



# Adjudication in Oncology Trials: A Concept Whose Time Has Come

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The gold standard clinical endpoint to demonstrate clinical benefit in oncology trials is overall survival (OS). However, evaluating OS in a clinical trial has several drawbacks. An analysis of OS requires large patient numbers and much longer follow-up compared to other endpoints. Trials based primarily on patient survival are therefore very expensive and time consuming, thus delaying approval as compared to using other accepted primary efficacy endpoints. In addition, overall survival may be confounded by subsequent therapies. Endpoints such as time to progression (TTP) or objective response rate (ORR) are not confounded by subsequent therapies and are often used in patients with solid tumors. These tumor assessment endpoints are based on subjective evaluations such as clinical or radiological observations and thus are not as objective as OS.

In addition to using these standards, certain design features can be incorporated into a clinical trial to minimize bias and increase precision and accuracy of potentially subjective observer-dependent assessments. To increase uniformity of efficacy endpoints based on tumor assessments, special attention must be given to blinding of patient data and the use of central (external) review committees is recommended. Without independent central review, bias stemming from the sponsor or study monitor's familiarity with particular patients may influence endpoint assessments. Moreover, the validity of the conclusions drawn may be questioned if stringent processes are not put in place to reduce the potential for bias.

Efforts to encourage uniform interpretation of endpoint data among assessors and minimize assessment variability across the study should be made and be part of the study design prior to patient enrollment. One study design intended to reduce variability of endpoint assessments is double-blind read with adjudication. In this design, radiological images are initially assessed by multiple, often two, independent blinded reviewers. If the reviewers disagree, then a third adjudicating (i.e., tie-breaker) assessment is made by an additional reviewer who may or may not be blinded to prior assessments. To further minimize variability, all independent reviewers should be uniformly trained and periodically tested to evaluate intra- and inter-reader variability.

Implementation of double-blind read with adjudication in Phase III oncology trials became more widespread in the late 90s based, in large part, on the need to have accurate, unbiased radiological assessment in patients with solid tumors. This need arose partly because of the addition of Subpart H to new drug approval regulations promulgated in 1992. These regulations allowed for accelerated drug approval using surrogate endpoints involving radiological assessment of tumor sizing. By the end of the millennium, however, it was becoming apparent that although endpoints such as ORR can support regulatory approval in select solid tumors, relief of tumor-related symptoms and drug toxicity should also be considered when making approval decisions.

Moving into the 21st century, solid tumor trials started using independent endpoint assessment committees that used the data from the independent imaging assessment committee in conjunction with information from the sites. Although these endpoint assessment and adjudication committees used a combination of independent blinded imaging data and clinical site data, their goals and processes were the same as the independent imaging assessment committee (listed below).

These processes are minimal requirements and additional important considerations may need to be addressed. For example, a defined procedure for adjudication between a site physician's assessment and assessments made by a central review committee may be required. These adjudications can be very complicated and must be prospectively defined and agreed upon by the Food and Drug Administration (FDA) in order for them to have any regulatory value.

For Phase III registration trials, the FDA and other regulatory agencies must be able to reach objective and definitive conclusions from data. Independence and consistency in the interpretation of the clinical endpoints across different geographic areas and over the course of the study is a primary challenge that is met by using a central assessment and adjudication committee. The successes of central review committees and, by extension, the success of the trials depend on

**INDEPENDENT  
IMAGING  
ASSESSMENT  
COMMITTEE**

**GOALS**

- Remove bias**
- Increase accuracy**
- Increase precision**

**PROCESSES NEEDED**

- **Prospectively defined documentation**
- **Quality control and quality assurance for handling data**
- **Criteria for selection of committee members and training plans for those members**
- **Clear definition of outcome categories**
- **Defined procedure for adjudication**

prospectively-defined procedures, which are agreed upon by the FDA. In addition, the FDA prefers that radiological assessments be done by a central review. This role is almost exclusively performed by an imaging core laboratory. Imaging core laboratories or central imaging laboratories have historically been focused on managing the collection of consistent, high-quality imaging data and ensuring minimal variability through a central reading committee. Integration of clinical data with radiological data is often required to make an assessment and thus quality control procedures, similar to those for imaging data, should be implemented.

WorldCare Clinical (WCC), LLC, in collaboration with sponsors and the FDA, has successfully implemented central review committees resulting in multiple drug approvals. The success of this collaboration is based in part on the rigorous approach WCC takes to remove bias and document data handling, endpoint assessment and adjudication procedures. WCC's recent advance in automating this process is the WorldPro® image and assessment data management platform. It consists of an anonymization image upload tool, a customizable database, and a comprehensive web portal that centralizes all trial activity via a fully-compliant, secure, web-based auditable technology. Among WorldPro's automated procedures is the ability to determine if a case needs adjudication and forward the image to an appropriate adjudication reviewer. In this manner, the adjudication reviewer can be distinct from the primary reviewer and can possess specified qualifications (e.g., certain level of training and/or experience). WorldPro's ability to provide a digital audit trail coupled with an interactive database that combines clinical information with the images and endpoint assessment committee and adjudication results is a unique capability of the system. Since use of WorldPro does not require specific hardware or in-depth training, it allows for easy transfer of the integrated database to the FDA or other regulatory agencies.

In conclusion, endpoint assessment and adjudication committees are becoming an important part of oncology drug development. Understanding the regulatory requirements of these committees and the process needed to make them successful is of critical importance. ❖

WorldCare Clinical (WCC) has a 17-year heritage of providing end-to-end imaging services for clinical trials in the pharmaceutical, biotechnology, and medical device industries. WCC's highly trained, full-service CRO team includes in-house radiologists, regulatory affairs specialists, biostatistics experts, data management professionals, advanced imaging scientists, and a project management team dedicated to solving the most complex trial study designs by maximizing the clinical value of imaging. Together with strategic partners at Massachusetts General Hospital and the University of Chicago Medical Center, WCC offers support for everything from study design to regulatory submission, to ensure an efficient and successful trial process and outcome.

We hope that you have enjoyed the inaugural issue of **FOCUS**. The field of clinical studies brings together participants from diverse disciplines: industry, research, academic, medical, government and financial. We have attempted to provide a representative sampling of their perspectives. Let us know how we have done by sending comments to [focus@pharmanet.com](mailto:focus@pharmanet.com). Let us know, too, if we can add you to the **FOCUS** mailing list – and if you have ideas you would like to contribute to future issues.

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