

Onsite Image Evaluations and Independent Image Blinded Reads: Close Cousins or Distant Relatives?

TO THE EDITOR: We respectfully submit the following letter is in response to the recent article by Dodd et al¹ in *Journal of Clinical Oncology* titled "Blinded independent central review of progression-free survival in phase III clinical trials: Important design element or unnecessary expense?"

In our view, the authors provided a unicameral view of issues surrounding the utilization of blinded independent image review. The title of the study suggests an evaluation of the performance of blinded reads using progression-free survival (PFS) in phase III clinical trials; however, their assumptions and conclusions are primarily based on a single-site phase II study. And while they posit that blinded reads may be an unnecessary expense, there was no cost/benefit analysis performed.

The authors acknowledge "differences in response rates determined by investigator and independent assessments,"¹ with the latter frequently reporting lower response rates. However, we disagree with their statement that "the extent to which these differences result in systematically biased comparisons is not obvious." We agree that there are differences, but there is no validity in attempting to compare these data sets as they are evaluated in completely different fashion.

While much attention has been paid to the need to standardize the performance and acquisition of imaging in oncology trials, the onsite image evaluation process remains uncontrolled. Onsite image evaluations are performed by personnel with variable medical imaging experience without dedicated training and/or testing of the site readers on the response criteria. Generally there is a pool of readers attached to each site who make measurements and complete case report forms. Because, not infrequently, radiologists are not coinvestigators and have not signed Form 1572, there is no imaging expert oversight on performing the image acquisitions, and there is no dedicated training for performing the image evaluations that conform to the requirements of a multicenter trial (eg, Response Evaluation Criteria in Solid Tumors, Cheson, and so on).

While the standard of care for clinical interpretation of images by a radiologist at a site is sufficient for patient management, a radiologist's clinical report is generally insufficient for selecting and measuring target and non target lesions required in a clinical trial. In many instances, the oncologist selects target lesions on images and makes tumor measurements. Our confidential communications with core laboratory officials reveal that at many sites, image evaluation is not even performed by a physician, but by the site coordinator.

On the contrary, in independent blinded evaluations, images on which efficacy is based are almost always read by radiologists

who are trained in the related specific indication. Before the readers may begin evaluation of the images, they are trained and tested in a standardized and transparent fashion, particularly on the response criteria or any variations to standard response criteria which may be present in a study. Bias is reduced by providing only necessary imaging information, and by omitting clinical data, dosing data, imaging site location, and so on. Bias is further reduced by a variety of blinded read designs, including multiple randomization schemata.

We agree that central review by a small number of reviewers with specific expertise lessens measurement variability. In addition, prospective trial-specific training and testing of readers further reduce measurement variability. Dodd et al¹ do not take into account the inherent variability in the appearance of lesions on imaging scans. While a nonradiologist may believe they can accurately measure a well-circumscribed round lesion, complex lesions with surrounding edema, hemorrhage, calcification, adjacent arterovenous shunting, or simply ill-defined margins require a trained radiologist to accurately distinguish tumor from nontumor imaging effects.

Since the imaging data is evaluated at the sites by untrained clinicians and trial personnel, any attempt to evaluate inter- and intrareader variability at the sites is futile. In contrast, inter- and intrareader variabilities are quantifiable in blinded readings.

Another reason that the comparison of onsite and blinded read data is invalid is that a single response per subject is derived from each site which is not just based on imaging data, but includes clinical data as well. These data are generated by a multitude of readers with varied experience who are located in different countries with different medical systems and clinical practices. Whereas the blinded read provides pure imaging data results which is agreed on by at least two expert radiologists who have similar qualification and experience in a particular indication.

We agree with the author that blinded reads performed at the end of the trial unfortunately can result in censorship of patients related to progression when PFS is an end point, and negatively affect the study outcome. New technologies have made it possible for near real-time independent image evaluation; however their use in clinical decision making should only be limited to the information offered by the image evaluations, and clinical and other data must be taken into account when the site makes a decision regarding patient management. (Blinded reads should not substitute for clinical judgment in patient management.)

Technology now allows for rapid turnaround of patient images within a few days at most and we believe should be employed to confirm progression before removing a patient from a study when PFS is an end point.

We believe that, even in double-blind trials, site image evaluations cannot substitute for independent evaluation because the latter is more controlled, more rigorous, and more transparent. The cost of blinded reads should be weighed against the cost of the quality of data created from uncontrolled evaluations at clinical sites as well.

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REFERENCE

1. Dodd LE, Korn BF, Jaffe CC, et al: Blinded independent central review of progression-free survival in phase III clinical trials: Important design element or unnecessary expense? *J Clin Oncol* 26:3791-3796, 2008

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