Guidance for Industry

Standards for Clinical Trial Imaging Endpoints

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Dr. Rafel Rieves at 301-796-2050 or (CBER) Office of Communication, Outreach, and Development at 301-827-1800 or 800-835-4709.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2011
Clinical/Medical

Guidance for Industry

Standards for Clinical Trial Imaging Endpoints

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
Tel: 301-796-3400; Fax: 301-847-8714; E-mail: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

or

Office of Communication, Outreach, and Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448
Tel: 800-835-4709 or 301-827-1800; E-mail: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2011
Clinical/Medical

TABLE OF CONTENTS

Guidance for Industry[1]
Standards for Clinical Trial Imaging Endpoints

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the use of endpoints that depend on the results of imaging tests in clinical trials of therapeutic drugs and biological products.[2] This guidance focuses on the imaging standards that we regard as important when imaging is used to assess a primary endpoint, or an endpoint component, in a clinical trial intended to confirm a drug's efficacy.[3] These standards can be used by sponsors to ensure that the 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. By considering the topics highlighted within this guidance, sponsors can obtain clinical trial imaging data in a manner that minimizes variability and enhances data quality and the ability to detect drug treatment effects.

This guidance describes the procedures recommended for collecting and interpreting medical images in efficacy trials. The guidance does not address whether or not specific measurements are clinically meaningful and are acceptable for drug approval.

[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 therapeutic biological products unless otherwise specified.

[3] A confirmatory trial is an adequately controlled trial in which the hypotheses are stated in advance and evaluated. Most phase 3 trials are confirmatory trials that use designs intended to confirm a drug's efficacy. Additional characteristics of a confirmatory trial are described within the guidance for industry *E9 Statistical Principles for Clinical Trials*. 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.

Even though many of the concepts within this guidance also can be applied to clinical trials of diagnostic products and devices, those clinical trials often involve more technical considerations. We encourage sponsors to consult guidances directed toward those types of products. For considerations involving development of imaging drugs, see the guidance for industry *Developing Medical Imaging Drug and Biological Products (Parts 1, 2, and 3).*

As part of the reauthorization of the Prescription Drug User Fee Act (PDUFA 4), we committed to certain performance goals (see letters from the Secretary of Health and Human Services to the Chairman of the Committee on Health, Education, Labor, and Pensions of the Senate and the Chairman of the Committee on Energy and Commerce of the House of Representatives, as set forth in the Congressional Record).[4] This draft guidance addresses one of these goals with the creation of a guidance document that addresses the "imaging standards for use as an endpoint in clinical trials." Although this guidance addresses imaging standards, it does not address the use of any specific imaging endpoints nor does it address a process of qualification of imaging biomarkers for use in clinical drug development. For issues that may be relevant to such a process, see the draft guidance for industry *Qualification Process for Drug Development Tools*.[5]

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 has long been used in therapeutic drug development, particularly in the early phases of drug development (e.g., phase 1 and phase 2 trials). More recently, imaging studies have been proposed for use in phase 3 trials, often as a component of the primary or secondary endpoints.

Imaging most commonly provides an assessment of human anatomy and/or physiology in the form of a pictorial assessment. If the clinical implications are not understood, simply generating an image may not confer benefit to a patient, and an outcome dependent on the interpretation of an imaging test may not be accepted by the Food and Drug Administration (FDA) as an appropriate endpoint for showing efficacy in a clinical trial. We addressed the evidentiary standards for imaging products in Parts 2 and 3 of the guidance for industry *Developing Medical Imaging Drug and Biological Products (Parts 1, 2, and 3)*. As stated in that guidance, acceptable indications for medical imaging agents include the following categories: structure delineation, disease or pathology detection or assessment; functional, physiological, or biochemical assessment; and diagnostic or therapeutic patient management.

[4] See Section A: PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 Through 2012 (http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119243.htm).

[5] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

In this guidance, we address the imaging standards for obtaining and interpreting medical images used to measure efficacy endpoints in confirmatory clinical trials. To illustrate the procedures applicable to imaging in a confirmatory clinical trial, we can divide imaging acquisition and interpretation standards into either a *medical practice* standard or a *clinical trial* standard, as follows:

- **Medical practice imaging standard.** For a medical practice imaging standard, the imaging acquisition and interpretation methods used in a clinical trial do not exceed those used in medical practice. For example, the imaging data incorporated into the clinical trial's final database may rely solely upon an investigator's response to a question about the report of a cardiac ejection fraction. This ejection fraction could be determined by any available medical practice method, depending upon the protocol's expectations (e.g., routine echocardiography or radionuclide imaging). Similarly, an adverse event report that cites a computed tomography finding of an intracranial hemorrhage is generally recognized as based upon the imaging standards typically used in the practice of medicine (i.e., a medical practice standard). A medical practice standard may prove useful for eligibility determination as well as safety monitoring and exploratory endpoint assessments in a confirmatory clinical trial. Sponsors are required to provide justification for the use of a medical practice standard when the imaging data form a component of a confirmatory trial's primary endpoint. The objective is to provide adequate assurance that the imaging methods for the assessment of the endpoint are well-defined and reliable.[6]

- **Clinical trial imaging standard.** With a clinical trial standard for image acquisition and interpretation, sponsors should address the features highlighted within the subsequent sections of this guidance. These features, including various aspects of data standardization, exceed those typically used in medical practice. A trial standard for image acquisition and interpretation is particularly important when an imaging outcome defines a primary endpoint in a phase 3 trial or when important quantitative outcomes are obtained from images. A clinical trial standard enhances the ability to detect a drug effect because of a reduction in the variability of the imaging data, and it also enhances the ability to verify data integrity.

In the following sections, we outline the topics sponsors should address when imaging is used within a clinical trial's primary endpoint to assess a drug's therapeutic efficacy. We emphasize here the nature of the processes that should be standardized. We further recommend that sponsors, in their materials being submitted for discussions with review divisions, describe specific technical aspects in great detail.

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

III. INITIAL CONSIDERATIONS

Logistical and technical factors may limit the ability to use imaging in a confirmatory clinical trial, regardless of whether the trial relies upon a medical practice standard or a clinical trial standard for imaging acquisition and interpretation. The use of imaging within clinical trials may be limited by the availability of imaging technology. Some clinical sites may lack the resources to support a trial's imaging expectations. Similarly, the frequency of imaging and the distance to a qualified imaging facility may preclude or limit a patient's participation in a 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 bioactivity and also demonstrate a mechanism to help monitor drug effects in clinical practice. The following questions illustrate some of the factors a sponsor may wish to consider before proposing the use of imaging in a confirmatory clinical trial.

A. Why Use Imaging in a Confirmatory Trial?

Imaging may assist in the assessment of efficacy and safety as well as patient eligibility. The value of an imaging-based efficacy endpoint is dependent upon the investigational drug's proposed benefit, the nature of the underlying clinical condition, and the precedents for use of imaging in the specific drug development therapeutic area, as well as unique trial design features. Sponsors should consult with individual review divisions when considering the use of imaging to measure an important endpoint in a confirmatory clinical trial.

We anticipate that a medical practice standard for image acquisition and interpretation will prove sufficient for many clinical trial eligibility and safety assessments. However, in some situations, even if the use of imaging does not involve assessment of efficacy, the use of a clinical trial standard should be considered. For example, a clinical trial standard for image acquisition and interpretation would probably apply to the eligibility criteria for a clinical trial of a drug to be used solely among patients with certain quantitative nuclear imaging features of metastatic disease. In this case, detailed imaging methods may be needed to ensure that all patients meet the quantitative imaging expectations for enrollment. Indeed, clinical use of the drug might ultimately require the use of the specialized imaging technology.

B. Are Imaging Standards Important?

The use of imaging within a clinical trial necessitates some form of standardization. For many trials, a medical practice imaging standard alone is sufficient such that no imaging methods (beyond those typically used in medical practice) need to be described in the clinical protocol or supportive trial documents. The importance of the imaging-based eligibility criteria or outcome is the key consideration in determining the extent of imaging standardization needed for a clinical trial.

C. Is Centralized Image Interpretation Important?

The need for a centralized (*core*) image interpretation process is contingent upon the role of imaging within the trial. In situations where image interpretation results in measurements

representing important components of trial eligibility determination or safety or efficacy endpoints, and these measurements are vulnerable to considerable variability among clinical sites, a centralized image interpretation process is needed. A centralized image interpretation process also is critical to controlling bias in open label trials. In general, compared to a site-based image interpretation, the centralized process can better provide verifiable and uniform reader training as well as ongoing management of reader performance, ensuring that the process is accurate and that bias and variability are minimized.

There are, however, situations where a site-based image interpretation might provide sufficient assessment of the images, even when these data define the trial's primary endpoint. For example, a site-based image interpretation may be reasonable in a randomized, double-blinded clinical trial of an investigational therapeutic drug where the imaging technology is widely available, the image is easily assessed by a clinical radiologist, and the investigational drug has shown little or no evidence of unblinding effects.[7] In this situation, the use of randomization and blinding controls bias in image interpretation.

D. Should Image Interpretation Be Blinded to Clinical Data?

The extent of blinding of readers depends upon the role of imaging in the clinical trial. Blinding is of little importance for images used to determine clinical trial eligibility in a controlled trial, because randomization follows this determination. However, in single-arm trials even image-based eligibility should be blinded to clinical data because unanticipated factors may inadvertently bias image interpretations and select patients who are not representative of the desired patient population.

In some situations, image interpretations should be performed with no knowledge of clinical data, including date of the image acquisition or knowledge of prior imaging observations. In other situations, a primary endpoint may require integration of clinical data into an image interpretation (Sargent, Rubinstein, et al. 2009). This determination requires a solid knowledge of the underlying clinical condition and the precedent for the use of imaging within a primary endpoint, as well as multiple logistical considerations, but it is critical that the image interpretation can be blinded to knowledge of treatment.

E. How Often Should Imaging Evaluations Be Performed?

The timing of imaging evaluations depends upon the role and nature of the primary endpoint, the feasibility of the imaging schedule, and overall trial design features, including the potential for unscheduled (*off-protocol*) imaging and the potential effect of missing data upon the primary endpoint. 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, imaging evaluations performed as infrequently as every 6 months may prove sufficient to assess progression-free survival among patients with a cancer known to have a slow progression and prolonged survival. However, in certain situations, relatively long intervals between scheduled imaging evaluations

[7] See the guidance for industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*.

might predispose the trial to bias if unscheduled imaging evaluations occur earlier in one of the treatment arms, potentially resulting in earlier disease detection (Amit, Bushnell, et al. 2010).

F. How Quickly Should Images Be Interpreted?

In clinical practice, images are typically interpreted on-site within minutes to several hours following acquisition for the purpose of clinical management. In a clinical trial, this *turnaround time* by a central image interpretation facility may prove impractical or inappropriate for the design.

The rapidity of image interpretation in a trial varies with the role of imaging in the trial. For example, when specialized, quantitative imaging is important for eligibility determination, a rapid turnaround time in image interpretation from a centralized image interpretation facility would be important for ensuring adequate enrollment. Inability to complete this turnaround on time may make the trial unfeasible.

Less urgency may accompany the turnaround time for image interpretation of efficacy endpoints, although these images too may need prompt evaluation by a centralized facility in certain trial designs. For example, the determination of cancer *progression* by a centralized image interpretation facility may be required to verify the appropriateness of initiation of a new therapy or cross-over administration of the investigational anti-neoplastic drug. Similarly, interim trial efficacy analyses that rely upon centralized image interpretations may necessitate a rapid turnaround in image interpretation.

G. What Procedures Should Be Standardized if Imaging Is an Important Aspect of a Clinical Trial Endpoint?

The procedures that should be standardized are determined by the role of imaging in the clinical trial. Therefore, no single set of detailed standards is readily applicable to clinical trials that differ in design and imaging objectives.

IV. BEFORE IMAGING: DEVELOPING A CHARTER

Sponsors should generally develop a document that provides a comprehensive, detailed description of the clinical trial imaging methodology if a trial standard for image acquisition and interpretation applies to the imaging data. We suggest sponsors refer to this document as an *imaging charter* and develop the document with the close vetting typically applied to the main components of a clinical protocol. Indeed, sponsors should generally regard the imaging charter as an integral component of the protocol, much as a statistical analysis plan is often developed as a component of a clinical protocol. The imaging charter can be attached to a clinical protocol as an appendix or developed as a section within the clinical protocol. For FDA review, we encourage submission of the charter simultaneously with a complete clinical protocol, including the final statistical analysis plan and any important supportive documents.

When imaging forms an important part of a clinical trial, we also encourage sponsors to discuss the imaging charter expectations at an end-of-phase 2 meeting. At this meeting, the sponsor can request advice on the development of an imaging charter and its role in a special protocol assessment submission.

Listed below are the suggested headings and subheadings for the elements within an imaging charter. Some of these elements may not apply to a particular clinical trial, while others may need considerable expansion to sufficiently describe the imaging methods. We encourage sponsors to list each of the elements within the imaging charter and elaborate upon the methods that address the element or briefly describe why the element does not apply to the trial. Compliance with the imaging charter can form an important aspect of the trial conduct verification process as well as the data quality assessment following completion of the trial.

Imaging technology rapidly evolves, can be highly technical, and varies markedly from measurement to measurement. For example, the technical specifications for obtaining reproducible echocardiographic measures of cardiac function profoundly differ 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 an imaging charter (Frank 2008; Boellaard, Oyen, et al. 2008). The complexity of technical standardization may preclude or markedly limit the use of imaging in a multicenter clinical trial even though the imaging methods have well-recognized value in clinical medicine (Keen, Mease, et al. 2010).

A. An Executive Summary of the Trial Design and the Role of Imaging in the Trial

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

Sponsors should provide an overview of the major aspects of the image acquisition, interpretation, and reader-defined deliverables to the sponsor. 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.

B. Image Acquisition Standards

Development of image acquisition standards involves having a broad knowledge of imaging modalities, including anticipation of imaging equipment upgrades or malfunction during the conduct of the clinical trial. In some situations, exploratory clinical trials may be needed 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

cardiac function; in this situation, the X-ray energy (kVp) must 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. The feasibility of maintaining technical consistency within and among clinical sites is particularly important when choosing and optimizing the imaging modality.

1. Equipment Standardization and Operation

The charter should identify the following.

a. Vendor-specific equipment/platforms (e.g., injectors, scanners, software)

The charter should identify the use of any investigational equipment. We recommend the use of only FDA-approved or cleared and marketed imaging equipment. The use of investigational equipment, including software, within a confirmatory clinical trial may necessitate special review and qualification considerations and, in some situations, may necessitate a process for obtaining FDA clearance or marketing approval of the equipment coincident with (or before) marketing approval of the investigational drug.

Sponsors should specify the important imaging equipment for the trial, including the imaging drug (contrast) injectors, scanners, and software. The importance of the equipment specifications varies with the role of imaging in the trial and may importantly 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, patient positioning, scan times, probe positioning, and technician-dependent procedures. We anticipate the need, in some situations, for detailed specification not only of the acceptable vendor-specific scanners but also of the model as well as any requisite upgrades to the equipment. 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. Another approach could identify the physical benchmarks and testing parameters that must be met by the imaging equipment in accordance with a prespecified protocol for the acquired images to be used in the trial.

Most three-dimensional imaging currently requires the raw data to be processed using proprietary software algorithms. Unknown, unplanned, or inadvertent software upgrades may affect how images are generated. Changes in an image may be caused by these unknown software changes, and be incorrectly attributed to actual clinical changes. The charter should specify 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 can 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. Indeed, ad hoc, unplanned interchange of modalities (including substitution of film for digitized imaging data) may compromise the objectives of a trial.

b. Equipment technical settings to be used at each site

The charter should state 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. Details critical to quantitative imaging, such as tomographic slice thickness, pulse sequence, and contrast agent injection time (especially for dynamic imaging), may importantly require specification.

c. The role of site imaging technicians in equipment operation, including identification of faulty or unacceptable images and the need to repeat imaging

The charter should describe the role of the imaging technician in the image acquisition process, including the minimum 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 because of technical failure. In some situations, such as ultrasound imaging, detailed procedures should describe the technician's role in manipulation of the imaging probe and opportunity to deviate from these minimum expectations. Depending upon the imaging modality and the technical demands, the charter may need to describe a technician training process that will help ensure consistency in image acquisition.

d. Phantoms to be used for site qualification and image quality monitoring

We regard the use of phantoms (i.e., prespecified objects for scanning) as a critical part of site qualification and image quality monitoring during the conduct of a clinical trial. 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 the specific imaging modality. In general, we do not regard equipment specifications and image acquisition details as a sufficient substitute for the use of a phantom. Standardization of image acquisition using imaging and dosimetry phantoms will likely enhance the consistent performance of the imaging equipment during the course of the trial.

e. Patient preparation, positioning, and comfort measures

Many imaging modalities require specific patient preparation (e.g., fasting or special dietary limitations), positioning (e.g., supine, right lateral decubitus), preparation (e.g., removal of jewelry and eyeglasses), and comfort measures (e.g., ear plugs or sedation). These common aspects of imaging may vary markedly among clinical sites. Allowing significant site-to-site variations in patient preparation can result in unacceptable levels of image data variability. Patient preparation might also be based on patient-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 patients may necessitate some form of sedation and description of the acceptable sedatives (including doses, route of administration, and potential for repeat dosing) may prove essential to quality imaging as well as the avoidance of missing images.

f. The date and time for imaging and alternatives

The charter should identify the planned dates and, if necessary, the times for imaging. In some situations, patients may need to be imaged at a specific time of day or night or following the development of certain clinical features (such as pain in a joint). The charter should describe these expectations and also identify the date and time windows that represent acceptable alternatives to the planned imaging evaluations.

g. Handling of off-protocol images

Patients 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. The charter should specify the handling of these off-protocol images. In some situations, the off-protocol images are essential for inclusion within a trial's imaging database (e.g., liver computed tomographic images obtained in response to patient signs or symptoms that develop during a trial of an antineoplastic drug), whereas other situations may justify exclusion of these images from a trial's imaging database (e.g., hand radiographs obtained following a motor vehicle accident for a patient enrolled in a trial that assesses ultrasound peripheral artery intimal thickness).

h. Imaging risks

Imaging may involve many important risks to patients, such as exposure to radiation and contrast agents. The charter should describe these risks and specifically identify the radiation dose to be administered during imaging as well as the risks associated with administration of imaging drugs. Additional risks may relate to noise exposure, thermal energy, or magnetic fields. The charter should briefly describe the extent to which these risks are to be described in the trial consent process.

Occasionally, imaging detects incidental findings that are important for further clinical evaluation. Some of these findings may represent false signals of disease and expose patients to invasive evaluations that would have otherwise been avoided. Some of these findings may also provide the first important signals of a clinically important condition. The charter should identify the process for handling these situations, including the areas to be highlighted within the trial consent process. In general, we anticipate that all incidental imaging findings that may have clinical consequences will be reported to the patient and the patient's physician.

i. Site qualification process

The charter should describe the process used to qualify clinical sites for trial participation, specifically describing the tests to be performed to verify equipment performance, technical

support, and capability for compliance with the 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 may need to build upon these expectations by imaging patients as part of a qualifying clinical trial. These types of site qualification 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.

j. Acquisition quality control monitoring process

The charter should describe the plan for periodic, on-site 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, it will probably involve some form of episodic imaging quality reporting from clinical sites. In general, we anticipate the need for periodic on-site inspection by trial 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.

k. Data storage, transfer, and site display

The charter should describe the expectations for imaging data storage, transfer to any separate facility (e.g., core laboratory or the sponsor) from the imaging site, and the plans for image display and interpretation at the clinical sites. 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 patient-identifying information)
- Specify the time period for storage of images at clinical sites and the format for data storage

2. Imaging Drug Standardization

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

- Preparative drugs
- Contrast agents
- Radionuclide agents

The charter should identify the important aspects of drug selection, dosage, and administration for each of these agents, as exemplified below. When describing the drug doses, the charter should state that the drugs should be administered in accordance with approved labeling or state justification for alternative dose regimens.

a. Preparative drugs

The charter should identify acceptable and/or requisite pre-imaging drugs, including sedatives, stimulants, intravenous fluids, or contrast agents. In some situations, the drugs may need to be identified by brand name and, in most situations, by dosages and routes of administration. These specifications can be particularly important for trials that enroll pediatric patients and for the imaging of patients following administration of drugs that may alter images (such as drugs essential for cardiac stress testing). For international trials, the charter may need to identify nation-specific drug options.

b. Contrast agents

Many modality-specific contrast agents are not interchangeable and differ importantly in doses, techniques for administration, and risks. The charter should identify acceptable and/or requisite contrast agents, including specific brand names if essential. 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 patients with acceptable renal function or other characteristics. The charter should identify any laboratory tests and outcomes critical for supporting the administration of contrast agents.

c. Radionuclide agents

In addition to specification of the dose and route of administration, the charter may need to briefly identify the major drug quality features for any clinical trial radionuclide agents manufactured at the site. Unlike preparative drugs and contrast agents, some radionuclides (e.g., positron emission tomography (PET) agents) are commonly produced at clinical sites and the composition as well as the quality of these drugs may importantly 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.

C. Clinical Trial Standards for Image Interpretation

Image interpretation generally is carried out by trained readers, such as radiology and/or nuclear medicine specialists, who review and interpret, or *read*, images obtained in the course of a clinical trial. For the purposes of this guidance, terms such as *image interpretation*, *image review*, or *image read* are used interchangeably, and image readers are sometimes referred to as image reviewers.

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

1. 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 core image interpretation facility, including the plan for:

- Verification of the image technical adequacy as defined in the protocol
- Transfer of images and supportive information to the core facility
- The core facility process for querying sites for missing images, data, or imaging technical problems
- Obtaining repeat images of patients
- The logging of images received at the core facility, including the patient-specific tracking system
- The format for image data transfer (e.g., Digital Imaging and Communications in Medicine 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 patient 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 patient-identifying information from images relayed over electronic communication (e.g., Internet or laptop computers) or other pathways that are vulnerable to a security breach.

2. 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 is usually 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.

a. 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 from the interpretation (read) process should be emphasized and justified. The charter should prespecify the following:

- Criteria for classifying an image as 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 interpreters have the responsibility of excluding certain images from the interpretation process, whether the image interpreters can also determine that an image is uninterpretable and the criteria used to make this decision

- Criteria for excluding images from the analysis and how missing imaging data will be accounted for (imputation scheme)

If images (or image sets for a patient at any specific time point) are to be randomized for display to readers, the charter should describe the randomization process. For example, one trial's image interpretation process may involve the time-sequential presentation of a patient's complete image set (from baseline through the follow-up evaluations) while another may involve the randomization of a patient's single time point image sets among those for many other patients' image sets. The randomization process is a key component of the overall image assessment plan.

b. Number of readers and their background qualifications

Sponsors should identify the number of image readers and their requisite background qualifications. In development of the plan, sponsors should consider:

- The extent of technical knowledge essential to image interpretation

- The avoidance of any other reader involvement in the clinical trial

- The avoidance of reader financial conflicts of interest with the sponsor[8]

- The need for confidentiality of image reads and/or the reading process

- The potential for reader fatigue and the need for substitute readers

- The time commitment of readers and reader availability

- Any unique considerations for identification of an adjudicating reader

- Any need for clinical readers (i.e., image interpretation by clinicians aware of non-imaging clinical trial information)

- The compensation plan for readers and avoidance of a compensation plan that may compromise or bias the quality of the read

The plan for documenting reader qualification should be described, including attestation of the extent of any conflicts of interest. The guidance for industry *Financial Disclosure by Clinical Investigators* describes the types of financial disclosure information, as well as the format, for submission within a marketing application.

c. Reader training and qualification

The reader training process should be described, emphasizing the use of any specific training materials (e.g., a training manual or training images), image display training sessions, any image read testing process, and the training documentation process. The origin (e.g., other clinical trials) of training images should be described, especially any images of patients anticipated for enrollment into the confirmatory clinical trial. In addition, the charter should prespecify whether any performance criteria will be used to qualify readers after training.

Sponsors should consider the importance of the following items in the development of the reader training process:

- **An overview of the major goals of the image interpretation.** In general, reader training should emphasize only the image-specific aspects of the image interpretation process unless the process also requires the integration of clinical information into the image interpretation process. The process should also minimize the potential for introduction of bias into image interpretation through knowledge of any potential image signatures that may break the desired blind to treatment assignment (e.g., if a PET ligand uptake is more common among the elderly, the co-registration of PET-computed tomography may bias the PET assessment because of recognition of aging-related cerebral atrophy on the tomogram).

[8] 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 industry *Financial Disclosure by Clinical Investigators*.

- **An overview of the major expectations for image manipulation, lesion measurement, and other image evaluations.** Readers may need special training in computer-assisted interpretation, measurement, or other analysis tools, and the process for performing and recording measurements, especially if this process involves unique software data lock features and password-protected features. The reading process may require 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 require 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 necessitate replacement of a reader with another trained and qualified reader. The charter should describe the reader testing and retraining or replacement procedure.

d. 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 for determining trial eligibility. In other situations, images are interpreted only following completion of all patient 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. The allowable time interval between the batch sessions should also be predefined.

The charter should provide a detailed description of the image review process. Among many other items, the following should 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 use of any clinical information in the read

- A definition 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 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 calibers, zoom, pan, alteration of window/level, and application of spatial features and adjustment of contrast or image inversions

- A description of any process for re-read of images

- 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 and temporal (for image stacks) and color resolution, and spatial and temporal noise. The charter may need to 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 manipulations of images, for instance, 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 and, in some situations, may generate all the information subsequently transferred to the imaging analytical database. The extent of computer assistance may vary widely but 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 then uses a computer-generated analysis tool to complement the reader's 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. To evaluate for systematic errors, we suggest that a subset of computer-generated analyses be verified by blinded external readers.

Sponsors should use an FDA-approved computer-assisted interpretation tool or a tool justified for use with a given imaging modality (for additional advice on investigational devices, see section IV.B.1.a., Vendor-specific equipment/platforms (e.g., injectors, scanners, software)). If there is a specific tool that is required for image interpretation for assessment of response to therapy or other patient monitoring, the use of this tool might need to be included in the eventual labeling for the investigational drug. The same computer-assisted interpretation tool should be available to all readers at a centralized read.

e. Imaging case report forms

We anticipate the need for specific imaging case report forms 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 subsequently be 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.

f. 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. Predetermination of 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 necessitate a re-read of previously interpreted images, including access to locked data. In all situations, the charter should describe the locking and any potential re-reads.

In general, we encourage the use of a sequential, locked 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 read outcome is documented and not altered.

g. 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, knowledge of such automatic compensation should be known and accounted for.

We recommend evaluating reader performance with defined and prespecified metrics. Evaluation should be ongoing during the interpretation process as well as retrospective.

Intra-reader variability as a measure of reader performance should, in many situations, be assessed by periodic blinded testing of the reader with a preselected set of images randomly interspersed with the clinical trial images. It is important that images from the trial being assessed are not used for reader testing. A drift in reader performance is not infrequently observed in clinical trials, therefore necessitating a periodic reader re-training and re-qualification. All details of reader testing, retraining, re-qualification, and possible replacement should be prespecified within the charter.

Image interpretation is inherently subjective. Therefore, inter-reader variability and the resulting need for adjudication are expected. The degree of variability among central readers leading to a certain adjudication rate observed in a given trial depends on multiple factors. Similarly, the same images might be interpreted differently by central as opposed to local readers at a clinical site. We recommend the use of quantitative measurement of reader variability as a valuable index of reader performance.

D. 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. The plan for submitting charter modifications to the FDA and other regulatory authorities should be described. 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.

E. 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.

F. Archiving of Images and Image Interpretations

Images should be archived as a usual component of patient 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.[9] 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 (by the site investigator for site-specific information and by the sponsor for all trial information) for a period of no less than 2 years following approval of a marketing application or termination of drug development, 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 core contractual facility or institution. Regardless of the physical storage route, the archiving process should address the following items:

- 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 are described in the guidance for industry *Computerized Systems Used in Clinical Investigations*.

V. DURING IMAGING: MONITORING PLANS AND CHARTER MODIFICATIONS

A. 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 a charter and verification of this compliance may prove an important component of the assessment of imaging data integrity.

B. Charter Modifications

During the clinical trial, circumstances may necessitate 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 anticipate the need to 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

[9] See the guidance for industry *Computerized Systems Used in Clinical Investigations* (http://www.fda.gov/regulatoryInformation/Guidances/ucm122046.htm).

meaningfulness of any size changes) and require reconsideration of the role of imaging in the trial as well as 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 patient 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 confirmatory trials.

VI. AFTER IMAGING: DATA TRANSFER, ARCHIVING, ANALYSIS, AND INTERPRETATION OF IMAGING INFORMATION

A. Data Transfer

It is important for sponsors to document fidelity to the charter-specified process of imaging information transfer from a site to a core facility and from the core facility to the sponsor throughout a clinical trial. Many clinical trials are likely to require transfer of imaging data to the sponsor only following completion of all image assessments and interpretations and some may require image data modification, tabulation, or even reinterpretation of images before this transfer. For example, the sponsor may supply certain prespecified clinical information for readers to consider as they reinterpret images. In these unique situations, audit trails can be especially critical and will likely form an integral component of data quality assessment.

B. 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 necessitate reassessment of images. We do not accept images as a component of new drug applications or biologics license applications. However, we may require sponsors to display images during inspections of the core image laboratory, or in presentations to FDA review staff or for use on laptop computer screens by individual reviewers (21 CFR 312.58(a)).

C. Analysis and Interpretation of Image Information

We anticipate that most analyses of imaging information will be performed by the sponsor in accordance with the clinical protocol specifications. In some situations, clinical sites or a core facility may analyze certain aspects of imaging (such as the determination of reader interpretation consistency) as a quality control measure. Sponsors should specify these site and core 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 this guidance, should all be thoroughly presented in the final study report submitted for review to the FDA.

REFERENCES

Amit, O, W Bushnell, L Dodd, N Roach, D Sargent, 2010, Blinded Independent Central Review of the Progression-Free Survival Endpoint, The Oncologist, 15:492-95.

Boellaard, R, W Oyen, C Hoekstra, O Hoekstra, E Visser, A Willemsen, B Arends, F Verzijlbergen, J Zijlstra, A Paans, E Comans, J Pruim, 2008, The Netherlands Protocol for Standardization and Quantification of FDG Whole Body PET Studies in Multi-Centre Trials, Eur J Nucl Med Mol Imaging, 35:2320-2333.

Douglas, P, J DeCara, R Devereux, S Duckworth, J Gardin, W Jaber, A Morehead, M Picard, S Solomon, K Wei, N Weissman, American Society of Echocardiography Standards, American College of Cardiology Foundation, 2009, Echocardiographic Imaging in Clinical Trials: American Society of Echocardiography Standards for Echocardiography Core Laboratories: Endorsed by the American College of Cardiology Foundation, J Am Soc Echocardiograph, 22(7):755-65.

Eisenhauer, E, P Therasse, J Bogaerts, et al., 2009, New Response Evaluation Criteria in Solid Tumors: Revised RECIST Guideline (version 1.1), Eur J Cancer, 45:228-247.

Frank, R, 2008, Quantitative Imaging Biomarkers Allicance FDG-PET/CT Working Group Report, Mol Imaging Biol, 10(6):305.

Keen, H, P Mease, C Bingham, J Giles, G Kaeley, P Conaghan, 2010, Systematic Review of MRI, Ultrasound, and Scintigraphy as Outcomes Measures for Structural Pathology in Interventional Therapeutic Studies of Knee Arthritis: Focus on Responsiveness, J Rheumatol, (epub), 38(1):1-13.

Sargent, DJ, L Rubinstein, L Schwartz, JE Dancey, C Gatsonis, LE Dodd, LK Shankar, 2009, Validation of Novel Imaging Methodologies for Use as Cancer Clinical Trial Endpoints, Eur J Cancer, 45:290-99.

Shankar, L, J Hoffman, S Bacharach, M Graham, J Karp, A Lammertsma, S Larson, D Mankoff, B Siegel, A Van den Abbeele, J Yap, D Sullivan, 2006, Consensus Recommendations for the Use of F18-FDG PET as an Indicator of Therapeutic Response in Patients in National Cancer Institute Trials, J Nucl Med., 47(6):1059-66.