ASE EXPERT CONSENSUS STATEMENT

Echocardiographic Imaging in Clinical Trials: American Society of Echocardiography Standards for Echocardiography Core Laboratories

Endorsed by the American College of Cardiology Foundation

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INTRODUCTION

Imaging with cardiac ultrasound is a critical element of cardiovascular clinical research. The noninvasive assessment of cardiac structure, function, and hemodynamics using echocardiography can provide essential data on the safety and efficacy of drugs and devices, as well as insight into mechanisms of disease and therapeutic benefit. Echocardiography may also be used to assess enrollment eligibility, provide surrogate endpoints, suggest future research directions, and assist in determining optimal patterns of clinical surveillance. However, the value of this information is highly dependent on the quality of the planning and performance of imaging, the quality of data analysis, and the appropriate incorporation of results into overall trial analysis.

Unlike other cardiac diagnostic tests, such as electrocardiography,[1] there are few guidelines or regulatory statements providing direction for the proper performance and analysis of echocardiography in clinical trials research. International standards such as

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Conflicts of Interest: The authors have no conflicts of interest to disclose except as noted above. Supporters of the authors' current core laboratory projects are listed below.

Research Support for Core Lab Projects: Pamela S. Douglas: Atritech (Plymouth, MA), Edwards Lifesciences (Irvine, CA), Osiris Medical (El Paso, TX), ABIOMED (Danvers, MA), Viacor (Wilmington, MA), and Amgen (Thousand Oaks, CA). Richard B. Devereux: National Heart, Lung, and Blood Institute (NHLBI; Bethesda, MD). Shelly Duckworth: Atritech, Edwards Lifesciences, Osiris Medical, ABIOMED, Viacor, Amgen. Julius M. Gardin: Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (NHLBI). Wael A. Jaber: Athersys (Cleveland, OH) Cardiovascular Cell Therapy Research Network (CCTRN), NHLBI, Aastrom Biosciences (Ann Arbor, MI) (in collaboration with ICON Medical Imaging, Warrington, PA), Juventas Therapeutics (formerly AcelleRX, Cleveland, OH), KAI Pharmaceuticals (South San Francisco, CA), Mannkind Corporation (Valencia, CA), and Medtronic (Minneapolis, MN). Annitta J. Morehead: Athersys, CCTRN, NHLBI, Aastrom (in collaboration with ICON Medical Imaging), Juventas Therapeutics (formerly AcelleRX), KAI Pharmaceuticals, Mannkind Corporation, and Medtronic. Michael H. Picard: Edwards Lifesciences. Scott D. Solomon: NHLBI, Abbott Laboratories (Abbott Park, IL), Boston Scientific Corporation (Natick, MA), Cardiac Dimensions (Kirkland, WA), Daiichi Sankyo (Tokyo, Japan), Forest Research Institute (New York, NY), Guided Delivery Systems (Santa Clara, CA), Hamilton Health Sciences (Hamilton, Canada), and Novartis. Neil J. Weissman: NHLBI, Spectranetics (Colorado Springs, CO), Labcoat Limited (Galway, Ireland), Boston Scientific Corporation, Atrium Medical Corporation (Hudson, NH), Cook Medical (Bloomington, IN), ATS Medical (Minneapolis, MN), Sorin/CarboMedics (Austin, TX), Edwards Lifescience, St Jude Medical (St Paul, MN), BIOTRONIK (Berlin, Germany), Novartis, Sunshine Heart (Tustin, CA), MitralSolutions (Fort Lauderdale, FL), Ample Medical (Foster City, CA), Evalve (Menlo Park, CA), Mitralign (Tewksbury, MA), Medispec (Germantown, MD), and Direct Flow Medical (Santa Rosa, CA).

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0894-7317/$36.00

doi:10.1016/j.echo.2009.05.020

International Organization for Standardization 9001:2000 for quality management or International Organization for Standardization/International Electrotechnical Commission 17025 for laboratory testing and quantification may be broadly considered to be relevant[2] but provide little specific guidance to echocardiography core laboratories (ECLs). Given the US Food and Drug Administration's (FDA) limited internal standards, regulatory requirements can vary from trial to trial and depend on which group within the FDA has oversight of the trial. This can lead to confusion on the part of sponsors and investigators and a failure to design and fund the imaging components of trials properly. Indeed, recent trials have shown the need for a more thoughtful, proactive approach to echocardiography to ensure the validity of the results of the overall trial. The results of the Predictors of Response to CRT (PROSPECT) study, an investigation of echocardiographic predictors of response to cardiac resynchronization therapy, proved difficult to interpret, because there was limited agreement between the 3 ECLs involved and poor reproducibility of some measures.[3,4] Similarly, the results of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, a study of the effect of lipid-lowering drugs on carotid intima-media thickness, were questioned because of the use of single-frame rather than moving images and a 17% rejection rate of ultrasound data.[5] As a result of these and other studies, ECLs are increasingly being used in large clinical trials and are usually required for large multicenter trials with imaging endpoints performed for regulatory submission.

The advantages of using an ECL are many; potential downsides include the associated cost and added complexity. Several studies have demonstrated the superiority of core lab interpretations for reducing variability and enhancing the precision of study results.[6-8] In large part, this is because core labs generally use a limited number of experienced observers, compared with local site readings by multiple observers with variable experience. Improved accuracy can be beneficial to trial efficiency because it may allow study of a smaller sample size. Indeed, the improvements in accuracy may be so significant as to alter the outcome of a trial. In one trial evaluating left ventricular volumes and function, only the ECL measurements had significant prognostic value for subsequent clinical endpoints.[6] In the field of cancer chemotherapy, a review of discrepancies between site and central interpretation of x-ray, computed tomographic, and positron emission tomographic images shows significantly altered trial results in some cases, with a subsequent impact on FDA approval in at least one case.[9] Thus, defining and implementing careful ECL best practices are essential steps toward performing more effective and efficient clinical trials research.

A previous American Society of Echocardiography statement, "Recommendations for Use of Echocardiography in Clinical Trials,"[10] describes the importance of high-quality imaging for research. It recommends methods for some of the common applications of echocardiography, such as determinations of left ventricular ejection fraction and mass, but it does not extensively address the roles and responsibilities of core laboratories or other issues such as personnel, study design, imaging review charters, site management, information technology, and statistical analysis. No other document or guidelines statement exists to fill these gaps. Thus, at the present time, there is great need for a clear and universally accepted set of "best practices" in these areas, which form the core of this consensus-driven standards document.

I. MATCHING TRIAL REQUIREMENTS TO OPTIMAL USE OF CORE LABORATORIES

Imaging in general, and echocardiography in particular, must be considered in the context of the overall trial, the regulatory requirements (if any), and the role that the imaging will fill. The role of the core lab will vary tremendously depending on the type of regulatory oversight involved (eg, FDA vs non-FDA), how echocardiography is used in a trial, the complexity of analysis required, how the data being developed will be analyzed and interpreted, and the type of trial. For example, the requirements of a small, investigator-initiated study in which echocardiography is used as an assessment, but does not contribute to a safety or efficacy endpoint, are very different from a large, pivotal or phase 3 trial performed for regulatory approval, for which complex echocardiography is both required and contributes to important safety and efficacy measures. Core lab activities and practices must be properly matched to the needs of each trial; best practices need to be customized accordingly. For the purposes of this document, 3 broad categories have been defined and are applied throughout the text (see Table 1).

These categories are intended to address clinical studies using echocardiography as a bioassay (such as a new drug with potential cardiovascular effects or assessments of new intracardiac prostheses). The categories are not rigid but are intended to provide a framework for the planning and execution of studies. Furthermore, they are also applicable to the core lab component of echocardiographic technology assessment trials (eg, contrast agent research), which may incorporate the performance characteristics of the entire echocardiographic acquisition process. In this latter case, the overall trial protocol must address the clinical efficacy and impact of the new technology, even though the core lab's function of interpreting images may remain similar to the "bioassay" trial.

We recognize that some trials will not be easily categorized and that changes in regulatory policies may vary. In addition, other factors should be considered and will also guide the specific application of echocardiographic and ECL activities. These include, but are not limited to, trial size, the number of sites, and the direct involvement of the ECL in image processing or interpretation. Furthermore, factors may change during the course of a trial (eg, the extent of site training and oversight required may be greater than originally anticipated), and operations of the ECL under best practices guidelines will require ongoing adjustments to meet these needs.

II. ECHOCARDIOGRAPHY CORE LABORATORIES: RESPONSIBILITIES AND ORGANIZATION

The ultimate objective of the ECL is to ensure that the echocardiographic data are robust enough to support or refute the hypothesis or objective of the trial or substudy. This goal is generally accomplished through the reduction of variability in assessment, which in turn contributes to an increase in the study's power. To this end, the specific services that an ECL may provide to a given trial extend beyond the collection, interpretation, and quantification of echocardiographic data for a clinical trial and include (1) development of the trial or substudy design, (2) training of sonographers and other personnel involved in image acquisition, (3) oversight of acquisition of images, (4) analysis of echocardiographic data, (5) providing quality assurance (QA), (6) information technology services (such as image management [digitization, transfer, storage] and data management), (7) interpretation of data, and (8) preparation of data reports, manuscripts, and

Table 1 Categories of echocardiography use in clinical trials

Category	Description
A	Any study that includes FDA or other regulatory body oversight or is performed for registration. Although specific guidance for imaging is lacking, the FDA's general requirements for regulatory compliance mandate the highest level of best practices.
B	Studies that do not involve FDA or other regulatory body oversight but involve complex imaging or include echocardiographic measures as primary or secondary efficacy or safety endpoints.
C	Studies that do not involve regulatory oversight, complex imaging, or echocardiographic endpoints.

support for regulatory submissions (see Figure 1). The ECL provides an independent, vital link between the trial sponsor and clinical sites, communicating with both to ensure mutual understanding of plans and successful execution. The exact services for any given trial depend on the type of regulatory oversight involved, the complexity of the trial, and the role of echocardiographic data within that trial.

Because both the operational and clinical aspects of the acquisition of echocardiographic images and the derivation of measurements from those images are dependent on the operator, human errors and inconsistencies inevitably introduce unwanted variability. A host of other major and minor factors that can adversely affect the use of echocardiography include missing data, nonuniformity in equipment, and lack of the expertise required for a particular trial. The main purposes of an ECL are to define and standardize processes for image acquisition and analysis, education and training of sonographers and overreaders, and image and data management, as well as actually performing the image analysis itself. These activities should be part of a broad program of quality assessment and improvement for all aspects of ECL operations, as well as study-specific QA activities. The overall QA program is discussed in greater detail below but includes systems, procedures, and definitions that provide confidence in the accuracy and integrity of all activities and data, as well as the development and periodic review of standard operating procedures, staff continuing education pertinent to clinical research, and adherence to good clinical practice. Although the design and implementation of QA programs to maximize the reproducibility and accuracy of echocardiographic data cannot eliminate all variability, they can ensure that errors in image acquisition and quantification are minimized.[8,11-13] Ideally, ECLs are either themselves certified by the Intersocietal Commission for the Accreditation of Echocardiography Laboratories or tightly linked to certified labs. Discussion of the specifics of overall and study-specific QA is interspersed through the recommendations below, because a successful ECL must integrate QA into day-to-day operations rather than consider it as a separate activity.

Core Lab Personnel

Although most core labs handling large registration trials include a variety of personnel, the director of an ECL is the central figure responsible for overseeing all aspects of the ECL. The director may also serve as the principal investigator (PI) of a specific trial, or that function may be performed by another qualified individual. The director is usually assisted by a project leader or a technical manager who ensures quality and operational excellence in the performance of overall ECL functions as well as an individual study. For each trial, the PI and project leader both interact closely with the sponsor and other

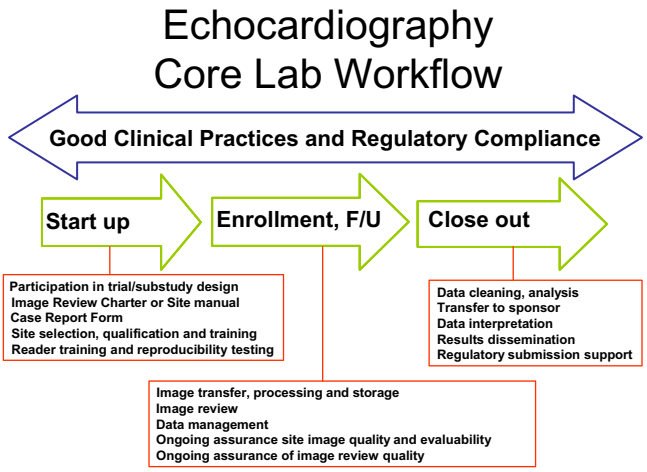

Figure 1 ECL work flow. *F/U*, Follow-up.

key personnel (such as a steering committee, data coordinating center, PIs, and managers and coordinators from clinical sites involved in the trial). Depending on the nature of the study, the ECL PI may or may not serve as the overall PI for the study. Depending on the size and services that are offered, other ECL personnel may include interpreting physicians and echocardiographers, the lead sonographer and interpreting sonographers, the clinical trial coordinator or assistants, information technology and data management personnel, and a biostatistician. An ECL may also consider appointing a QA or audit officer. Depending on the size and complexity of a particular ECL, a single person may assume more than one of the positions above. For example, a lead sonographer may assume the responsibilities of a project leader and a clinical trial coordinator. Core lab personnel and titles may vary among labs, and which personnel are required will depend on the exact services that a core lab is providing for a sponsor. A range of possible core lab services and personnel for each category of trial is provided in Table 2. It is important to note that there is no single "best" core lab organizational structure or process and that the roles of various personnel in Table 2 are intended to represent only one of many possible configurations of an ECL. More important than the specific organization is ensuring the assignment of responsibility both for the processes and procedures involved as well as for ensuring clinical excellence.

III. OVERALL APPROACH TO SPECIFIC CLINICAL TRIALS: IMPORTANCE OF THE IMAGE REVIEW CHARTER

All category A clinical trials require the development and maintenance of documentation that adequately supports all aspects of the ECL operations. Such documentation is typically contained in an image review charter but can also be accomplished in a series of other documents (such as standard operating procedures, a prespecified analysis plan for primarily echocardiographic endpoints, task-oriented protocols, and/or specific recording logs) at the discretion of the ECL and the sponsor. As used in this document, an image review charter is an all-encompassing document that lists imaging resources; imaging criteria; processes for the receipt, handling, preparation, and archiving of images; the process steps for the review and assessment of images; and the various methodologies for QA and quality control (Table 3). Such a document is typically submitted to or available for review by

Table 2 Functions of ECLs and Key Personnel

Service	Examples	Key personnel	Study category
Trial design and support			
Interactions with clinical research organization and sponsor	Ensure initial and ongoing agreement on the processes and work flow to be undertaken by the core lab; development and approval of an imaging charter	PI, PL	A, B, C
Trial design	Development of overall clinical and echocardiographic protocol, policies, and procedures; selection of clinical sites; providing advice on equipment, etc	PI	A, B
Biostatistics	Sample size calculations, statistical methods	PI, statistician	A, B
Ongoing communications	Updating steering committee or sponsor, communications with study sites, participation in teleconferences, monitoring, providing progress reports, etc	PI	A, B, C
Post-trial support	Abstract and manuscript development for both primary and secondary manuscripts, sharing of data, etc	PI, PL	A, B
Representation on committees	Ex officio position on the trial's executive/steering committee; membership on trial publications committee	PI	A, B
Image acquisition			
Develop echocardiographic protocol, site policies and procedures	Determine echocardiographic parameters to be used for trial, develop an echocardiographic site manual, etc	PI, LS	A, B, C
Develop and implement study materials	Image acquisition protocol, site manual, analysis protocol and instructions, case report or data collection forms with work instructions, etc	PI, PL,LS, CTC, statistician	A, B, C
Develop and implement training programs	Site qualification; develop training manuals and materials for image acquisition and transfer; train site sonographer and echocardiographer; train sonographer and reviewer at core lab	PI, PL, LS, CTC	A, B, C
Biostatistics	Review of data forms and instructions, data transfer formats, etc	PI, statistician	A, B
Image analysis			
Data receipt and uploading	Review received images, QA feedback to sites; upload to analysis workstation	SS, CTC	A, B, C
Data analysis	Select clips for analysis, analysis of data per protocol, perform quantitative analyses, interpret studies, etc	PI, LS, SS, SE	A, B, C
Data transcription	Transfer data to case report forms or other databases, etc	LS, CTC, PL, statistician	A, B, C
Biostatistics	Data queries and cleaning	Statistician	A, B, C
QA			
Study data	Ensure accurate acquisition of high-quality echocardiographic images, reproducibility, monitoring of sites, provide feedback to clinical sites, sonographer retraining if required, etc	LS, CTC	A, B, C
Reviewers	Determine and minimize intraobserver and interobserver variability, prevent drift, monitoring, retraining if required, etc	SS, SE	A, B, C
Equipment	Regular analysis calibration of echocardiographic systems	LS	A, B
Biostatistics	Development of statistical methods to evaluate intraobserver and interobserver variability and drift, plan any necessary remediation, etc	PI, statistician	A, B, C
Standard operating procedures	Develop methods for tracking, processing and analysis of studies, internal quality assurance, training procedures, blinding methods, etc	PI, PL, QAO	A, B, C
Compliance	Regulatory assurance that staff members are properly trained and all standard operating procedures are observed	PL, QAO	A
Audits	Regular review and inspection of overall core lab and study-specific processes, procedures, equipment and documentation to ensure adherence to good research practices and regulatory requirements	QAO	A, B, C
Information technology			
Image management	Digitization of studies from videotape, processing (deidentification) of images, secure image transfer following CFR part 11 guidelines, data storage, etc	CTC, SS	A, B, C
Data transfer and management	Develop plans for electronic or other method of data transfer from study sites to ECL, ensure part 11 compliance, handling and verifying data, maintenance of audit and data trails, data storage and backup, etc	PL, CTC	A, B, C
Results communication			
Manuscript authorship	Member of core lab as author on main trial results paper; development of publications plan	PI	A,B

CFR, Code of Federal Regulations; *CTC*, clinical trial coordinator; *LS*, lead sonographer; *PL*, project leader; *QAO*, QA officer; *SS*, study sonographer or physician primary reader; *SE*, study echocardiographer or physician overreader.

Table 3 Image review charter topics

Definition and purpose of imaging charter
Role of imaging in study design
Image acquisition and collection
Receipt tracking and quality control of image data
Design of independent review
Methodology for independent review
Selection and training of independent reviewers
Communication with sites and sponsor
Additional materials
References
Image acquisition protocol
Tracking forms and documents
Image flow charts

regulatory agencies to document and support the use of imaging in the clinical trial. It is also an important tool to enhance communication between core lab personnel, the sponsor, and trial leadership. This section addresses the documentation necessary for an ECL performing a category A trial. If the required documentation is incorporated into separate documents, they must be aligned and coordinated with each other and with the clinical protocol. Thus, a single document serving as a comprehensive image review charter is often the preferred approach.

Role of Echocardiography in the Trial

The image review charter must link the clinical protocol to the use of echocardiography and clearly define why echocardiography is involved, how it is to be used, and how it will be interpreted so as to link back to the main clinical study objectives. The role of echocardiography drives the operational requirements of the ECL and its interaction with clinical sites, the sponsor, the contract research organization, and/or regulatory agencies.

Echocardiography Acquisition. The ECL should develop the echocardiography acquisition protocol that provides instructions for the clinical sites as to how echocardiography should be performed. Therefore, part of the ECL imaging charter should specify how site training will be accomplished and how training success will be ensured. It should also address how sites are to store the images acquired. For example, options for saving images include (1) digital or analog format, (2) Digital Imaging and Communications in Medicine (DICOM) standards or not, and (3) the specific type of media.

Receipt, Tracking, and Quality Control. The image review charter should address image storage at the clinical site and transport to the ECL, including the creation of an audit trail. The image review charter should also address processes for the deidentification, labeling, and resolution of missing media or missing documentation. Any forms used for tracking and addressing deviations should be included in the image review charter.

Independent ECL Review Design and Methods. The ECL director, in conjunction with the leadership of the clinical trial, will need to design the core lab analysis and document how that analysis will be performed. All aspects of the design and methodology issues should be addressed prior to study initiation and documented in the image review charter.

ECL Reviewer Training. Qualifications and required training for all personnel involved in the interpretation of echocardiography should be specified and documented, including ongoing training and procedures for replacing reviewers and correcting deficiencies.

IV. CLINICAL TRIAL STUDY DESIGN

Echocardiography may play a number of roles within clinical trials, and how echocardiography is integrated into the overall study plan depends on its specific role in achieving the goals of that particular study. It is recommended that the core lab PI interact closely with the trial steering committee, often as a regular or ex officio member of this group and especially for category A and B trials. Such involvement is essential if echocardiography is to be used for selecting or confirming patient eligibility for study entry or for providing primary or secondary efficacy or safety endpoints and may also be beneficial if echocardiography is used to provide mechanistic data to complement primary endpoints, especially if complex imaging is planned. In all trials, ECL leadership should be involved in the development and execution of an echocardiographic data analysis plan that is coordinated with the overall study analysis plan. The analysis of the echocardiographic data should adhere to American Society of Echocardiography standards as defined in currently available documents.

When echocardiography is used as an efficacy or safety measure in a clinical trial, the specific endpoints and measures should be prespecified in the study protocol. If these endpoints represent primary efficacy measures, detailed statistical justification for the sample size needed for these specific measures should be provided on the basis of prior knowledge of the variance of these measures in the ECL and assumptions about the clinically meaningful detectable difference between treatment groups and the desired type I error and power for detecting the assumed clinical meaningful difference. For category A trials, ongoing review of yield of evaluable images is essential to ensure that the study sample size is achieved for echocardiographic data as well as patient enrollment. Finally, some trials (especially those with negative results) may wish to recalculate their power retrospectively as part of the final analyses using the actual sample sizes accrued and variability measured during the conduct of the studies.

V. CLINICAL SITES

The ECL interfaces with clinical sites throughout the study, and the quality and content of these interactions are critical to the success of the research. In addition to providing scanning protocols and qualification, the ECL can serve as a "coach" to encourage the sites' continuous attention to quality and compliance with the protocol.

Site Selection

Because the production of quality images is critical to a trial, and careful site selection can improve echocardiographic data quality,[14] requirements for site selection and qualification are critical to the trial. However, they will vary with the complexity of imaging required and on the category of trial. For category A and B trials, it should not be assumed that any clinical laboratory is capable of reliably producing the necessary data. Ideally, the site-ECL interaction would begin with site selection, because the core lab's assistance can be essential in helping the sponsor locate, select, and qualify sites capable of providing correct and timely images of high quality (see below for more detail). The site must be able to identify an echocardiographer who can serve as the PI.

Site Personnel

The inclusion of echocardiographers is essential for category A trials, either as the site PIs or as co-PIs, and should be included on site institutional review board applications. Ideally, one or two sonographers who are specifically trained in the echocardiographic protocol of a particular study will perform all the echocardiographic examinations for that study, but the protocol should specify whether this is requirement or whether the site may use any qualified sonographer. Site sonographer training, experience, and credentialing requirements should be commensurate with the complexity of the imaging required and the category of trial. Every ECL should maintain a database of the individual site sonographers and, ideally, perform qualification of and provide feedback to sites when necessary regarding study quality or protocol adherence.

Site Manual

The ECL provides a site instruction manual specific to the echocardiographic protocol of the study, which includes all forms and instructions required for the successful completion and transmission of the study images. The image acquisition protocol is part of the site manual and guides the site sonographers in performing the echocardiographic examination according to the specific needs of the trial, including which echocardiographic views to obtain, where to obtain Doppler and color-flow data, how to select specific machine settings, and so on. The site manual can also include abbreviated protocols that can be referred to easily during an examination (sonographer checklist), echocardiographic images, and technical tips, instructional material such as DVDs, or training Web sites. In addition, the site manual provides detail on the transmission of echocardiographic data to the ECL, including tracking forms, other echocardiography-specific case report forms, and QA feedback processes and definitions. The site manual must be approved by the sponsor and would be part of the image review charter if one is created for the study.

Site Training

Because sites are identified, the ECL is responsible for training the lead site sonographer and other critical site personnel, including conducting an in-depth review of the image acquisition protocol and image transmission. Initial training may be by conference call, on-site visit, or at a study initiation meeting and can be supplemented with Web or hard-copy training materials.

Site Qualification and Initial Site QA

Once training has been accomplished, the ECL will qualify each site using, at a minimum, documentation of the availability of machines, software, and scanning expertise needed to adequately gather the required views for the protocol and capabilities regarding data format and transmission (eg, videotape, CD-ROM, DICOM). It is recommended that each site perform at least one qualification echocardiographic study following the acquisition protocol for approval by the ECL before subject recruitment begins. For very complex, category A studies, each participating site sonographer may be required to qualify through the submission of an echocardiogram acquired according to the acquisition protocol. However constructed, this process serves as a "dry run" as well as a training tool and allows the site and ECL to address promptly and proactively any potential imaging, personnel, technical, or transmission problems requiring attention prior to subject enrollment and the collection of trial data. After review of the qualifying echocardiogram(s), the ECL should send a critique to the site and the sponsor indicating the results of the qualification process. Poorly performing sites should be instructed regarding the critical components that were missed. Should a site or sonographer not qualify initially, the opportunity then exists for protocol review and resubmission.

Ongoing Site QA

The ECL should maintain a continuous quality assessment and improvement program throughout the study period. For studies with ongoing submission of images during the trial, the ECL should periodically submit a report regarding image quality and acquisition acceptability to the site and sponsor within a mutually agreed upon timeframe. The ECL should track and report the quality and yield of evaluable echocardiograms to the sponsor and sites on a regular basis and have a plan for communicating with the sponsor and sites should the quality of submitted exams become suboptimal. Sites should be required to perform at or above a designated acceptability level; if a site falls below this level, remedial training should be completed. If this does not correct the problem, the study sponsor should be prepared to censure the site, including consideration of discontinuing enrollment at the site.

VI. IMAGE ANALYSIS

Image Analysis Plan

An image analysis plan is a written document developed by the ECL and approved by the sponsor describing each step of data analysis and is an important component of the imaging review charter. It includes information regarding personnel (physician reviewers, technical staff members, replacement plans), training plans, analysis tools (vendor software brand and version), echocardiographic measurements (definitions, calculations, and applicable references), echocardiographic analysis (number of cardiac cycles to be measured, definitions of suboptimal or unreadable), and quality assessment and control strategies (interobserver and intraobserver variability, reader drift).

There are many decisions required to construct an image analysis plan, beyond how best to measure a specific parameter. For example, in a longitudinal study, a determination needs to be made whether echocardiograms are interpreted independently over time or batch read so as to avoid temporal bias or temporal drift. If a longitudinal study is designed to detect change over time, echocardiograms may be either interpreted independently with a subsequent statistical comparison over time or interpreted side by side at the end of the trial to maximize sensitivity for detecting change in a particular parameter. Most other aspects of the analysis process should be determined in advance and should be approved by the sponsor. These may include, but are not limited to, exact analysis methods, software, and analysis equipment; the number of readers who will interpret each echocardiogram, along with whether they will perform preliminary measurements of some or all parameters; the adjudication process for discrepancies; method of assessing intrareader and interreader variability; the type of blinding that is necessary (site, time, etc) and how it will be accomplished; and the need for an interim analysis, along with who will know the results.

The echocardiography case report form is used by the ECL to collect pertinent echocardiographic image data and must be approved by the study sponsor and the ECL PI before study startup. Data fields may include all echocardiographic measurements themselves, identifiers (site identification, subject identification, visit date and type

[ie, baseline, 30 days postprocedure], site sonographer name, image modality [ie, transthoracic echocardiography, transesophageal echocardiography]), subject information (eg, height, weight, blood pressure, medications, if relevant), space for comments, and names and dates of interpretation. Of note, the overall study data collection may not include any echocardiographic measurements if these are not critical to the trial.

Image Analysis Personnel

Echocardiographic analysis should be performed by a small group of sonographers and physicians. All readers must be documented to have been fully trained in the study's image analysis protocol and should demonstrate adequate intraobserver and interobserver variability before performing any analyses.

Primary Reader Role and Qualifications

The primary reader performs the initial QA reading of a study and completes feedback to the site. If images are acceptable, the primary reader performs study-specific measurements according to the analysis plan blinded to clinical aspects of the study. ECL primary readers must have a comprehensive understanding of clinical research with documented current training in the principles and practices of human research trials and ideally should maintain current credentials (from the American Registry of Diagnostic Medical Sonography or Cardiovascular Credentialing International in the discipline applicable to the study [adult echocardiography, pediatric echocardiography, and/or vascular sonography]). The primary readers must have a high degree of expertise specific to the study requirements, whether simple, such as measuring ejection fraction, or more complex, such as perfusion imaging or cardiac resynchronization therapy analysis.

Physician Overreader Role and Qualifications

The reviewing physician's role is to perform the final review and sign off on the echocardiographic study, whether as a primary reader or after review of the accuracy of the primary read. The extent to which measurements are performed or repeated by the physician reviewer depends on the complexity of the measurement, the category of the trial, and ECL policies. In category A trials, 100% physician review should be performed, and in other studies, at least a subset of primary reader studies should be overread for QA purposes. The physician overreader must have documented training and expertise specific to the study image requirements, a comprehensive understanding of clinical research, and documented current training in the principles and practices of human research trials and good clinical practice. Other, more general credentials, such as Core Cardiology Training Symposium level III training and current National Board of Echocardiography credentials, are desirable.

Inclusion of New Personnel

Many large trials will inevitably require the addition or substitution of additional personnel during their courses, requiring that the ECLs have staffing replacement plans. For longer term studies, the maintenance of a historical timeline listing study-specific personnel and their roles may be useful. As at the clinical sites, new ECL sonographers and physicians should be oriented to all study-specific documents and procedures and should have received task-specific training before beginning analysis. Further, their intraobserver and interobserver variability should be tested and confirmed to be acceptable.

Principles and Practices for Image Review and Analysis

Digital imaging enables acquisition and storage solutions for core labs, allows remote review and analysis of images, electronic calibrations and calipers, storage of reference images, provides random access to files and data, and eliminates the degradation in image quality associated with conversion from an analog recording. However, extra care must be taken in recording images, because the processing and storage requirements of digital clip format may cause sonographers to limit the number of cardiac cycles acquired in each view. It is important that an ECL create a set of rules to ensure compliance with good clinical practice and federal regulations, including

- limiting access to the images and data files to the sonographer-physician team involved in analyzing a specific study;
- keeping an electronic audit trail of each access and modification of the images or data, including each measurement that enters the database; and
- avoiding changes to acquisition format or reading software or computer monitors (altering spatial resolution) throughout a given study.

Strategies that improve the quality of review include requiring viewing the totality of the study before choosing the "best frame or cardiac cycle" to make a specific measurement; recording still frames of all 2-dimensional, Doppler, or M-mode measurements; and implementing QA strategies (see additional discussion below).

VII. IMAGE HANDLING AND DATA MANAGEMENT

Image Transfer Standard

Optimal image transfer to the ECL should use digital technology and DICOM format with intrinsic calibration. Because some site laboratories may use videotape, CD-ROM, or DVD and non-DICOM formats, the ECL should be able to handle images transferred in all formats. The ECL must have a schema for labeling and deidentifying images. In the case of digital imaging, it is encouraged that the original echocardiogram be kept at the clinical site and a copy sent to the ECL via mail. If videotaped images are to be transferred, consideration should be given to forwarding the original while the site retains the copy, so that the ECL data will be derived from the higher quality recordings. If echocardiographic data are used for patient enrollment criteria, echocardiography data should be transferred to the ECL electronically using a Web-based application to minimize the time for image transfer. Eventually, electronic or digital systems should be the standard for image transfer to the ECL and for communication back to clinical sites for queries, quality control, and compliance to a specific protocol.

Image Management

When a study is received at the core lab, it should be logged in the ECL database, which includes the following information: protocol name, clinical site, study identification, echocardiography date, date received, location of storage, tracking number, date reviewed, and information regarding any queries generated. This log should be reconciled with the overall study database. Received studies are copied to ECL workstations and stored on an image server as digital clips using a unique identification number. Videotape and CD-ROM or DVD media may be stored, returned to sites, or sent to the sponsor as prearranged. Core lab images and data should be stored in a secure environment according to applicable institutional or federal regulations for the retention of study-related documents after the completion of the study.

Data Management

Measurement data and derived variables are entered into the core lab case report form either manually or, preferably, electronically using data records consistent with the case report form. If performed manually, double entry of data is preferred if the data entry error rate is >0.5%, but this may not be possible, because of cost and personnel constraints. The data then undergo QA using prespecified range limit checks and other logic, with verification (and correction if necessary) of outlying values by re-review of primary images. Quality-assured data are then exported to the trial sponsor or to the data coordinating center through an electronic export file in a predetermined, sponsor-approved format. The prespecification of data format may require a data transfer agreement between the ECL and sponsor. It is desirable to perform a test data transfer early in the trial to confirm export file format and compatibility of electronic data bases. The core lab should maintain its own database with appropriate audit trail verification, for QA purposes, data backup and for generating progress reports, QA, and manuscripts.

VIII. QUALITY ASSURANCE

A large portion of the variability in any echocardiographic study is determined by differences in the image acquisition. The methods discussed above are designed to reduce this. In addition, each core lab must define how variability in measurement and analysis will be assessed and minimized.

Ongoing QA for Image Measurement and Interpretation

Ongoing, study-specific quality control measures for study measurement and interpretation are critical aspects of any ECL analysis (see above for site QA). To this end, a plan should be prospectively developed for each core lab project describing methods and definitions being used and planned reproducibility analyses, including image selection and measurement and any planed accuracy assessments. The plan can then be supplemented over the course of the trial with QA results and corrective actions, if any are required. Although there is no universally agreed upon process, each laboratory must plan to perform, at a minimum for category A and B trials, determination of intraobserver and interobserver variability for each primary and secondary reader for a core set of variables. This should be performed prior to the start of analysis, so that any confusion with regard to the analysis protocol can be eliminated and any deficiencies corrected. It is then repeated at intervals over the course of a multiyear study to ensure that variability is maintained at an acceptable level. Such comparisons can help "calibrate the eye," so that qualitative assessments are similar from reader to reader. Most important, adherence to a well-constructed QA plan will prevent the loss of data and ensure confidence in the final results.

The identification of a difference between groups in cross-sectional and longitudinal analyses depends on both the expected effect size (difference between groups) and the variability within the groups in absolute values or their changes over time. It is therefore important to adopt procedures that minimize data variability while ensuring that undue biases are not introduced. The following strategies may assist in this process.

Temporal Drift

Temporal drift can be a problem when echocardiography readers change their measurement methods between serial echocardiographic studies separated by intermediate or longer intervals. For example, in the Coronary Artery Risk Development in Young Adults (CARDIA) study, one of the readers had significantly (and unknowingly) changed his approach to making measurements of the left ventricle between two examinations separated by 4 years (J. Gardin, personal communication, 2008). This problem was resolved by having this reader reread the first and second studies, in a blinded fashion, to eliminate any influence of temporal drift. Protocols for reading echocardiograms in trials need to embed quality control measures to monitor for temporal drift and have designated corrective actions should drift occur.

Side-by-Side Versus Batch Readings

Extensive evidence from echocardiography and other imaging modalities indicates that side-by-side versus batch reading of serial studies reduces variability. This has been most striking for qualitative grading of valvular regurgitation,[15] with less consistent effects for left ventricular ejection fraction, left atrial area, and tissue Doppler indices.[16] However, in one study,[17] side-by-side reading reduced the standard deviation of the primary echocardiographic outcome measure but reduced the change of that variable in response to treatment by even more. This suggests that side-by-side readings may not automatically enhance study power if the treatment effect is smaller than expected. One potential disadvantage of side-by-side reading is the introduction of bias when therapeutic blinding is not possible, such as in evaluation of percutaneous valve therapy.

IX. STATISTICAL ANALYSIS PLAN

Measuring Precision and Accuracy

Verification of the precision of key measurements should be obtained within any large study by assessment of interreader and intrareader variability. In-depth studies to verify the accuracy of echocardiographic measurements can rarely be obtained in the course of clinical trials, but appropriate data regarding interstudy variability for some echocardiographic measurements can be taken from published literature.[13]

If in the unusual case that a more complete examination of measurement precision is desirable, it can be obtained by performing duplicate echocardiographic studies without intervening treatment or other change in participant characteristics and determining differences in key measurements. More precise determination of accuracy of echocardiographic measurements is out of the scope of this document and is reviewed in the previous American Society of Echocardiography statement, "Recommendations for Use of Echocardiography in Clinical Trials."[10] Briefly, accuracy may be tested by comparison with a phantom, which is of a known size but does not pose the same imaging difficulties as a beating human heart, or by comparison of echocardiographic data with those obtained by another modality, such as cardiac magnetic resonance image. In practice, the use of phantoms in trials has gradually declined because accuracy is generally excellent, and accuracy is generally safely assumed if precision is carefully addressed.

Handling of Missing and Censored Data

It is not uncommon to have echocardiographic measurements planned at several time points during the course of a study but have missing data at one or more of these intervals in some patients.

Plans for handling missing data should be part of the overall study analysis plan. One approach to dealing with missing baseline data is to exclude these patients from analyses of in-trial changes in echocardiographic measures as "missing at random" data. If postbaseline measurements are missing, one can either exclude patients with missing data at a specified follow-up point from analyses of change to that time point—ensuring a comparable interval between measurements but reducing study power—or carry forward the last available measurement. Although methods exist to estimate missing data from available measurements, such as imputation, they have not been widely used in trials using imaging, and the accuracy of the imputed values may be suboptimal compared with a separate reference standard.[18] The assessment of whether there are systematic differences between patients in whom specific measures are missing and those with available measures is also an essential part of the analysis plan.

Adjudication Process: When and How

The adjudication of echocardiographic measures may be needed in the minority of studies that use designs with two parallel readers, with prespecified thresholds used to trigger the adjudication process. Procedures may either rely on joint consensus review of the images by both readers or use referral to a third reader, perhaps the director of the ECL, for a definitive determination. In studies that use a single primary reader or experienced overreader of echocardiograms, re-review of the study to verify or correct measurements may be triggered by values that fall outside prespecified ranges (QA described above prior to data transfer) or that show physiologically implausible relations to other echocardiographic measures. In all cases, these processes should be conducted blinded to clinical information.

X. REGULATORY CONSIDERATIONS

The FDA defines good clinical practice as "an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects." Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.[19] Good clinical practice guidelines apply to the standards on how ECLs should operate, define the roles and responsibilities of ECL investigators, and apply in detail to the functioning of the ECL as a clinical research laboratory. It is critical that all personnel in the ECL are familiar with good clinical practice and that its tenets are followed in every aspect of operations.

Audits

Audits are exhaustive reviews of every aspect of the ECL personnel, policies, practices, procedures, and equipment. An audit may be performed to verify that a specific clinical study is being conducted properly and that the data produced by the site are accurate and complete, or it may be directed at assessing the ECLs overall adherence to good clinical practices. Internal audits may be initiated by the ECL to monitor the quality of its processes and therefore allow identification and correction of any problems in advance of more formal audits. Such internal audits can be invaluable for refining lab organization and operations.

Many sponsors will require an audit as part of a category A or B trial, and these should be initiated by the sponsor in consultation with the relevant regulatory body. Auditors review case report forms and all supporting materials for some, or all, of the patients enrolled in a specific trial (or in several trials, if the audit is investigator oriented). The audit will review documentation of who performed which study-related tasks and where, how the data were recorded and with what accuracy, how image and data security were maintained, and so on. Once an audit is performed, the ECL will have a limited time to correct any observed minor deficiencies, while major deficiencies may cause the lab to be removed from the trial. Although the FDA can perform an audit on any core lab performing regulatory trials, this is highly unusual.

Firewalls and Data Protection

A firewall is necessary between the ECL and clinical sites to ensure that clinical patient care is not governed by ECL interpretations of images. Sites should routinely perform a local review of research studies for the purposes of clinical care and to detect incidental findings. If sites wish to use research echocardiograms for clinical care, a separate interpretation should be performed and documented locally. The ECL should be maintained in a secure environment protected from access by unauthorized personnel. Data and images must be stored in redundant format with a physical separate backup location.

XI. MEASUREMENT OF CORE LAB EFFICIENCY AND ACCURACY

In addition to adherence to regulatory requirements, each ECL must be able to demonstrate the efficiency of its work, including operational processes and accuracy of echocardiographic measurement and interpretation. Although no specific metrics exist, draft measurements are under discussion by a consortium of industry, imaging contract research organizations, and the FDA.[20] This group has proposed categories of measurement spanning the entire range of core lab activities:

A. Operations and workflow
   a. Sites: percentage of sites qualified, time from qualification to first image acquisition, time from image acquisition to image receipt at the ECL, time from image receipt to site QA feedback, percentage of queries by site, and time to resolution of each query
   b. Image and data handling: time required for image processing and uploading, time required for completion of image review, procedures for database cleaning, time from last patient analysis to cleaned database delivery, adherence to an approved schedule
   c. Data completeness: percentage of missing images, percentage of nonevaluable baseline images, percentage of nonevaluable follow-up images, and percentage of suboptimal images
B. Clinical: time required to develop and write an image review charter, number and importance of any protocol deviations, and intrareader and interreader variability for categorical and continuous data points
C. Administrative: variance from approved budget, timeliness and revisions of contracts, and number of protocol drafts and scope changes

It is critically important that whatever parameters are eventually crafted serve to further the overall goals of producing high-quality data for the trial rather than simply to emphasize efficient processes. Efficiency without attention to quality may have unintended consequences that are ultimately counterproductive. The use of properly crafted metrics, once defined, will provide an information and discussion tool for sponsor and core lab decision makers to improve all aspects of clinical trial imaging.

XII. PROFESSIONAL AND PRACTICAL CONSIDERATIONS

Intellectual Property

Issues of intellectual property need to be discussed beforehand between the ECL and sponsor and should be codified in the form of contracts between them before the study begins. In many cases, these property rights are determined by the PI's institution and cannot be modified. The sponsor has a legal obligation to adhere to the contractual definitions of intellectual property. In doing so, consideration needs to be given to the sponsor's role in developing the trial design and endpoints and contracting with sites to obtain the images. In many cases, the sponsor can reasonably be seen as owning the images along with controlling the right to use these data, unless otherwise specified in the contract. Conversely, if, during the analysis of the images, ECL personnel make new intellectual observations that are different from those initially specified or requested, then the core lab would also reasonably expect to a share in the rights to these novel observations.

Representation to Trial

In many circumstances, the ECL PI will have a better understanding than other trial personnel of the results, implications, and limitations of the ultrasound data, especially if other trial investigators do not understand the full potential of echocardiography. If ECL ultrasound data are key to the hypotheses being tested, the core lab PI's position on the trial steering committee can be used to ensure correct specification of the imaging endpoints during trial design and ensure that the imaging data are used to their fullest potential in addressing trial hypotheses. The ECL PI's participation also helps explain the implications of the imaging data at all phases of the trial and to ensure correct interpretation of the imaging endpoints.

Publication Rights

The ECL role on a trial publications committee will vary as a function of the role of the images in the trial. For category A and B trials, the ECL PI should have a position on the trial publications committee and thus assist in development of the trial publication plan (see Table 2). To recognize the contribution of the ECL and oversee proper interpretation of echocardiographic results, at least one member of the core lab should serve as an author on the main trial paper if echocardiographic endpoints are critical in the primary or secondary analyses discussed in such papers (see Table 1). With this assignment, it would be expected that this author would assist in at least the portion of manuscript that focuses on the echocardiographic data, including methods, results, and discussion. The ECL PI or designee is expected to work with members of trial leadership and assist them with interpretation of imaging data used for additional analyses and reports.

Independent Analyses

With appropriate prior approval, the ECL has the right to use the submitted images to make additional measurements relevant to the trial but not requested by the trial leadership. Such data could be used for secondary analyses by the core lab after the main trial paper has been completed. However, these additional projects should only proceed after clearance from the trial publications committee and should be coordinated with the trial's executive committee and with the timing of the primary manuscripts and any potential regulatory proceedings.

Secondary Use of Research Images

Core labs may wish to use images submitted to them to test hypotheses unrelated to the conducted research. Such intent should be discussed with the sponsor and included in the contract. For example, this might include use of the images to assess accuracy of a new image analysis software or hardware. If the images can be deidentified and cannot be reidentified, this would be considered research but would not require review and approval by an institutional review board under the federal regulations (45 CFR 46). However, local institutional review boards may have institutional policies that differ and may require that a determination be made for each project on a case-by-case basis. The core lab director should be familiar and in compliance with federal and local regulations in regard to secondary uses of research images.

XIII. FUTURE RESEARCH

At the present time, many of the best practices contained in this document have been developed by creative and practical core labs, determining what works best by trial and error. Thus, much of the content of this document has been derived from experience rather than prospective investigation. Although empirically derived, this document does represent the thoughtful consensus of leading ECLs. Although research to investigate practical aspects of work flow is unlikely to be performed, several aspects of the best practices recommended are amenable to testing. Indeed, the general question of whether adherence to best practices improves research results can be addressed by observation and case studies if not by a randomized trial.

Further investigation is recommended in areas critical to overall trial design, including those that have an impact on sample size determination if echocardiographic endpoints are included. Among these areas are determination of reasonable expectations regarding site production of measureable images, so that the likelihood of missing endpoints can be accounted for in sample size calculations.[14] Also important is the development of accepted standards for accuracy and precision for different types of commonly measured echocardiographic variables. This could lead to acceptance of key indicators of core lab quality. At the present time, limited information exists in the literature.[7,11-13] Finally, statistical methods for evaluating reproducibility are still in evolution[21,22] but represent an area ripe for prospective investigation.

XIV. SUMMARY

The improvement of echocardiographic imaging in clinical trials research requires optimal core lab practices but goes beyond these to include all stakeholders in the research process: sponsors, trialists, clinical sites, information technology specialists, statisticians, regulators, and imagers. In this expert consensus document, we have outlined the roles and responsibilities of core labs, their relationships to other components of the trial, and, most important, procedures by which ECLs can optimize results and improve the accuracy and precision of the information they provide to parent studies. This has been shown prospectively to improve the efficiency and quality of clinical research. It is hoped that these best practices are broad enough to be applicable to other forms of cardiovascular imaging, if not all imaging used in clinical trials research.

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