



Best Practices for Implementing Image Analysis Software in Clinical Trials

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Pharmaceutical developers are increasingly asked by regulators to include quantitative image analysis as part of the study Imaging Charter for evaluating clinical trial data. In fact, imaging in clinical trials has grown by an astonishing 700% since 2001. This phenomenal growth adds a whole new level of risk and complexity to clinical trials. From compliance challenges, site image acquisition inconsistencies, reader measurement variability, and image transfer issues to 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 quantitative imaging endpoint data.

Each clinical study with a primary, secondary, and/or exploratory imaging endpoint will have many qualitative observations and quantitative measurements to sift through. The larger the study, and the more complex the therapeutic area and indication, the more sponsors and contract research organizations (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 original vendor or developer may have previously validated the software, 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 challenges can be addressed by following a few simple – yet essential – steps:

1. Get on the Same Page. If multiple clinical experts (e.g., readers) 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 image interpretation standards (IIS).
2. Ensure Consistent Measurements. Make sure all of the expert readers are performing their image measurements and observations in the same manner. A well-written IIS is a great start and will harmonize image analysis quality across all readers. Tailoring the image analysis software (and method/workflow) 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



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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 performing 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 IIS) 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 standards (IAS) and could potentially impact image quality and downstream image assessment by the readers and/or software.

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, IIS, image analysis software, and other imaging-related tools (e.g., imaging management solution) implemented in the trial will be valuable documentation for the clinical 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 assessing 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 are not often evaluated in clinical practice.

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 the data generated definitively match the known

values (e.g., physical characteristics) of the imaging phantom. Preexisting image data, from a previous study, can also be leveraged to support image analysis software validation if/when the phantom approach is not feasible

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 of 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 implementing and centralizing imaging measurements 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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