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IMAGING PERSPECTIVES

Use of Imaging Endpoints in Clinical Trials

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ABSTRACT

Cardiovascular imaging is an integral component of many clinical trials beyond those for which the primary goal is to evaluate or validate imaging technologies. The scope of such trials is broad, ranging from those in which a medical, surgical, or interventional cardiovascular device or drug is being evaluated to those in which there is concern about cardiovascular adverse events complicating treatment for noncardiac conditions. This paper discusses study design as it pertains to the incorporation of imaging elements, the important role played by imaging core laboratories, the rationale for and approaches to involvement of imagers in clinical trials, and guidance by the U.S. Food and Drug Administration on imaging endpoints in clinical trials. (J Am Coll Cardiol Img 2017;10:296–303) © 2017 by the American College of Cardiology Foundation.

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DESIGN OF IMAGING ASSESSMENTS

The design of the imaging elements of multicentered cardiovascular clinical trials must take into consideration the technical and diagnostic capabilities of different imaging modalities, their accuracy and reproducibility, relative risks and costs, availability, and, the likelihood that the expertise exists at each of the study sites to provide adequate images for analysis. Where site-reported rather than core laboratory-adjudicated imaging results are to be used, the skill of the interpreting physicians at study sites must also be a consideration. For these reasons, the study design team should include or consult with those who are not only imaging experts but who also have an awareness of what might reasonably be expected in terms of local site technical and interpretive expertise. These considerations can influence overall trial design and the decision to include imaging data as principle study endpoints. As an example, the degree of left ventricular reverse remodeling as determined by transthoracic echocardiographically derived indexed left ventricular end-systolic volume was chosen as the primary endpoint in the Cardiothoracic Surgery Network studies of mitral regurgitation (1,2).

The selection of imaging elements in a trial must, of course, be based on the degree to which imaging can provide a robust and reproducible assessment of

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parameters that are relevant to the questions being posed by the study. At times, there may be multiple options among available modalities (e.g., when the objective is to measure left ventricular ejection fraction). At other times, the options may be more limited. For example, there is no practical alternative to transthoracic echocardiography for multiple assessments of transvalvular gradients after aortic valve replacement. When multiple options exist, a thoughtful comparison of modalities as to accuracy and reproducibility, risks, costs, and site capabilities can be used to finalize modality selection. Considerations of accuracy and reproducibility should include issues of spatial and temporal resolution, interobserver and intraobserver variability, and performance of the modality under consideration relative to a gold or reference standard.

Depending on the question being posed of the imaging data, test-retest and beat-to-beat variability should also be considered. For some parameters (e.g., echocardiographically derived strain), inter-vendor variability may also be a consideration that could drive a decision to ensure that all images are acquired with equipment of a single manufacturer. All other considerations being equal, the modality or application within a modality (3-dimensional [3D] vs. 2-dimensional, contrast vs. noncontrast imaging) that provides the most accurate and reproducible findings should be used. Risks that must be evaluated include those associated with vascular access and contrast agents, esophageal intubation (transesophageal echocardiography), and radiation exposure. Both risk and cost considerations are particularly important if study-mandated imaging cannot be considered standard of care.

Modern computed tomography (CT), afforded by its isotropic voxels, is capable of reconstructed images in any plane without compromising its spatial resolution. In addition, the technical aspects are highly standardized with well-defined and established acquisition protocols. Imaging is relatively independent of local expertise even when local interpretation may not be feasible. This relative operator independence and standardized acquisitions make it an excellent tool to allow a core laboratory to provide noninvasive imaging procedural guidance and for its images to serve as an anatomic endpoint in clinical trials. Although these features make CT scanning an increasingly popular imaging tool to support cardiovascular clinic trials, significant limitations remain with this technique, particularly the lack of hemodynamic data, the inability to integrate CT scanning at the time of a procedure in the absence of meaningful fusion imaging, and the need to administer iodinated contrast medium. Nonetheless, CT is essential in trials of transcatheter aortic and mitral valve replacement, for example, in which precise and reproducible anatomic measurements are required.

Magnetic resonance imaging (MRI), conversely, offers opportunities in which CT is lacking. Although not as standardized and far more operator dependent, MRI offers hemodynamic evaluation and does not rely on iodinated contrast material or ionizing radiation, thus making it a robust imaging tool for patients with abnormal renal function. MRI has become the reference standard for ventricular volumes and mass as well as myocardial fibrosis.

In contrast, echocardiography has important limitations due to its operator and subject dependence, particularly when 3D acquisitions are required for volumetric assessments. However, it has high spatial and temporal resolution and remains the procedure of choice for assessing valvular function and hemodynamic variables, including pulmonary artery systolic pressure. As a technique that is radiation free, relatively inexpensive, and capable of real-time imaging, it is widely used in trials of native and prosthetic valves as well as those for which an impact on valvular structure and function might be anticipated (e.g., anorectic drugs), and those in which subtle alterations of global ventricular function might be encountered (e.g., strain imaging for assessing the impact of chemotherapeutic agents). Although there is active work in expanding the clinical and research capabilities of radioisotope molecular imaging, in trials for which imaging serves as a tool rather than the major focus of the investigation, nuclear techniques are largely limited to the assessment of myocardial perfusion at rest or with stress.

In some situations, the framework for the use of imaging has been established by independent expert consensus (3,4) or through the need to provide information similar to that in relevant historical trials. As discussed in the following section, the FDA may also have input into the design of imaging elements of trials.

An overarching consideration in imaging study design should be the degree to which a change detected by imaging is meaningful, recognizing that statistical significance can be reached even when the measured changes are within the sampling error of the technique. Where valid quantitative alternatives exist, subjective semi-quantitative measures should not be used. However, there may be instances in which subjective measures are clinically relevant and

ABBREVIATIONS AND ACRONYMS

3D = 3-dimensional

CT = computed tomography

FDA = Food and Drug Administration

MRI = magnetic resonance imaging

SOP = standard operating procedure

TAVR = transcatheter aortic valve replacement

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