Clinical Trial Imaging Endpoint Process Standards

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Revision 1

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Clinical Trial Imaging Endpoint Process Standards Guidance for Industry[1]

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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in optimizing the quality of imaging data obtained in clinical trials intended to support approval of drugs and biological products.[2] This guidance focuses on imaging acquisition, display, archiving, and interpretation process standards that we regard as important when imaging is used to assess a trial's primary endpoint or a component of that endpoint.

Considerable standardization already exists in clinical imaging. There are a variety of sources, including the Picture Archiving and Communication System and the Digital Imaging and Communications in Medicine (DICOM) standards for the handling and transmittal of clinical imaging information, that describe the standards generally employed by clinical practitioners. This guidance recommends additional standards regarding important aspects of imaging endpoint process standardization that are more specific to clinical trials. Imaging process standards help sponsors ensure that imaging data are obtained in a manner that complies with a trial's protocol, that the quality of imaging data is maintained within and among clinical sites, and that there is a verifiable record of the imaging process. Minimization of imaging process variability may importantly enhance a clinical trial's ability to detect drug treatment effects.

This guidance does not address whether specific imaging measures would be acceptable in submissions used to support approval of a drug or biologic. These considerations should be discussed with the FDA review division responsible for drug development.

[1] This guidance has been prepared by the Division of Medical Imaging Products in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and biological products unless otherwise specified.

Many of the imaging process standard considerations for clinical trials of therapeutic drugs can also be applied to clinical trials that evaluate the performance of diagnostic drugs. For considerations involving the development of diagnostic imaging drugs, see the guidance for industry *Developing Medical Imaging Drug and Biological Products (Parts 1, 2, and 3)*.[3]

This guidance revises the draft guidance for industry *Standards for Clinical Trial Imaging Endpoints* issued in August 2011. The guidance has been revised to clarify that:

- The guidance pertains to clinical trials intended to support the approval of drugs and biological products and focuses upon the trials' primary endpoint imaging process standards.

- Clinical trial imaging endpoint process standards vary along a continuum that extends from existing medical practice imaging process standards through augmented processes that create trial-specific imaging process standards.

- Trial-specific imaging process standards should be detailed in the clinical protocol or in a clinical trial methodology document(s) typically referred to as an *imaging charter*. An imaging charter can be a single process document or an ensemble of documents.

- The risk to subjects from imaging procedures is best described in the clinical protocol and consent documents instead of the imaging charter.

- This guidance does not address whether clinical trial endpoints ascertained through imaging measures would meet the standard for drug approval.

- When considering imaging process standards, the use of specially designed objects (phantoms) to evaluate image acquisition may or may not be important, depending on the nature of the imaging endpoint, clinical site-specific modality considerations, and the clinical trial design.

- The clinical protocol, not the charter, should describe how incidental findings detected in the course of imaging will be handled in a clinical trial.

- The imaging process standards should identify any use of investigational imaging equipment. Note that the investigational device exemption requirements under 21 CFR part 812 apply to investigational devices.

- The clinical trial sponsor should ensure the fidelity of all imaging charter components to the clinical protocol and statistical analysis plan.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Imaging provides human anatomic and/or physiologic information of variable clinical meaningfulness, ranging from indisputably interpretable information to information that is of uncertain value. For example, the clinical meaningfulness of an image showing a fractured long bone is readily apparent while an image showing the distribution of an uncharacterized ligand receptor in the cerebral cortex may be of uncertain meaning. If the clinical implications of an image are not understood, generating the image may not produce clinical information that helps to assess a drug's effect.

Almost all medical imaging processes involve some aspects of standardization established by those within the practice of medicine. In medical practice, images of human anatomy and/or physiology typically are acquired and interpreted, often with limited or no formal quantification, by a single facility's imaging professional staff. The images typically achieve the medical practice's diagnostic purposes even though the acquisition, display, and interpretation methods may vary somewhat among imaging facilities and imaging professionals. This variability may have little or no medical practice diagnostic significance, yet in a clinical trial, imaging process variability may result in increased variability in endpoint measurements and may limit the ability of the trial to achieve its objectives.

Although the medical practice of diagnostic imaging already follows many standardized procedures, we recommend that some trials augment these existing standards to create *trial-specific* imaging process standards. We define these trial-specific imaging process standards as standards that extend beyond those typically performed in the medical care of a patient (i.e., the process standards are implemented solely for the purposes of the clinical trial). The extent of trial-specific imaging process standards can range from minimal processes that are described solely in the clinical protocol, such as obtaining noncontrasted and contrasted images in all subjects, to more detailed imaging process standards for image acquisition, display, interpretation, and archiving that are detailed in an imaging charter (see Appendixes A through C).

A clinical trial's design and clinical context are critical determinants of the extent that imaging process standards could be important to the trial. Trial-specific imaging process standards may not be critical to some phase 3 clinical trials even when a trial's primary endpoint is based entirely on the imaging results. For example, it is the FDA's view that a radiologist's report of a hip fracture on standard radiography generally would provide sufficient verification for the primary endpoint of rate of hip fracture, assuming that all clinical trial sites maintain the imaging standards expected of contemporary medical practice. This assumption should be verified for a large clinical trial where practice standards may differ across regions.

In a clinical trial where the imaging process and imaging primary endpoint measures are not well standardized in medical practice, and particularly where the images should be interpreted quantitatively (rather than *yes/no*, as in the hip fracture case), trial-specific standards become important. For example, trial-specific standards have been important for clinical trials that used a primary endpoint measure of carotid artery intima media thickness (CIMT) as measured by ultrasound. Changes in CIMT over time have been used to assess the activity of lipid-altering drugs as indicated by the CIMT anatomical alterations. These trials have involved highly standardized imaging acquisition protocols as well as trial-specified endpoint measures performed by centralized imaging centers (Crouse, Raichlen, et al. 2007; Dogan, Plantinga, et al. 2011).

The following sections outline the imaging process topics sponsors should address when an imaging primary endpoint is used within a clinical trial intended to support the approval of a proposed drug.[4]

III. LOGISTICAL AND TECHNICAL CONSIDERATIONS

Use of an imaging-based primary endpoint in a clinical trial, regardless of whether the trial relies upon existing medical practice imaging process standards or trial-specific standards, can pose logistical and technical difficulties. Some clinical sites may lack the resources to support a trial's imaging expectations. The frequency of imaging and the distance to a qualified imaging facility may preclude or limit some patients' participation in the clinical trial. These factors may discourage the use of imaging in a clinical trial or limit the role of imaging within the trial. Nevertheless, imaging data may provide particularly persuasive evidence of a drug's effectiveness and also help characterize a means of monitoring drug effects in clinical practice. The following questions are some of the factors a sponsor should assess when considering the use of an imaging-based primary endpoint in a clinical trial intended to support approval of a drug. Further, the sponsor should contact the assigned FDA review division to discuss the clinical meaningfulness of the primary endpoint imaging information to be obtained in the trial.

A. Why Use an Imaging-Based Primary Endpoint?

Clinical trials of drugs typically rely upon primary endpoints that are widely accepted measures of clinical benefit, such as survival or other readily detected important clinical outcomes (e.g., occurrence of stroke or myocardial infarction), or measures of improved function or decreased symptoms. In some of these situations, an imaging-based outcome may define the clinical outcome, as in the above hip fracture example. In many situations, a clinically important symptomatic outcome, such as the prevention of asthma exacerbations or reduction of pain, cannot be assessed with imaging. The usefulness of an imaging-based primary endpoint is dependent upon multiple factors, such as:

[4] Evidentiary standards for diagnostic imaging products are addressed in Parts 2 and 3 of the guidance for industry *Developing Medical Imaging Drug and Biological Products (Parts 1, 2, and 3).*

- The investigational drug's proposed benefit
- The nature of the underlying clinical condition
- What is known about the relationship between the investigational drug's effect on the image-based endpoint and typical measures of clinical benefit
- The precedent for use of an imaging-based primary endpoint in the specific therapeutic area
- Unique trial design features, such as randomization, subject evaluation schedule, masking, and choice of a comparator therapy
- Logistical and feasibility issues, such as the availability of imaging modalities and the clinical site's ability to maintain these modalities

If an imaging-based primary endpoint is chosen for a phase 3 trial, the choice of the imaging modality (such as echocardiography versus single photon emission computerized tomography) may prove an especially important consideration. Imaging modality upgrades and malfunctions are sometimes unpredictable. Clinical sites may also experience unforeseen limitations on the use of the modality or modality-specific imaging drugs and processes, such as the interchange of certain contrast agents that may not affect typical diagnostic imaging but may alter trial-specific quantitative imaging measures.

B. Is Centralized Image Interpretation Important for an Imaging-Based Primary Endpoint?

In clinical trials, images are interpreted either at the clinical site or at a centralized facility that receives images from the clinical sites. Sometimes, both site and centralized imaging interpretation may be performed. Image interpreters are sometimes referred to as *readers*, and we use that term in this guidance.[5]

The usefulness of a centralized image interpretation process is determined by the role, variability, and susceptibility to bias of imaging within the trial as well as modality-specific image quality considerations and overall trial design features. Centralized image interpretation is not always critical, even for a phase 3 trial primary endpoint that uses some aspects of quantitative imaging, if the quantitative measures are widely performed and reported in clinical medicine, little imaging acquisition or interpretation variability is anticipated, and the trial design features control potential biases in image interpretation. However, these characteristics may not apply to some clinical trials, such as those that might be subject to bias and cannot be blinded, those that use imaging modalities vulnerable to image quality problems, and those that use specialized imaging measures.

[5] Terms such as *image interpretation*, *image review*, or *image read* are used interchangeably in this guidance, and image readers are sometimes referred to as image reviewers.

In unblinded clinical trials, clinical information may bias a site-based image interpretation because the expected relation of clinical features to outcome is known and, therefore, local reading will raise concern about potential unblinding. A centralized image interpretation process, fully blinded, may greatly enhance the credibility of image assessments and better ensure consistency of image assessments. Some imaging modalities also may prove vulnerable to site-specific image quality problems, and a centralized imaging interpretation process may help minimize these problems. For example, the National Lung Screening Trial's experience with computed tomography of the chest suggested that centralized image quality monitoring was important to the reduction of imaging defects (Gierada, Garg, et al. 2009). Hence, a centralized image interpretation process may be used to help control image quality as well as to provide the actual imaging-based endpoint measurements.

Some image interpretation methods, such as trial-specific measures of bone or joint disease in arthritic diseases, rely upon centralized imaging because of the extent of reader training recommended for the specialized image interpretation.

As compared to site-based image interpretations in multicenter clinical trials, we anticipate that a centralized image interpretation process may provide more verifiable and uniform reader training as well as ongoing management of reader performance, helping to ensure quality control of the images and their interpretation and to decrease variability in image interpretations, leading to a more precise estimate of treatment effect. Nevertheless, the overarching trial design features and the other previously described features may justify the use of site-based imaging interpretations even in large phase 3 multicenter clinical trials, so long as blinding of image interpretation to treatment can be assured or bias is otherwise controlled.

C. Should Image Interpretation be Blinded to Clinical Data?

The extent of blinding of image readers to clinical data depends upon the role of imaging in the clinical trial, the specific disease and clinical setting, and the potential for unblinding effects (e.g., toxicity) of the investigational drug. In a randomized controlled trial, we anticipate that clinical trial primary endpoint image readers will be blinded to a subject's treatment assignment, because knowing the assignment would be presumed to create bias. Further, we anticipate that many, if not most, clinical trials using imaging-based primary endpoints will be conducted with no reader knowledge of individual-level clinical data because this knowledge also may bias the reader. In unique situations, a primary endpoint may rely upon integration of clinical data into an image interpretation, but this is not expected to be common (Sargent, Rubinstein, et al. 2009).

To determine whether image readers should be blinded to clinical information, sponsors should have knowledge of the underlying clinical condition, an understanding of the precedent for the use of imaging as a trial's primary endpoint, and detailed insight into the trial's unique image interpretation procedures (such as a plan for sequential *locked-read* image interpretation where an assessment cannot be altered versus an option for modification of prior image interpretations). In certain disease conditions, readers also should be blinded to the image acquisition date and/or knowledge of prior imaging observations. Again, we note that even if the image reader is aware of individual-level clinical information, blinding to treatment assignment is almost always critical.

D. How Often Should Imaging Evaluations be Performed?

When a medical image serves as a trial's primary endpoint, its timing and frequency of ascertainment depends upon the underlying condition being studied, the feasibility of the imaging schedule, and the overarching trial design features. For a trial using time point-based imaging measures as a primary endpoint, the frequency of imaging evaluations should be the same in all trial arms. Asymmetric imaging evaluation time points can introduce bias in the treatment effect assessment.

For a primary endpoint that uses a time-to-event analytical approach, imaging evaluations should be performed at baseline and at sufficient frequency to provide a reasonably precise measure of the time to the expected clinical event. For example, it is the FDA's view that imaging evaluations performed as infrequently as every 6 months may prove sufficient to assess progression-free survival among subjects with a cancer known to have a slow progression and prolonged survival. We think that in some oncologic drug trials, chemotherapy toxicity may necessitate delay of a cycle and the coincident imaging evaluation. We think that the use of a calendar-based schedule or a window of assessment may help to avoid bias in this situation due to asymmetry of evaluation intervals.

E. How Soon After Acquisition Should Images be Interpreted?

In diagnostic medical imaging practice, images typically are interpreted onsite within several hours following acquisition. In contrast, in clinical trials using centralized imaging interpretation, image interpretation may require a longer time frame. Therefore, image interpretation timing typically is more of a consideration when clinical trials use centralized imaging interpretation. When planning a clinical trial that uses an imaging primary endpoint, the *turnaround time* by a central image interpretation facility should be appropriate for the anticipated trial design. For example, prompt image interpretation may be an important consideration for trials that use centralized image interpretations as a component of interim analyses, as may occur when imaging-based analyses are important to accommodate prespecified sample size adjustment plans. Similarly, image interpretation expediency may prove critical when centralized imaging interpretation is used to help control imaging quality; in this situation, the centralized imaging readers should promptly identify technical flaws that necessitate repeat imaging of a subject. In other circumstances, interpretation of batches of randomized images at specified intervals during a study may be appropriate. Sponsors should consider the timeliness of centralized image interpretation when developing a clinical trial protocol that uses an imaging-based primary endpoint.

F. What Procedures Should be Standardized for an Imaging-Based Clinical Trial Primary Endpoint?

No single set of detailed imaging process standards is readily applicable to every clinical trial because they differ in design and objectives. When usual medical practice imaging process standards are acceptable in a trial, these plans should be stated in the clinical protocol. Considerations of what to standardize beyond these minimal expectations should be driven by

consideration of the imaging processes that might introduce variability and inaccuracy to the endpoint as well as by consideration of the other items outlined below. When determining the extent of imaging process standardization critical for a phase 3 clinical trial that uses an imaging-based primary endpoint, sponsors should consider the following factors:

- Imaging modality availability and the modality's implicit technical performance variation across trial sites
- Performance features of the imaging modality at the trial sites or any other locations where subjects may undergo imaging
- Qualifications of the imaging technologists and any special technological needs for the trial
- Whether the proposed imaging measures rely upon phantoms and/or calibration standards to ensure consistency and imaging quality control among clinical sites
- Any unique image acquisition features of the trial design (including subject positioning, anatomical coverage of imaging, use of contrast, timing of imaging, the importance of subject sedation, scanner settings for image acquisition)
- Image quality control standards, including those specifying the need for repeat imaging to obtain interpretable images
- Procedures for imaging display and interpretation, including technical variations in reader display stations
- The nature of the primary endpoint image measurement, including the importance, if any, of training image readers in trial-specific quantification methods
- The extent that image archiving could be important to the trial's conduct, monitoring, and data auditing
- The potential for imaging modality upgrades or modality failures, as well as the potential variation in imaging drugs (such as contrast agents) across trial sites
- The precedent for use of the imaging-based primary endpoint measure in investigational drug development, especially previously observed imaging methodological problems

If the existing medical imaging practice standards should be augmented to create trial-specific imaging process standards and those trial-specific standards are too lengthy to be described in the clinical protocol, then we encourage sponsors to develop an imaging charter that details the trial-specific imaging process standards (see Appendix A). An imaging charter can consist of a single document or an ensemble of technical documents. Overall, the charter should describe how potential sources of imaging bias and variability are controlled and how imaging process standards are implemented to a level appropriate to the trial design.

IV. THE EXTENT OF IMAGING PROCESS STANDARDS

The extent of imaging process standards in a phase 3 clinical trial runs on a continuum from the standards already in place in imaging medical practice to trial-specific considerations of image acquisition, image display, transmittal, interpretation, database development, and image archiving. Similarly, the effort and expense associated with clinical trial imaging standardization may range from relatively minor through challenging. At a minimum, the sponsor should consider the following questions when developing primary endpoint imaging process standards for a clinical trial.

A. Are Existing Medical Practice Imaging Process Standards Sufficient for the Trial's Primary Endpoint?

To rely solely on existing medical practice imaging process standards to support an imaging-based clinical trial primary endpoint, the sponsor should anticipate the variability inherent in clinical site-based image acquisition, display, interpretation, and archiving. Consequently, for sponsors to rely solely on existing imaging process standards, the trial's imaging endpoint measure or outcome should be readily apparent on an image that is acquired, displayed, and interpreted using imaging processes that do not importantly vary among clinical sites. For example, existing medical practice imaging process standards may be reasonable for an endpoint focused upon the detection of a long bone fracture or intracranial hemorrhage — an indisputable outcome that is readily determined with well-accepted and widely implemented imaging methods that do not importantly vary among clinical sites.

With medical practice imaging process standards, the images might be interpreted and archived at the clinical site such that the imaging outcome may be documented in clinical trial records solely by an investigator's response on a case report form and/or appended clinical imaging report. These limited process and image documentation features typically are insufficient for a clinical trial endpoint that relies upon quantitative imaging assessment unless the quantitative measure is widely accepted as reliable and consistently reported to clinicians as a component of medical practice. The more complex the image endpoint quantification process, the more likely it is that existing medical practice imaging process standards will benefit from augmentation to create trial-specific standards that minimize variability and document image endpoint measurements.

B. What Should be Considered When Augmenting Existing Medical Practice Imaging Process Standards to Create Trial-Specific Imaging Process Standards?

We anticipate that most phase 3 clinical trials using an imaging-based primary endpoint will profit from some aspect of trial-specific imaging process standardization. In some situations, this standardization may be confined to a clinical protocol's brief statement about the nature of the imaging to be performed in the trial and the frequency of the imaging evaluations. For example, the protocol may include a statement that all subjects will be imaged both with and

without contrast enhancement. In other situations, an imaging charter should be developed to standardize an array of imaging procedures among the clinical sites, such as the timing of imaging during the trial, subject sedation and positioning, image display and interpretation, as well as image archiving. Appendix A describes the various components of imaging process standards a sponsor should consider when augmenting medical practice imaging processes. In comparison to medical practice imaging process standards alone, trial-specific standards may provide better assurance that the imaging methods for the assessment of a trial imaging endpoint are well defined and reliable.[6]

[6] See 21 CFR 314.126(b)(6).

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APPENDIX A: BEFORE IMAGING: CHARTER CONSIDERATIONS

This Appendix outlines some of the imaging methodology factors for sponsors who may be considering using specific imaging standards for a particular clinical trial. We refer to these augmented imaging process standards as trial-specific standards. Relatively uncomplicated trial-specific standards can be described in the body of a clinical protocol. If the trial-specific standards are too cumbersome or inappropriate for the body of a clinical protocol, then we encourage the development of an imaging charter.

An imaging charter (hereafter, *charter*) can consist of either a single document or an ensemble of documents that describe the clinical trial imaging methodology, such as modality-specific technical details, image interpretation, and image archiving procedures. Sponsors should develop the document(s) with the same rigorous standards typically applied to the clinical protocol. Indeed, sponsors can choose to develop the charter as an appended component of a clinical protocol. In this situation, the charter can be attached to a clinical protocol as an appendix or cited as a supplementary document. The charter can also consist of a freestanding, overarching summary of the imaging methodology with references to multiple other imaging-specific documents that form a component of the charter, such as *imaging acquisition protocols*, *data transfer plans*, or *image submission guidelines*. These documents provide detailed information on the methodology for acquiring images, and for transferring and archiving the images and the image interpretation data.

Generally, we do not regard the charter as part of the protocol unless the sponsor specifically designates it as a component. We encourage sponsors to submit the charter for FDA review as soon as possible and well in advance of trial enrollment initiation. In the unusual situation where review of a charter is critical for completing either a special protocol assessment or review of a trial's clinical protocol, the review division can specifically request submission of the charter along with the trial's clinical protocol. Submission of a charter for FDA review helps to support the plan for verification of the trial's data integrity because compliance with the charter may form an important aspect of the trial conduct verification process as well as of the data quality assessment procedure.

When imaging forms an important part of a phase 3 clinical trial's primary endpoint (or some other important part of a trial), we encourage sponsors to briefly discuss at an end-of-phase 2 meeting whether or not imaging standardization procedures are appropriate.

There is no specific format or content required for a charter. When developing a charter, sponsors should define the requirements for standardization based on the trial's imaging objectives and the sponsor-required imaging methods at the participating clinical sites. Consequently, sponsors should specify key requirements for imaging equipment, and image quality, as well as the processes for image acquisition, display, interpretation, storage, and data transfer.

Imaging technology evolves rapidly and can be highly technical. Images may vary markedly from one acquisition time point to another. For example, the technical specifications for

obtaining reproducible echocardiographic measures of cardiac function differ profoundly from the methods essential to intercenter standardization of F18 fludeoxyglucose standard uptake value measures (Shankar, Hoffman, et al. 2006; Douglas, DeCara, et al. 2009). Imaging professional societies have developed or are developing publications that detail modality-specific standards and we encourage sponsors to become familiar with these documents when developing a charter (Frank 2008; Boellaard, Oyen, et al. 2008). The complexity of technical standardization may markedly limit the use of imaging in a multicenter clinical trial even if the imaging methods have well-recognized value in clinical medicine (Keen, Mease, et al. 2010).

Listed below are the suggested headings and subheadings for the elements within a charter. Some of these elements may not apply to a particular clinical trial, while others may profit from expansion to sufficiently describe the imaging methods. We encourage sponsors to list each of these elements within the charter, and either elaborate upon the methods that address the element or briefly state how the element does not apply to the trial.

Executive Summary of the Trial Design and the Role of Imaging in the Trial

The charter should summarize the role of imaging within the clinical trial and provide a description of the imaging database variables (*deliverables*) to be incorporated into the analysis of the primary endpoint. It should describe how important trial design features may affect the proposed imaging database variables (e.g., procedures to minimize missing data, and plans for the use of off-protocol images).

The Executive Summary should also provide an overview of the major aspects of the image acquisition, interpretation, and reader-defined deliverables. Presentation of a flow chart that identifies the specific steps in the process can be especially useful in summarizing the flow of the imaging information.

Standards for Image Acquisition

Development of image acquisition standards involves a broad knowledge of imaging modalities, including knowledge of anticipated imaging equipment upgrades or malfunctions during the conduct of the clinical trial. In some situations, exploratory clinical trials may be important to identify the most important imaging technical details, including those vulnerable to technical failure and charter noncompliance. For example, an explicit description of the imaging acquisition time may be critical when rapid dynamic cardiac arteriography is used to assess coronary artery disease; in this situation, the X-ray energy (kVp) should be standardized and appropriate for imaging iodinated contrast agent within the heart. Similarly, optimization of X-ray energy is essential for breast imaging because a high kVp will obscure the signal intensity differences between adipose, glandular, or cancerous tissue, and variations in kVp among clinical sites may increase variability in the imaging endpoint. In addition to equipment settings, other imaging acquisition parameters critical to the trial imaging endpoint (e.g., the number, angle, and magnification level of radiographic views in assessing arthritis) should be standardized in the charter. The feasibility of maintaining technical consistency within and among clinical sites is particularly important when choosing and optimizing the imaging modality.

Equipment standardization and operation

The charter should typically identify the following.

- **Vendor-specific equipment/platforms (e.g., injectors, scanners, ultrasound probes, software).** The charter should identify the use of any investigational equipment. For sites in the United States, we recommend the use of FDA-approved or cleared and marketed imaging equipment. Investigational equipment, including software, used within a clinical trial must comply with FDA regulations, and may necessitate FDA clearance or marketing approval of the equipment coincident with (or before) marketing approval of the investigational drug. Investigational devices that have not been approved or cleared are subject to the investigational device exemption requirements under 21 CFR part 812.

  The charter should specify the important imaging equipment for the trial, including the imaging drug (contrast) injectors, scanners, ultrasound probe selection/settings, and software. This is particularly important for certain functional and quantitative imaging tasks that benefit from the use of specific scanners and models that are able to perform the imaging and allow the control that ensures the standardization. The importance of the equipment specifications varies with the role of imaging in the trial and may limit the number of qualifying clinical sites. For example, imaging scanners may differ in technical details that can influence image quality, such as image reconstruction software programs and techniques for respiratory and cardiac gating, subject positioning, scan times, probe positioning, and technician-dependent procedures.

  In trials using quantitative imaging procedures, an ongoing site qualification process may be important to maintain control of changes in imaging hardware and software. In other trials (e.g., large multinational trials using standard computed tomography or magnetic resonance imaging modalities), the ongoing control of hardware and software versions across all sites may be inapplicable or impractical. The charter should provide a justification for the approach proposed by the sponsor. The sponsor can provide routine extensive technical details in companion manuals (e.g., imaging acquisition and processing manuals) rather than in the charter.

  In situations where it is critical to minimize variability of imaging data, we encourage the use of a tabular listing of the acceptable imaging equipment, including the key characteristics of the acquisition, processing, and display components of each scanner or review workstation. Another approach could be to identify the physical benchmarks and testing parameters that should be met by the imaging equipment in accordance with a prespecified protocol for the acquired images to be used in the trial. When developing these specifications, sponsors are encouraged to perform exploratory analyses of imaging outcomes grouped by imaging platforms.

  Most three-dimensional imaging technology currently relies upon raw data processing using proprietary software algorithms. Software upgrades within the study period may affect how images are generated. Changes in an image may be caused by these software

changes and be incorrectly attributed to actual clinical changes. The charter should specify minimum requirements for important software and also identify any situations when alternatives are acceptable.

Occasionally, requisite imaging equipment may become unavailable at a qualified site because of equipment malfunction or unavailability of technical support. In these situations, a clinical site might choose to substitute one imaging modality for another (such as magnetic resonance for computed tomography). The charter should identify the situations when these changes are acceptable. We anticipate that, in many situations, modalities will not prove interchangeable (such as arteriography for ultrasound) when the endpoint assessment involves a quantitative imaging measurement. Ad hoc, unplanned interchange of modalities (including substitution of film for digitized imaging data) may compromise trial objectives if changes occur during the course of the clinical trial for a given subject.

- **Equipment technical settings to be used at each site.** The charter should summarize the technical settings for image acquisition for each type of important imaging equipment and identify any acceptable deviations from these settings. We encourage sponsors to identify these settings based upon the findings from exploratory clinical trials or other trials that attempted to standardize the technology among multiple clinical sites. Typically, such information is included in site imaging manuals. Details critical to quantitative imaging, such as tomographic slice thickness, pulse sequence, and contrast agent injection time (especially for dynamic imaging), should be specified in the charter.

- **Role of site imaging technicians in equipment operation, including identification of faulty or unacceptable images and the importance of repeating imaging.** The charter should describe the role of the imaging technician in the image acquisition process, including the recommended qualifications and the role of the technician, if any, in the initial assessment of image quality. Situations should be identified when repeat imaging is critical (and exposure to additional radiation dose is justified) because images are uninterpretable due to technical failure. In some situations, such as ultrasound imaging, detailed procedures should describe the technician's role in manipulation of the imaging probe. Depending upon the imaging modality and the technical demands, the charter can describe or reference the trial documents describing a technician training process that will help ensure consistency in image acquisition. In this situation, the charter should specify that trial sites will document modality-specific training standards and maintain records that show the technologists participating in the trial have met all training requirements specified by the charter.

- **Phantoms to be used for site qualification and image quality monitoring.** In many situations, the use of phantoms (i.e., prespecified objects for scanning) is a critical part of site qualification and image quality monitoring during the conduct of a clinical trial. In other situations, phantoms may not be important if the equipment and imaging acquisition parameters are well standardized. Phantoms can simulate a variety of conditions and have been developed for a range of imaging modalities (e.g., magnetic resonance, nuclear medicine, radiography). The choice of the specific phantom type

depends upon the imaging objectives as well as upon the specific imaging modality. Standardization of image acquisition using imaging and dosimetry phantoms often enhances the consistent performance of the imaging equipment during the course of the trial.

- **Subject preparation, positioning, and comfort measures.** Many imaging modalities require specific subject preparation (e.g., fasting or special dietary limitations), positioning (e.g., supine, right lateral decubitus, weight-bearing status for lower extremity radiographs), preparation (e.g., removal of jewelry and eyeglasses), and comfort measures (e.g., ear plugs or sedation). These common aspects of imaging could vary markedly among clinical sites. The charter's specifications for these items may prove especially useful because significant site-to-site variations in subject preparation can result in unacceptable levels of image variability. Subject preparation also might be based on subject-specific factors, such as age, weight, and physical condition; the importance of standardization of these aspects may widely vary. For example, a trial conducted among pediatric subjects may call for some form of sedation. A description of the acceptable sedatives (including doses, route of administration, and potential for repeat dosing) may prove essential to quality imaging as well as to the avoidance of missing images.

- **Schedule for imaging and alternatives.** Typically a trial's clinical protocol would outline the schedule for imaging evaluations; hence, the charter might not include the schedule. In other situations, the clinical trial protocol may include only a superficial description of the imaging schedule, so the charter should include more details about imaging times. For example, in certain circumstances subjects should be imaged at a specific time of day or night or following the development of certain clinical features (such as pain in a joint) that prompt imaging-specific procedures (such as region-of-interest imaging). The charter should describe these expectations and also identify the date and time windows that represent acceptable alternatives to the planned imaging evaluations.

- **Off-protocol imaging.** Subjects in a clinical trial lasting many months are likely to undergo imaging examinations in addition to the ones intended to assess the response to therapy or to detect disease progression. These off-protocol images may or may not be made available to image readers and considered as part of the trial's imaging-based outcomes. The clinical protocol may address some of the off-protocol imaging plans, but we anticipate that the charter will elaborate upon these plans to minimize the potential for mishandling of these images.

- **Imaging risks.** Imaging may involve risks to subjects, such as exposure to radiation and contrast agents. These risks should be described in the trial's clinical protocol so that they can be considered by institutional review boards (IRBs) and appropriately described within consent documents (see 21 CFR parts 50 and 56). Therefore, we anticipate that most charters will not contain a section that describes imaging risks.

Occasionally, clinical trial imaging detects incidental findings that may be important for further clinical evaluation. Incidental image findings may result in health benefits as well as risks for subjects. For example, some incidental findings may needlessly prompt invasive diagnostic evaluations. If the detection of incidental findings is likely with clinical trial imaging, the clinical protocol and consent documents should describe the procedures for handling the incidental findings. The charter also should summarize how these incidental findings will be handled based upon the description within the clinical protocol. A description of these plans within the clinical protocol is important to ensure that the process is reviewed by IRBs and, as necessary, summarized within trial consent documents (see 21 CFR parts 50 and 56). Similar to the handling of important incidental laboratory findings, we anticipate that clinically important incidental image findings will be disclosed to the site investigator who, in turn, will evaluate the role of the image finding in patient management.

- **Site qualification process.** The charter should address the process used to qualify clinical sites for trial participation, specifically describing and/or referencing the tests to be performed to verify equipment performance, technical support, and capability for compliance with charter expectations. We anticipate that phantom imaging, on-site inspection, and training will provide sufficient site qualification for many trials. In some situations, the site qualification process should build upon these expectations by imaging subjects as part of a qualifying clinical trial. These types of site qualifications can be particularly important for highly technical imaging modalities or international trials that include countries where the imaging technology might be uncommon in clinical practice.

- **Acquisition quality control monitoring process.** The charter should describe the plan for periodic, quality control monitoring of imaging acquisition, storage, and transfer, including the plan for repetitive phantom imaging and the correction of deviations from the quality expectations. The importance and nature of this type of monitoring varies, depending upon the nature of the imaging technology, but, at a minimum, should involve some form of episodic imaging quality reporting from clinical sites. In instances where imaging is particularly complex or novel, we anticipate periodic on-site inspection by the trial's imaging-specific monitors to assess the imaging technical compliance of each clinical site or a subset of all the sites. Situations should be identified in which sites will be requalified or terminated because of failure to comply with image quality expectations. Any requalification procedures should be described.

- **Data storage and transfer.** The charter should describe the expectations for imaging data storage and transfer to any separate facility from the imaging site (e.g., centralized laboratory or the sponsor). In general, the charter should:

  – Specify the storage of imaging data at the clinical site

  – Describe any and all plans for transfer and storage of imaging data outside the clinical site

- Describe any image alteration procedures to be performed at the site (such as removal of all subject-identifying information (i.e., *anonymization*))

- Specify the time period for storage of images at clinical sites and the format for data storage

Imaging drug standardization

Drugs are commonly used as a component of imaging and often require administration procedures related to the scanning of a subject. Most notable are:

- Preparative drugs
- Contrast agents
- Radiopharmaceutical agents

Depending upon the nature of the imaging evaluation, the charter should identify the important aspects of drug selection, dosage, and administration for each of these drugs, as exemplified below.

- **Preparative drugs.** In situations where preparative (or other) drugs may interact with the planned imaging evaluations, the charter should identify acceptable and/or requisite pre-imaging drugs, including sedatives, stimulants, beta-blockers, vasodilators, intravenous fluids, or contrast agents. The drugs should be identified by brand name and by dosages and routes of administration. These specifications can be particularly important for trials that enroll pediatric subjects and for the imaging of subjects following administration of drugs that will affect images (such as drugs essential for cardiac stress testing).

- **Contrast agents.** Many modality-specific contrast agents are not interchangeable and differ importantly in doses, techniques for administration, and risks. If critical to the imaging evaluation, the charter should identify acceptable and/or requisite contrast agents, including specific brand names. The charter should also identify the doses, routes of administration, rates of administration, and any special administration procedures (such as automatic injectors or administration times that may trigger scanning).

  Some contrast agents can be safely administered only to subjects with acceptable renal function or other characteristics. The charter should identify any laboratory tests and outcomes critical for supporting the administration of contrast agents. Risks associated with imaging, including those associated with contrast agents, are best described in the clinical protocol.

- **Radiopharmaceutical agents.** In addition to specification of the administered activity, mass, and route of administration, the charter should briefly identify the major drug quality features for any clinical trial radiopharmaceutical manufactured at clinical sites. Unlike preparative drugs and contrast agents, some radiopharmaceuticals (e.g., positron emission tomography (PET) agents) are commonly produced at clinical sites and the

quality of these drugs may vary from site to site. Standardization of these drug attributes may be important in achieving the trial's imaging objectives. The charter should identify any site-specific production considerations for site qualification.

Standards for Image Interpretation

Image interpretation generally is carried out by trained readers, such as qualified radiology, nuclear medicine, and/or clinical specialists, who review and interpret, or *read*, images obtained in the course of a clinical trial.

The following elements pertain predominantly to the use of a centralized facility for image interpretation in a clinical trial. Whether images are interpreted solely at the clinical site or at both the clinical site and a centralized facility, we regard these elements as important aspects to address within the charter when a centralized facility is used.

Image transfer, receipt documentation, and initial quality assessment

The charter should identify the process for transfer of imaging data from each clinical site to the centralized image interpretation facility, including the plans for:

- Verification of the image technical adequacy
- Transfer of images and supportive information to the centralized facility
- The centralized facility process for querying sites for missing images, data, or imaging technical problems
- Obtaining repeat images of subjects
- The logging of images received at the centralized facility, including the subject-specific tracking system
- The format for image data transfer (e.g., DICOM compact disc sent by courier)
- Digitization of received images or data
- Any technical evaluation (or pre-interpretation) or alteration of images, including de-identification of subject information, biasing marks, or other undesired image signals
- Monitoring compliance with the transfer, receipt, and initial image assessment process
- Correction of deficiencies and failures in the transfer, receipt, or initial image assessment process

The process should be highlighted for removal of all subject-identifying information from images relayed over electronic communication (e.g., Internet or laptop computers) or other

pathways that are vulnerable to a security breach (e.g., courier or postal transfer of hard copy images or digital images on disk).

Image display and interpretation

The paradigm shift from film-based to filmless imaging has redefined clinicians' processes of image display, and interpretation of images within a clinical trial may critically depend on the quality of the displayed image. Image display in many digital systems is a flexible and dynamic process whereby radiologists directly interact with the soft-copy image, which is displayed on a computer workstation. The hardware component of a display system usually is composed of a display device and a display driver or graphics card. The specifications given for a system are valid only for that particular combination of devices. Another important aspect of the display system is the hardware and software components used for maintaining the display presentation mapping between image values and luminance levels under a desired calibration model. Information regarding the calibration hardware, software, and procedures, including frequency and nature of the performed tests, should be identified in the charter and referenced as appropriate to a standard operation manual.

- **Selection of images for interpretation, display sequence, and randomization.** The charter should identify the nature and extent of images to be interpreted (e.g., all scheduled images as well as off-protocol images) as well as any important sequence aspects (e.g., baseline images followed by subsequent time point images). The appropriateness of excluding images or portions of images from the interpretation (read) process should be emphasized and justified. The charter should prespecify the following:

  – Criteria for classifying an image as uninterpretable based on a *technical failure* or other classification that leads to the exclusion of an image from the interpretation process

  – The qualification of individual(s) who are to make the determination of whether an image is included or excluded in the reading queue

  – If individual(s) other than the actual image readers have the responsibility of excluding certain images from the interpretation process, whether the image readers can also determine that an image is uninterpretable and the criteria used to make this decision

  – Criteria for how uninterpretable or missing imaging data will be accounted for (imputation scheme) in the data analyses

  – The potential for reader interpretation drift (i.e., deviation from study-specific image interpretation criteria on which readers have been trained) if images are assessed on an ongoing basis for a trial that includes multiple images obtained over time

  The randomization process is often a key component of the overall image presentation plan. If images (or image sets for a subject at any specific time point) are to be

randomized for display to readers, the charter should describe the randomization process. For each type of image presentation, the charter should describe the data locks (i.e., procedures that prevent modification of a reader's final interpretation) to be used at the subject image set level. These locks generally are critical to evaluating the contribution of each image examination to the overall assessment of a subject's image set. The following are examples of a trial's image presentation process:

- In a time-sequential presentation, a subject's complete image set (from baseline through the follow-up evaluations) is shown in the order in which the images were obtained. In this process (unless prespecified and justified in the charter), the reader does not initially know the total number of time points in each subject's image set.

- In the simultaneous image presentation, a subject's complete image set is displayed (there is no blinding of date, sequence, or total number of images).

- In the simultaneous, randomized temporal image presentation, a subject's complete image set is shown at the same time in a random order with respect to the date (there is no blinding to total number of images).

- In the simultaneous time point presentation, a subject's single time point image set is randomized among many other subjects' image sets.

- In a hybrid, randomized image presentation, a subject's complete image set (or only the postbaseline images) are shown fully randomized. After the read results have been locked for each time point, the images are shown again in known chronological order for re-read. Changes in any of the randomized assessments are tracked and highlighted in the final assessment. In within-subject-control trials (e.g., comparative imaging), images obtained before and after the investigational drug should be presented in fully randomized unpaired fashion and in randomized paired fashion in two separate image evaluations. The minimum number of images in each randomized block necessary to minimize recall should be considered.

- **Readers and their background qualifications.** When developing the charter, sponsors should identify the number of image readers and their requisite background qualifications. The developers should consider:

  - The extent of technical knowledge essential to image interpretation.

  - The avoidance of any other reader involvement in the clinical trial (e.g., participation as an investigator) that might bias the interpretation of the images.[7]

[7] Sponsors should also determine whether image readers should be considered to be clinical investigators. Under the applicable regulations (21 CFR parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860), a sponsor is required to submit to the FDA a list of clinical investigators who conducted covered clinical trials and certify and/or disclose certain financial arrangements. Additional information is available in the guidance for clinical investigators, industry, and FDA staff *Financial Disclosure by Clinical Investigators*.

907 – The importance of confidentiality of image reads and/or the reading process.
908
909 – The potential for reader fatigue and the use of substitute readers. Decline in the
910 quality of image interpretation caused by reader fatigue has been reported in clinical
911 medicine (Krupinski, Berbaum, et al. 2012). Similarly, in clinical trials, reader
912 performance may be compromised if the readers are assigned an excessive number of
913 images to examine within a short period of time. The charter developers should
914 consider whether to specify a maximum number of images to be read in a session if
915 reader fatigue is an important consideration for image interpretation.
916
917 – The time commitment of readers and reader availability.
918
919 – Any unique considerations for identification of a reader that adjudicates discordance
920 in image interpretation between readers and determines the final assessment.
921
922 – The importance, if any, of clinical readers (i.e., image interpretation by clinicians
923 aware of nonimaging clinical trial information).
924
925 • **Reader training and qualification.** The reader training process should be described,
926 emphasizing the use of any specific training materials (e.g., a training manual or training
927 images), image display training sessions, any image read testing process, and the training
928 documentation process. The origin (e.g., other clinical trials) of training images should
929 be described. In addition, the charter should prespecify whether any performance criteria
930 will be used to qualify readers after training and over the course of the trial. Reader
931 training manuals are key documents that contain more details of the reader training
932 procedures and should be provided with the charter for FDA review.
933
934 Sponsors should consider the importance of the following items in the development of
935 the reader training process:
936
937 – *An overview of the major goals of the image interpretation.* In general, reader
938 training should emphasize only the image-specific aspects of the image interpretation
939 process unless the process also involves the integration of clinical information into
940 the image interpretation process. The process should also minimize the potential for
941 introduction of bias into image interpretation through knowledge of any potential
942 image signatures that may break the desired blind-to-treatment assignment (e.g., if a
943 PET ligand uptake is more common among the elderly, the co-registration of PET-
944 computed tomography may bias the PET assessment because of recognition of aging-
945 related cerebral atrophy on the tomogram).
946
947 – *An overview of the major expectations for image manipulation, lesion measurement,*
948 *and other image evaluations.* Readers may benefit from special training in computer-
949 assisted interpretation, measurement, or other analysis tools, as well as in the process
950 for performing and recording measurements, especially if this process involves
951 unique software data lock features and password-protected features. The reading
952 process may assume knowledge of unique assessment tools, such as Response

Evaluation Criteria in Solid Tumors (RECIST) outcome expectations (Eisenhauer, Therasse, et al. 2009). The charter should describe these expectations in detail and address situations when images may not be conducive to the requisite lesion measurement or other tool expectations.

- *Identification of any unique read definitions and/or criteria, including the use of image case report forms.* Some clinical trials may benefit from predefined criteria for reads (e.g., identification of the specific basis for an unreadable image) and these criteria may differ from commonly used clinical criteria. Training and verification of training (with mock image reads) may be important in documenting reader proficiency.

- *Description of any reader retraining procedures.* Some image interpretation processes may include the use of test images intermixed among the clinical trial images such that readers are intermittently tested as to the proficiency and/or consistency in their reads. Failure to sustain proficiency may result in replacement of a reader with another trained and qualified reader. The charter should describe the reader testing and retraining or replacement procedure.

- **Timing of image reads and the read process.** The charter should describe the timing of image reads with respect to the clinical trial conduct. In some situations, prompt interpretation of images is important (e.g., for determining trial eligibility or confirming disease progression in trial subjects). In other situations, images are interpreted only following completion of all subject evaluations. Perhaps most commonly, readers can interpret images in batches periodically during the trial. If readers interpret images in batches, the size of the batches should be specified and the batch size justified to minimize recall bias. The allowable time interval between the batch sessions also should be predefined.

  The charter should provide a detailed description of the image review process. We recommend that the following be identified:

  - The review setting (e.g., a room with a controlled lighting system that allows for minimizing ambient illumination to a certain level, with eight computer display panels of a certain size and available only to the reader).

  - Whether readers interpret images independent of any other individuals. If not, the individuals who may be present during the read should be specified and their role in image interpretation described. Any consensus read process should be detailed.

  - A description of any image adjudication process.

  - Detailed description of the use of any clinical information in the read.

- A description of the read outcome information to be described on case report forms and any special procedures in this process (e.g., an initial read followed by a redisplay of images to form a global reassessment).

- The assessment tools to be used and qualitative and/or quantitative measurements to be performed during the image read (e.g., modified RECIST criteria assessment of each image set).

- A description of any computer software or other electronic processes involved in image interpretation, such as an automatic calculation of progression.

- Any lesion tracking system (e.g., certain requisite target lesions), particularly any nuances related to the appearance of new lesions for tracking, or inability to identify any previously tracked lesions (e.g., imaging problems or lesion resolution).

- Options and/or requirements for image manipulation, including application of calipers, zoom, pan, adjustment of window/level, contrast inversion, and application of image enhancement features.

- A description of any process for re-read of images. For example, a reader may experience a sudden illness that results in an incomplete image interpretation. A prespecified plan for the re-reading of incompletely read images helps to verify the integrity of the read process.

- The reader's role in citation of missing images or technical deficiencies within the images.

- A description of the plan to ensure that all original read outcome information is locked and available for subsequent verification and comparison to any re-read outcomes.

When developing the image display process, sponsors should consider, as appropriate for the chosen modality, the key performance characteristics of medical displays such as luminance range; viewing angle; contrast ratio; reflection coefficients; grayscale; spatial, temporal (for image stacks), and color resolution; and spatial and temporal noise. The charter should specify these details as well as other modality-specific items, such as the process for displaying dynamic images in relation to static images and any software manipulation of images for the minimization of degradations that may occur along the imaging process or transfer chain.

Computer-assisted image interpretation may form an important component of the read process. The extent of computer assistance generally should be described explicitly within the charter, including a plan for quality-control checks upon any critical software functions. For example, the image interpretation may be driven primarily by a reader who uses a computer-assisted analysis tool to complement the reader's initial assessment. Such reliance on computer assistance can be algorithmic, with prespecified parameters

for the use of a tool, or can be elective. In either case, such use should be defined within the charter in a manner that results in a sufficient audit trail and assessment of the roles of reader and reading tool. To evaluate for systematic errors, we suggest that a subset of computer-generated analyses be verified by blinded external readers.

If interpretation tools are to be used, the charter should specify the use of FDA-approved computer-assisted interpretation tools. Alternatively, an unapproved (investigational) tool justified for use with a given imaging modality can be used in some situations if it is compliant with all applicable FDA regulations, including the investigational device exemption requirements under 21 CFR part 812. Charter developers should review the software development process and testing (for additional advice on investigational devices, see the vendor-specific equipment/platforms element under the Equipment standardization and operation subheading). The same computer-assisted interpretation tool should be available to all readers at a site or centralized facility.

If the investigational imaging interpretation tool will prove an important component of monitoring the drug's effects after it is approved, the sponsor should consider that investigational interpretation tools that do not have FDA approval or clearance must comply with the investigational device exemption requirements under 21 CFR part 812. The developers of the charter should emphasize this consideration to the sponsor during the charter development, if the consideration is not otherwise addressed in trial documents.

- **Imaging case report forms.** We anticipate that specific imaging interpretation case report forms could be important for many clinical trials, particularly trials that involve quantitative imaging within endpoint construction. The charter should briefly describe the content of the case report form and emphasize the specific data content or notations that will be subsequently transferred to the sponsor to form the imaging database for the trial's endpoint analyses. We encourage the attachment of a case report form example to the charter. On this case report form, sponsors should denote the specific items to be transferred to the sponsor to form the imaging analytical database. In some situations, the case report form may consist of a tabular display of numbers (such as lesion measurements) or categories (such as predefined categories of bone erosion). An example of the tabular display within the charter may help lessen the potential for errors during the imaging flow process.

- **Imaging data lock process.** At a predetermined point during the image review process, the image interpretation data (case report form information and any other important reader notations, including notations on images) generated by the readers should be *locked*. Locking data means that no further modification of image assessment is allowed. The data locking process and timing should be closely linked with the image read process. Data can be automatically locked by the imaging display equipment or triggered in response to reader notations. In some situations, the reading process may include a re-read of previously interpreted images, including access to locked data. In all situations, the charter should describe the locking of data and any potential re-reads.

We encourage the use of an image lock approach to the read process whereby readers interpret the assigned image (or image set) and lock their read (e.g., lesion measurements, response category, lesion severity) such that the contribution of each image read to the read outcome in each image set is documented and not altered.

- **Quality control of the image display and interpretation process.** The charter should describe the process for monitoring compliance with the image display and interpretation process. This monitoring should include technical assessment of equipment, such as display systems and data locking software, as well as the reader interpretation process.

  Digital test patterns for quality control purposes can be used on a daily basis to ensure consistent performance and to detect changes in the hardware or software that can degrade image quality. In some instances, automatic luminance corrections might compensate for the reduction in luminance that is expected over time. Some of these quality control approaches offer the convenience of centralized reporting that facilitates the comparison of different display systems used in a given trial. In some circumstances, these automatic adjustment features may actually complicate measurements if they are unaccounted for. In either case, information about such automatic compensation should be known and accounted for.

  In some clinical trials, evaluation of reader interpretation performance will likely prove essential to help assess the extent to which readers are consistent in image interpretation and comply with the trial specifications. We recommend evaluating intra- and inter-reader performance with defined and prespecified metrics based upon evaluations that are ongoing during the image interpretation process.

  In many situations, intra-reader variability as a measure of reader performance should be assessed by periodic blinded testing of the reader with a preselected or predefined set of images interspersed with the clinical trial images. These *reader testing images* can come from a source external to the trial or, with proper data locking methods, from reinterpretation of selected clinical trial images. If clinical trial images will be used as reader testing images, then prespecified methodology should ensure that the original image interpretation is considered final and, for intra-reader variability, there is a sufficient period between reading and rereading of the images to minimize recall bias. A change in reader performance is not infrequently observed in clinical trials and, depending upon the role of imaging in the trial, periodic reader retraining and requalification may be critical. All details of reader testing, retraining, requalification, and possible replacement should be prespecified within the charter and/or supporting trial documents.

  Image interpretation is inherently subjective and readers of the same image may justifiably disagree in their interpretations of the image. In these situations, an adjudicator should resolve the discordant image interpretation to provide a final image outcome. In some situations, the frequency of this reader adjudication may provide a sense of the inherent subjectivity within the image outcome. Knowledge of the adjudication rate may be important for interpreting the results. When developing clinical

trial protocols and the charter/supporting documents, the trial developers should consider the potential effect of reader interpretation variability upon the clinical trial outcomes and, if the image adjudication rate is regarded as an important consideration, then the trial documents (protocol and statistical analysis plan) should prespecify this rate determination process.

Charter Modifications Before Imaging

The charter should briefly describe the process for modifying the charter in response to potential deficiencies within the imaging process or need to improve the process. Sponsors should describe the plan for submitting charter modifications to the FDA and other regulatory authorities. In general, we anticipate charter revisions to be uncommon, particularly if imaging has been used in exploratory clinical trials and the imaging processes follow precedents. To assess the sufficiency of the imaging plans for a phase 3 trial, sponsors can conduct pilot reading studies to test the reading and image lock process, the report form, and other important aspects of imaging. If so, these pilot studies should not involve images or data that will be used in the phase 3 trial.

Imaging Data Transfer Process to the Sponsor

Image interpretation should result in the completion of a case report form and/or tabular display of numbers, measures, or categories of responses. The charter should describe the process for transfer of this information to the sponsor and the time point(s) for transmission of this information. The charter should describe how the sponsor will use the transferred information to establish the variables used in the analysis of the primary endpoint.

Archiving of Images and Image Interpretations

Images should be archived as a usual component of subject care as well as for use as the source documentation in clinical trials. Electronic source data should meet the same elements of data quality that are expected of paper records and should comply with all applicable statutory and regulatory requirements. The FDA's acceptance of data from clinical trials for decision-making purposes relies upon verification of the quality and integrity of data, generally based upon the findings from audits and inspections.[8] In addition to images themselves, the image interpretations (case report forms or assessment tabulations) represent source data and should be retained for potential inspection and auditing. All source records, whether electronic or paper, must be retained for a period of no less than 2 years following approval of a marketing application or discontinuation of shipment and delivery of the drug for investigational use, as described in 21 CFR 312.57(c) and 21 CFR 312.62(c).

The charter should describe the process for archiving imaging information by the site investigator as well as the sponsor. In some situations, the sponsor may choose to archive the imaging at a centralized contractual facility or institution. Regardless of the physical storage route, the archiving process should address the following items:

[8] See the guidance for industry *Computerized Systems Used in Clinical Investigations*.

- Limiting access to ensure images and data are retained in their original form
- Back-up storage
- Archiving in a manner conducive to a clear audit trail, including date and time stamps

Additional information regarding systems and personnel controls for computerized source data is described in the guidance for industry *Computerized Systems Used in Clinical Investigations*.

Verification of Fidelity of Charter Documents With the Clinical Protocol and Statistical Analysis Plan

Because the charter may consist of an ensemble of technical documents, the developers of the charter should include a final step in which all the documents are reviewed to ensure that the charter's technical specifications do not contradict or modify the protocol-specified imaging endpoints. Many individuals and organizations may be involved in the development of a charter. These entities may offer perspectives and proposals that may be thought to enhance or functionally adapt technical specifications in response to clinical protocol imaging expectations. These alterations and interpretations may, in fact, redefine important trial endpoints via the proposed imaging technical details. We encourage sponsors to include in their charters a brief section that states all imaging technical documents will be reviewed to ensure that the imaging-specific details produce imaging outcomes consistent with the trial's clinical protocol and statistical analysis plan.

APPENDIX B: DURING IMAGING: MONITORING PLANS AND CHARTER MODIFICATIONS

A plan for ongoing monitoring of the imaging process is critical to ensure the quality of the acquired images. Revisions to the imaging procedures might be recommended if unanticipated technical issues arise.

Monitoring Plans

The charter should outline the complete plan for monitoring the imaging process. The extent of monitoring is anticipated to vary widely, dependent upon the use of imaging within a trial. In some situations, monitoring will be minimal, while in other trials, intense monitoring (to include requalification of equipment with phantoms and periodic retesting of readers) will be critical. Sponsors should comply with the monitoring plan described within the charter. Verification of this compliance may prove an important component of the assessment of imaging data integrity.

Charter Modifications

During the clinical trial, circumstances may prompt modification of the imaging procedures. For example, unanticipated technical features may obscure a portion of an image or preclude one of the expected quantitative assessments. In these situations, we recommend the sponsor revise the charter to correct the problem and to maintain a record of the modification. The revision should identify any potential effect of the modification upon the trial's important endpoint analyses. In some situations, modification of the charter may affect the definition of the primary endpoint (e.g., alteration of the method for lesion measurement may call into question the clinical meaningfulness of any size changes) and result in reconsideration of the role of imaging in the trial or premature termination of the trial. To avoid these difficulties, we encourage sponsors to thoroughly consider the role of imaging (including the technical aspects) in a clinical trial, especially if the imaging is highly technical and/or relies upon quantitative assessments that require vigilant subject and site cooperation with the imaging process. The use of imaging in early phases of drug development may help lessen the challenges associated with wider use of the technology within trials intended to support a drug's approval.

APPENDIX C: AFTER IMAGING: DATA TRANSFER, ARCHIVING, AND ANALYSIS OF IMAGING INFORMATION

A description of the procedures for the transfer of imaging data (e.g., from a trial site to a centralized facility for image interpretation or from a centralized facility to a sponsor for analysis) is critical for verification of data quality and integrity.

Data Transfer

It is important for sponsors to document fidelity to the charter-specified process of imaging information transfer from a site to a centralized facility and from the centralized facility to the sponsor throughout the clinical trial. Many clinical trials are likely to involve transfer of imaging data to the sponsor only following completion of all image assessments and interpretations, and some may involve image annotations before this transfer (such as a documented caliper-based lesion measurement). In these situations, documentation of image and imaging information transfer may greatly facilitate the completion of audits of the clinical trial's imaging procedures.

Archiving

Sponsors and investigators should comply with the charter-specified plan for imaging source data archiving. Deviations from this plan and/or loss of imaging information may compromise the ability of the FDA to verify data quality and/or prompt reassessment of images. We do not accept images as a component of new drug applications or biologics license applications. However, we may request sponsors to display images, as part of records and reports relating to a clinical investigation; upon our request, sponsors must permit the FDA to have access to these records (see 21 CFR 312.58(a)).

Analysis of Image Information

We anticipate that most analyses of imaging information will be performed by the sponsor (or the sponsor's designated analysts) in accordance with the clinical protocol specifications. In some situations, clinical sites or a centralized facility may analyze certain aspects of imaging as a quality control measure (such as the determination of reader interpretation consistency). Sponsors should specify these site and centralized facility roles in the charter. Clinical trial imaging data should not be analyzed in an ad hoc, unplanned manner.

Imaging processes that had taken place during the conduct of the trial, such as image acquisition, image interpretation, data transfer, and other processes described in the guidance, should be thoroughly presented in the final report submitted for FDA review.