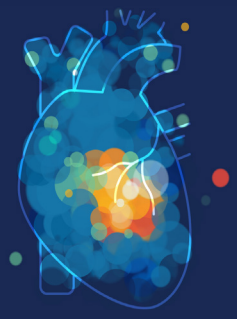
Whitepaper:

ADVANCES IN MULTIMODALITY CARDIOVASCULAR IMAGING: ENHANCING CLINICAL TRIALS FOR PRECISION MEDICINE

Authors: Hans Jonker, Rina Ariga, MBBS, DPhil, Laetitia Vanhoutte, MD, PhD, Sal Zabbatino, MD, and Scott Holland, PhD



Cardiovascular diseases are one of the leading causes of mortality and morbidity worldwide. Clinical trials are essential to evaluate the safety and efficacy of new interventions for the prevention and treatment of these conditions. Imaging techniques are essential tools for cardiovascular research, as they allow visualization and quantification of structure and function of the heart and blood vessels. Each imaging technique has its own advantages and limitations; thus, the choice of the most appropriate approach depends on the research question, the availability of resources, and ethical considerations. This article underscores the value of imaging endpoints in cardiovascular studies, illuminating their role in refining therapeutic approaches and enhancing the predictability and success of clinical outcomes. For potential trial Sponsors, this narrative offers a perspective on the contribution of imaging endpoints in advancing the efficacy and precision of cardiovascular interventions.

ADVANCES IN CARDIOVASCULAR IMAGING

The cardiovascular imaging field is rapidly evolving at an accelerating pace. Advanced imaging has improved the diagnosis, prognosis, and management of cardiovascular diseases, such as coronary artery disease, heart failure, valvular heart disease, and congenital heart disease. Some of the major recent advances include:

Hybrid Imaging Techniques: Integration of multimodality imaging combines the strengths of modalities, such as PET/CT, PET/MRI, and US/MRI, to provide comprehensive information on anatomy, physiology, and molecular biology.

Contrast Enhancement: Novel contrast agents, tracers and better exploitation of intrinsic tissue properties for magnetic resonance imaging (MRI) and positron emission tomography (PET) has improved the assessment of myocardial perfusion, inflammation, fibrosis, and metabolism.

High-Resolution: Improvement of image quality and temporal and spatial resolution of computed tomography (CT), MRI and ultrasound (US) by using new hardware, software, and reconstruction algorithms has reduced noise and artifacts.

Improving Scan Time: In MRI, use of specific equipment and algorithms (partial Fourier imaging, non-cartesian imaging, reduced data acquisition methods, etc.) have led to significant decrease in acquisition time reducing need for apnea and patient sedation.

Reduction of Radiation Exposure: Lower radiation exposure due to technological advancements has improved accessibility to techniques that utilize ionizing radiation. E.g.: improvements in gating techniques for CT or advances in detector technology.

Artificial Intelligence and Machine Learning: Application of artificial intelligence (AI) and machine learning (ML) to cardiovascular imaging data can automate analysis and enhanced image acquisition, interpretation, quantification, and even decision making.

Imaging at Scale: Expansion of cardiovascular imaging and infrastructure for big data analysis has initiated population-level screening and prevention. Other settings include telemedicine, point-of-care, and decentralized trials.

These advances in cardiovascular imaging have improved patient care and outcomes in primary cardiovascular diseases and in cardiovascular complications from other diseases and treatment. In parallel, these advances impact clinical trials on various levels, such as availability, complexity, use of imaging biomarkers, outcome measures, and endpoints.

Traditional "hard" endpoints from clinical trials such as mortality and morbidity data are considered the gold-standard for evidence-based medicine. However, these endpoints may not capture the full spectrum of benefits and harm of a given therapy. Large sample sizes and/or long follow-up periods are required, increasing the cost and complexity of clinical trials. These challenges have catalyzed the need for novel "intermediate" or "surrogate" endpoints that reflect disease progression and predict risk. Such endpoints have enabled faster and more efficient trials, facilitating a timelier translation of research findings into clinical practice.

Both qualitative and quantitative imaging biomarkers enable the early detection of pathological features and subtle changes in patients, often before they manifest as clinical complications. This early detection facilitates timely intervention, potentially leading to improved patient outcomes. When applied to imaging endpoints in cardiovascular research, these provide an opportunity for a more nuanced understanding of disease mechanisms, progression, and response to treatment and offers a critical bridge between preclinical investigations and clinical outcomes. Acceptance of imaging derived clinical trial endpoints by regulators offers the potential to accelerate development of cardiovascular therapies by providing earlier signals about safety and efficacy.

MULTIMODALITY IMAGING

Multimodality imaging in cardiovascular clinical trials, involves the use of multiple imaging techniques to gather comprehensive data about the cardiovascular system. Imaging modalities commonly used in clinical trials include CT, Echocardiography, MRI, X-Ray Angiography, Intravascular Imaging, and Nuclear Medicine. For example, Invasive Coronary Angiography (ICA, figure 1) is a primary tool in the assessment of Coronary Artery Disease (CAD), which provides guidance for interventions and is often considered a golden standard. The invasive nature, radiation exposure, and contrast dye, however, make it a cumbersome technique for the patient, furthermore there are limitations to the features it can visualize and the information it can provide. Through Cardiac CTA (figure 2) a complete assessment of the coronary anatomy can be obtained noninvasively, and plaque can be characterized. Radiation exposure and contrast dye are still a factor though and the ability to evaluate the tissue of the myocardium itself is limited. Cardiac MR (figure 3) can both assess function of the heart and evaluate the myocardium on a tissue level. Cardiac MR in its turn is a time consuming and costly imaging modality with limited availability; also, it lacks the ability to effectively evaluate the coronary arteries. This example highlights the key benefit of multimodality approach: the unique insight each modality provides for precise disease phenotyping, crucial for patient selection in clinical

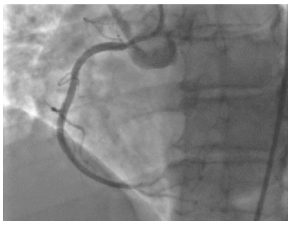


Figure 1. *Angiography PCI showing the right coronary artery.*

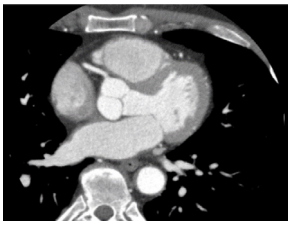


Figure 2. *ECG gated contrast enhanced Cardiac CTA.*

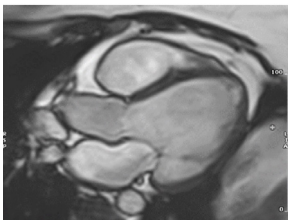


Figure 3. *Cardiac MR, LGE imaging.*

trials, and the detailed monitoring of disease progression, adverse effects, and response to treatment. For example, multimodality imaging can help to assess the pharmacokinetics, biodistribution, target engagement, and pharmacodynamics of a drug candidate. Multimodality imaging can enhance the quality and reliability of clinical trial data by combining the benefit of more than one of these imaging techniques to provide improved precision assessments and endpoints of cardiovascular function compared to what a single modality may provide, as explored in the following case study. Multimodality cardiovascular imaging also poses some challenges, such as the need for data integration and analysis of multimodal data, patient compliance with multiple exams, and of course the cost. Therefore, multimodality imaging requires careful planning, design, execution, and interpretation of clinical trials.

CASE STUDY – AMYLOIDOSIS

To highlight the design, utility, and importance of multimodal imaging in cardiovascular clinical trials we examine a case study involving a hypothetical clinical trial of a new treatment of cardiac amyloidosis. Amyloidosis is a group of diseases characterized by the abnormal accumulation of amyloid proteins in various tissues and organs in the body. These proteins can disrupt normal tissue structure and function, leading to organ damage and dysfunction.

The progression of amyloidosis can vary depending on the type and severity of the disease. However, in general, amyloidosis tends to progress slowly over time as the amyloid deposits accumulate in different parts of the body. Symptoms may initially be mild or nonspecific, such as fatigue, weakness, and weight loss. As the disease advances and more organs are affected, symptoms may become more severe and specific to the affected organs, including the heart, kidneys, liver, brain, spleen, stomach, and intestines.

Early detection and appropriate management can help slow the progression of the disease, thus reducing the occurrence of serious complications (organ failure) and improve the quality of life and long-term health care costs for these patients. Besides the clinical benefits, early detection can provide opportunities to develop new treatment strategies and therapies for early-stage patients. Treatment options may include medications to reduce the production of amyloid proteins. Examples are chemotherapy, stem cell transplantation, and supportive therapies to manage symptoms and complications.

Several modalities may be used in the diagnosis and follow-up of cardiac amyloidosis, most commonly these are Echocardiography, Cardiac MR, and Radionuclide Imaging. Used separately, each have their own advantages and disadvantages or limitations. The optimal imaging tests for quantification of disease progression are still uncertain. However, current and future studies are aimed to illuminate these knowledge gaps. Accurately and specifically measuring disease progression and treatment effect using non-invasive imaging, opens the possibilities to develop imaging endpoints that can be implemented in future studies.

Echocardiography assesses the structure and function of the heart, and can detect signs of amyloid infiltration, which may manifest as increased wall thickness, biatrial enlargement, pericardial effusion, and reduced global longitudinal strain. Echocardiography can also measure diastolic function, filling pressures, and atrial and ventricular dysfunction, which are important for prognosis and management of cardiac amyloidosis. However, echocardiography cannot differentiate between subtypes, i.e., primary amyloidosis (AL) and transthyretin amyloidosis (ATTR). By itself, echocardiography might not be sufficient to determine patient eligibility or stratification for clinical trial participation. Also, it may have limitations in image quality and tissue characterization.

CMR provides high-resolution images of the heart which allows us to evaluate biventricular anatomy, mass and function and tissue properties. CMR can also detect amyloid deposits by using relaxometry and late gadolinium enhancement (LGE). In amyloidosis, native T1 values are typically elevated, even in some patients where conventional classifications suggest there is no cardiac involvement. The LGE technique is sometimes complicated with difficulty to null the signal of the healthy myocardium. LGE pattern is classically subendocardial and then transmural, with a non-coronary distribution. MRI not only helps to differentiate amyloidosis from sarcomeric hypertrophic cardiomyopathy, but also to discriminate between AL and ATTR subtypes by using T1 and ECV thresholds, providing more specific classification for eligibility for a given clinical trial. Unfortunately, MRI may not be feasible in patients with renal failure or carrying MR-unsafe devices (i.e., old generation pacemakers,

abandoned leads, some cochlear implants or ventriculoperitoneal shunts, etc.).

Radionuclide imaging uses bone-avid radiotracers, such as 99mTc-PYP, 99mTc-DPD, or 99mTc-HMDP, to visualize amyloid deposits in the heart. Radionuclide imaging can reliably distinguish between AL and ATTR subtypes, as ATTR amyloidosis shows avid uptake of these tracers, whereas AL amyloidosis shows minimal or no uptake. Radionuclide imaging can also quantify the amyloid load by using standardized uptake values (SUV) or heart-to-contralateral lung ratios (H/CL), which correlate with prognosis and response to therapy. Radionuclide imaging is widely available and has lowered its radiation footprint over time, it may still have lower spatial resolution and specificity than CMR. In the setting of randomized clinical trials these features make SPECT imaging a good candidate for assessment of response to treatment in amyloidosis clinical trials, and a useful tool for patient eligibility and selection.

When used in a multi-modality imaging setting several advantages can be leveraged.

Cardiac MRI

Overview:

- Detailed assessment of structure and function
- Tissue characterization
- High cost
- Available at specialized centers

Applied Techniques:

- LV function and morphology
- Amyloid Imaging
- Amyloid Quantification

Suggestive Parameters:

- Increased LV wall thickness, increased LV mass, biatrial enlargement, typical diffuse or global LGE pattern, difficulty in achieving myocardial nulling, significantly increased ECV (>0.40), small pericardial and pleural effusions

Echocardiography

Overview:

- Detailed assessment of structure and function and valves
- No tissue characterization
- Low Cost
- High Availability

Applied Techniques:

- 2D, Color and Spectral Doppler Imaging
- Tissue Doppler Imaging
- Strain Imaging
- Aging

Suggestive Parameters:

- Increased LV wall thickness, increased LV mass, typical LV longitudinal strain pattern, mitral annular TDC <5cm/s, biatrial enlargement, small A-wave in sinus rhythm, small pericardial and/or pleural effusions

99Tc-PYP/DPD/HMDP Imaging

Overview:

- High diagnostic sensitivity
- Intermediate cost
- Available at specialized centers

Applied Techniques:

- Visual scan interpretation
- Semi-quantitative interpretation in relation to rib uptake
- Quantitative findings H/CL lung ratio

Suggestive Parameters:

- Myocardia uptake of 99Tc-PYP/DPD/HMDP is visually confirmed, a semi-quantitative visual grade of 2 or 3

Echocardiography, CMR, and radionuclide imaging can provide complementary information on cardiac structure, function, tissue characterization, and amyloid type, leading to more accurate and timely diagnosis of cardiac amyloidosis and better assessment of prognosis and treatment response. Radionuclide imaging with bone-avid radiotracers and MRI to a lesser extent can differentiate ATTR from AL cardiac amyloidosis without the need for endomyocardial biopsy, which is invasive, costly, and not widely available. Enabling of non-invasive sub-typing of amyloidosis is especially important for assessing eligibility and stratification in clinical trials according to specified inclusion criteria.

Multimodality imaging offers unique advantages for clinical trials in amyloidosis. Information from echocardiography, cMRI, and cardiac SPECT can be integrated by investigators and medical monitors to determine whether patients meet criteria for enrollment, as well as to fulfill recruitment requirements for specific sub-types of disease. Further, multiple assessments can be entered into statistical analysis to provide highly specific measures of response to treatment. Moreover, echocardiography and CMR can provide quantitative measures of cardiac strain, ejection fraction, mass, and extracellular volume, which are associated with survival and can guide treatment decisions. In clinical trials, multimodality imaging supports novel therapeutic development and evaluation. As new therapies for cardiac amyloidosis emerge, multimodality imaging can serve as a valuable tool for monitoring their efficacy and safety, as well as for identifying optimal candidates and dosing regimens. Multimodality imaging can also help to explain the mechanisms of action and the effects of novel therapies on cardiac amyloid burden and remodeling.

THE NEED FOR STANDARDIZATION

The standardization of imaging biomarkers in clinical trials is crucial for ensuring consistency, reliability, and comparability of data across different study sites and over time. Standardized imaging biomarkers enable consistent and reproducible measurements, reducing variability in data collection across various imaging centers. This consistency is essential for drawing meaningful conclusions from study results, especially when using multiple imaging modalities across many clinical trial sites.

Standardization facilitates comparisons between different clinical trials, allowing researchers to evaluate the efficacy and safety of interventions across studies. This is particularly important for meta-analyses and systematic reviews. Standardized biomarkers ensure that the measured parameters are repeatable, reliable, and reflect meaningful aspects of the disease or intervention under investigation. This enhances the validity and translatability of study findings to real-world clinical practice.

In multicenter trials, where data is collected from multiple sites, standardized imaging protocols and biomarkers enhance collaboration and data integrity. This is crucial for large-scale studies involving diverse patient populations. Longitudinal studies and follow-up assessments benefit significantly from standardized imaging biomarkers. Consistency over time allows researchers to monitor disease progression or treatment effects accurately. Standardization provides a basis for establishing rigorous quality control and assurance measures. Importantly, standardization of image acquisitions and analysis of multi-modality cardiac imaging data in clinical trials reduces noise in the clinical trial endpoints, resulting in better signal-to-noise at the output of statistical analysis models and better-quality data submitted to regulatory agencies. Working groups can develop guidelines and protocols to ensure that imaging procedures meet predefined standards, enhancing the overall quality of data.

STANDARDIZATION BY WORKING GROUPS

Working groups, consortiums, and consensus papers are important drivers behind standardization, for multiple reasons. By bringing together experts in the field who can collaboratively define and refine imaging biomarker standards, the collective expertise ensures that standards are evidence-based and reflect the latest advancements in the field.

Standardization of imaging biomarkers through working groups, consortiums, and consensus papers is especially important in multi-modality cardiac imaging for clinical trials. With the multiple imaging modalities outlined above offered by multiple vendors to multiple sites, the number of permutations of imaging exams collected by clinical sites are likely to vary widely. To enable meaningful comparisons of multi-center data and provide reliable input to statistical analysis models, standardization of imaging modalities and acquisition is critical.

One example of such a workgroup is ESR's European Imaging Biomarkers Alliance (EIBALL) initiative, a project that aims to facilitate the development, standardization, and use of imaging biomarkers in clinical trials and practice. EIBALL is a collaboration of the ESR with other specialist societies, international standards agencies, and trials organizations to create a network of excellence in the field of imaging biomarkers. EIBALL coordinates all ESR activities concerning imaging biomarkers, maintain an inventory of existing imaging biomarkers and their evidence as well as defining new possible imaging biomarkers for different body regions and diseases. EIBALL encourages the clinical use of biomarkers by setting standards for data acquisition and image processing and collaborate with other initiatives such as RSNA's QIBA and EORTC. EIBALL helps to improve the quality and comparability of imaging data and to support the advancement of medical imaging research and practice.

In the context of cardiovascular health and procedures, ARC, VARC, and NARC are examples to specific initiatives or criteria developed by experts in the field to standardize, evaluate, and improve cardiovascular treatments and outcomes.

ARC refers to the Academic Research Consortium, which is a collaboration of academic researchers, clinicians, and industry professionals focused on developing standardized definitions and criteria for clinical trials in cardiovascular research. Key contributions include:

- Standardized Endpoints: Creating uniform definitions for endpoints in clinical trials, such as major adverse cardiac events (MACE).
- Evaluation Criteria: Providing guidelines for assessing the safety and efficacy of cardiovascular devices and therapies.
- Collaboration: Promoting collaboration among academic institutions, regulatory bodies, and industry partners to advance cardiovascular research.

VARC is the Valve Academic Research Consortium, which focuses on standardizing the evaluation of transcatheter valve interventions, particularly transcatheter aortic valve replacement (TAVR). Key initiatives include:

- Standardized Definitions: Developing consensus definitions for clinical endpoints in studies involving transcatheter valve therapies.
- Clinical Guidelines: Providing recommendations for the conduct and reporting of clinical trials involving valve interventions.
- Outcome Measures: Establishing criteria for measuring procedural success, complications, and long-term outcomes in valve interventions.

NARC is the Nomenclature for Aortic Root and Valve Complex, which is an initiative aimed at standardizing the terminology and definitions related to the aortic root and valve complex. Key aspects include:

- Consistent Terminology: Developing a uniform language for describing the anatomy and pathology of the aortic root and valve complex.
- Diagnostic Criteria: Establishing clear criteria for diagnosing conditions related to the aortic root and valve.
- Communication: Enhancing communication among clinicians, researchers, and educators by providing a common framework for discussing aortic root and valve-related issues.

These cardiovascular initiatives aim to improve the quality and consistency of research, diagnosis, and treatment in the field of cardiology. They help ensure that clinical trials are comparable, outcomes are accurately measured, and healthcare professionals are on the same page when it comes to terminology and procedures.

THE ROLE OF A CORE LAB

The core lab is an essential component of clinical trials, providing the standardization described above, as well as consistent, high-quality, and timely data that can support the safety and efficacy of new therapies. Additionally, it can offer expertise, guidance, and innovation in the design, execution of clinical trials that make use of multi-modality cardiovascular imaging. The core lab further contributes to analysis of imaging data for clinical trials, as well as regulatory compliance and quality assurance. By partnering with a core lab, Sponsors can benefit from the added value of having access to a global network of sites, technologies, and resources that can enhance the quality and efficiency of their clinical trials.

The utilization of qualified central readers in imaging trials managed by a core lab presents numerous advantages that significantly contribute to the reliability, consistency, and quality of trial outcomes. Central readers, often comprising experienced and specialized experts, bring a standardized and meticulous approach to the interpretation of imaging data. This not only minimizes variability in assessments but also ensures a more robust and objective evaluation across diverse study sites. The expertise of central readers is particularly crucial in studies that utilize multiple imaging modalities, such as echocardiography, MRI and/or CT scans, where nuanced interpretations and integration of imaging data sets can impact trial results. Additionally, their independence from individual study sites fosters impartiality, reducing potential bias, and enhancing the overall credibility of trial findings. By adhering to rigorous imaging protocols, central readers contribute to the generation of high-quality data, facilitating regulatory approvals, and bolstering the scientific validity of the trial results. Overall, the engagement of qualified central readers emerges as a strategic imperative for imaging trials, elevating the standards of precision, consistency, and reliability in the assessment of medical imaging data.

As shown by the Amyloidosis example case, multimodality imaging can provide comprehensive and complementary information for the clinical trials in cardiovascular disease therapies. However, multimodality imaging also poses a challenge due to the added complexity to the trial, but Medpace Core Laboratories (MCL) addresses these challenges by:

- Providing specialized expertise and training in different imaging modalities and software tools.
- Harmonization and validation of image acquisition protocols and analysis methods across different imaging centers and vendors.
- Multi-layered quality control and assurance of image quality and data integrity.
- A unique in-house designed ecosystem designed with efficient and secure data transfer, storage, and archiving in mind, allowing for interoperability and integration of image data with other clinical data sources.
- Proven compliance with ethical and regulatory standards and guidelines.
- A multidisciplinary team approach, involving experts from different imaging modalities, clinical specialties, biostatistics, informatics, qualified central readers, and project management.
- Clear and consistent communication with the imaging centers, sponsors, investigators, and regulators.
- Leveraging the advances in artificial intelligence, cloud computing, and big data analytics to enhance the efficiency, accuracy, and value of multimodality imaging.

MCL is a one-stop shop for all Sponsor's imaging needs, from protocol design and site selection to image acquisition and analysis. Our team of experts have extensive experience in various therapeutic areas and imaging modalities, and can provide Sponsors with high-quality data and insights from our medical imaging scientist technologists. Whether you need MRI, CT, PET, ultrasound, or any other imaging technique, we have the expertise to support your clinical trial.

MCL offers medical imaging services, working with Medpace or other clinical teams to ensure that imaging components are seamlessly integrated into the complex structure of the overall clinical trial. Medpace provides core lab services for either stand-alone or fully integrated projects with Medpace's full-service, scientifically driven clinical teams. Our approach has led to FDA approvals, highlighting MCL's ability to manage the most complex and innovative trials.

Do you have an upcoming clinical trial that needs seamless execution? Contact us today to discuss how Medpace can help accelerate your clinical development.

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