Ensuring Clinical Trial Success:
The Vital Role of BICR Imaging Reviews for Eligibility and Confirmation of Progression

Clinical trials are the bedrock of drug development, and their success is contingent on a multitude of factors. Among these, high-quality blinded independent central reviews (BICRs) for eligibility and confirmation of progression play pivotal roles, providing evidence that can determine the course of a program.

This white paper focuses on two essential applications of imaging in clinical trials: 1) imaging eligibility reviews, and 2) disease confirmation of progression reviews. BICR imaging reviews are far from being mere procedural steps or "nice-to-haves"; they are fundamental to the accuracy, efficacy and integrity of clinical trials, enhancing outcomes and ensuring adherence to scientific rigor – critical for accurate drug assessments and productive interactions with regulatory bodies.

1. Imaging Reviews for Patient Eligibility: A Critical Gateway to Clinical Trial Integrity

Central imaging review for clinical trial patient eligibility is a process by which a participating site sends screening images to a central imaging core lab to be evaluated, determining patient suitability for participation. In most trials that utilize imaging to support drug efficacy – especially oncology trials – there are imaging-based requirements that patients must meet prior to being enrolled. These requirements could include:

- At least 1 tumor measuring minimum 1cm in longest diameter (e.g., RECIST 1.1 trials[1])
- No residual tumor at screening (e.g., tumor recurrence trials)
- Tumor in a specific location

Often, these determinations are made by the site trial personnel who lack specialized training in RECIST criteria, or who are not imaging experts.

As emphasized in the RECIST 1.1 guidelines, maintaining the scientific validity of a trial, in addition to ensuring patient safety and ethical conduct, are paramount.[1] These guidelines provide a standardized framework for tumor response evaluation, underscoring the importance of accurate and consistently applied imaging criteria in oncology trials. The role of independent reviewers in interpreting these criteria is indispensable for maintaining the objectivity and standardization of patient eligibility, thereby safeguarding the integrity of clinical trials.[2]

Objective Patient Selection

The assessment of imaging data for clinical trial patient eligibility can be performed at the site or by independent reviewers. In multicenter trials, performing patient eligibility assessments at the site can introduce variability due to the involvement of several reviewers with differing levels of trial-specific training. To mitigate this variability, independent imaging reviews for patient eligibility are performed by selected readers who are trained on trial-specific criteria and blinded to the patients' clinical data. This is critical for maintaining objectivity in patient selection, enhancing the standardization of eligibility and avoiding the risk of including ineligible patients, which could lead to censoring patient data.

In one report, data from more than 10% of a large cohort of oncology patients were censored at the time of analysis, indicating the costly potential fallout of omitting eligibility reviews.[3] Given that experts who are not involved in direct patient care conduct these reviews, potential biases linked to personal or institutional interests can be eliminated from concern.[2] Objective assessments ensure that every patient enrolled meets the defined criteria precisely, a necessity for the scientific integrity of any trial. Including patients who do not meet eligibility criteria can skew trial results, potentially leading to misinformed conclusions about treatment efficacy or safety.

Omitting Patient Eligibility Reviews: Cost Breakdown

To further elucidate the impact of including ineligible patients in trials, consider the following:

- **Numerical cost analysis:** In a hypothetical 500 patient oncology trial, where the per-patient cost is $80,000, the financial impact of a 10% ineligibility rate translates to a significant monetary loss
  - > **Cost of ineligible patients:** 10% of 500 is 50 patients; at $80,000 per patient, the direct financial loss amounts to $4 million
  - > **Broader implications:** Beyond the direct costs, the inclusion of ineligible patients carries substantial risks, including the potential for trial failure or delays; such setbacks can lead to delayed market entry, jeopardizing the product's competitive edge

Enrolling Subjects With Incorrect Imaging Eligibility Assessment: Breakdown of Risks

Accurate imaging eligibility assessments are foundational to preventing enrollment of patients in a trial who do not meet the protocol-required specifications, thereby reducing the risk of trial protocol deviations and maintaining scientific integrity.[2]

- **Reduced evaluable population:** Enrolling subjects not meeting imaging criteria necessitates censoring their response assessments, which shrinks the evaluable population, jeopardizing the trial's regulatory approval prospects
- **Ethical and legal concerns:** Inclusion of ineligible patients risks ethical breaches and legal repercussions by administering investigational drugs outside protocol specifications, potentially delaying appropriate treatment options
- **Increased trial costs:** The enrollment of noncompliant subjects elevates trial expenses due to the management and analysis adjustments required for unevaluable patients

Regulatory Risks of Imaging Eligibility

Cohort Integrity and Variability

Protocol deviations can lead to variability in the study population, complicating data analysis and interpretation. Ensuring participant conformity to set criteria maintains tight study cohort(s) and ensures the collection of relevant and consistent data. This adherence is vital for the validity of the study's findings and its broader applicability to the intended patient population.[4]

Regulatory Scrutiny and Trial Approval

Regulatory bodies, including the FDA, meticulously review clinical trials for protocol adherence, especially concerning patient eligibility criteria. Noncompliance can trigger regulatory inquiries, potentially jeopardizing the trial's approval process. This underscores the importance of rigorous eligibility assessments to uphold trial integrity and meet regulatory expectations.

Unique Insights From Eligibility Criteria Study

A study published in the *Journal of Clinical Oncology* highlighted the impact of eligibility criteria on oncology trials.[3]

- **Prospective vs. retrospective review impact:** The study illuminated the stark contrast in ineligibility findings between prospective and retrospective reviews. Specifically, a proactive review identified only 2% (n = 89 out of 3,812) of subjects as ineligible, compared to a 12% (n = 614) ineligibility rate identified through retrospective BICR. This highlights the effectiveness of prospective reviews in significantly reducing ineligible participant inclusion
- **Statistical power and trial integrity:** The 10% difference in ineligibility rates underscores the critical role that thorough eligibility reviews play in preserving the statistical power and integrity of clinical trials; such reviews ensure that only qualified subjects are included, thereby upholding the scientific validity and ethical standards of the research

These findings emphasize that independent eligibility reviews can substantially improve the standardization of subject eligibility.

Ethical and Legal Risks Associated With Incorrect Determination of Imaging Eligibility

Enrolling patients who do not meet the imaging eligibility criteria not only exposes them to potential risks without the benefits of investigational therapies, thus violating ethical principles of beneficence and nonmaleficence, but also undermines patient autonomy by not respecting their right to make informed decisions. This practice carries legal risks, as administering investigational therapies to ineligible patients breaches clinical trial protocols and regulatory standards. Ethical and legal challenges in imaging eligibility emphasize the need for transparency, informed consent and adherence to guidelines to mitigate participant risks and ensure trial validity.[5]

2. Imaging-Based Disease Confirmation of Progression Reviews: Ensuring Accurate Patient Continuation or Stoppage

In clinical trials, particularly in oncology, the process of disease confirmation of disease progression can be a critical component, particularly when progression-free survival (PFS) and disease-free survival (DFS) are important study endpoints. This process involves evaluating whether and when a patient's disease has advanced significantly, potentially necessitating their withdrawal from the trial.

Confirmation by Sites vs. Central Imaging Vendors

Site Confirmation of Progression

The site determination of progression can be biased by a number of factors that are used to determine if and when a patient's disease has progressed to a predefined extent, which might necessitate their withdrawal from the trial.[1] This process is conducted by submitting all scheduled and unscheduled imaging data to a central imaging vendor

who then performs a rapid review to independently confirm whether progression has occurred at the current assessment.

Centralized Independent Confirmation

The central imaging vendor plays a crucial role in verifying radiologic disease progression, providing an expedited and independent confirmation of progression, separate from the central radiologist group assessing images for efficacy. Central confirmation of progression has been widely used for more than a decade in oncology trials. More recently, so-called "live" blinded central independent reviews, have even been proposed to rapidly provide central confirmation of progression to the investigational sites.

Independent Assessment and Timeliness

Upon identification of radiographic progression by an investigator (per the criteria being used in the trial), all current and previous images are sent to the central imaging vendor for an expedited review. The FDA emphasizes the importance of prompt interpretation of images to determine disease progression in trial subjects, as delays or inaccuracies in this process can significantly alter the course of the trial and the decisions made regarding a patient's further participation in the trial.[6]

To uphold the integrity of the trial and safeguard patient safety, a rapid review process for progression reviews delivers timely data for critical decision-making regarding patient treatment. This swift response is essential for maintaining the trial's timeline and ensuring that any needed adjustments are appropriately based on the patient's current *objective disease status*, a point the FDA has emphasized in these scenarios to maintain trial integrity and patient safety.[6]

Financial and Statistical Impact of Progression Assessment

The accuracy of disease progression assessment – especially where progression-free survival (PFS) is a primary endpoint – carries significant financial and statistical implications for clinical trials.[3,7] Incorrect appraisals of a patient's progression status, influenced by potential site investigator bias, can precipitate informative censoring – a significant concern in central review settings.[8]

Potential site investigator bias on the determination of disease progression is well documented and the potential source of serious errors.[7] Patients censored based on site assessments might indeed progress sooner if evaluated without bias, skewing the analysis of PFS. The introduction of informative censoring undermines the reliability of trial outcomes, necessitating meticulous central verification of progression to mitigate these risks. Studies underscore the necessity of this verification to maintain the integrity and accuracy of trial data, indicating that even in well-conducted trials, a notable discrepancy exists between site and central reviews regarding patient progression.

Furthermore, the financial implications of not addressing this discrepancy are significant. Misjudged progression assessments can affect the sample size, impacting not only the trial's statistical power but also escalating its financial burden. Addressing these challenges through robust central confirmation processes can substantially reduce the risk of costly trial errors, underscoring the essential nature of these reviews for trial success and fiscal prudence.

The Cost of Incorrect Progression Assessments

Premature subject terminations due to incorrect site progression assessments that are not subsequently confirmed centrally can pose substantial financial costs. For instance, *each patient in a stage 3 cancer trial can cost about $80,000*. As such, removing patients erroneously from a trial due to inaccurate progression judgments can mean losses potentially amounting to hundreds of thousands – if not millions – of dollars. For example, in a trial with 500 patients, if only 5% were removed incorrectly, based on site assessments, that would amount to 25 patients and $2 million.

The Case for Centralized Eligibility and Progression Reviews Cost of Implementing Centralized Reviews

Imagine a clinical trial designed to evaluate a new cancer treatment with a total enrollment of 500 subjects. The cost of managing each subject within the trial is estimated at $80,000, covering all aspects from recruitment, treatment and monitoring to data analysis.

The incorrect management of 10% of the subjects (i.e., 50 out of 500 subjects) due to inaccurate imaging interpretations leads to a financial loss. Assuming each subject incurs a cost of $80,000, the total loss amounts to $4 million (50 subjects x $80,000 per subject).

If implementing the centralized review process costs, for instance, $500,000 (only 12.5% of the $4 million potential loss), this investment would prevent the incorrect management of 50 subjects and the associated $4 million in losses. *And this estimate does not account for lost time.*

Accurate progression assessment is pivotal not for ensuring overall trial financial viability, but for mitigating financial losses specifically by minimizing informative censoring. This precision in determining progression directly impacts the integrity and cost-effectiveness of clinical trials, especially in late-phase studies where the financial implications of inaccurate patient status assessments are most pronounced.

Conclusion: Elevating Clinical Trial Standards

Meticulous image reviews are much more than a good idea; they can be the difference between success and failure. By ensuring accurate assessments before determining eligibility, removing a patient or concluding a trial, these reviews can preserve data integrity and ensure that substantial financial resources are appropriately utilized.

In clinical drug trials, the precision of imaging reviews for eligibility and disease progression not only bolsters scientific accuracy, but also addresses critical financial and regulatory considerations. Imagine a scenario where a trial with 100 patients is set to stop when 80% reach disease progression. If the trial concludes based on inaccurate progression assessments, and it's later discovered that only 60% had genuinely progressed, the premature termination of the trial could result in a significant financial loss.

The speed of bringing a drug to market is directly tied to success of the drug, and in a competitive landscape where multiple companies may be developing similar drugs, the accuracy and timeliness of these reviews are supremely important. If patients must be added to a trial due to the removal of others based on incorrect progression assessments, this adds additional cost and time to the development or, alternatively, sponsors may opt for maintaining timelines but sacrificing some of the power of the trial results. The investment in a second set of expert eyes for image analysis, therefore, is not an added cost, but a vital safeguard.

Moreover, there are serious potential medical, ethical and legal implications associated with administering a drug to a participant who doesn't meet the trial's eligibility criteria. Ensuring the right patient is included in the trial is both a regulatory requirement and an ethical imperative.

In conclusion, the key to successful outcomes in trials that involve imaging lies in prioritizing the quality of image analyses. This approach involves a thorough, expert interpretation of imaging data to make accurate judgments about patient eligibility and disease progression, and this means relying on highly trained and experienced independent readers who are not involved with the care of a trial's patients. By securing analyses that are highly precise, sponsors can make better decisions, improving the likelihood of reaching accurate conclusions about the efficacy and safety of their drug, while protecting the patients involved.

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