Six Steps to Ensuring Successful Clinical Trial Imaging

By Amit Vasanji, PhD and Brett A. Hoover

Pharmaceutical developers are increasingly asked by regulators to include imaging analysis when evaluating clinical trial data. In fact, imaging in clinical trials has grown by an astonishing 700% since 2001. This phenomenal growth also adds a whole new level of risk and complexity to clinical trials. From compliance challenges, site measurement inconsistencies, and image transfer issues to subjective assessments, incomplete data, and timeline delays, study teams need to manage and evolve their imaging strategies to position trials for success.

That said, clinical trial sponsors need not fret about the inclusion of imaging in their clinical development programs. As with many of today’s clinical research activities, technological advancements are often leveraged by trial sponsors to overcome these challenges and accelerate their research. Here, we present the rationale behind the utility of image analysis software and suggest best practices for sponsors looking to leverage this technology to ensure successful extraction of clinical trial imaging endpoints.

How Technology Is Changing Clinical Trials

The addition of imaging to a clinical trial, regardless of the therapeutic area, indication, or treatment, creates a layer of complexity and produces new regulatory and workflow compliance challenges. A given trial can have any number of images from a variety of modalities that require review by clinical expert readers (e.g., radiologists, pathologists, dermatologists, cardiologists), typically at multiple sites. The more variables present, the more opportunities exist for error(s), compliance missteps and subjective, often biased, data.

Fortunately, technology exists to help guide the imaging evaluation process. For example, image analysis software can be implemented to direct and guide a reader through the analysis of each imaging time point and even pre-process and segment anatomical structures of interest in lock-step with the study’s imaging charter and image evaluation protocol (IEP). This minimizes protocol deviations and ensures that each reader’s unique bias does not creep into the analysis process by focusing the reader on targeted endpoints whose workflows are outlined in the trial specific IEP. Software-guided reads are becoming an important part of trial design and the development of the trial’s IEP to help ensure all images are read uniformly and consistently, minimizing inter-/intra-reader variability and the potential for imaging-related queries. Simply stated, image analysis software brings a myriad of benefits to clinical studies, including accuracy, consistency, adaptability, and compliance.

Accuracy & Consistency

By designing an IEP that includes software-guided reads tailored to the trial’s imaging charter, trial
leaders help enable and protect the accuracy and reproducibility (i.e., quality) of imaging endpoint data. Image readers are prompted by the software when exams are ready to be read—each reader interfacing with the software, imaging exams, and measurement and viewing tools within a unified imaging management system. And, the software requires the reader to comply with the IEP’s workflow—minimizing the introduction of reader-specific bias and unintended protocol deviations. As image observations and measurements are completed, the software captures each read (i.e., automated eCRF field population and corresponding image measurement overlays), providing a clear audit trail, eliminating eCRF transcription errors, and reducing data queries to accelerate database lock at study completion.

Adaptability
Very few trials run entirely smoothly. Unexpected challenges always seem to arise, such as the introduction of new or replacement readers. Utilizing image analysis software also facilitates the transition to or introduction of new clinical expert readers into the imaging evaluation process, while minimizing any potentially negative impact this might have on final data quality and consistency. And, if the new reader makes an error, the software helps identify, document and correct the anomaly, and signal if additional IEP training and/or image evaluation workflow adjustments may be required. Tracking of reader assessments by the software can provide real-time rates of discordance and can be particularly helpful for studies with batched reads.

Compliance
While urging trial sponsors to incorporate more rigorous, controlled imaging methods and objectives into their studies, the FDA and other regulators want to see consistency and objectivity in all facets of any clinical trial. Consistent image acquisition, processing, and evaluation processes are not only important for ensuring imaging endpoint data quality, objectivity and reproducibility, these elements are also crucial for meeting regulatory standards for obtaining marketing approval. Surprisingly, many trials conducted today often have little or no traceability for imaging-related measurements. For example, reader delineation of a tumor on a lung CT is often not saved and documented. This prevents a sponsor or monitor from auditing the read consistency. More importantly, not being able to visually recall prior measurements in a longitudinal study prohibits accurate assessment of therapeutic efficacy.

Best Practices for Implementing Image Analysis Software
Each clinical study with a primary, secondary, and/or exploratory imaging endpoint will have many image observations and measurements to sift through. The larger the study, and the more complex the therapeutic area and indication, the more sponsors and CROs risk acquiring a potentially overwhelming number of imaging data points, which can lead to problems if the study team is not well prepared. Key to preparedness is comprehensive, purposeful, and well documented validation of the image analysis software (method) to be implemented in the study. While the software may have been previously validated by the original vendor or developer, that doesn’t necessarily mean it’s the most effective tool for a particular study and associated workflows.

Validating the image processing and analysis software method specifically for the study’s protocol, site acquisition equipment, and imaging endpoints is necessary for two key reasons: 1) to ensure the software method is optimal for your study and will produce accurate, objective, quantitative data, and 2) to avoid regulatory and compliance hang-ups. These issues can be addressed by following a few simple—yet essential—steps:

1. Get on the Same Page. If multiple clinical experts are providing image evaluation for a study, demand and ensure that all expert readers are utilizing the same software and methods tailored to the study’s IEP.

2. Ensure Consistent Measurements. Make sure all of the expert readers are performing their image measurements and observations in the same...
way. A well-written IEP is a great start and will harmonize image analysis quality across all readers. Tailoring image analysis software (and method) to the study’s therapeutic area, indication, and imaging endpoints will provide confidence in the image evaluation process and generate accurate, objective, complete data. Ideally, both reader and software consistency and competence should be tested periodically using a library of phantom scans or subject scans germane to trial endpoints.

3. **Ensure Validation.** When using a non-standard technique, such as new software (or method) developed specifically for the study, request that the radiology team—or the team doing the imaging analysis—provide a testing and validation report that describes and supports the non-standard technique being applied. Noting that software and/or methodological testing and validation was performed (and how) in the overall trial report (and linking this to the study’s IEP) will help explain and justify the image analysis strategy to the FDA and other regulatory agencies.

4. **Qualify and Log it.** Maintain a log documenting all imaging equipment qualified for use in the study. This includes the make, model, and software version of each imaging modality scanner, and the specific hardware and software details for the setup at each qualified study site. It is also important to document and track equipment and software upgrades that deviate from the approved image acquisition protocols and could potentially impact image quality and assessment.

5. **Verify Training.** Collect the training records and credentials of all image readers in the study. Any and all information that reflects and represents their expertise with the study’s therapeutic area, indication, IEP, image analysis software, and other imaging related tools (e.g., imaging management solution) implemented in the trial will be valuable documentation to the trial report. Further, this information can be particularly important if implementing a non-standard image analysis technique (e.g., new imaging biomarker) such as in Step 3 above. It is important to note that performing an assessment for clinical care is not the same as reading for a clinical trial. Readers should have relevant experience in evaluating a trial’s specific imaging endpoints that aren’t often evaluated in clinical practice.

6. **Test it.** Take the time to empirically validate the image analysis software to be utilized in the trial. One way to accomplish this is for a technician to scan an imaging phantom or healthy volunteer, and then test the image analysis methods against this data set. Be sure to choose a phantom that closely matches the needs of the study’s indication and anatomical region-of-interest in terms of tissue type, size, shape, density, etc. Have the image analysis team perform image measurements and observations on the phantom-generated exams with the image analysis software so that that the data generated definitively matches the known values (e.g., physical characteristics) of the imaging phantom.

By following these steps, trial leaders can have confidence that image analysis software will deliver accurate and reproducible data that will satisfy the regulatory approval requirements of clinical development programs.

**Conclusion**

Clinical trial leaders need to be prepared to meet the growing need for incorporating imaging into their clinical development plans. Trial sponsors who continue to take a traditional, de-centralized approach to imaging may be placing their trial at unnecessary risk, as well as incurring delays and added expense. By centralizing this important endpoint measurement with advanced technology solutions, sponsors and CROs can meet regulators’ increasing interest in clinical trial imaging and ensure data accuracy while mitigating risks and improving trial efficiencies.

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