May 14, 2015

Division of Dockets Management (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA–2011–D–0586 -- Clinical Trial Imaging Endpoint Process Standards; Draft Guidance for Industry

Dear Sir/Madam:

The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 110,000 employees engaged in research activities around the world, ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research.

Each year, ACRO member companies conduct more than 9,000 clinical trials involving nearly two million research participants in 142 countries. On average, each of our member companies works with more than 500 research sponsors annually, and we have a broad and unique understanding of the roles, responsibilities and behavior of all the stakeholders – research sponsors, investigators, Institutional Review Boards, clinical trial participants and ancillary providers of all types – that are part of the research enterprise. Representing companies that routinely interact with IRBs, clinical investigators and sponsors, ACRO thanks the FDA for the above-referenced draft guidance.

ACRO member company imaging expertise includes medical imaging CRO services for efficacy and/or safety endpoints; full-service solutions for diagnostic contrast agents and imaging device trials; and electronic solutions for safety, endpoint and adjudication committees – just to name a few.

ACRO is pleased to provide specific recommendations in the table below.

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ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

Line Number(s)	Current Language	Suggestion/Comment
	Incidental Findings (General Comments)	Anyone involved in managing data in clinical trials has an implied obligation to the well-being of study subjects. Part of this care involves the careful review, reporting and action when noticing incidental findings. However, those best positioned to fulfill that obligation are the treatment teams directly involved in the patient's care and associated healthcare professionals. This expectation is rooted in the direct relationship the treating team has with the individual patient, their access to patient history, and current symptoms. Accordingly, the reporting of incidental findings should be the responsibility of the clinical site where the imaging was acquired. The process should be anchored in the study protocol and consent forms. ACRO believes this approach ensures the most timely and most robust process. The FDA guidance should reflect this approach. The language suggesting that independent reviewers have an obligation to report incidental findings may also create unintended legal consequences that put independent reviewers at a risk for malpractice suits and may disallow European reviewers to read in such clinical trials. ACRO's specific language change is suggested in the referenced line below (please see Lines 71-72).
	Incidental Findings (General Comments)	Central Reviews are not always conducted in real time and therefore should not be used to address acute patient care issues. Central readers' licenses do not allow for clinical care across all governing bodies and locales.

20-23	Introduction	The guidance states that it applies when imaging is part of the trial's primary endpoint. ACRO recommends clarification of expectations around secondary endpoints (which often include imaging), and when this guidance would not apply in registration studies.
26	Considerable standardization already exists in clinical imaging. There are a variety of sources, including the Picture Archiving and Communication System and the Digital Imaging and Communications in Medicine (DICOM) standards . . .	In order to provide clarity, Picture Archiving and Communication System (PACS) is not a standard. PACS systems may support a standardized output format, but PACS systems themselves are not a standard.
30-33	Imaging process standards help sponsors ensure that imaging data are obtained in a manner that complies with a trial's protocol, that the quality of imaging data is maintained within and among clinical sites, and that there is a verifiable record of the imaging process.	ACRO recommends expanding this to say that imaging process standards guide sponsors in identifying critical imaging parameters that should be specified in their protocol.
71-72	The clinical protocol, not the charter, should describe how incidental findings detected in the course of imaging will be handled in a clinical trial.	Lines 71-72 contradict the language in lines 688-690. In lines 71-72, the Guidance says incidental findings should be described in the protocol but lines 688-690 say they should be summarized in the Charter. Therefore, ACRO suggests removing "not the charter" as lines 688-690 states: *"The charter also should summarize how these incidental findings will be handled based upon the description within the clinical protocol."* In addition, ACRO proposes adding text to state that *it is the responsibility of the investigator sites to review the images of each patient, to ensure timely and accurate treatment, based on imaging finding that are incidental to the trial endpoints.*

108-117	Although the medical practice of diagnostic imaging already follows many standardized procedures, we recommend that some trials augment these existing standards to create trial-specific imaging process standards. We define these trial-specific imaging process standards as standards that extend beyond those typically performed in the medical care of a patient (i.e., the process standards are implemented solely for the purposes of the clinical trial). The extent of trial-specific imaging process standards can range from minimal processes that are described solely in the clinical protocol, such as obtaining non-contrasted and contrasted images in all subjects to more detailed imaging process standards for image acquisition, display, interpretation and archiving that are detailed in an imaging Charter (see Appendices A through C).	The Charter is a component of the ensemble of study-specific documents that may include the Charter, Site Manual, the Data Transfer Plan, Communication Plan, etc. In order to avoid redundancy across documents, specifics should be located in the appropriate document based on the intended audience (e.g., trial-specific imaging process standards should be in the Site Manual, data export variables should be in the Data Transfer Plan, Independent Review assessment procedures should be in the Charter). All other documents can then provide a high level summary and reference the appropriate document. One of the issues with having redundant language across all study documents is that if a document is amended, then all documents need to be amended.
119-125	This assumption should be verified for a large clinical trial where practice standards may differ across regions.	ACRO recommends providing an example or a clarification on what may be considered adequate as verification in this context
247-248	"In unique situations, a primary endpoint may rely upon integration of clinical data into an image interpretation, but this is not expected to be common (Sargent, Rubinstein, et al. 2009)."	ACRO requests additional clarity. There are oncology response criteria where clinical information can affect the image interpretation itself (such as, in the RANO criteria, the spatial and temporal proximity of the assessment to the completion of radiation therapy, which affects how likely a particular change is to be pseudo progression rather than true early tumor growth).

250-254	To determine *whether image readers should be blinded to clinical information*, sponsors should have knowledge of *the underlying clinical condition*, an understanding of the precedent for the use of imaging as a trial's primary endpoint, and detailed insight into the trial's unique image interpretation procedures (such as a plan for sequential *locked-read* image interpretation where an assessment cannot be altered versus an option for modification of prior image interpretations).	This section may benefit from some expansion/clarification regarding the underlying clinical condition, as we often find this a difficult topic. ACRO recommends that sponsors clearly define potential sources for unblinding (for example, unblinding side effects of the treatment) in their protocol.
292-293	"centralized imaging readers should promptly identify technical flaws that necessitate repeat imaging of a subject"	Because readers are often looking at the scans only much later, ACRO recommends that the word "readers" be changed to "trained personnel", so that other staff at a core lab could perform this function, especially if it is time-sensitive.
469-470	In this situation, the charter can be attached to a clinical protocol as an appendix or cited as a supplementary document.	In many ACRO members' experience, the charter is developed after the protocol --and is not included as an appendix. However, we would be highly in favor of earlier engagement with sponsors and earlier charter development.
478-479	We encourage sponsors to submit the charter for FDA review as soon as possible and well in advance of trial enrollment initiation.	While this would be ideal, in the experience of many ACRO members, charter documents commonly are not completed in advance of trial enrollment initiation. Therefore, ACRO suggests that it would be appropriate to change to: "We encourage sponsors to submit the charter for FDA review as soon as possible and well in advance of the need of image and trial data interpretation"

491	There is no specific format or content required for a Charter.	This conflicts with comments that FDA provided to the Pharmaceutical Imaging Group (PIG) during the first Medical Imaging FDA/PIG meeting in 2006. FDA, at that point, had specified that in order to facilitate quicker reviews, it would be best if all Charters had similar sections and language. In 2006-2007, break-out groups were formed and a standardized Medical Imaging Charter Template Table of Contents was created, so that all Imaging Core Labs would have similar sections in their Charters. In this manner, Sponsors and FDA would be looking at similar documents across different core labs and would both be comfortable with the content of the Charter and know when certain sections were or were not included.
494-496 See also 697-705 See also 707-717	Consequently, sponsors should specify key requirements for imaging equipment and image quality, as well as the processes for image acquisition, display, interpretation, storage and data transfer.	While Sponsors should certainly be concerned that both sites and the independent review facility (IRF) have equipment adequate to the needs of the study, they may not be able to specify requirements. Site Qualification ensures that equipment at sites have met minimum standards and that the use of phantoms for certain modalities (e.g., FDG-PET, bone scan) are used. Since equipment qualification is a standard process at imaging facilities, it may be better suited for these facilities to continuously monitor equipment qualification and performance during the life of the study. Qualification and performance can then be verified during site monitoring visits.
509	Listed below are the suggested headings and subheadings for the elements within a Charter.	Appendix A is loosely laid out like the agreed-upon Medical Imaging Charter Template, but it is not specifically geared towards an Independent Review, unlike the draft Medical Imaging Charter Template Table of Contents.

597-605	Requisite imaging equipment – unavailability due to equipment malfunction or unavailability of technical support	The imaging charter and site imaging manual should list potentially acceptable imaging substitutes (e.g., for Bone scans whole body MRI and or FDG/PET CT or NaF PET/CT).
607	Equipment technical settings to be used at each site	The Sponsor should provide guidance recommendations, but final settings should be at the discretion of the site provided they meet acceptable radiation dose levels. Because technology evolves, required (hard set) parameters may be inefficient.
616-620	**Role of site imaging technicians in equipment operation, including identification of faulty or unacceptable images and the importance of repeating imaging.** *The charter should describe the role of the imaging technician in the image acquisition process*, including the recommended qualifications and *the role of the technician,* if any, in the initial assessment of image quality.	ACRO recommends adding text to state that *providing technicians with adequate qualifications is the investigator site's responsibility*.

683-695	Reporting of Incidental Findings	ACRO offers three recommendations: First, we suggest the language recommends this is per Sponsor discretion based on type of read design and timing for reads. If the Sponsor decides to comment on incidental findings back to the sites, we suggest this should be included in informed consent and the specific incidental findings are defined. Second, incidental findings should not be part of the CRO responsibility as images may not be analyzed for months or years after acquisition. The protocol should contain language that the local site has the responsibility to identify and communicate incidental findings noted during imaging procedures conducted at their contracted facility. Third, this should be described in the protocol and if detection will be communicated to the sites, it should then be summarized in charter.

688-690	The *charter also should summarize how these incidental findings will be handled* based upon the description within the clinical protocol.	ACRO notes that several concerns arise when an imaging CRO is asked to report incidental findings. Any incidental imaging findings identified during the Independent Review, without any other clinical data, will be circumstantial at best and may prove minimally helpful, if brought to the attention of the investigator. There are multiple legal and regulatory reasons why Independent Reviewers cannot be involved in patient care and all precautions must be taken to avoid the practice of medicine by an Independent Reviewer, which includes not incorporating language into Charters that may allude to medical decisions being made based on data generated from the Independent Review, incidental or not. If incidental findings are observed during the study, IRFs may, after internal discussion, inform the Sponsor. The Sponsor can then determine how to handle these findings (e.g., contact the site, etc.). Additionally, most reads performed by the Independent Review would not be performed in *"real time*." By the time the independent reviewer suspects a finding, it could be months or later (or in some cases, years, if reads are performed in batch mode). The expectation is that the investigator would have noted any findings during visits and would have treated the subject appropriately. The Independent Review should not be involved in patient care since the independent reviewers are not involved in treating subjects.

688-690 (continued)	The *charter also should summarize how these incidental findings will be handled* based upon the description within the clinical protocol.	Because of concerns about licensing, liability, limited information about patients, and the absence of "real-time" review, ACRO recommends that a process be put in place at the beginning of the study to ensure that investigator sites are reviewing the images of each patient to ensure timely and accurate treatment. And, we propose adding text to state that *finding and acting on incidental findings is the responsibility of site investigators – not the independent reviewers.*
692-695	Similar to the handling of important incidental laboratory findings, we anticipate that clinically important incidental image findings will be disclosed to the site investigator who, in turn, will evaluate the role of the image finding in patient management.	ACRO recommends clarification by rephrasing as: "We anticipate that a process will be established at the site that ensures that those clinically important incidental image findings will be disclosed to the site investigator who, in turn, will evaluate the role of the image finding in patient management."
723	Specify the storage of imaging data at the clinical site	ACRO recommends that this be modified or removed. Storage of imaging data should be a site requirement based on participating in a clinical research protocol with a pharmaceutical company, as opposed to falling under the jurisdiction of the charter and the BICR Core Lab.

747-754	Preparative drugs. In situations where preparative (or other) drugs may interact with the planned imaging evaluations, *the charter should identify acceptable and/or requisite pre-imaging drugs,* including sedatives, stimulants, beta-blockers, vasodilators, Intravenous fluids, or contrast agents. The drugs should be identified by brand name and by dosages and routes of administration. These specifications can be particularly important for trials that enroll pediatric subjects and for the imaging of subjects following administration of drugs that will affect images (such as drugs essential for cardiac stress testing).	These details are not typically captured in the imaging charter, (outside of specifying things like whether or not CT should be performed with contrast, or specifying that PET imaging will be done with F18 FDG) as these details would be expected in the protocol. In addition, specifying acceptable imaging drugs by brand name may prove very challenging and may not be feasible in global, multi-national trials. ACRO proposes language stating that *the medical staff at the investigator site is responsible for avoiding known drug interactions that would adversely affect the patient.* Finally, In situations where preparative (or other) drugs may interact with the planned imaging evaluations, the charter should identify acceptable and/or requisite pre-imaging drugs, including sedatives, stimulants, beta-blockers, vasodilators, intravenous fluids, or contrast agents.
756-761	Contrast agents. Many modality-specific contrast agents are not interchangeable and differ importantly in doses, techniques for administration, and risks. If critical to the imaging evaluation, the charter should identify acceptable and/or requisite contrast agents, including specific brand names.	Charters specify whether or not contrast is to be used, but ACRO recommends removing the requirement for specifying by brand names, as this would be very challenging for multi-national trials.

818-821	*"The process should be highlighted for removal of all subject-identifying information from images relayed over electronic communication (e.g., Internet or laptop computers) or other pathways that are vulnerable to a security breach (e.g., courier or postal transfer of hard copy images or digital images on disk)."*	ACRO notes that some proprietary DICOM tags cannot be easily removed. However, these are unlikely to be patient-identifying.
925ff	Reader Training and Qualification	The guidance provided on the extent of training is adequate. However a helpful addition might be clarification of what would indicate that additional training is required. Clinical radiologists typically do not know or use standard assessment tools.
985-987	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).	ACRO suggests relaxing this language as many central reviewers have home workstations, or reading centers in their respective facilities.
1028- 1031	When developing the image display process, sponsors should consider, as appropriate for the chosen modality, the key performance characteristics of medical displays such as luminance range; viewing angle; contrast ratio; reflection coefficients; grayscale; spatial, temporal (for image stacks), and color resolution; and spatial and temporal noise.	This may only be feasible if a central lab is reviewing the images. ACRO recommends broadening the language here to set expectations appropriately. In addition, the viewing angle cannot be controlled, not even in the central lab setting

1071-1073	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.	The applications may commonly be developed later than the charter documents. ACRO recommends rephrasing to: "We encourage a clear tabulation of the specific items that are to be transferred to form the imaging analytical data base within the charter documents. Alternatively a case report form example may be attached."
1111- 1113	We recommend evaluating intra- and inter-reader performance with defined and pre specified metrics based upon evaluations that are ongoing during the image interpretation process.	This may only be feasible if a central lab is reviewing the images.
1175-1176	The charter should describe the process for archiving imaging information *by the site* investigator as well as the sponsor.	The charter covers how a CRO will store data, but does not specify how a site will store data. ACRO suggests that the process for archiving imaging information by the investigator site be documented by the investigator site or sponsor.
1190-1193	Because the charter may consist of an ensemble of technical documents, *the developers of the charter should include a final step in which all the documents are reviewed* to ensure that the charter's technical specifications do not contradict or modify the protocol-specified imaging endpoints.	Because each ensemble is managed by separate groups with respective expertise, this may not be feasible. ACRO's recommendation is that this be the responsibility of the sponsor.
1270	Sponsors should specify these site and centralized facility roles in the charter.	The charter is typically written by the central imaging lab to describe the role of the imaging lab, and would not go into detail about the role of the site, outside of what the site is asked to do with the imaging being centrally reviewed.

In conclusion, ACRO appreciates this opportunity to comment on this guidance, and we look forward to further dialogue with the FDA about the important issues raised in this Request for Comments. Please do not hesitate to contact ACRO if we can be of any assistance (knoonan@acrohealth.org).

Respectfully submitted,

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