the method of measurement are also captured for non-target lesions.

The basic rules of tumor evaluation are as follows:

- Any lesion recorded at baseline should continue to be followed even if the lesion disappears. If a target lesion disappears, its length should be marked as 0; if a non-target lesion disappears, this should be recorded in its assessment.
- Any new lesion observed at post-baseline visits should be assigned a new lesion number.
- If a lesion disappears at an assessment point and then re-appears later it should be treated as a new lesion and, as such, given a new lesion number.
- For each lesion, the method of measurement should remain the same as at baseline for evaluable results.
- For each lesion, the lesion location should be the same as at baseline for evaluable results.

Following RECIST rules, the overall tumor response to treatment can be calculated for each subject at each visit cycle/assessment. Typically, the tumor response is manually calculated by the investigator and recorded on a CRF page. For this evaluation to be valid, the basic rules listed above must be met.

Site	Subject	Lesion Number	Location	Visit Number/ Cycle	Assessment Number	Assessment Date	Method of Measurement	Assessment
07	002	1	Rib	1	1	7-Feb-10	Spiral CT	
07	002	1	Rib	2	1	1-Apr-10	Spiral CT	SD
07	002	1	Rib	3	1	11-May-10	Spiral CT	SD
07	002	1	Rib	4	1	24-Jun-10	Spiral CT	SD
07	002	1	Rib	5	1	9-Aug-10	Spiral CT	SD
07	002	2	Spine	1	1	7-Feb-10	Spiral CT	
07	002	2	Spine	2	1	1-Apr-10	Spiral CT	SD
07	002	2	Spine	3	1	11-May-10	Spiral CT	SD
07	002	2	Spine	4	1	24-Jun-10	Spiral CT	SD
07	002	2	Spine	5	1	9-Aug-10	Spiral CT	SD

Table 1. Example of a Non-Target Lesion Dataset

Site	Subject	Lesion Number	Location	Visit Number/ Cycle	Assessment Number	Assessment Date	Method of Measurement	Size
07	002	1	Adrenal Gland	1	1	7-Feb-10	Spiral CT	3
07	002	1	Adrenal Gland	2	1	1-Apr-10	Spiral CT	1.8
07	002	1	Adrenal Gland	3	1	11-May-10	Spiral CT	1.7
07	002	1	Adrenal Gland	4	1	24-Jun-10	Spiral CT	1.9
07	002	1	Adrenal Gland	5	1	9-Aug-10	Spiral CT	1.9
07	002	2	Liver	1	1	7-Feb-10	Spiral CT	1.6
07	002	2	Liver	2	1	1-Apr-10	Spiral CT	0.9
07	002	2	Liver	3	1	11-May-10	Spiral CT	0.9
07	002	2	Liver	4	1	24-Jun-10	Spiral CT	0.9
07	002	2	Liver	5	1	9-Aug-10	Spiral CT	0
07	002	3	Spine, T3	1	1	11-Feb-10	PET/CT	1.5
07	002	3	Spine, T3	2	1	1-Apr-10	Spiral CT	1.5
07	002	3	Spine, T3	3	1	11-May-10	Spiral CT	0
07	002	3	Spine, T3	4	1	24-Jun-10	Spiral CT	0
07	002	3	Spine, T3	5	1	9-Aug-10	Spiral CT	0
07	002	4	Lung, left	5	1	9-Aug-10	Spiral CT	1.8

Table 2. Example of a Target Lesion Dataset

In some cases, a programmatically calculated tumor response can be derived and compared to the manually calculated response recorded on the CRF. The rules that apply to the manually calculated response also apply to the programmatically calculated response.

DATA QUALITY WITH RECIST

The authors of this paper have developed a set of standard data checks to determine the integrity of the captured data. Utilizing these checks can yield a larger and cleaner set of data. These checks can be introduced into the CRF edit checks or can be implemented as SAS checks performed on post-extract data.

Before considering these checks, though, it is important to point out the value of good CRF design: ensuring high quality data begins with CRF design. For RECIST evaluations, this involves ensuring that, at a minimum, the following information is captured for each lesion at each visit cycle/assessment.

Target and Non-Target Lesions:

- Lesion identifier (unique tracking number)
- Visit cycle and assessment number within cycle
- Date of assessment
- Location of lesion
- Method of measurement

Target Lesions:

- Size (or "Not Done" if not assessed)

Non-Target Lesions:

- Assessment (e.g., stable, progressive, complete response or "Not Assessed")

DATA CHECKS

Below is a list of the standard data checks employed by the authors. These data checks can be used to verify the integrity of data used for the investigator's manual evaluation of response or for a programmatically derived response.

Checks of Target Lesions:

Check 1: List of target lesions records where no size measurement is present but "Not Done" is not checked. This check ensures that all data are accounted for and that an explanation is present for any missing data.

Check 2: List of target lesions where the first assessment is not at the baseline visit. The first assessment for target lesions should always be at baseline so that changes in size can be tracked. This is critical for the overall response, best response and the time to progression calculations. Subjects whose first assessment was not at baseline cannot be evaluated even if their subsequent post-baseline assessments are per protocol. Any subjects with lesions failing this check should be queried so that the maximum set of data can be utilized.

Checks of Non-Target Lesions:

Check 3: List of post-baseline non-target lesion records where an assessment is not present but "Not Done" is not checked.

Checks of Target and Non-Target Lesions:

Check 4: List of lesion records where the method of measurement does not match the method used for the lesion at baseline. With few exceptions, if the method of measurement changes from that used at baseline, then the data could be unusable or the results not evaluable.

Check 5: List of lesion records where the method of measurement is not from the set of approved methods for the study. If the method of measurement is not from the set of approved methods for the study, then the data could be unusable or the results not evaluable.

Check 6: List of lesion records where the location of the lesion does not match the location listed at baseline. This list identifies potential lesion tracking issues and such records need to be queried to ensure that the data are usable.

Check 7: List of lesion records where visit or assessment number is missing. It is important for the visit information to be recorded correctly at every assessment. This check ensures that all data are present and are available to be utilized in the response assessment.

Check 8: List of lesion records that are complete duplicates. This is a surprisingly common occurrence.

Check 9: Gaps in visit or assessment sequences. This check identifies potentially missing data.

Checks of Investigator's Manual Evaluation of Response:

Check 10: List of records where the visit is missing. The lesion responses as calculated on the site and entered on the CRF need a corresponding visit value for the data to be usable. This can also be programmed into the CRF to make it compulsory for the visit record to be entered before the assessment is entered.

Check 11: List of records without corresponding target/non-target lesion information at the same assessment.

Check 12: List of records that are complete duplicates. Duplicates should be eliminated from the source data.

Check 13: List of records with investigators response recorded on the CRF is not equal to the programmatically calculated response.

CONCLUSION

RECIST is a widely accepted evaluation criteria for oncology studies involving solid tumors. Although somewhat complex, RECIST can be used to determine primary or secondary efficacy end points. The set of data collected to calculate the RECIST response is fairly large and there is the potential for inconsistencies in the data which would negatively impact tumor evaluations. The intent of the authors is not to provide a deep understanding of the RECIST guidelines, but to equip the reader with a basic understanding of data collection issues and forewarn about potential inconsistencies in the data that can lead to difficulty in determining end-points. The authors have presented several checks that should be implemented at the CRF design stage or within the subsequent SAS checks. Satisfactory resolution to most of the queries generated through these checks should result in a larger pool of data being available for analysis and also result in better quality results. Cleaner data should also lessen the complications and complexity of analytic programming.

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