



A “Second Opinion” for Subjective Endpoints: The Case for an Endpoint Assessment Committee

Introduction to EAC

The FDA's recent guidance on imaging standards and increased frequency of requests for a Blinded Independent Central Review (BICR) for registration trials and other Phase III studies have made Endpoint Assessment Committees (EAC) more important to securing regulatory approval. Often the primary endpoint of these trials is based on a subjective assessment of the patient's overall status determined by a physician-rated or even patient-reported assessment of imaging, laboratory, pathology, biopsy, and clinical data. In the recent past, these assessments were the purview of the principle investigator at the site. This has always been a problem in an open-label trial, where a potential for bias exists. In these cases, regulatory agencies request that the data be subjected to a BICR.

BICRs have the potential to minimize bias and increase the precision of trial data by utilizing multiple independent readers (in a multi-reader BICR). Currently most multi-reader BICRs are performed primarily for radiological assessments. This is in part attributed to both an understanding of the variability associated with image interpretations and the growth of teleradiology, which allows multiple readers to make rapid assessments of imaging data with software that can automatically send discrepant reads to an adjudicator¹. Rapid multi-reviewer BICRs of other subjective trial data (safety, pathology and/or dermatology data) have been hampered by the timely completion of assessments and are often challenged by the logistics of performing these reviews in a paper environment. An additional lengthy review and, if needed, adjudication process limits sponsors' ability to make timely decisions based upon BICR findings. As telemedicine improves, the cost of an external expert review of complex and variable subjective data becomes more practical, thus facilitating the growth of digital EACs^{2,3}.

EACs and BICR: When and Why?

EACs can be of tremendous help in ensuring not only accuracy and objectivity of assessment, but also comprehensiveness of efficacy results for regulatory submission. No specific FDA guidance documents have been issued in draft or final form that provide recommendations regarding the use of EACs and BICRs. But the FDA's 2011 draft Guidance Standard for Clinical Trial Imaging Endpoints can be used as an effective road map in exploring the value and use of BICR⁴.

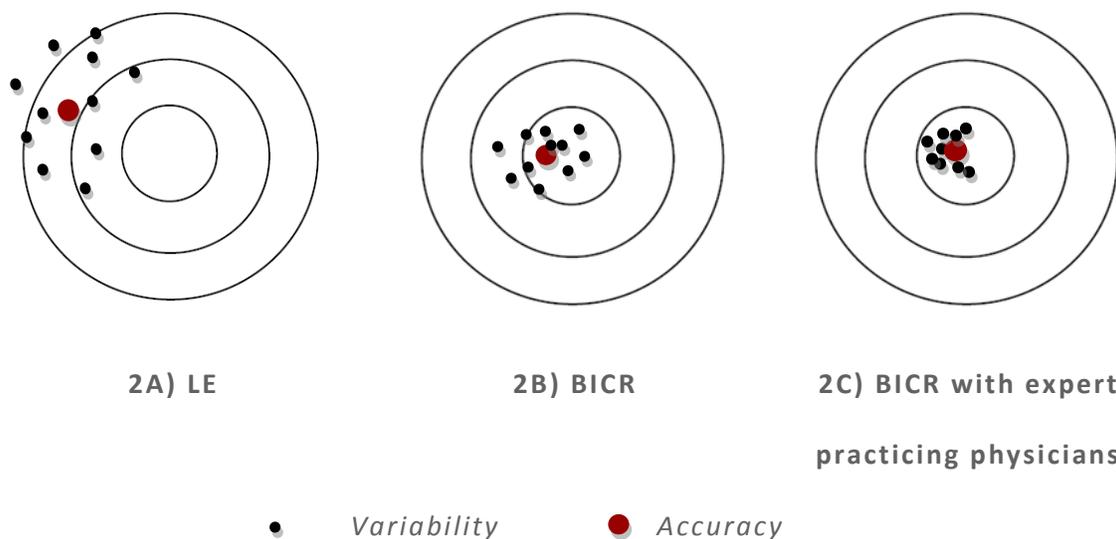
The draft guidance document suggests that in registration trials, when clinical site data interpretation is variable and results of measurements are important to trial success, a BICR can provide consistent results through verifiable and uniform reader training as well as ongoing management of reader performance.

The FDA takes an even stronger stance regarding open-label trials, saying BICRs are critical to the control of bias and can provide reader training and performance management to minimize variability⁴. The BICR acts as a mechanism not only to eliminate bias in open-label trials, but also to potentially increase accuracy and precision of interpretation. The minimization of variance in the assessments made by a BICR is attributed to the ability to train, test and retrain, if needed, a small, cohesive group of independent reviewers (IR) (<10) as compared to a large number (>100) of local evaluations (LE). IR precision can be honed through an iterative process of testing and then team training with a focus on difficult cases (i.e., adjudicated cases). This type of "selective performance testing" allows ongoing inter-reader assessments of performance at any time with all or a subset of IRs. Independence and consistency in the interpretation of the clinical endpoints across different geographic areas and throughout the course of a study are primary challenges that can be addressed using a BICR.

The increased accuracy anticipated from a BICR is attributable to the use of a unified team of board-certified, subspecialty-trained practicing physicians who have research experience in performing complex assessments.

Figure 2 is a pictorial representation of different read environments. Figure 2A represents the LE with relatively high variability (black dots) and moderate accuracy (red dot). Figure 2B represents a BICR where variability is better controlled through better training and testing, but the accuracy is lower since BICR are not subspecialty-trained, practicing physicians. Figure 2C represents a BICR that demonstrates better accuracy and precision than 2A or 2B since training and testing can be performed and readers are board-certified, sub-specialists.

Figure 2: The Effect of Experience and Training on Accuracy and Precision



Interpreting Subjective Data

When considering the need to support an EAC, sponsors should review the same issues addressed by the draft FDA imaging guidance document regardless of the type of data. Data can be a clinical outcome determined by an oncologist, skin lesion size determined by a dermatologist, or even histopathology assessed by a pathologist. If the subjective information is critical to the trial’s success, then the following questions must be addressed:

Does the subjective information require quantification that is difficult to perform at the site level?

When analyzed by site personnel, is the subjective information variable?

Is the trial open-label? Or, if the trial is blinded, is there potential for the treatment arm to become un-blinded by specific treatment-related toxicity?

And most importantly, can a BICR composed of experts potentially increase precision and decrease variability of the assessment?

If the answer to these questions is yes, sponsors should seriously consider a BICR. Since all trials aim to minimize bias and variability and maximize accuracy, a BICR of important subjective data is integral to a trial's success, even when imaging is not a primary component. The FDA itself touches on this broader use of BICR in its guidance document on data monitoring committees⁵. Furthermore, working with a specialized imaging CRO with EAC expertise across multiple clinical areas can streamline the planning and implementation process of an EAC review.

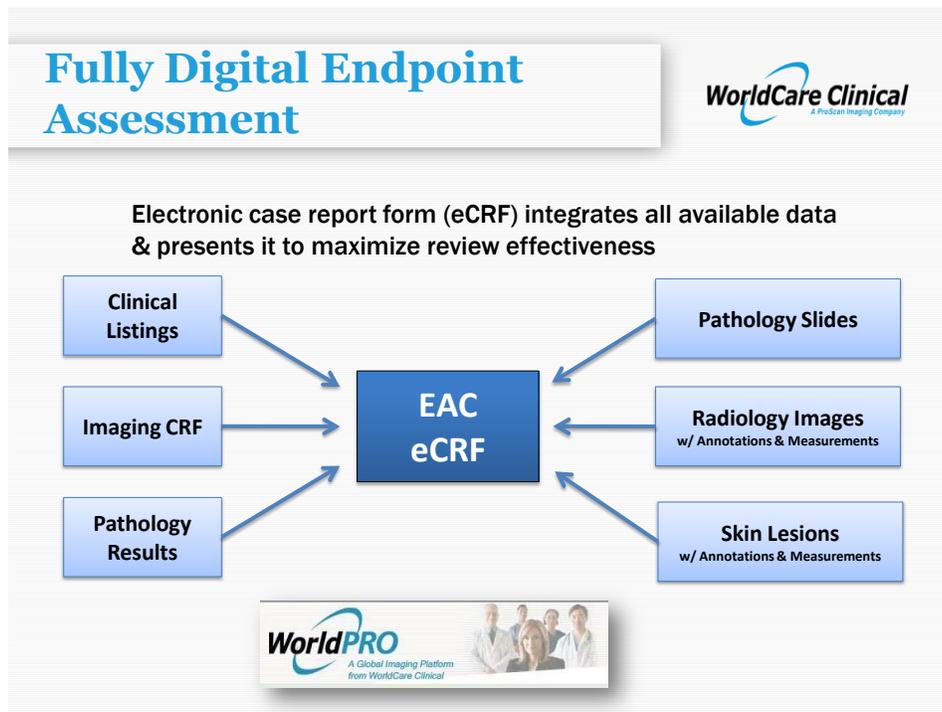
Role of the Contract Research Organization (CRO)

Identifying which subjective assessments should be independently reviewed is not always straightforward. A general rule is to focus only on primary and important secondary endpoints. CROs with experience in EACs possess the knowledge and experience in both determining if the subjective assessment needs to be independently reviewed and understanding what type of training and retesting of independent reviewers needs to be performed during the trial to ensure precision and accuracy are maintained. Understanding variability requires the ability to deal with complex data sets and statistically account for chance agreement. CROs with EAC experience regularly deal with a limited pool of IRs (i.e., subspecialty-trained physicians) and have criteria for testing and retraining. This requires both strategic relationships with leading academic and tertiary care institutions and advanced digital portals so that a review of images and other data can be done at remote locations.

The CRO's technological approach can also have a critical impact on the successful implementation of an EAC and subsequent acceleration of the drug development process. The right approach can help facilitate the coordination of data collection and the integrated assessment process to optimize workflow and ensure data validity. A fully-digitized process that removes bias in document data handling is especially important for regulatory submission.

Portals that are part of a larger, web-based, auditable technology can provide a central point for all trial activity and allow project managers, EAC members, and on-site clinicians to coordinate the assessment procedure. Particularly important are automated procedures for quality control, such as the ability to determine the need for adjudication on a specific case and to forward the data to an appropriate adjudication reviewer. This way, the adjudication reviewer can be distinct from the primary reviewer and can possess specified qualifications (e.g., certain level of training and/or experience). These kinds of specialized capabilities will become increasingly important as clinical data and the accompanying reports go digital. Additionally, the ability to provide a digital audit trail coupled with an interactive database that combines clinical information with images, EAC and adjudication results will be a necessity for FDA submission and approval.

CROs with an automated data management system in place can streamline all data capture and transmission, while displaying and launching all relevant data from the electronic case report form (see Figure 2).



When conducting a melanoma trial, for example, the data can include clinical site data, independent radiological images with annotations and measurements, pathology reports with histology images, and skin lesion images with annotations and measurements.

Looking Ahead

EACs are helping to reformat the landscape of complex drug development. Understanding how EACs fit into the trial process and their potential for improving the chances of regulatory success will become a priority for sponsors in the coming years, and so the quality control measures and technology requirements necessary for their effective implementation demand our serious attention. For regulatory review, a prudent “second opinion” utilizing a BICR may be the key to success.

WCC Delivers the Definitive Second Opinion with Independent Review Services from World-class, Practicing Specialists

WorldCare Clinical's Endpoint Assessment Committee (EAC) services are designed to efficiently manage the EAC and independent assessment process for sponsors looking to improve validity of subjective endpoint assessment by incorporating a more holistic and experienced evaluation of effect important to the FDA.

WCC leverages its relationship with Massachusetts General Hospital (MGH) to provide subspecialty-trained physicians from across departments for reads. From radiology and dermatology to oncology, cardiology and neurology, WCC provides blinded independent assessments by subspecialty-trained, board-certified experts, who are trained by WCC under a uniform system to maximize the precision and accuracy of data interpretation.

Using WCC's WorldPRO technology, WCC performs a digital assessment that collates all clinical data, including radiology, pathology slides, photography, patient feedback and more, in a user-friendly format, for a digital central review and streamlined submission to the FDA. Unique to WCC, EAC reviewers are able to make their own assessment, saving measurements on radiology, dermatology and pathology images to maintain critical audit trails.

WCC offers total planning and execution of an EAC for any study with subjective endpoints. Specific services include:

- Sourcing of members based on WCC recommendation or sponsor preferences
- Training for all members under a committee chair to minimize variability between assessments
- Allocation of roles and responsibilities for each member, including oncologists or other therapeutic specialists, radiologists, and pathologists
- Design of the EAC charter, including decision algorithms for response assessment
- Determining work load and time estimates, including training and testing programs, in conjunction with the sponsors and EAC chair
- Automated data collection and management, including clinical site data, independent radiological assessments, pathology reports with histology images, etc.
- Automated quality control, including adjudication, digital audit trails, and interactive database with all clinical information and assessment data for FDA review.

To learn more about how partnering with WCC will help you improve the validity of your subjective endpoint assessments, please visit: <http://www.wcclinical.com/our-expertise/#page-EAC-Services> or call 1 (888) 816-4721.

About WorldCare Clinical

WorldCare Clinical (WCC) is a leading imaging CRO that employs imaging expertise, innovative technology and operational excellence to maximize the precision and accuracy of a blinded independent central review of clinical trial data. Originally founded in 1992 by the Massachusetts General Hospital (MGH) Department of Radiology, WCC has evolved as an independent company while maintaining a strategic relationship with MGH. With a 20-year focus on imaging trials and their specific requirements, WCC provides sponsors with extensive medical, operational, and image management expertise in support of even the most complex study designs. For more information, visit www.wcclinical.com.

¹ Walovitch R, Tomera J. A Team Approach: How independent endpoint assessment committees can overcome imaging limitations. *Applied Clinical Trials* 2010 May 1.

² Tyner C, El-Assi Z. Electronic Endpoint Adjudication: How an integrated, EDC-based system can optimize the endpoint process. *Applied Clinical Trials Supplement* 2010

³ Walovitch R, Memisoglu A, Walsh D. Adjudication in Oncology Trials: A Concept Whose Time Has Come. *Applied Clinical Trials* 2009.

⁴ FDA. Guidance for Industry: Standards for Clinical Trial Imaging Endpoints (DRAFT Guidance). 2011 Aug 8

⁵ FDA. Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees. (2006).