BEST PRACTICES GUIDE

OVERCOME IMAGING CHALLENGES THROUGH TECHNOLOGY

Strategies to minimize risk and generate higher-quality data
EVOLVE IMAGING STRATEGIES TO MEET REGULATORY GUIDELINES AND ENSURE SUCCESS

Regulatory agencies are increasingly asking sponsors to include quantitative image analysis for the evaluation of clinical trial data. However, variability across images collected (and subsequent analyses) leads to a need for larger sample sizes, longer timelines and bigger budgets. This means imaging data must adhere to quality standards — not only to meet regulatory expectations, but also to ensure trial outcomes success.

Study teams need to manage and evolve their imaging strategies to minimize risks such as compliance challenges, site image acquisition inconsistencies, image transfer issues, human bias during subjective assessments, incomplete (or missing) data and timeline delays. While advances in imaging technology have helped reduce these risks, a plan should be in place to ensure the imaging is appropriate, performed consistently within — as well as between — sites and analyzed objectively.
GROWTH IN CLINICAL TRIAL IMAGING

The use of imaging in clinical trials has increased by 700% since 2001.¹ In many instances, regulatory agencies, including the FDA, now require imaging for pre-market approval for certain medical devices. This trend is also starting to grow in drug trials, where imaging is incorporated into exploratory, secondary and even primary endpoints.

Imaging provides the tangible benefits of additional safety and efficacy data for regulatory agencies through visual representation of local and/or global disease response to treatment and the ability to more longitudinally measure and track changes that occur with the more subtle and sophisticated drugs in development today. However, an increase in the use of imaging in clinical trials brings a higher level of risk and complexity and an even greater demand for improved imaging technology and expertise.

¹. https://brackendata.com/blog-posts/medical-imaging-clinical-trials-growth-rate
TRADITIONAL IMAGING METHODS CREATE CHALLENGES AND RISKS

Traditional imaging methods, especially those typically seen in non-research environments (e.g., diagnostic medicine), amplify challenges with collecting and analyzing images in clinical trials because they are characterized by non-standardized and manual image collection, management and assessment processes. What’s more, imaging in clinical trials is usually performed in addition to the typical standard-of-care procedures and must adhere to the stricter data-quality standards found in clinical research. However, site staff naturally view imaging trial procedures as a distraction from day-to-day patient care. Compliance is often negatively affected, resulting in inconsistent image acquisition and missed or lost imaging time points.

Stringent data quality requirements also introduce new challenges for regulatory and workflow compliance, complicated by more sophisticated imaging modalities and more complex image processing and management workflows. Unlike other standard tests or patient reports, poor image quality can render any downstream image analysis useless for clinical trial purposes. In imaging, “Garbage in is garbage out.”
New and expanding imaging modalities create technical challenges, compliance issues and subjective, biased data

Traditional imaging modalities include, but are not limited to, computed tomography (CT), ultrasound (US), magnetic resonance imaging (MRI), positron emission tomography (PET) and X-ray (XR). More non-traditional imaging modalities include magnetic resonance elastography (MRE), optical coherence tomography (OCT) and structured-light imaging (SLI). As drug and device research continues to explore ways to generate stronger, more definitive safety and efficacy data, the need to expand current approaches or develop new imaging modalities, technology and expertise will grow.

With this trend comes increased risk, more compliance challenges and an even greater requirement for scientific oversight. General sources of risk from different imaging modalities stem from the level of expertise required (e.g., PET imaging), speed to complete an acquisition (e.g., brain MRI), imaging resolution (e.g., CT vs X-ray) and validation procedures (e.g., new image analysis algorithms). The more variables present, the more opportunities exist for error(s), compliance missteps and subjective — often biased — data. Better data simply demand stronger science and purpose-built technology.
Additionally, a clinical trial can have any number of images from a variety of these modalities that require review and evaluation by clinical expert readers (e.g., radiologists, pathologists, dermatologists, cardiologists, etc.), typically from remote locations. The more people involved in a study’s image processing and evaluation workflow, the more likely there will be errors, protocol deviations, inconsistent results and discordance between readers.

**Diagnostic and image capture systems not designed for clinical research**

While there are many diagnostic PACS or image capture systems available, take caution before adopting them for clinical research. Most diagnostic and image capture systems lack strong (or any) audit trail capabilities and are not designed to manage clinical trial data. This can lead to unpredictable compliance challenges.

When companies realize these systems are not suitable for clinical research, they often revert back to traditional image collection methods, burning images on CDs and shipping through commercial delivery. This ultimately results in time delays, higher costs, lost images and unnecessary queries.
Study results undermined by insufficient validation or poor documentation

Validation issues also present unique challenges with clinical trial imaging. Study results can be undermined by insufficient process validation or poor validation documentation to support and justify the image analysis software implemented or a lack of standardization of the site procedure manual (SPM) to harmonize image quality across many study sites. In many instances, there is a disconnect between the steps within a study’s image collection, processing and analysis workflow due to the use of multiple, non-integrated third-party technologies to individually manage each step. This process and technology disconnect will often lead to lost, mismanaged or non-interpretable imaging data.

Transfer and transport create lost and damaged images

Images are often lost or corrupted during their transport to a central location for processing, analyses and regulatory reporting. This typically stems from either sub-par image collection and transfer technology or the use of manual methods of image transfer like burning and shipping digital media such as CDs. Further difficulties with transferring files occur when there are multiple vendors and systems managing the imaging activities, or when the image transfer technology requires local installation of hardware or software that is non-compliant with a study site’s IT policy.
STRATEGIES TO DECREASE IMAGING-RELATED RISK

Given the growing importance and complexity of imaging data for clinical trial efficacy and safety endpoints, it’s imperative to plan ahead and mitigate these risks. Transitioning to technology-driven processes is easier when a few key actions and appropriate planning are implemented.

Engage imaging experts to optimize protocols

Engaging imaging experts to assist with the development of dedicated SPMs and independent review manual (IRM)s can dramatically lower imaging-related risk in a clinical trial. Imaging experts can help determine how to best minimize potential issues — or prevent them altogether — to generate higher-quality data given specific study constraints.

WATCH THIS VIDEO TO SEE HOW IMAGING TECHNOLOGY CHANGES CLINICAL TRIAL IMAGING AND WHERE IT FITS IN TRADITIONAL IMAGING PROCESSES.
Experts help define which imaging modality, or combination of modalities, to implement and how to best acquire images in a study relative to the therapeutic area and indication. The same experts can help decide which imaging management solution is ideal for the study and map out the image processing and evaluation process that is best suited to the study’s desired imaging objectives and outcomes. These decisions depend on the study design, the imaging modalities involved, equipment available at each site, the indication studied and the staff skill level required to successfully execute the study protocol. This is, in part, why study site qualification is such a critical first step when initiating a clinical trial that will involve imaging.

When developing the image processing and evaluation protocol, imaging experts will consider objective qualitative assessments, incorporation of image processing, co-registration and analysis software into the reading protocol, and clear justification and validation of imaging processes and workflows. Regulatory agencies expect these elements to be in place prior to study start to ensure that the resulting data are objective and accurately represent the study outcomes.
Weigh the level of risk when developing the protocol
The lowest-risk protocol is one that chooses to use standard-of-care methods; there are little or no changes required to existing study site workflow or staff training. At the other end of the spectrum, the highest level of risk exists with an imaging protocol that is fully customized to the unique research needs of a given study. Modifications to imaging parameters and subject positioning, for example, may deviate from the site staff’s daily operations, which increases the likelihood for compliance challenges. The best imaging experts will know how to strike the right balance when developing protocols.

CASE STUDY
A top 50 pharmaceutical company was struggling to objectively and reproducibly measure the location and concentration of its contrast agent for the evaluation of pulmonary embolism. Additionally, the company wanted a better way to visualize and detect pulmonary emboli.

By engaging imaging experts to develop a software-based image processing and analysis method for use with contrast-enhanced CT imaging, the sponsor measured and longitudinally tracked contrast agent location and concentration. They also were able to detect the disease earlier because pulmonary emboli with smaller diameters could be more accurately measured—something not possible with traditional processing and analysis methods. Learn more here.
Assess methods to collect and analyze imaging data

Thinking about the methods used to collect, process and analyze imaging data in advance will help minimize data variability and mitigate data quality and validity questions during the regulatory submission process. Pairing the right image collection and transfer process and technology can make or break a study. Doing this correctly will depend on many factors, such as study site location, local IT infrastructure, image format and image size. The effect of risk stemming from subjective or non-validated image scoring criteria can be minimized by working with experts to explore and properly validate the criteria (or new biomarkers) and implement a technology-guided workflow to remove subjectivity from the image evaluation process.

IMAGING RISK VARIES BY MODALITY
Consider a centralized, electronic imaging approach

Centralized electronic data collection facilitates better data access, integrity, interpretation, reporting and transmission. Centrally processing and evaluating images is less risky compared to a localized approach with image reading and evaluation occurring at each site across a multitude of different readers.

Regardless of how images are read or interpreted, there are multiple strategies that can reduce the risk — starting with regular training of the readers and establishing clear read variability threshold criteria for when re-training is necessary. During IRM development, consider an objective assessment with well-defined measurements and observations, incorporating image processing and analysis software into the reading workflow and a clear definition of how read adjudication will occur, if multiple readers are involved. Finally, staff- and technology-driven data and image annotation edit checks provide independent adaptive quality control (QC) throughout the image processing workflow to ensure consistent reading and data quality.

IMAGING RISK VARIES BY HOW IMAGES ARE INTERPRETED
Let image analysis software do the heavy lifting

Embracing technology in imaging trials becomes much easier when purpose-built technology is used to do the “heavy” lifting, guiding the image evaluation process to where greater attention and expert eyes are needed—allowing the reader to be more focused, objective and efficient during the image evaluation. In this way, image analysis software streamlines the process, minimizes data queries, prevents protocol deviations and helps to harmonize the imaging results. This is particularly useful when evaluating pathology biopsies. Software can quickly process the large field-of-view image, identify critical regions-of-interest and triage for reader attention and a deeper review. In this way, reading sessions that used to take hours can be reduced to minutes, while increasing the accuracy of the review.
Incorporate comprehensive validation to avoid submission and compliance issues

Comprehensive, purposeful and well-documented processes and technology validation avoids issues with regulatory submission and compliance, particularly related to questions about data accuracy and validity. Validation should be specific to the study protocol, the imaging modalities, the imaging endpoints and the image scoring criteria to ensure that the software method is optimal for the study.

CASE STUDY

A top 50 pharmaceutical company needed to enroll hundreds of subjects with traumatic brain injury, but were contraindicated to MRI, the gold standard imaging modality for this condition. With the assistance of imaging experts, the necessary processes and methods were put in place for imaging and quantitatively measuring edema using CT imaging. The sponsor successfully executed the study and generated unique, valuable efficacy endpoint data.

Learn more here.
GETTING STARTED

All of the strategies outlined on the prior pages will position an imaging trial for success, but taking these small — yet important — steps will likewise go a long way to minimizing risk and generating higher-quality data:

> **Maintain an imaging equipment log**

Maintain a log of all imaging equipment that will be used in the study, including the make, model, software version and update/upgrade schedule. This information can help imaging experts predict if/when a software or hardware change could disrupt the study and potentially cause data continuity issues.

> **Facilitate QC review and analyses with digital storage in a centralized platform**

Once collected, data should be quarantined, scrubbed of protected health information (PHI) and then stored digitally in a centralized platform to facilitate QC checks and centralized analyses, if required.
> **Develop a comprehensive IRM**
A well-written IRM ensures that image processing and analysis software is properly configured and implemented and all expert readers are adequately trained and performing image measurements and observations in the same way, harmonizing the quality of image analyses across readers. The consistency and competence of the reader and software can be continually verified through the periodic blinded reading of phantom or subject scans relevant to the trial endpoints.

> **Document reader training records**
It’s critical to document the training records and credentials for all image readers specific to the clinical trial assessments and the imaging endpoints. This strategy is important in the event regulators want verification that readers are appropriately trained for the specific trial protocol and endpoints.

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ADVANTAGES OF TECHNOLOGY-DRIVEN IMAGING
Technology-driven imaging solutions differ greatly from traditional approaches — and provide quantifiable tangible benefits.

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<thead>
<tr>
<th>Traditional approaches:</th>
<th>Technology-driven solutions:</th>
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<tbody>
<tr>
<td>Time-consuming, labor-intensive, error-prone</td>
<td>Faster, less expensive, higher quality</td>
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<td>Manual image collection and management</td>
<td>Sophisticated algorithm generation for each specific protocol</td>
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<td>Time-consuming manual image assessments</td>
<td>Validation and QC as the reader focus rather than reading every image</td>
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<td>Unnecessary risk and delays from inconsistencies and errors</td>
<td>Guided and intuitive read platform enables complete and consistent data</td>
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<td>Subjective assessment with arbitrary scoring</td>
<td>Objective results — without the typical human bias</td>
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TRADITIONAL VS TECHNOLOGY-DRIVEN IMAGING APPROACHES IN CLINICAL TRIALS
There are many benefits to technology-driven imaging collection, analysis and management. Sponsors and CROs should consider different aspects of their clinical development approach to realize their full potential.

<table>
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<th>Approach</th>
<th>Benefits</th>
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| Streamlined process           |  > Guides reader through analysis of each imaging exam to avoid protocol deviations  
                               |  > Simplifies and accelerates image evaluation through image pre-processing and segmentation of anatomical region of interest (ROI)  
                               |  > Ensures the correct image, time point and demographics have been acquired through adaptive edit checks during upload  
                               |  > Confirms each image is ready for evaluation  
                               |  > Simplifies transition if new or replacement readers are required                                                                                                                                 |
| Harmonized imaging results    |  > Ensures consistent image and data quality across sites, readers and time points  
                               |  > Provides both a data and visual (i.e., image annotations) audit trail of record edits and image measurements                                                                                       |
| Automated workflows           |  > Alerts sites when exams fail the QC check and provides suggestions for improving protocol compliance  
                               |  > Facilitates verifiable, reproducible, quantitative, objective and more accurate analyses  
                               |  > Prevents individual reader unique bias from influencing image analysis outcomes                                                                                                                                 |
| Secure image transport        |  > Moves images from sites to storage locations in a compliant, efficient and predictable way  
                               |  > Ensures patient data privacy through image quarantine and PHI removal                                                                                                                             |
BENEFIT NOW – AND LATER

Regulatory agencies are increasingly driving sponsors to include imaging in their clinical trials and to generate more quantitative data to support their efficacy and safety claims. This trend will continue to grow, so now is the time to prepare.

Trial leaders can reduce the inherent imaging-related risks by implementing an expert-driven protocol and purpose-built imaging technology. This includes engaging an imaging expert to ensure the right imaging modality and processes are selected, establishing a solid baseline of technology for image collection, processing and management and strongly considering how images will be interpreted. All of this will enable the generation of accurate, objective, quantitative, imaging data, which mitigate risks and uncertainties.

Streamlined regulatory compliance, shorter approval timelines, less rework and greater efficiencies provide a competitive edge. Adopting the right technology today positions companies and the patients they serve to reap immediate benefits — and allows for additional benefits as new technological advancements are introduced.

Learn how ERT minimizes imaging risk through high-quality data. To learn more, go to ert.com or email info@ert.com.
ABOUT ERT

ERT is a global data and technology company that minimizes uncertainty and risk in clinical trials so that customers can move ahead with confidence. With nearly 50 years of clinical and therapeutic experience, ERT balances knowledge of what works with a vision for what’s next, so we can adapt without compromising standards.

Powered by the company’s EXPERT technology platform, ERT’s solutions enhance trial oversight, enable site optimization, increase patient engagement and measure the efficacy of new clinical treatments while ensuring patient safety. In 2017, ERT supported 60% of all FDA drug approvals. Pharma companies, biotech and CROs have relied on ERT solutions in 13,000 studies spanning more than three million patients to date. By identifying trial risks before they become problems, ERT enables customers to bring clinical treatments to patients quickly — and with confidence.