PEER REVIEWED

Cardiac Imaging in Clinical Development: The Benefits of Advanced Imaging Management Systems

Individuals involved in drug development are faced with many different challenges along the process of seeking regulatory approval. Imaging plays an important role in the assessment of the effectiveness and safety of new drugs or medical devices, and this article will focus on the role of cardiac imaging in clinical trials while acknowledging imaging's role may also span non-clinical drug development.

Successful drugs have a well understood and positive risk-benefit profile in terms of safety and efficacy. Cardiac safety adverse events, such as ventricular fibrillation, ventricular tachycardia or Torsades de Pointes, are a major point of emphasis in drug development[1]. As such, the US Food & Drug Administration (FDA) requires cardiac safety monitoring during the clinical development of new medical treatments[2]. Cardiac imaging is often used to meet this important safety requirement, and also has an obvious role in evaluating the efficacy of cardiovascular drugs during clinical development.

The cardiovascular system can be assessed through a wide variety of imaging modalities which provide objective and reproducible methods to evaluate the clinical effectiveness of the study drug, i.e., impact of therapy on the disease state or heart function. These techniques include non-invasive and invasive techniques, such as:

- Ultrasound (echocardiography, intravascular ultrasound or IVUS)
- Multiplanar anatomic, functional (e.g. stress testing techniques)
- Quantitative imaging techniques including angiography, CT, MRI, molecular medicine SPECT and PET imaging

Experienced clinical development teams understand and apply the evolving body of clinical research and therapeutic-level recommendations to clinical trial protocols in order to monitor for these cardiac conditions. Yet, the imaging required to monitor for cardiotoxicities during clinical development can, at times, be treated as a perfunctory task.

The fact is, for cardiac safety and efficacy trials, as in all multi-centred trials involving imaging: it matters how images are taken, how they are analysed, and how the process is monitored. The quality and capabilities of the imaging management system – the process and tools used to collect, share, interpret, and store images – has an appreciable impact on patient safety as well as trial costs and timelines. Importantly, clinical teams must understand the regulatory requirements or guidances available and apply the correct approaches to collecting the relevant clinical study information.

"Ensuring that imaging is managed expertly – including the use of the latest technology and careful oversight – has a broad implication for patient safety as well as trial cost and timing." – Joseph Pierro, M.D.

Cardiac Imaging: Essential in Clinical Trials

Imaging is commonly used as a biomarker for safety in clinical development and in many trials is the primary efficacy endpoint. Echocardiography is widely used to assess symptomatic and asymptomatic cardiac dysfunction and to grade the severity of the condition; the results are surrogate markers for cardiac safety or efficacy.

The rapid development and availability of modern imaging technology being deployed in clinical trials allows for the identification of potential pathological changes earlier (e.g., decline in left ventricular ejection fraction (LVEF) or end systolic volume, acute myocarditis, and valve leaflet thickening). Given the complexity of imaging services being required in today's trial designs, study sponsors reach to the expertise provided by imaging core to fill internal team knowledge gaps.

Such assessments are performed in order to (Figure 1):

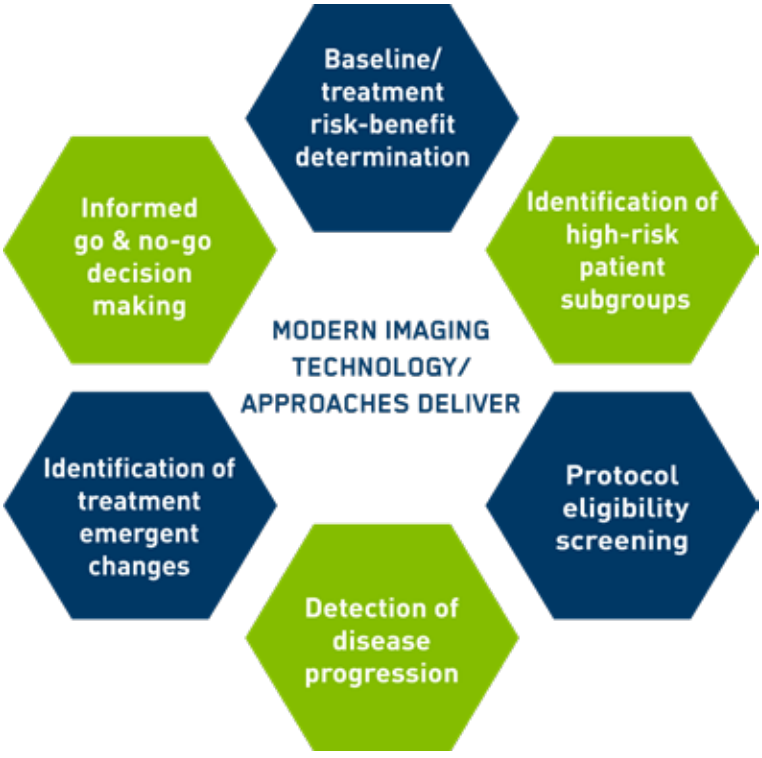

Figure 1: Modern imaging technology allows for the identification of potential pathological changes earlier in clinical trials

- Make go/no-go decisions for continued drug development
- Understand baseline and post-treatment risk-benefit determination
- Assist in identifying high-risk subgroups within the population (for example risk stratification of subjects with low ejection fraction, low or ventricular volume or coronary artery calcification score)
- Screen subjects for protocol eligibility
- Detect disease progression or lack of treatment efficacy
- Monitor patients for treatment-emergent changes which may indicate treatment effect or necessitate the need for dose adjustment or treatment discontinuation.

The study team will recommend the monitoring frequency based on an understanding of the drug's mechanism of action, the intended patient population(s), the therapeutic or toxicity profile, and a review of prior clinical and non-clinical data. As mentioned earlier, regulatory precedents in terms of prior approvals of similar drugs, i.e. a similar therapeutic class, as well as relevant guidance documents should be incorporated into the planning processes to meet FDA's increasing expectations that imaging be performed in a robust manner.

Early detection and diagnosis of the lack of cardiac efficacy or potential cardiotoxicity is, of course, important, as the goal in the latter example is to be able to medically intervene, prevent delayed effects, and improve outcomes for the patients when appropriate. And, should the investigational product need to be re-engineered in the lab, it is better to determine this as early as possible in the development path.

Increasingly, echocardiography is the primary assessment tool for cardiac safety assessments, given its advantages of wide availability, lower cost, and the improved detection three-dimensional methods afford.

Imaging: A Critical Factor in Patient Care and Data Integrity

Several factors can impact the quality of data produced through echocardiography, as with other imaging modalities.

First, the imaging technologist is the person acquiring the images and the individual's skill, experience, and knowledge can influence the quality of the image. Second, there can be variations in how the image is acquired, such as the display, resolution, and scanner parameters that are related to the equipment itself. And third, how individual readers interpret the images can – and does – vary.[3]

This point is important when considering the inclusion of site-determined image interpretations. Numerous studies have reported on the diagnostic or interpretative differences between site physician readings and those performed by a centralised imaging core lab, where higher levels of process standardisation and adjudicated imaging reports (i.e. 2 + 1 reader model) may be provided to the sponsor.[4,5]

Studies conducted since 1947 have measured diagnostic discordance in the 25 per cent to 40 per cent range and the clinical team should understand or consult with available imaging or statistical experts regarding the potential impact that this level of discordance may have on study power and endpoints.[4,6,7]

In fact, FDA's guidance document (2018) recommends that sponsors use multiple independent reviewers to evaluate each subject to control for errors, variability, and read quality, stating "We anticipate that a centralised image interpretation process may provide more verifiable and uniform reader training as well as ongoing management of reader performance, helping to ensure quality control of the images and their interpretation and to decrease variability in image interpretations, leading to a more precise estimate of treatment effect."[8]

Additionally, wide variability in both quantitative and qualitative echocardiography assessments is recognised in recent expert society guidance publications offered by both The European Society of Cardiology (ESC) and The American Society of Echocardiography (ASE).

Errors and inconsistencies can have a direct impact on patient care, as well as on the chance of regulatory approval for the investigational product. Thus, there's a need for a comprehensive approach to ensuring that image acquisition techniques are standardised, that images are appropriately collected to the highest quality standard across multiple sites, and that the images are evaluated consistently to support study protocol endpoints.

That's why imaging documentation, imaging management systems and active reader management practices are critical. Further emphasising the above point, the recent ASE Echocardiography Report recommends the use of a centralised echo-reading laboratory in multicentre clinical trials.[9]

Imaging Management Technology: Added Transparency, Reduced Risk

Today's imaging technology platforms can help reduce the chance of human error, speed the assessment process, increase objectivity and consistency, and improve patient safety. A single system is used to collect the source data (which is input directly by the clinical trial site staff), manage image analysis, report on the results, and archive records. Because the data are always contained in the same system, there are no delays or errors caused by transferring it between different platforms to perform various operational tasks. This, in fact, eliminates virtually 100 per cent of transcription errors. Furthermore, a consistent process is applied using standardised procedures in a common viewing platform.

The best systems available provide:

- **Real-time Safety and or Efficacy Monitoring.** Imaging results are collected at the clinical site and are immediately available at the clinical institution, so safety and efficacy signals can be identified at once for clinical decision-making. They are also immediately available to ensure images are performed according to professional standards/guidelines and are available to the independent or blinded readers (BICR) so that they can make their independent assessments. The results can also be shared with other stakeholders such as sponsors, cardiac advisory boards, and data and safety monitoring committees.

- **Visibility to all Study Data in Near Real Time.** Trial managers and medical directors have total visibility to all study imaging data, throughout the imaging life cycle. They can:
  - View reader assessments
  - Monitor intra-/inter-reader variability
  - Measure the degree of discordance between site-based and blinded, central readers
  - Track the number of cases requiring adjudication
  - Monitor for selection bias in adjudicated cases

  Such insight into reader workloads and performance makes it possible to quickly address issues around reader drift, variability, and bias, thus minimising their impact. If, for example, it becomes clear from the metrics that a reader's approach has changed, re-training can be provided so that the reader's performance is consistent with others in the reader pool.

- **Automated Workflows.** The system delivers reminders and gives users automatic prompts so that images pass through the agreed-upon workflow from reader to reader to adjudicator as efficiently as possible. The process is not dependent upon a project manager to keep it on track.

- **Software-guided & AI-Assisted Reads.** Image analysis software can direct a reader through the analysis of each imaging time point and even pre-process and segment anatomical structures of interest in lockstep with the study's imaging charter and image evaluation protocol (IEP). This minimises 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. Artificial intelligence (AI) can be used to augment human assessment. Using AI in this way can reduce read times by as much as 50 per cent and the need for adjudication by 20 per cent. It would, in the process, increase speed and reduce costs.

Ensure image acquisition techniques are standardised, that images are appropriately collected to the highest quality standard across multiple sites, and that the images are evaluated consistently to support study protocol endpoints.

Active Reader Management: Added Efficiency and Effectiveness

An imaging core lab will be concerned with all of the controllable factors that impact data quality, from data collection to image review and data analysis. The best practices of an imaging core lab include:

- Ensuring that the imaging endpoints support the protocol
- Selecting a limited number of independent readers based on their training and experience
- Managing the image assessment – starting with standardising the imaging protocol, training on the system and reading endpoints or study criteria
- Monitoring reader performance periodically during the study to lower variability and adjudication rates (readers are asked to re-read cases to identify performance drift)
- Reporting on imaging status and reader performance with recommendations for discussion with the sponsor and intervention(s) if needed

The lab's ability to monitor reader performance and oversee imaging progress is dependent upon the capabilities of the imaging management software.

Achieving Success: Tips for Sponsors

Ensuring the validity of cardiac imaging data points is difficult, and the challenge must be addressed early in trial planning to both protect patients and the integrity of the trial itself. Sponsors should:

- Look to both positive and negative results in early trials to determine the potential predictive value of cardiac endpoints.
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- Identify patients likely to benefit from drug treatment or are at risk for cardiotoxicity and determine the risk-benefit balance, for example, balance survival benefits with reduced cardiac risk relative to a patient's quality of life. (There is a higher tolerance for adverse events in oncologic treatments, and the benefit/risk balancing point is different than in other disease states.)

- Clearly define the protocol-required cardiac assessments and measurement parameters to be obtained during the echocardiogram or other imaging modalities. This will help the clinical team understand the patients' clinical course and inform decisions on treatment adjustments that may be needed to maintain or restore normal cardiac function. The protocol should include details on the number of imaging findings required, together with information based on statistical analysis to assist investigators in managing patients.

- Establish a baseline of cardiac performance prior to treatment, perform serial assessments during the trial, and conduct a follow-up assessment post-therapy.

- Pay particular attention to the technologies and processes used to ensure accuracy in how images are taken and interpreted (See Box: Questions to Ask Your Imaging Partner).

Questions to Ask your Imaging Partner in Cardiac Imaging Trials

- Which system is used to collect imaging endpoints?
- How quickly is data available? How easy is the analysis?
- How precise are the assessments?
- What is the expected rate of reader discordance?
- What is the optimal number of independent readers for the trial?
- What has the adjudication rate been on similar trials?
- What process is used to monitor the timeliness and accuracy of reads?
- What process/technology is in place for creating an audit trail and ensuring compliance?
- What systems and training are in place to ensure that sites know how to follow the imaging protocol?
- What process or standards are used for the image archive process?

Conclusion

Ensuring that imaging in cardiac safety and efficacy trials is managed expertly and with the benefit of the latest technology and careful oversight has broad implications for patient safety as well as trial cost, timing and trial success. Overall error rates can be reduced by as much as 20 per cent, read times can be reduced by up to 50 per cent, and adjudication rates can be cut by 20 per cent.

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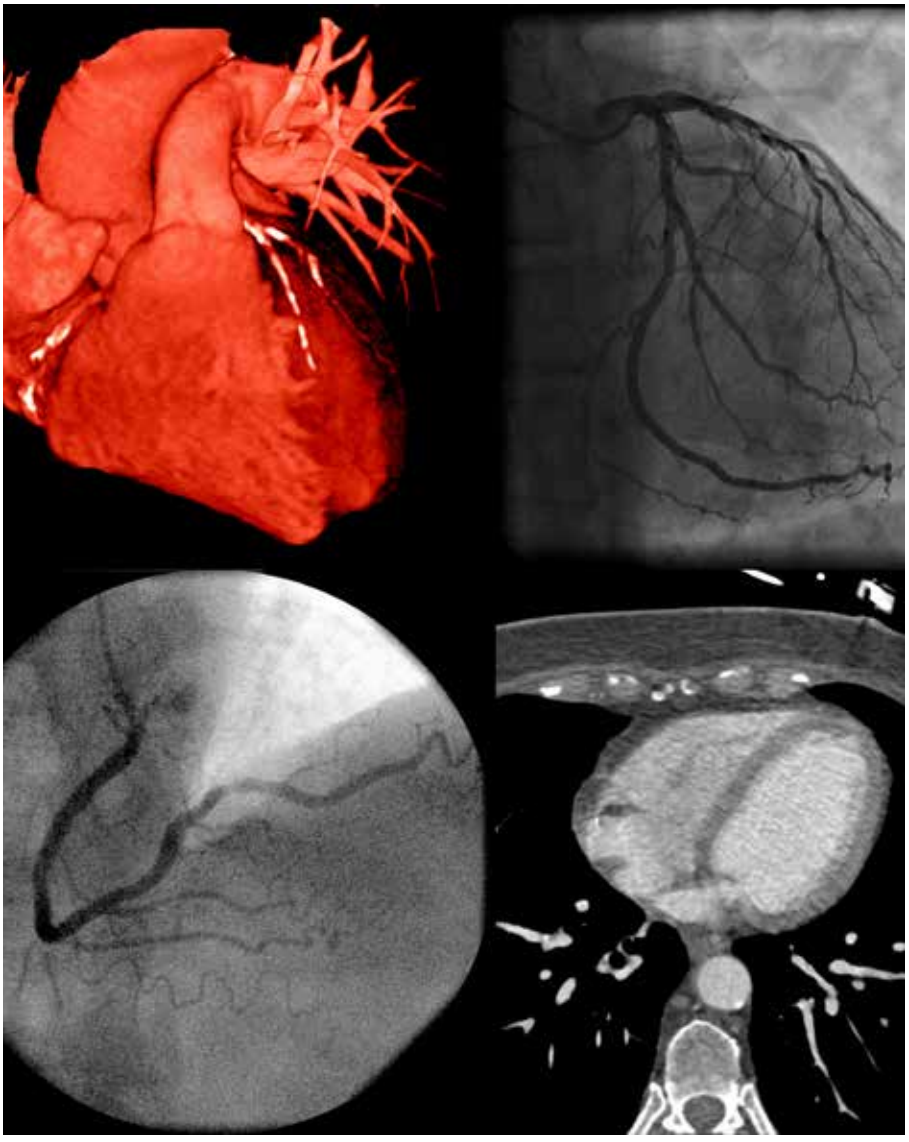

Joseph Pierro

Dr. Joseph Pierro, MD Medical Director, Imaging, has over 30 years of expertise in the field of radiology and over 20 years of clinical trial research & development experience, which includes global senior level positions held within the pharmaceutical industry and as a medical reviewer at the FDA Center for Drug Evaluation and Research. In his current role, Dr. Pierro provides scientific, clinical and radiologic imaging guidance that enables biopharmaceutical companies to successfully implement ERT's advanced imaging solution during the clinical development of new medical products.

David Raunig

David has Raunig, PhD, Senior Principal Imaging Statistician, ERT. 20+ years of experience integrating current medical, scientific and statistical techniques into the collection and analysis of imaging data during the development of new medical products. As Sr. Principal Imaging Statistician, David is responsible for driving the quality of ERT's imaging solution by integrating regulations, operations and statistics into the conduct of clinical trials. Previously, David held senior leadership positions with global pharmaceutical and clinical research organizations, including Bristol Myer-Squib, Icon Medical Imaging, and Pfizer.