

APPLIED CLINICAL TRIALS

YOUR PEER-REVIEWED GUIDE TO GLOBAL CLINICAL TRIALS MANAGEMENT

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The Role of Independent Review in Oncology Trials

Independent experts help reduce variability and bias in trials that use medical imaging.



PHOTOGRAPHY: COMSTOCK

Medical imaging in oncology trials is already well documented. Techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and conventional radiography can provide insights into drug safety and efficacy faster than traditional clinical endpoints. Adopting an imaging strategy, however, introduces challenges, particularly around the potential variability of imaging data collected in multicenter trials and the interpretation of that data. Centralized independent review of imaging data can reduce the variability and bias inherent in these types of trials.

The need for independent review

Ensuring consistency and lack of bias in clinical trials is a critical issue for sponsors and regulatory authorities such as the FDA. This is particularly relevant when medical imaging is utilized for the evaluation of surrogate endpoints in multicenter trials, a practice increasingly adopted in the management of oncology trials. Image acquisition protocols can vary across sites, and each center may interpret data somewhat differently according to local practice. Radiological assessment of images is often subjective, resulting in high interobserver variability among radiologists

viewing the same images. In a study involving 50, 60, or 100 sites, significant variability and inconsistency with interpretation is inevitable. While there remains a requirement for on-site evaluation by the local oncologist and radiologist when making a diagnosis or providing patient care, a central review allows an auditable, rigorous, and uniform process of evaluation. This provides greater consistency across sites, patients, and timepoints, achieving higher confidence levels in data generated.

Coordinating the review process

Trials involving medical imaging and the associated need for independent review require a significant operational and technological infrastructure, considerable expertise and foresight, as well as the ability to coordinate such undertakings. The process should include:

- Standardization of imaging and image management at the sites
- Image collection at a central location and management of the blinding process
- Developing and documenting the independent review criteria and independent reviewer roles and responsibilities
- Subcontracting independent reviewers

- Coordinating the overall logistics of independent review.

The format of the independent review and the makeup of the panel of experts is dependent on many factors, including disease indication and study phase. For registration studies, the independent review process may require a double read by two independent radiologists, unassociated with the study sites or sponsor. A third radiologist acts as adjudicator to resolve differences of interpretation between the two readers. There may also be a requirement for a separate review of clinical and laboratory data by an independent oncologist.

The process must demonstrate that no bias was introduced during the administration of the independent review. Highly qualified therapeutic experts with no vested interest in the outcome of the study should serve as independent reviewers. When designing an independent review process for an imaging trial, certain factors should be considered, such as the implications of different types of indications within oncology, suitability of assessment criteria, regulatory preferences, lesion selection rules, the appropriate modality for the image used to document disease response, and proper blinding of the reviewer. The study team must also decide how the study objectives and endpoints impact the type of independent review recommended, by addressing questions such as: Is it appropriate to implement a modification to a published response criterion? Is it appropriate to use more than one reviewer? What specific interpretations should the reviewers make so that the necessary data is collected to derive all study endpoints?

Independent review in oncology trials

When applying independent review to oncology trials, the study team must take into account the type of cancer and the characteristics of lesions inherent to that type of cancer, the type and schedule of images for assessing disease, and the clinical data that the independent reviewers should consider to make an accurate, unbiased assessment (see Table 1).

Lesion selection. Rules for what constitutes a measurable lesion at baseline or a new lesion, how lesions that become confluent or split will be handled, and how nonmeasurable lesions such as pleural effusions and ascites will be assessed must be defined prospectively. In lung cancer, mediastinal nodes can be clustered, limiting a reviewer's ability to accurately measure these lesions, while atelectasis and pleural fluid can blur margins of a tumor. Likewise, head and neck cancers can produce lesions in the neck that are often matted and small, also limiting an accurate measurement of these lesions. Conversely, colorectal cancer produces tumors that are ideal for measurement since they are typically large and round.

A finite number of lesions can be selected as measurable based on their size, location, shape, and relationship to other lesions. All remaining lesions should also be accounted for and followed qualitatively. The radiologist follows both lesion types throughout the review process; however, the types of assessments that can be made are dependent on the nature of the lesion and whether the reviewer is making a qualitative or

quantitative assessment. Further complexity arises when skin lesions are involved, which are common in melanoma and breast cancer trials. These may be assessed and even measured by an independent oncologist, who will then take both the assessments made by the radiologist as well as his/her own assessment of skin lesions into account along with the clinical data history of the case.

Clinical data. Since a radiologist reviews cases with little or no clinical data available on the subject, an oncologist may be employed to review the results of the radiology assessment, as well as clinical data on the subject, for a more comprehensive independent review that mimics the clinical environment, without the inherent bias. For some oncology trials the clinical data may have a significant impact on the overall assessment of the case. The oncologist may assess clinically detected lesions, performance status, the results of pathology or cytology reports, tumor markers, as well as any abnormal laboratory results taken at the investigative site. Ovarian cancer trials will often require that the tumor marker, CA-125, return to normal in order for a response to be considered a complete response. In lymphoma and leukemia trials, clinical data such as organ size and bone marrow biopsy results may

Case Study—Melanoma Trial

Melanoma presents an interesting case for independent review in oncology trials. The methodology for following lesions by imaging and the types of assessments performed by the independent radiologist reviewer are similar to other oncology trials that rely on stand-alone imaging assessments of typical modalities such as CT, MRI, and X-ray. However, in many subjects with melanoma, the skin lesion burden may be greater than the radiographic lesion burden, suggesting that an independent review heavily laden with radiology review may not give full visibility to skin lesion assessment, which should be performed by the oncologist reviewer.

RECIST based trials suggest that a maximum of 10 measured target lesions should be selected and followed, while other lesions should be assessed qualitatively. The limited number of "selectable" lesions adds complexity to an independent oncology review where different types of reviewers (i.e., radiologist and oncologist) are responsible for selecting measurable lesions. Should the number of measured lesions be split equally between radiographic and skin? Should more than the recommended number of lesions be measured, such as up to 10 lesions for the radiologist and 10 for the oncologist? Can the reviewers work together to select lesions? Can cases be treated differently based on the subject specific lesion, or should all subject cases be treated the same regardless of lesion location?

The underlying factor for resolving all of these questions is in determining how the objectivity of the independent review process would be impacted while allowing the review to remain scientifically sound.

be required to make a truly accurate response assessment.

Modalities and imaging schedule. Missing or incomplete images can dramatically impact study outcomes by resulting in unconfirmed responses as well as multiple assessments of “unknown” and in some cases progressive disease called earlier than actually present. The review of an image that is not part of the required imaging outlined in the study protocol can

change the outcome of an assessment. This impacts study end-points, such as overall response assessments, and affects time-driven endpoints derived from imaging review, such as time to progression, progression-free survival, and time to response. For example, breast cancer may infiltrate the skin, lung, liver, and bone. As a result, imaging for breast cancer may require bone scans and skin lesion photographs in addition to CT or

Table 1. An overview of oncology indications and assessments from an independent review perspective

Indication	Assessment Criteria Recommended	Modalities	Anatomy of Lesion Appearance	Important Considerations
Breast Cancer	RECIST, WHO	<ul style="list-style-type: none"> • CT (or MRI) • Bone Scan • Skin Photos 	Chest, Abdomen, Pelvis, Brain, Skin, Bone	May infiltrate skin, lung, and liver as well as bone without a discrete mass lesion.
Chronic Lymphocytic Leukemia	NCI-WG	<ul style="list-style-type: none"> • CT (or MRI) 	Neck, Chest, Abdomen, Pelvis	Oncology review of clinical data with radiological results critical.
Colorectal Cancer	RECIST, WHO	<ul style="list-style-type: none"> • CT (or MRI) 	Chest, Abdomen, Pelvis	Ideal tumor for measurement (large and round).
Head and Neck Cancer	RECIST, WHO	<ul style="list-style-type: none"> • CT (or MRI) 	Head and Neck	Lesions in neck nodes are often matted and small, limiting the ability to accurately measure.
Lung Cancer	RECIST, WHO	<ul style="list-style-type: none"> • CT (or MRI) • Bone Scan 	Chest, Abdomen, Pelvis, Brain, Skin, Bone	Mediastinal nodes are clustered, limiting the ability to accurately measure. Atelectasis and pleural fluid can blur margins of tumor.
Liposarcoma	RECIST, WHO	<ul style="list-style-type: none"> • CT (or MRI) • Bone Scan 	Neck, Chest, Abdomen, Pelvis, Extremities	Often grows around aorta and spine (must not include these normal structures in the measurements).
Melanoma	RECIST, WHO	<ul style="list-style-type: none"> • CT (or MRI) • Bone Scan • Skin Photos 	Chest, Abdomen, Pelvis, Brain, Skin, Bone	Oncologist review of skin lesion photos useful.
Non-Hodgkin’s Lymphoma	IWC, IWC+PET	<ul style="list-style-type: none"> • CT (or MRI) • PET 	Neck, Chest, Abdomen, Pelvis	Oncology review of clinical data with radiological results useful.
Ovarian Cancer	RECIST, WHO	<ul style="list-style-type: none"> • CT (or MRI) • Bone Scan 	Chest, Abdomen, Pelvis, Brain, Skin, Bone	Oncology review of clinical data and tumor markers useful.
Renal Cell Carcinoma	RECIST, WHO	<ul style="list-style-type: none"> • CT (or MRI) • Bone Scan • CT Perfusion 	Chest, Abdomen, Brain, Bone	Ideal tumor for measurement (large and round).
Solid Tumors (Anti-angiogenesis)	Values such as K^{trans} , V_e , iAUC	<ul style="list-style-type: none"> • DCE-MRI 	Any	Used in early phase studies.

Response Evaluation Criteria In Solid Tumors (RECIST)

World Health Organization (WHO)

Transfer Constant (Extraction Fraction Product) (K^{trans})

Extravascular extracellular space volume (V_e)

Integrated Area Under the Curve (iAUC)

National Cancer Institute-Sponsored Working Group Guidelines for Chronic Lymphocytic Leukemia (NCI-WG)

International Workshop to Standardize Response Criteria for Non-Hodgkin’s Lymphomas (IWC)

Positron Emission Tomography (PET)

Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI)

Case Study—Independent Review of Bone Lesions

The protocol of a breast cancer study clearly included the acquisition of bone scans in addition to chest, abdomen, and pelvis CT or MRI scans for all patients. However, head CT or MRI scans were acquired only at baseline for screening purposes because brain metastases were one of the exclusion criteria. An investigative site acquired a head CT scan of a patient due to a clinical indication during the study. The head CT scan showed bone lesions in the skull. The required bone scans of the same patient (not acquired on the same date as the head CT scan) did not show bone lesions in the skull. What should be presented for independent review? Should the head CT be presented to the radiologist? Should a local (site) radiology report of the head CT scan be provided to the independent oncologist?

MRI. If any of these modalities were present at screening but then missing at follow-up timepoints, the reviewer may not be able to make a clear assessment for the case, resulting in a call of “unknown.” Conversely, a lesion seen on an image at a follow-up timepoint that was not imaged at baseline may result in a call of progressive disease. Hence, ensuring clear assessment rules for all modalities and the implications of missing imaging are key to a successful independent review.

Defining the independent review process. Prospectively defining the process for independent review early on in the study start-up process is of utmost importance in oncology trials. The Independent Review Charter (IRC) is the cornerstone of the independent review process and allows the sponsor and imaging CRO to not only define the process up front, but also present a document to the regulatory authorities for review and agreement. The IRC is particularly important in pivotal trials for registration where the primary endpoint or important secondary endpoints are based on imaging data.

The IRC is a document that the imaging core lab and sponsor develop together, which:

- Describes the role and responsibilities of the imaging contract research organization
- Outlines the process for the independent review of imaging and clinical data to ensure consistency and objectivity of the independent reviewers
- Serves as good business practice for the sponsor in order to understand and be critical of the independent review process.

A primary challenge in developing a solid independent review process is to anticipate unforeseen problems that may arise during the independent review. Hence, writing a successful IRC requires a fine balance between describing the process comprehensively and providing as much detail as possible, while also allowing flexibility for problems that may not be foreseen.

Conclusion

Process control and independent review play an important and ever increasing role in the clinical development of oncology therapeutics. A review of the imaging and clinical data by independent experts skilled in the therapeutic area is critical to reducing variability and bias, thus giving the data greater validity. Throughout the process, careful thought must be given to the collection, processing, reporting, and export of data for final statistical analysis and integration into the full submission.

Independent review in oncology trials is influenced not only by sponsor requirements and the phase of the study, but also by the complexity of the review process, which is impacted by the type of cancer. The assessment criteria, type and number of reviewers, and methodology of the review process are affected by the clinical particulars indicative of the disease. Anticipating the unexpected is a critical aspect of independent review in oncology clinical trials. Prospectively defining the process as comprehensively as possible, while keeping in mind that other unanticipated scenarios may arise, is key to a successful independent review in oncology clinical trials. Furthermore, by allowing the process to be reviewed and approved by regulatory authorities, the sponsor can further ensure the validity of the independent review.

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