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# Guidance for Industry Standards for Clinical Trial Imaging Endpoints

## *DRAFT GUIDANCE*

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**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

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**Guidance for Industry<sup>1</sup>**  
**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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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.<sup>2</sup> 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.<sup>3</sup> 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.

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<sup>1</sup> 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.

<sup>2</sup> For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

<sup>3</sup> 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>.

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34 Even though many of the concepts within this guidance also can be applied to clinical trials of  
35 diagnostic products and devices, those clinical trials often involve more technical considerations.  
36 We encourage sponsors to consult guidances directed toward those types of products. For  
37 considerations involving development of imaging drugs, see the guidance for industry  
38 *Developing Medical Imaging Drug and Biological Products (Parts 1, 2, and 3)*.  
39

40 As part of the reauthorization of the Prescription Drug User Fee Act (PDUFA 4), we committed  
41 to certain performance goals (see letters from the Secretary of Health and Human Services to the  
42 Chairman of the Committee on Health, Education, Labor, and Pensions of the Senate and the  
43 Chairman of the Committee on Energy and Commerce of the House of Representatives, as set  
44 forth in the Congressional Record).<sup>4</sup> This draft guidance addresses one of these goals with the  
45 creation of a guidance document that addresses the “imaging standards for use as an endpoint in  
46 clinical trials.” Although this guidance addresses imaging standards, it does not address the use  
47 of any specific imaging endpoints nor does it address a process of qualification of imaging  
48 biomarkers for use in clinical drug development. For issues that may be relevant to such a  
49 process, see the draft guidance for industry *Qualification Process for Drug Development Tools*.<sup>5</sup>  
50

51 FDA’s guidance documents, including this guidance, do not establish legally enforceable  
52 responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should  
53 be viewed only as recommendations, unless specific regulatory or statutory requirements are  
54 cited. The use of the word *should* in Agency guidances means that something is suggested or  
55 recommended, but not required.  
56

57

## **II. BACKGROUND**

58

59  
60 Imaging has long been used in therapeutic drug development, particularly in the early phases of  
61 drug development (e.g., phase 1 and phase 2 trials). More recently, imaging studies have been  
62 proposed for use in phase 3 trials, often as a component of the primary or secondary endpoints.  
63

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

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

<sup>5</sup> 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>.

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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.<sup>6</sup>
- **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.

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<sup>6</sup> See 21 CFR 314.126(b)(6).

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### **115 III. INITIAL CONSIDERATIONS**

116  
117 Logistical and technical factors may limit the ability to use imaging in a confirmatory clinical  
118 trial, regardless of whether the trial relies upon a medical practice standard or a clinical trial  
119 standard for imaging acquisition and interpretation. The use of imaging within clinical trials  
120 may be limited by the availability of imaging technology. Some clinical sites may lack the  
121 resources to support a trial's imaging expectations. Similarly, the frequency of imaging and the  
122 distance to a qualified imaging facility may preclude or limit a patient's participation in a clinical  
123 trial. These factors may discourage the use of imaging in a clinical trial or limit the role of  
124 imaging within the trial. Nevertheless, imaging data may provide particularly persuasive  
125 evidence of a drug's bioactivity and also demonstrate a mechanism to help monitor drug effects  
126 in clinical practice. The following questions illustrate some of the factors a sponsor may wish to  
127 consider before proposing the use of imaging in a confirmatory clinical trial.

128

#### **129 A. Why Use Imaging in a Confirmatory Trial?**

130

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

137

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

147

#### **148 B. Are Imaging Standards Important?**

149

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

156

#### **157 C. Is Centralized Image Interpretation Important?**

158

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



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

168  
169 There are, however, situations where a site-based image interpretation might provide sufficient  
170 assessment of the images, even when these data define the trial's primary endpoint. For  
171 example, a site-based image interpretation may be reasonable in a randomized, double-blinded  
172 clinical trial of an investigational therapeutic drug where the imaging technology is widely  
173 available, the image is easily assessed by a clinical radiologist, and the investigational drug has  
174 shown little or no evidence of unblinding effects.<sup>7</sup> In this situation, the use of randomization and  
175 blinding controls bias in image interpretation.

### **D. Should Image Interpretation Be Blinded to Clinical Data?**

176  
177  
178  
179 The extent of blinding of readers depends upon the role of imaging in the clinical trial. Blinding  
180 is of little importance for images used to determine clinical trial eligibility in a controlled trial,  
181 because randomization follows this determination. However, in single-arm trials even image-  
182 based eligibility should be blinded to clinical data because unanticipated factors may  
183 inadvertently bias image interpretations and select patients who are not representative of the  
184 desired patient population.

185  
186 In some situations, image interpretations should be performed with no knowledge of clinical  
187 data, including date of the image acquisition or knowledge of prior imaging observations. In  
188 other situations, a primary endpoint may require integration of clinical data into an image  
189 interpretation (Sargent, Rubinstein, et al. 2009). This determination requires a solid knowledge  
190 of the underlying clinical condition and the precedent for the use of imaging within a primary  
191 endpoint, as well as multiple logistical considerations, but it is critical that the image  
192 interpretation can be blinded to knowledge of treatment.

### **E. How Often Should Imaging Evaluations Be Performed?**

193  
194  
195  
196 The timing of imaging evaluations depends upon the role and nature of the primary endpoint, the  
197 feasibility of the imaging schedule, and overall trial design features, including the potential for  
198 unscheduled (*off-protocol*) imaging and the potential effect of missing data upon the primary  
199 endpoint. For a primary endpoint that uses a time-to-event analytical approach, imaging  
200 evaluations should be performed at baseline and at sufficient frequency to provide a reasonably  
201 precise measure of the time to the expected clinical event. For example, imaging evaluations  
202 performed as infrequently as every 6 months may prove sufficient to assess progression-free  
203 survival among patients with a cancer known to have a slow progression and prolonged survival.  
204 However, in certain situations, relatively long intervals between scheduled imaging evaluations

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<sup>7</sup> See the guidance for industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*.

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

207

### **F. How Quickly Should Images Be Interpreted?**

209

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

214

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

220

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

228

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

229

230  
231  
232 The procedures that should be standardized are determined by the role of imaging in the clinical  
233 trial. Therefore, no single set of detailed standards is readily applicable to clinical trials that  
234 differ in design and imaging objectives.

235

236

## **IV. BEFORE IMAGING: DEVELOPING A CHARTER**

237

238  
239 Sponsors should generally develop a document that provides a comprehensive, detailed  
240 description of the clinical trial imaging methodology if a trial standard for image acquisition and  
241 interpretation applies to the imaging data. We suggest sponsors refer to this document as an  
242 *imaging charter* and develop the document with the close vetting typically applied to the main  
243 components of a clinical protocol. Indeed, sponsors should generally regard the imaging charter  
244 as an integral component of the protocol, much as a statistical analysis plan is often developed as  
245 a component of a clinical protocol. The imaging charter can be attached to a clinical protocol as  
246 an appendix or developed as a section within the clinical protocol. For FDA review, we  
247 encourage submission of the charter simultaneously with a complete clinical protocol, including  
248 the final statistical analysis plan and any important supportive documents.

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

254  
255 Listed below are the suggested headings and subheadings for the elements within an imaging  
256 charter. Some of these elements may not apply to a particular clinical trial, while others may  
257 need considerable expansion to sufficiently describe the imaging methods. We encourage  
258 sponsors to list each of the elements within the imaging charter and elaborate upon the methods  
259 that address the element or briefly describe why the element does not apply to the trial.

260 Compliance with the imaging charter can form an important aspect of the trial conduct  
261 verification process as well as the data quality assessment following completion of the trial.

262  
263 Imaging technology rapidly evolves, can be highly technical, and varies markedly from  
264 measurement to measurement. For example, the technical specifications for obtaining  
265 reproducible echocardiographic measures of cardiac function profoundly differ from the methods  
266 essential to intercenter standardization of F18 fludeoxyglucose standard uptake value measures  
267 (Shankar, Hoffman, et al. 2006; Douglas, DeCara, et al. 2009). Imaging professional societies  
268 have developed or are developing publications that detail modality-specific standards and we  
269 encourage sponsors to become familiar with these documents when developing an imaging  
270 charter (Frank 2008; Boellaard, Oyen, et al. 2008). The complexity of technical standardization  
271 may preclude or markedly limit the use of imaging in a multicenter clinical trial even though the  
272 imaging methods have well-recognized value in clinical medicine (Keen, Mease, et al. 2010).

### 273 274 **A. An Executive Summary of the Trial Design and the Role of Imaging in the** 275 **Trial**

276  
277 Sponsors should summarize the role of imaging within the clinical trial and provide a detailed  
278 description of the imaging database variables (*deliverables*) to be incorporated into the analysis  
279 of the primary endpoint. Sponsors should describe how important trial design features may  
280 affect the proposed imaging database variables (e.g., procedures to minimize missing data, and to  
281 handle missing data in the analysis plan and plans for the use of off-protocol images).

282  
283 Sponsors should provide an overview of the major aspects of the image acquisition,  
284 interpretation, and reader-defined deliverables to the sponsor. Presentation of a flow chart that  
285 identifies the specific steps in the process can be especially useful in summarizing the flow of the  
286 imaging information.

### 287 288 **B. Image Acquisition Standards**

289  
290 Development of image acquisition standards involves having a broad knowledge of imaging  
291 modalities, including anticipation of imaging equipment upgrades or malfunction during the  
292 conduct of the clinical trial. In some situations, exploratory clinical trials may be needed to  
293 identify the most important imaging technical details, including those vulnerable to technical  
294 failure and charter noncompliance. For example, an explicit description of the imaging  
295 acquisition time may be critical when rapid dynamic cardiac arteriography is used to assess

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296 cardiac function; in this situation, the X-ray energy (kVp) must be standardized and appropriate  
297 for imaging iodinated contrast agent within the heart. Similarly, optimization of X-ray energy is  
298 essential for breast imaging because a high kVp will obscure the signal intensity differences  
299 between adipose, glandular, or cancerous tissue and variations in kVp among clinical sites may  
300 increase variability in the imaging endpoint. The feasibility of maintaining technical consistency  
301 within and among clinical sites is particularly important when choosing and optimizing the  
302 imaging modality.

303

### 304 1. *Equipment Standardization and Operation*

305

306 The charter should identify the following.

307

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

309

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

316

317 Sponsors should specify the important imaging equipment for the trial, including the imaging  
318 drug (contrast) injectors, scanners, and software. The importance of the equipment  
319 specifications varies with the role of imaging in the trial and may importantly limit the number of  
320 qualifying clinical sites. For example, imaging scanners may differ in technical details that can  
321 influence image quality, such as image reconstruction software programs and techniques for  
322 respiratory and cardiac gating, patient positioning, scan times, probe positioning, and technician-  
323 dependent procedures. We anticipate the need, in some situations, for detailed specification not  
324 only of the acceptable vendor-specific scanners but also of the model as well as any requisite  
325 upgrades to the equipment. We encourage the use of a tabular listing of the acceptable imaging  
326 equipment, including the key characteristics of the acquisition, processing, and display  
327 components of each scanner. Another approach could identify the physical benchmarks and  
328 testing parameters that must be met by the imaging equipment in accordance with a prespecified  
329 protocol for the acquired images to be used in the trial.

330

331 Most three-dimensional imaging currently requires the raw data to be processed using  
332 proprietary software algorithms. Unknown, unplanned, or inadvertent software upgrades may  
333 affect how images are generated. Changes in an image may be caused by these unknown  
334 software changes, and be incorrectly attributed to actual clinical changes. The charter should  
335 specify important software and also identify any situations when alternatives are acceptable.

336

337 Occasionally, requisite imaging equipment may become unavailable at a qualified site because of  
338 equipment malfunction or unavailability of technical support. In these situations, a clinical site  
339 can choose to substitute one imaging modality for another (such as magnetic resonance for  
340 computed tomography). The charter should identify the situations when these changes are  
341 acceptable. We anticipate that, in many situations, modalities will not prove interchangeable

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342 (such as arteriography for ultrasound) when the endpoint assessment involves a quantitative  
343 imaging measurement. Indeed, ad hoc, unplanned interchange of modalities (including  
344 substitution of film for digitized imaging data) may compromise the objectives of a trial.

345

346 b. Equipment technical settings to be used at each site

347

348 The charter should state the technical settings for image acquisition for each type of important  
349 imaging equipment and identify any acceptable deviations from these settings. We encourage  
350 sponsors to identify these settings based upon the findings from exploratory clinical trials or  
351 other trials that attempted to standardize the technology among multiple clinical sites. Details  
352 critical to quantitative imaging, such as tomographic slice thickness, pulse sequence, and contrast  
353 agent injection time (especially for dynamic imaging), may importantly require specification.

354

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

358

359 The charter should describe the role of the imaging technician in the image acquisition process,  
360 including the minimum qualifications and the role of the technician, if any, in the initial  
361 assessment of image quality. Situations should be identified when repeat imaging is critical  
362 because of technical failure. In some situations, such as ultrasound imaging, detailed procedures  
363 should describe the technician's role in manipulation of the imaging probe and opportunity to  
364 deviate from these minimum expectations. Depending upon the imaging modality and the  
365 technical demands, the charter may need to describe a technician training process that will help  
366 ensure consistency in image acquisition.

367

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

369

370 We regard the use of phantoms (i.e., prespecified objects for scanning) as a critical part of site  
371 qualification and image quality monitoring during the conduct of a clinical trial. Phantoms can  
372 simulate a variety of conditions and have been developed for a range of imaging modalities (e.g.,  
373 magnetic resonance, nuclear medicine, radiography). The choice of the specific phantom type  
374 depends upon the imaging objectives as well as the specific imaging modality. In general, we do  
375 not regard equipment specifications and image acquisition details as a sufficient substitute for the  
376 use of a phantom. Standardization of image acquisition using imaging and dosimetry phantoms  
377 will likely enhance the consistent performance of the imaging equipment during the course of the  
378 trial.

379

380 e. Patient preparation, positioning, and comfort measures

381

382 Many imaging modalities require specific patient preparation (e.g., fasting or special dietary  
383 limitations), positioning (e.g., supine, right lateral decubitus), preparation (e.g., removal of  
384 jewelry and eyeglasses), and comfort measures (e.g., ear plugs or sedation). These common  
385 aspects of imaging may vary markedly among clinical sites. Allowing significant site-to-site  
386 variations in patient preparation can result in unacceptable levels of image data variability.  
387 Patient preparation might also be based on patient-specific factors, such as age, weight, and

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388 physical condition; the importance of standardization of these aspects may widely vary. For  
389 example, a trial conducted among pediatric patients may necessitate some form of sedation and  
390 description of the acceptable sedatives (including doses, route of administration, and potential for  
391 repeat dosing) may prove essential to quality imaging as well as the avoidance of missing  
392 images.

393

394 f. The date and time for imaging and alternatives

395

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

401

402 g. Handling of off-protocol images

403

404 Patients in a clinical trial lasting many months are likely to undergo imaging examinations in  
405 addition to the ones intended to assess the response to therapy or to detect disease progression.  
406 The charter should specify the handling of these off-protocol images. In some situations, the off-  
407 protocol images are essential for inclusion within a trial's imaging database (e.g., liver computed  
408 tomographic images obtained in response to patient signs or symptoms that develop during a trial  
409 of an antineoplastic drug), whereas other situations may justify exclusion of these images from a  
410 trial's imaging database (e.g., hand radiographs obtained following a motor vehicle accident for a  
411 patient enrolled in a trial that assesses ultrasound peripheral artery intimal thickness).

412

413 h. Imaging risks

414

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

421

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

429

430 i. Site qualification process

431

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

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434 support, and capability for compliance with the charter expectations. We anticipate that phantom  
435 imaging, on-site inspection, and training will provide sufficient site qualification for many trials.  
436 In some situations, the site qualification process may need to build upon these expectations by  
437 imaging patients as part of a qualifying clinical trial. These types of site qualification can be  
438 particularly important for highly technical imaging modalities or international trials that include  
439 countries where the imaging technology might be uncommon in clinical practice.

### j. Acquisition quality control monitoring process

442  
443 The charter should describe the plan for periodic, on-site quality control monitoring of imaging  
444 acquisition, storage, and transfer, including the plan for repetitive phantom imaging and the  
445 correction of deviations from the quality expectations. The importance and nature of this type of  
446 monitoring varies, depending upon the nature of the imaging technology, but, at a minimum, it  
447 will probably involve some form of episodic imaging quality reporting from clinical sites. In  
448 general, we anticipate the need for periodic on-site inspection by trial monitors to assess the  
449 imaging technical compliance of each clinical site or a subset of all the sites. Situations should  
450 be identified in which sites will be requalified or terminated because of failure to comply with  
451 image quality expectations. Any requalification procedures should be described.

### k. Data storage, transfer, and site display

452  
453 The charter should describe the expectations for imaging data storage, transfer to any separate  
454 facility (e.g., core laboratory or the sponsor) from the imaging site, and the plans for image  
455 display and interpretation at the clinical sites. In general, the charter should:

- 456 • Specify the storage of imaging data at the clinical site
- 457 • Describe any and all plans for transfer and storage of imaging data outside the clinical  
458 site
- 459 • Describe any image alteration procedures to be performed at the site (such as removal of  
460 all patient-identifying information)
- 461 • Specify the time period for storage of images at clinical sites and the format for data  
462 storage

## 2. *Imaging Drug Standardization*

470  
471  
472 Drugs are commonly used as a component of imaging and often require administration  
473 procedures intimately related to the scanning of a patient. Most notable are:

- 474 • Preparative drugs
- 475 • Contrast agents
- 476 • Radionuclide agents

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

483

484 a. Preparative drugs

485

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

493

494 b. Contrast agents

495

496 Many modality-specific contrast agents are not interchangeable and differ importantly in doses,  
497 techniques for administration, and risks. The charter should identify acceptable and/or requisite  
498 contrast agents, including specific brand names if essential. The charter should also identify the  
499 doses, routes of administration, rates of administration, and any special administration  
500 procedures (such as automatic injectors or administration times that may trigger scanning).

501

502 Some contrast agents can be safely administered only to patients with acceptable renal function  
503 or other characteristics. The charter should identify any laboratory tests and outcomes critical  
504 for supporting the administration of contrast agents.

505

506 c. Radionuclide agents

507

508 In addition to specification of the dose and route of administration, the charter may need to  
509 briefly identify the major drug quality features for any clinical trial radionuclide agents  
510 manufactured at the site. Unlike preparative drugs and contrast agents, some radionuclides (e.g.,  
511 positron emission tomography (PET) agents) are commonly produced at clinical sites and the  
512 composition as well as the quality of these drugs may importantly vary from site to site.  
513 Standardization of these drug attributes may be important in achieving the trial's imaging  
514 objectives. The charter should identify any site-specific production considerations for site  
515 qualification.

516

### **C. Clinical Trial Standards for Image Interpretation**

517

518  
519 Image interpretation generally is carried out by trained readers, such as radiology and/or nuclear  
520 medicine specialists, who review and interpret, or *read*, images obtained in the course of a  
521 clinical trial. For the purposes of this guidance, terms such as *image interpretation*, *image*  
522 *review*, or *image read* are used interchangeably, and image readers are sometimes referred to as  
523 image reviewers.

524



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

529

### 530 1. *Image Transfer, Receipt Documentation, and Initial Quality Assessment*

531

532 The charter should identify the process for transfer of imaging data from each clinical site to the  
533 core image interpretation facility, including the plan for:

534

535 • Verification of the image technical adequacy as defined in the protocol

536

537 • Transfer of images and supportive information to the core facility

538

539 • The core facility process for querying sites for missing images, data, or imaging technical  
540 problems

541

542 • Obtaining repeat images of patients

543

544 • The logging of images received at the core facility, including the patient-specific tracking  
545 system

546

547 • The format for image data transfer (e.g., Digital Imaging and Communications in  
548 Medicine compact disc sent by courier)

549

550 • Digitization of received images or data

551

552 • Any technical evaluation (or pre-interpretation) or alteration of images, including de-  
553 identification of patient information, biasing marks, or other undesired image signals

554

555 • Monitoring compliance with the transfer, receipt, and initial image assessment process

556

557 • Correction of deficiencies and failures in the transfer, receipt, or initial image assessment  
558 process

559

560 The process should be highlighted for removal of all patient-identifying information from images  
561 relayed over electronic communication (e.g., Internet or laptop computers) or other pathways  
562 that are vulnerable to a security breach.

563

### 564 2. *Image Display and Interpretation*

565

566 The paradigm shift from film-based to filmless imaging has redefined clinicians' processes of  
567 image display, and interpretation of images within a clinical trial may critically depend on the  
568 quality of the displayed image. Image display in many digital systems is a flexible and dynamic  
569 process whereby radiologists directly interact with the soft-copy image, which is displayed on a  
570 computer workstation. The hardware component of a display system is usually composed of a

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571 display device and a display driver or graphics card. The specifications given for a system are  
572 valid only for that particular combination of devices. Another important aspect of the display  
573 system is the hardware and software components used for maintaining the display presentation  
574 mapping between image values and luminance levels under a desired calibration model.  
575 Information regarding the calibration hardware, software, and procedures, including frequency  
576 and nature of the performed tests, should be identified.

577

578 a. Selection of images for interpretation, display sequence, and  
579 randomization

580

581 The charter should identify the nature and extent of images to be interpreted (e.g., all scheduled  
582 images as well as off-protocol images) as well as any important sequence aspects (e.g., baseline  
583 images followed by subsequent time point images). The appropriateness of excluding images  
584 from the interpretation (read) process should be emphasized and justified. The charter should  
585 prespecify the following:

586

587 • Criteria for classifying an image as a *technical failure* or other classification that leads to  
588 the exclusion of an image from the interpretation process

589

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

592

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

597

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

600

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

607

608 b. Number of readers and their background qualifications

609

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

612

613 • The extent of technical knowledge essential to image interpretation

614

615 • The avoidance of any other reader involvement in the clinical trial

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- 617 • The avoidance of reader financial conflicts of interest with the sponsor<sup>8</sup>
- 618
- 619 • The need for confidentiality of image reads and/or the reading process
- 620
- 621 • The potential for reader fatigue and the need for substitute readers
- 622
- 623 • The time commitment of readers and reader availability
- 624
- 625 • Any unique considerations for identification of an adjudicating reader
- 626
- 627 • Any need for clinical readers (i.e., image interpretation by clinicians aware of non-
- 628 imaging clinical trial information)
- 629
- 630 • The compensation plan for readers and avoidance of a compensation plan that may
- 631 compromise or bias the quality of the read
- 632

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

### 637 c. Reader training and qualification

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

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

- 646
- 647 • **An overview of the major goals of the image interpretation.** In general, reader  
648 training should emphasize only the image-specific aspects of the image interpretation  
649 process unless the process also requires the integration of clinical information into the  
650 image interpretation process. The process should also minimize the potential for  
651 introduction of bias into image interpretation through knowledge of any potential image  
652 signatures that may break the desired blind to treatment assignment (e.g., if a PET ligand  
653 uptake is more common among the elderly, the co-registration of PET-computed  
654 tomography may bias the PET assessment because of recognition of aging-related  
655 cerebral atrophy on the tomogram).
- 656
- 657
- 658

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<sup>8</sup> 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*.

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- **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

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- 705 • Detailed use of any clinical information in the read
- 706
- 707 • A definition of the read outcome information to be described on case report forms and
- 708 any special procedures in this process (e.g., an initial read followed by a redisplay of
- 709 images to form a global reassessment)
- 710
- 711 • The assessment tools and qualitative and/or quantitative measurements to be performed
- 712 during the image read (e.g., modified RECIST criteria assessment of each image set)
- 713
- 714 • A description of any computer software or other electronic processes involved in image
- 715 interpretation, such as an automatic calculation of progression
- 716
- 717 • Any lesion tracking system (e.g., certain requisite target lesions), particularly any
- 718 nuances related to the appearance of new lesions for tracking or inability to identify any
- 719 previously tracked lesions (e.g., imaging problems or lesion resolution)
- 720
- 721 • Options and/or requirements for image manipulation, including application of calibers,
- 722 zoom, pan, alteration of window/level, and application of spatial features and adjustment
- 723 of contrast or image inversions
- 724
- 725 • A description of any process for re-read of images
- 726
- 727 • The reader's role in citation of missing images or technical deficiencies within the images
- 728
- 729 • A description of the plan to ensure that all original read outcome information is locked
- 730 and available for subsequent verification and comparison to any re-read outcomes
- 731

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

740

741 Computer-assisted image interpretation may form an important component of the read process  
742 and, in some situations, may generate all the information subsequently transferred to the imaging  
743 analytical database. The extent of computer assistance may vary widely but should be described  
744 explicitly within the charter, including a plan for quality-control checks upon any critical  
745 software functions. For example, the image interpretation may be driven primarily by a reader  
746 who then uses a computer-generated analysis tool to complement the reader's assessment. Such  
747 reliance on computer assistance can be algorithmic, with prespecified parameters for the use of a  
748 tool, or can be elective. In either case, such use should be defined within the charter in a manner  
749 that results in a sufficient audit trail. To evaluate for systematic errors, we suggest that a subset  
750 of computer-generated analyses be verified by blinded external readers.

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751  
752 Sponsors should use an FDA-approved computer-assisted interpretation tool or a tool justified  
753 for use with a given imaging modality (for additional advice on investigational devices, see  
754 section IV.B.1.a., Vendor-specific equipment/platforms (e.g., injectors, scanners, software)). If  
755 there is a specific tool that is required for image interpretation for assessment of response to  
756 therapy or other patient monitoring, the use of this tool might need to be included in the eventual  
757 labeling for the investigational drug. The same computer-assisted interpretation tool should be  
758 available to all readers at a centralized read.

759  
760 e. Imaging case report forms

761 We anticipate the need for specific imaging case report forms for many clinical trials,  
762 particularly trials that involve quantitative imaging within endpoint construction. The charter  
763 should briefly describe the content of the case report form and emphasize the specific data  
764 content or notations that will subsequently be transferred to the sponsor to form the imaging  
765 database for the trial's endpoint analyses. We encourage the attachment of a case report form  
766 example to the charter. On this case report form, sponsors should denote the specific items to be  
767 transferred to the sponsor to form the imaging analytical database. In some situations, the case  
768 report form may consist of a tabular display of numbers (such as lesion measurements) or  
769 categories (such as predefined categories of bone erosion). An example of the tabular display  
770 within the charter may help lessen the potential for errors during the imaging flow process.  
771

772  
773 f. Imaging data lock process

774 At a predetermined point during the image review process, the image interpretation data (case  
775 report form information and any other important reader notations, including notations on images)  
776 generated by the readers should be *locked*. Locking data means that no further modification of  
777 image assessment is allowed. Predetermination of the data locking process and timing should be  
778 closely linked with the image read process. Data can be automatically locked by the imaging  
779 display equipment or triggered in response to reader notations. In some situations, the reading  
780 process may necessitate a re-read of previously interpreted images, including access to locked  
781 data. In all situations, the charter should describe the locking and any potential re-reads.  
782

783 In general, we encourage the use of a sequential, locked approach to the read process whereby  
784 readers interpret the assigned image (or image set) and lock their read (e.g., lesion  
785 measurements, response category, lesion severity) such that the read outcome is documented and  
786 not altered.  
787

788  
789 g. Quality control of the image display and interpretation process

790 The charter should describe the process for monitoring compliance with the image display and  
791 interpretation process. This monitoring should include technical assessment of equipment, such  
792 as display systems and data locking software, as well as the reader interpretation process.  
793

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

803  
804 We recommend evaluating reader performance with defined and prespecified metrics.  
805 Evaluation should be ongoing during the interpretation process as well as retrospective.

806  
807 Intra-reader variability as a measure of reader performance should, in many situations, be  
808 assessed by periodic blinded testing of the reader with a preselected set of images randomly  
809 interspersed with the clinical trial images. It is important that images from the trial being  
810 assessed are not used for reader testing. A drift in reader performance is not infrequently  
811 observed in clinical trials, therefore necessitating a periodic reader re-training and re-  
812 qualification. All details of reader testing, retraining, re-qualification, and possible replacement  
813 should be prespecified within the charter.

814  
815 Image interpretation is inherently subjective. Therefore, inter-reader variability and the resulting  
816 need for adjudication are expected. The degree of variability among central readers leading to a  
817 certain adjudication rate observed in a given trial depends on multiple factors. Similarly, the  
818 same images might be interpreted differently by central as opposed to local readers at a clinical  
819 site. We recommend the use of quantitative measurement of reader variability as a valuable  
820 index of reader performance.

### **D. Charter Modifications Before Imaging**

821  
822  
823  
824 The charter should briefly describe the process for modifying the charter in response to potential  
825 deficiencies within the imaging process or need to improve the process. The plan for submitting  
826 charter modifications to the FDA and other regulatory authorities should be described. In  
827 general, we anticipate charter revisions to be uncommon, particularly if imaging has been used in  
828 exploratory clinical trials and the imaging processes follow precedents.

### **E. Imaging Data Transfer Process to the Sponsor**

829  
830  
831  
832 Image interpretation should result in the completion of a case report form and/or tabular display  
833 of numbers, measures, or categories of responses. The charter should describe the process for  
834 transfer of this information to the sponsor and the time point(s) for transmission of this  
835 information. The charter should describe how the sponsor will use the transferred information to  
836 establish the variables used in the analysis of the primary endpoint.

### **F. Archiving of Images and Image Interpretations**

837  
838  
839  
840 Images should be archived as a usual component of patient care as well as for use as the source  
841 documentation in clinical trials. Electronic source data should meet the same elements of data  
842 quality that are expected of paper records and should comply with all applicable statutory and

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843 regulatory requirements. The FDA’s acceptance of data from clinical trials for decision-making  
844 purposes relies upon verification of the quality and integrity of data, generally based upon the  
845 findings from audits and inspections.<sup>9</sup> In addition to images themselves, the image  
846 interpretations (case report forms or assessment tabulations) represent source data and should be  
847 retained for potential inspection and auditing. All source records, whether electronic or paper,  
848 must be retained (by the site investigator for site-specific information and by the sponsor for all  
849 trial information) for a period of no less than 2 years following approval of a marketing  
850 application or termination of drug development, as described in 21 CFR 312.57(c) and 21 CFR  
851 312.62(c).

852  
853 The charter should describe the process for archiving imaging information by the site  
854 investigator as well as the sponsor. In some situations, the sponsor may choose to archive the  
855 imaging at a core contractual facility or institution. Regardless of the physical storage route, the  
856 archiving process should address the following items:

- 857
- 858 • Limiting access to ensure images and data are retained in their original form
- 859 • Back-up storage
- 860 • Archiving in a manner conducive to a clear audit trail, including date and time stamps
- 861

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

864  
865

### **V. DURING IMAGING: MONITORING PLANS AND CHARTER MODIFICATIONS**

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#### **A. Monitoring Plans**

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870  
871 The charter should outline the complete plan for monitoring the imaging process. The extent of  
872 monitoring is anticipated to vary widely, dependent upon the use of imaging within a trial. In  
873 some situations, monitoring will be minimal, while in other trials, intense monitoring (to include  
874 requalification of equipment with phantoms and periodic retesting of readers) will be critical.  
875 Sponsors should comply with the monitoring plan described within a charter and verification of  
876 this compliance may prove an important component of the assessment of imaging data integrity.

877

#### **B. Charter Modifications**

878  
879

880 During the clinical trial, circumstances may necessitate modification of the imaging procedures.  
881 For example, unanticipated technical features may obscure a portion of an image or preclude one  
882 of the expected quantitative assessments. In these situations, we anticipate the need to revise the  
883 charter to correct the problem and to maintain a record of the modification. The revision should  
884 identify any potential effect of the modification upon the trial’s important endpoint analyses. In  
885 some situations, modification of the charter may affect the definition of the primary endpoint  
886 (e.g., alteration of the method for lesion measurement may call into question the clinical

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



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887 meaningfulness of any size changes) and require reconsideration of the role of imaging in the  
888 trial as well as premature termination of the trial. To avoid these difficulties, we encourage  
889 sponsors to thoroughly consider the role of imaging (including the technical aspects) in a clinical  
890 trial, especially if the imaging is highly technical and/or relies upon quantitative assessments that  
891 require vigilant patient and site cooperation with the imaging process. The use of imaging in  
892 early phases of drug development may help lessen the challenges associated with wider use of  
893 the technology within confirmatory trials.

894  
895

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

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899

#### **A. Data Transfer**

900

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

909

#### **B. Archiving**

910

911 Sponsors and investigators should comply with the charter-specified plan for imaging source  
912 data archiving. Deviations from this plan and/or loss of imaging information may compromise  
913 the ability of the FDA to verify data quality and/or necessitate reassessment of images. We do  
914 not accept images as a component of new drug applications or biologics license applications.  
915 However, we may require sponsors to display images during inspections of the core image  
916 laboratory, or in presentations to FDA review staff or for use on laptop computer screens by  
917 individual reviewers (21 CFR 312.58(a)).

918

#### **C. Analysis and Interpretation of Image Information**

919

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

926

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

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## *Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

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