Although the value of The Response Evaluation Criteria in Solid Tumors (RECIST) in standardizing response evaluations in clinical trials is well recognized, the practical use of RECIST together with the rapid development of imaging techniques and cancer treatments have highlighted the limitations of RECIST and the need for updated criteria. This white paper is a review of the most important differences between the original RECIST and RECIST 1.1. Moreover, it anticipates some of the practical challenges and shortcomings with RECIST 1.1 along with PAREXEL’s recommended clarifications or adaptations for correct and consistent application of RECIST 1.1 to specific trial indications.
The Response Evaluation Criteria in Solid Tumors (RECIST) were introduced in 2000 by a task force set up by the European Organization for Research and Treatment of Cancer (EORTC), the National Cancer Institute of the United States, and the National Cancer Institute of Canada. Key features of the original RECIST included definitions of minimum size of measurable lesions, instructions on how many lesions to follow (up to 10; a maximum five per organ site), and the use of unidimensional, rather than bidimensional, measures for overall evaluation of tumor burden.

The RECIST Working Group, consisting of representatives from academic research organizations, government and industry, together with imaging specialists and statisticians, has recently updated RECIST (to version 1.1) and published the revised criteria in the European Journal of Cancer (Eisenhauer et al). A >6500 patient database was compiled, from which inferences were made that inform the revisions. RECIST 1.1 aims towards providing answers and clarity on a series of issues that have arisen since RECIST first came out in 2000. Amongst these were whether fewer than 10 lesions can be assessed without affecting the evaluation of treatment response; how to apply RECIST in trials where the primary endpoint is progression based (not response); how to handle the assessment of lymph nodes; and, whether response confirmation is truly needed.

Unidimensional measurements remain the backbone of RECIST 1.1. Several publications have confirmed the validity of unidimensional measurements (in contrast to bidimensional or three-dimensional) and they seem to perform well in most solid tumors as noted in the RECIST 1.1 publications.

RECIST 1.1 remains grounded in the anatomical assessment of disease. Although the group acknowledged the need for continuous appraisal of rapidly advancing imaging technologies, such as functional imaging, they did not believe that there is at present sufficient standardization and widespread availability to recommend adoption of these alternative assessment methods. The only exception to this is in the use of FDG-PET imaging as an adjunct to determination of progression.
DETERMINATION OF OVERALL TUMOR BURDEN

MEASURABILITY OF TUMOR AT BASELINE

While the original RECIST defined measurable lesions as \( \geq 20 \) mm with conventional techniques or as \( \geq 10 \) mm with spiral CT scan, RECIST 1.1 defines measurable tumor lesions as those with a minimum size of:

- **10mm by CT scan** (CT scan slice thickness no greater than 5 mm). When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans but not for chest). If MRI is performed, the minimum size for a measurable lesion should be 10 mm or twice the slice thickness (plus any gap), whichever is largest.

- **10mm caliper measurement by clinical exam** when lesions are superficial (e.g., skin nodules). Lesions which cannot be accurately measured with calipers should be recorded as non-measurable. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken.

- **20mm by chest X-ray.** Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

MALIGNANT LYMPH NODES

While the original RECIST didn’t include specific considerations for assessment of lymph nodes, RECIST 1.1 defines:

- **Pathologically enlarged lymph node as a node \( \geq 10 \) mm in the short axis**

- **Measurable lymph node as a node \( \geq 15 \) mm in the short axis when assessed by CT scan**

- **Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed**

- **Only the short axis of these nodes will contribute to the baseline sum. Nodal size is normally reported as two dimensions in the plane in which the image is obtained.**

- **Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. Thus, when lymph nodes are included as target lesions, the ‘sum’ of lesions may not be zero even if complete response criteria are met. In order to qualify for CR, each node must achieve a short axis <10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.**

Figure 2. Image A corresponds to a baseline CT scan showing an enlarged lymph node in the right axilla that measures 23 mm in the long axis and 19 mm in the short axis. Given its size in the short axis, the node is both abnormal and measurable. Image B represents a follow-up timepoint after treatment has been started and the node now measures 11 x 7 mm and it is therefore consistent with complete response.


Lymph node involvement by tumor is different from other soft tissue tumor sites. It is well recognized, that lymph nodes should be measured in the short axis as this is the best predictor of the presence of metastatic disease\(^3,4\). Moreover, when they are no longer involved with cancer, lymph nodes return to normal size yet they may remain visible.

The procedure for measurement of lymph nodes can be further clarified as follows: Measure the longest diameter of the node first. Then, determine the longest dimension perpendicular to the longest diameter and report that measurement as the short axis.

RECIST 1.1 does not provide a recommended minimum measurable lymph node size when slice thickness is greater than 5 mm. In the interest of consistency, it seems prudent to prospectively define if lymph nodes with a short axis of 15 mm can be considered measurable regardless of slice thickness or if the slice thickness should be doubled similarly to non-nodal target lesions (e.g., if slice thickness is 10 mm, measurable lymph nodes should be 20 mm in short axis).

**NON-MEASURABLE LESIONS**

RECIST 1.1 considers the following non-measurable lesions: All lesions with longest diameter <10 mm or pathological lymph nodes with >=10 to <15 mm short axis as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques. Of note, cystic and bone lesions from the original RECIST were removed from this list.

**BONE LESIONS**

Assessment of bone lesions in RECIST 1.1 is as follows:

- **Lytic bone lesions or mixed lytic-blastic lesions**, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability previously described.

- **Blastic bone lesions** are non-measurable.
Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

The authors are commended for clarifying the assessment of bone disease and defining the role and adequacy of specific imaging methodologies.

**Cystic Lesions**

Considerations in RECIST 1.1 for assessment of cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability previously described. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

It is well recognized that many lesions develop cystic/necrotic centers as the result of treatment and metastases in the liver may be cystic de novo (e.g., non-seminomatous germ cell tumors, ovarian cancer). On the other hand, it is known that certain 'cystic tumors' increase in size because of the treatment itself or when treatment is effective (e.g., non-seminomatous germ cell tumor metastases). Therefore, it might be advisable to provide comments documenting changes in tumor composition.

**Lesions with Prior Local Treatment**

RECIST 1.1 provides additional guidance for the assessment of lesions that have undergone local treatment as follows:

- Lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Although lesion progression may be readily documented at investigator sites, for logistical reasons it may be challenging for independent reviewers to determine such lesion progression (e.g., evaluation of lesion progression requires collection of an additional scan that predates the baseline/screening scan).

RESPONSE ASSESSMENT

METHOD OF ASSESSMENT

RECIST 1.1 includes the following details: The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

There is a caveat to RECISTT 1.1’s statement that the same method should be used to assess each lesion. There may be instances where MRI is considered the modality of choice to image patients that develop a medical condition preventing them from receiving iodinated contrast agents while on-study. In these cases, a follow-up MRI will be compared to a baseline CT scan. Therefore, it would be of importance to define how the MRI scan will be assessed and whether measurements can be performed or not. Typically, we rely on the independent reviewer’s expertise to decide whether any measurements rendered on the MRI scan would be accurate (e.g., baseline CT and follow-up MRI have comparable parameters).

TUMOR MARKERS

Although according to RECIST 1.1, tumor markers alone cannot be used to assess objective tumor response, if markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis.

Generally, PAREXEL recommends allowing patients with non-measurable disease only in certain settings/indications (e.g., ovarian cancer) and have Regulators prospectively endorse the protocol design, as applicable. Despite Protocols requiring presence of measurable disease at baseline for patient inclusion, it is advisable to define how patients, for whom independent reviewers cannot verify presence of measurable disease, will be assessed during independent review. While deciding whether to allow patients without measurable disease at baseline, Sponsors may want to consider the likelihood that progression related endpoints may be slightly biased in favor of no progression (e.g., non-target lesions assessed as non-CR/non-PD could qualify for progressive disease if they would have been measured).

CYTOLOGY, HISTOLOGY

RECIST 1.1 suggests that these techniques be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

PRESENCE OF MEASURABLE DISEASE AT BASELINE

RECIST 1.1 proposes that only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. In studies where the primary endpoint is progression related, the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

TARGET LESIONS

The original RECIST recommended that all measurable lesions up to ten [10] lesions in total and a maximum of five [5] lesions per organ be identified as target lesions. RECIST 1.1 advocates for a maximum of five lesions total (and a maximum of two lesions per organ). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the
largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters.

The RECIST Working Group provided evidence attesting to the comparability of the response assessments between 10 and 5 target lesions. Given that intra- and inter-reader variability is known to increase as the number of target lesions decreases, site and central interpreters are strongly encouraged to select 5 target lesions when possible.

**TARGET LESIONS THAT BECOME “TOO SMALL TO MEASURE”**

While there was no specific guidance in the original RECIST, RECIST 1.1 recommends that target lesions that become too small to measure be handled in the following manner: While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being ‘too small to measure’. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. This default value is derived from the 5mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error.

**TARGET LESIONS THAT SPLIT OR COALESCE**

In contrast to the original RECIST, RECIST 1.1 provides specific guidance for the assessment of splitting and merging target lesions. When non-nodal lesions ‘fragment’, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the ‘coalesced lesion’.

**NON-TARGET LESIONS**

As in the original RECIST, RECIST 1.1 states that measurements of non-target lesions are not required and they should be followed qualitatively as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’. The article also points out that it is possible to record multiple nontarget lesions involving the same organ as a single item on the case report form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).
The concept of progression of non-target disease is explained as follows: When the patient also has measurable disease, to achieve ‘unequivocal progression’ on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest ‘increase’ in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare. When the patient has only non-measurable disease, the same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in ‘volume’ (which is equivalent to a 20% increase in diameter in a measurable lesion). While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it often impossible to do so, therefore the increase must be substantial.

NEW LESIONS

RECIST 1.1 provides additional insight with respect to new lesions. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient’s baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a ‘new’ cystic lesion, which it is not.

Furthermore, a lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient’s brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

LESION REAPPEARANCE

In contrast to the original RECIST, RECIST 1.1 includes detailed guidance for assessment of lesion reappearance. If a [target] lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient’s response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient’s tumor had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumor status was a PR or SD and one [target] lesion which had disappeared then

Figure 5. Image A represents a baseline CT scan showing diffuse peritoneal nodularity (long and short arrows), as well as, enlarged lymph nodes in the retroperitoneum (arrowhead), all of which were classified as non-measurable (non-target) lesions. Image B corresponds to a subsequent CT scan demonstrating unequivocal progression of non-target disease, in particular, the peritoneal involvement on the left side of the abdomen (short arrow).
reappears, its maximal diameter should be added to the sum of the remaining (target) lesions for a calculated response and PD can only be declared based on the sum of all (target) lesions.

While no specific guidance is offered for the assessment of non-target lesion re-appearance, PAREXEL Informatics would typically recommend that the same principle be applied and that if the prior response status was either PR or SD, response at the current timepoint be determined based on the status of non-target lesions as a whole and the overall disease context. Conversely, if the prior overall response status was CR, the re-appearance of a non-target lesion would typically result in progressive disease provided that it is clearly unequivocal. Another aspect that is worth clarifying prospectively is how lesion re-appearance affects the nadir (smallest value since baseline). Our proposal would be to continue using the timepoint with the smallest sum of diameters as the reference to determine progression of target lesions even if it is different from the timepoint of target lesion disappearance. While the nadir for assessment of a reappearing non-target lesion would be the timepoint of lesion disappearance, we would recommend that response be determined in the context of the overall disease status at the timepoint of reappearence.

RESPONSE CRITERIA FOR TARGET LESIONS

The original RECIST and RECIST 1.1 share the same target response assessment guidelines, with the exception of lymph node assessment and progressive disease requirements, as described below.

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to <10 mm.

- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

It is anticipated that the implementation of an absolute increase in the sum of the diameters for progressive disease in target lesions will offset the potential for PD being called early or inappropriately as result of a fewer number of target lesions in RECIST 1.1.

RESPONSE CRITERIA FOR NON-TARGET LESIONS

Non-target lesion response is assessed in a similar manner in the original RECIST and RECIST 1.1, with the exception of lymph node assessments, as described below. Also of note, the category of Incomplete Response/Stable Disease (SD) in the
original RECIST has been replaced with non-CR/non-PD in RECIST 1.1.

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions (as previously described). (Note: the appearance of one or more new lesions is also considered progression).

**TIMEPOINT RESPONSE**

The principles behind response assessment at each protocol specified timepoint are comparable in the original RECIST and RECIST 1.1. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2 should be used.

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

Interestingly, according to RECIST 1.1, the timepoint response may be PR or SD despite the fact that one or more non-target lesions were not evaluated. This reflects an overall shift in the importance of non-target lesion status in the overall response assessment and is in line with the new language in the article that recommends a cautious approach to declaring progressive disease on the basis of non-target lesions, especially in the face of response or stability in target lesions. In such circumstances it may

| 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 = in evaluable**

| 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* |
| Not all evaluated | No | NE |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |

**CR = Complete Response, PD = Progressive Disease, and NE = in evaluable**

*’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.*
be appropriate to assume that any non-target lesions that were not evaluated have not progressed.

Specifically, if target lesions are in complete remission and not all non-target lesions were evaluated, downgrading the overall response to PR is more conservative than concluding CR based on target lesions.

**FDG-PET**

According to RECIST 1.1, the use of FDG-PET scans is to be carefully considered, however, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible ‘new’ disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- **Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.**
- **No FDG-PET at baseline and a positive FDG-PET at follow-up:**
  - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD. Moreover, FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that FDG-PET may lead to false positive CR due to limitations of FDG-PET resolution/sensitivity.

While RECIST 1.1 defines a FDG-PET focus as positive if the uptake is greater than twice that of the surrounding tissue on an attenuation corrected image, at this time it does not allow for quantitation or change in magnitude over time of the PET loci. The new criteria also do not describe how to handle the scenario where a hot spot on PET corresponds to a target lesion that has markedly increased in size on the CT scan but the collective sum of diameters of all target lesions does not qualify for PD. Similarly, RECIST 1.1 fails to suggest what the response at the present timepoint should be for cases where there is a hot spot on PET during follow-up that is not associated with a new CT (or MRI) lesion and a baseline PET was not available. While timepoint response cannot be PD, it might be advisable to proactively define what timepoint response should be (e.g., NE, response assigned based on the status of the disease on all remaining imaging modalities, other).

**CONFIRMATORY MEASUREMENT**

While the original RECIST required confirmatory scans for response (CR or PR), RECIST 1.1 states the following: In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

There is a caveat to the guidance in RECIST 1.1. If secondary response related endpoints are of interest despite the primary endpoint being based on progression, it would be advisable to incorporate confirmatory scans for response or seek Regulatory endorsement of the Protocol design in a prospective manner. PAREXEL Informatics would also suggest that for trials with central review, sites perform a ‘confirmatory’ scan when PD is detected unless PD is clearly unequivocal. Alternatively, it might be worth considering independent review for ‘confirmation’ of PD. Both measures may reduce the incidence of informative censoring, based on patients being removed from the trial prematurely or inappropriately.
The following considerations could potentially be added for proper and consistent implementation of RECIST 1.1.

**RECOMMENDATIONS FOR APPROPRIATE AND CONSISTENT EVALUATION AND MEASUREMENT OF LESIONS:**

- Given that different window settings result in significant variations in the size and consistency of lung lesions, it is important that lung lesions be measured in optimal window settings based on their location and that consistent window settings are used for subsequent assessments of a given lesion. We would generally recommend lung windows, except for lesions that are peripherally or centrally located, which may be best evaluated in soft tissue windows.

- There are several potential pitfalls in the assessments of liver lesions. Not only administration of intravenous contrast for CT scanning is critical for evaluation of lesions in the liver, but also selection of the optimal scanning phase for evaluation. In addition to using the same scanning phase for subsequent lesion assessments, PAREXEL Informatics typically recommends that the ‘enhancing rim’ be consistently included in the measurement, when present.

Hypervascular tumors, such as Neuroendocrine tumors or Hepatocellular carcinoma, may benefit from the acquisition of triphasic CT scans of the liver. In this context, it would be important to prospectively define the scanning phase to be used for measurement of hepatic lesions.

The phase that may display the tumors more consistently and reproducibly may not be the phase showing the full extent of the tumors. Even if tumors are slightly undermeasured, reproducibility would typically be given preference. However, MRI is likely to show the boundaries of hypervascular liver.
lesions in a more consistent and predictable manner and is less dependent on the administration of intravenous contrast and timing of the scan. Therefore, MRI scanning may be a good alternative to image hypervascular tumors provided adequate availability and proficiency at participating centers.

- Certain types of tumors may be difficult to measure accurately in one dimension. An example of this is en-plaque lesions. Depending on their location, en-plaque lesions can have their long axis in the imaging plane or outside of it, thus, linear measurements do not always capture the full extent of the lesions. Furthermore, en-plaque lesions frequently regress in the short axis plane rather than in their long axis.

- Another aspect that should be factored into the evaluation of response to treatment is the development of intra-tumor calcification or hemorrhage, which may develop during treatment and could influence changes in tumor size. The interpreter should be encouraged to provide comments on the development of such tumor changes as response may not be well assessed by simple measurements in these cases. Calcification in response assessment may be seen in metastases to the lymph nodes, liver or peritoneum.

**CONSIDERATION FOR CONSISTENT TARGET LESION SELECTION:**

- RECIST 1.1 does not provide specific guidance on the definition of ‘organ’ in relation to the maximum number of target lesions that can be selected per organ. We would recommend that such detail be prospectively defined and would typically consider bilateral organs (e.g., lungs, kidneys, adrenals) as one organ. Similarly, it would seem pertinent to define the concept of ‘organ’ as it relates to lymph nodes. PAREXEL Informatics would typically consider all lymphatic chains or subregions as one organ.

**SUGGESTIONS FOR PROPER DETERMINATION OF RESPONSE ASSESSMENT:**

- Similar to the RECIST 1.1 guidelines for assessment of lymph nodes, we would recommend that specific assessment guidelines be implemented to designate complete response in other structures that are present under normal conditions but that may become diffusely involved with tumor, such as, the adrenal glands and the bladder wall.

- Given that most tumors within the body (except for lung nodules) grow and regress irregularly and some cancers may display mixed responses, the sum of all lesions measured may ‘disguise’ differential tumor responses or not truly reflect the overall disease status. In such circumstances, the interpreter should be encouraged to provide detailed comments to explain possible response ‘discrepancies’. Also, misclassification of response can often be the result of the selection of fewer and smaller target lesions and so interpreters should be encouraged to select the maximum number of target lesions and give preference to large lesions, whenever possible.
If the adoption of RECIST 1.1 is unworkable for practical or other purposes, the major objective is unlikely to be realized. Therefore, site training and coaching seems more important now than it was during the original RECIST era.

As with any other criterion involving tumor measurements, the key to accurate, reproducible assessment of response to treatment in both clinical practice and clinical trials is the involvement of a radiologist experienced in oncological imaging. The assessment of response not only requires precise tumor size measurements, but also requires an in-depth understanding of the complications of cancer therapies and a detailed knowledge of the disease-specific patterns of tumor worsening.

Sponsors may be wondering when it would be appropriate to transition to RECIST 1.1. Typically, our advice is if a comparison to historic data or previous trials of the same compound or other indications are planned, one may want to continue applying original RECIST. If RECIST 1.1 contains features that are particularly important for a specific trial and indication (e.g., assessment of progression, bone lesions, non-measurable disease at baseline only, lymph nodes, etc.), then it may be worth considering adopting RECIST 1.1. Importantly however, while regulatory feedback is still limited, sponsors may opt to incorporate RECIST 1.1 features into the original RECIST as ‘modifications’ or ‘clarifications’. This may be particularly relevant for late phase and registration studies. On the other hand, for early phase trials (I – II) sponsors may consider ‘trying’ the advantages of RECIST 1.1 and pursue Regulatory endorsement, as applicable.
WHEREVER YOUR JOURNEY TAKES YOU, WE’RE CLOSE BY.