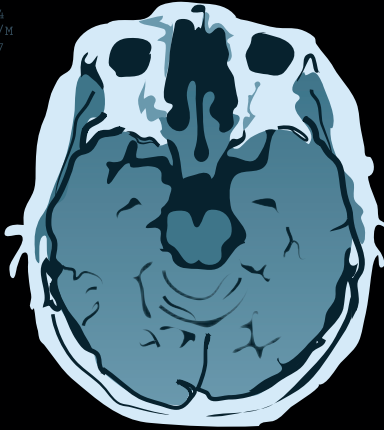
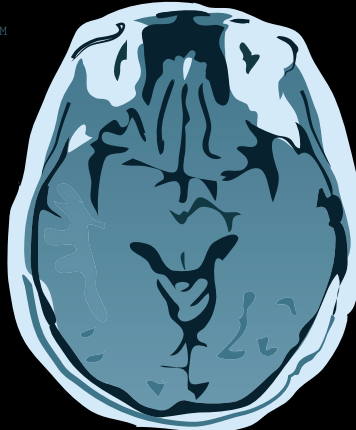


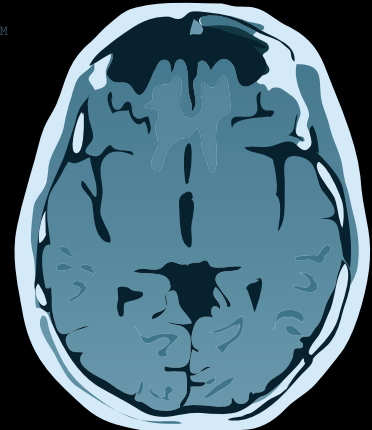
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# Image Conscious

Medical imaging is increasingly being used for establishing endpoints in clinical trials. The FDA's new guidance document advises how best to manage the research process.

Over the past few decades pharmaceutical companies have been searching extensively for biomarkers or surrogate endpoints that can decrease development times. Medical imaging has played an increasingly important role in this paradigm. Some surrogate endpoints, such as lesion size in oncology, have been accepted by regulatory authorities. Others, such as changes on MRI scans in rheumatoid arthritis, are still under debate and can be used in early phase trials for internal decision making, but have not yet been accepted as endpoints for regulatory approval.

The increasing importance of imaging has also given rise to the formation of

so-called imaging core labs; companies (or academic groups) that specialise in the logistical management and centralised review of medical images (1).

In light of all these developments there is also increased interest from the regulatory authorities in the way that medical images are handled in clinical trials. After a number of open meetings and discussions and prior guidances for devices and biologics, the FDA issued the new draft document in August 2011 entitled Guidance for Industry: Standards for Clinical Trial Imaging Endpoints (2-6).

This article evaluates this new FDA draft guidance document, highlighting the

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issues sponsors need to consider when setting up a trial with imaging as an endpoint. The guidance document is not yet final but the stage has been set and the expectation is that the final version will be close to this well thought-out draft.

## Introduction and Background

"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... The 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 acceptable for drug approval."

The FDA does not identify when and why an imaging endpoint can be used. This will remain a discussion point depending on the specific indication, the treatment, the design of the trial and the potential for imaging to serve as a surrogate marker.

The FDA notes a difference between medical practice imaging standards and clinical trial imaging standards. Clinical trial imaging standards "do not exceed those used in medical practice." They may be useful in eligibility assessments, safety monitoring and for exploratory end points. However, sponsors would be required to justify the use of these standards when they use imaging for a confirmatory trial's primary end point.

A clinical trial imaging standard 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."

This section in the draft guidance document emphasises the important role that a central review of images can play in decreasing variability. It would be useful to evaluate if the same standards should apply if imaging is used for secondary end points and earlier phase trials. The basic idea of decreasing variability applies in these trials as well and may help in detecting a true difference between groups.

In a later part of the draft guidance document the FDA expands on this idea, saying "The use of imaging in early phases of drug development may help lessen the challenges associated with wider use of the technology within confirmatory trials." This reinforces the view that using clinical trial imaging

standards should be given careful consideration in every trial with imaging endpoints.

### Initial Considerations

Several key aspects are discussed in this part of the draft guidance document. The FDA states that "Logistical and technical factors may limit the use of imaging... nevertheless, imaging data may provide particularly persuasive evidence of a drug's bioactivity and also demonstrate a mechanism to help monitor drug effects in clinical practice."

The reasons for using imaging are discussed in the guidance, and interesting comments regarding when the clinical trial imaging standard should be considered while using imaging end points are made: "For example, a clinical trial standard for image acquisition and interpretation would probably apply to the eligibility criteria for a clinical trial of a drug to be used solely among patients with certain quantitative nuclear imaging features of metastatic disease. In this case, detailed imaging methods may be needed to ensure that all patients meet the quantitative imaging expectations for enrolment. Indeed, clinical use of the drug might ultimately require the use of the specialised imaging technology."

In other words, depending on the use of imaging as an endpoint and the potential further use of imaging in the treatment of patients, it may be necessary to apply more stringent standards.

### Is Centralised Image Interpretation Important?

The need for a centralised (core) image interpretation process is contingent upon the role of imaging within the trial. A centralised image interpretation process is needed in situations where image interpretation results in measurements representing important components of trial eligibility determination, safety or efficacy endpoints, and these measurements are vulnerable to considerable variability among clinical sites. A centralised image

interpretation process is also critical to controlling bias in open label trials.

Again, the basic reason for the use of centralised image review (that is decreasing variability) is recognised. In addition, it is mentioned that bias may occur in assessments from radiologists who have knowledge of the patient's treatment, which means that open label trials should have an independent central review.

The FDA further mentions several key aspects of image management which are dependent on the overall role of imaging in the clinical trial. Depending on this role, the following issues need to be addressed in more or less detail:

- The importance of imaging standards and standardisation of procedures
- The blinding of the reviewers for clinical data
- The frequency of imaging
- The turnaround time for central review of imaging

This means that even with the draft guidance document there is ample room for discussions based on the exact set-up of the trial. It would therefore be advisable to seek expert help before starting with a trial with imaging endpoints. This expert help should be provided by people that have intimate knowledge of the technical aspects of the radiological imaging technique as well as knowledge of the regulatory consequences and logistical aspects of the use of imaging in trials. Most of the larger imaging core labs should be able to help in these fields.

### Developing a Charter

A large section of the guidance document is dedicated to the development process and content of the imaging charter. The FDA defines an imaging charter as "a document that provides a comprehensive, detailed description of the clinical trial imaging methodology if a trial standard for image acquisition and interpretation applies to the imaging data." It is believed that this should generally be developed if clinical trial standards apply to the image

data management in a trial. The FDA encourages that the imaging charter be a part of the protocol, either as an appendix or part of the body of the protocol.

From a practical perspective it can be debated how much detail of the operational aspects should be included in the charter if it truly becomes a part of the protocol. The protocol is usually finished months before the sites are initiated and all the details of the scanning equipment are known.

This sets the bar much higher and requires the operational aspects to be completed sooner; if this remains in the guidance, it will change the face of clinical trials development.

### Charter Headings and Subheadings

In the draft guidance there is a list of headings and subheadings that should be incorporated in the imaging charter (unless the sponsor can justify why they are left out or deemed not applicable).

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

This is an executive summary describing the imaging variables (deliverables) that will be incorporated in the analysis and all aspects that may affect these imaging variables. It should also provide an overview of the flow of imaging information.

### Image Acquisition Standards

The following issues regarding equipment standardisation and operation need to be addressed:

- Issues such as the timing after contrast injection or equipment standardisation, where only specific manufacturers are used. The equipment specifications can have far-reaching consequences since it may exclude certain sites from participation
- The use of phantom scanning. The FDA states "We regard the use of phantoms (that is, pre-specified objects for scanning) as a critical part of site qualification and image quality

monitoring during the conduct of a clinical trial. Phantom scanning can simulate a variety of conditions and have been developed for a range of imaging modalities (such as magnetic resonance, nuclear medicine and radiography). The choice of the specific phantom scanning type depends upon the imaging objectives as well as the specific imaging modality"

- The description of imaging risks (such as radiation exposure). The risk involved with the imaging (such as radiation exposure, contrast agent exposure, and so on) should also be part of the informed consent and it would therefore be good to discuss this before finalisation of the protocol and patient information leaflet
- The acquisition quality control monitoring process. Here the FDA anticipates "the need for periodic on-site inspections by trial monitors to assess the imaging technical compliance of each clinical site or a subset of all the sites"

The statement regarding periodic on-site inspection means that the scope of the charter goes beyond the work normally considered the responsibility of an imaging core laboratory and extends to the CRO or the clinical operations department of the sponsor.

Imaging drug standardisation also needs to be considered. "Drugs (such as contrast agents or preparative drugs) are commonly used as a component of imaging and often require administration procedures intimately related to the scanning of a patient." The charter should describe the exact use and specifications of these drugs.

The use of preparative drugs, such as sedatives, in certain procedures can be very site specific. It seems that such use is linked to everyday practice and may not have a major impact on the image quality or the outcomes of the trial. It is likely that these aspects are left to the discretion of the investigator/local radiologist. They could potentially add this information to the eCRF to allow further evaluation, but it may not be practical to try and describe all the local procedures in the charter.

### Clinical Trial Standards for Image Interpretation

This section deals with the issues that need to be considered while (centrally) reviewing images. It emphasises the standardisation and planning of the image interpretation and touches on issues such as:

- The image transfer process
- The image display (and quality of the display monitors)
- Reader training issues
- Evaluation of intra-reader variability
- Timing of the reads

A specific point is made about computer assisted image interpretation. The FDA states "The extent of computer assistance may vary widely but should be described explicitly within the charter, including a plan for quality-control checks upon any critical software functions."

### Charter Modifications before Imaging

The FDA states: "In general, we anticipate charter revisions to be uncommon, particularly if imaging has been used in exploratory clinical trials and the imaging processes follow precedents."

From experience we know that most sponsors regard a charter as a living document that only needs to be finalised before the actual start of the review of images. Based on the increased importance of the charter, this idea of a living document seems no longer feasible and the charter will need to be viewed as a type of protocol that needs to be well thought through and finalised before the start of the trial.

### Imaging Data Transfer Process to the Sponsor

This section of the charter should describe how image interpretation results are transferred to the sponsor and what analysis will be done with them.

### Archiving of Images and Image Interpretations

"The FDA's acceptance of data from clinical trials for decision-making purposes relies upon verification of the quality and integrity of data, generally based upon the findings

from audits and inspections. In addition to images themselves, the image interpretations (case report forms or assessment tabulations) represent source data and should be retained for potential inspection and auditing. All source records, whether electronic or paper, must be retained (by the site investigator for site-specific information and by the sponsor for all trial information) for a period of no less than two years following approval of a marketing application or termination of drug development, as described in 21 CFR 312.57(c) and 21 CFR 851.312.62(c). The charter should describe the process for archiving imaging information by the site investigator as well as the sponsor."

### Monitoring Plans and Charter Modifications

This section of the draft guidance deals with potential modifications of the charter. It suggests that the charter truly becomes a document that has a similar status as the trial protocol and cannot be changed without proper discussion between parties and full agreement on final versions.

The need for a description of a monitoring plan is also outlined here as the document states that "The use of imaging in early phases of drug development may help lessen the challenges associated with wider use of the technology within confirmatory trials." This is a key statement, as early use of imaging may indeed help to identify any unsuspected issues with the specific imaging end points selected for a particular indication area and treatment.

### Data Transfer, Archiving, Analysis and Interpretation of Imaging Information

The role of the imaging core lab (ICL) should be defined in the charter. The FDA clearly states that "clinical trial imaging data should not be analysed in an *ad hoc*, unplanned manner (1)." This not only confirms the role of the ICL but clearly defines the requirements for well-planned and blinded reads. There has

been some debate in academic literature about the need for an independent read but this replaces the debate with a regulatory requirement (7,8).

#### References

1. Miller CG, Medical imaging core laboratories, *Applied Clinical Trials*, October 2005, <http://appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/CRO%2FSponsor/Medical-Imaging-Core-Laboratories/ArticleStandard/Article/detail/182766>
2. Guidance for Industry, Providing clinical evidence of effectiveness for human drugs and biological products, Food and Drug Administration May 1998, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf>
3. Notes for guidance on postmenopausal osteoporosis in women, Committee for Proprietary Medicinal Products, 2001, <http://www.rshata.com/updateguidance/emea/old/055295.pdf>
4. Guidance for Industry, Developing medical imaging drug and biological products, Food and Drug Administration June 2004, *Part 1: Conducting Safety Assessments*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory>
- Information/Guidances/ucm078930.pdf, *Part 2: Clinical Indications*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071603.pdf>, *Part 3: Design, Analysis and Interpretation of Clinical Studies*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071604.pdf>
5. Guidance for Industry, Clinical trial endpoints for the approval of cancer drugs and biologics, Food and Drug Administration May 2007, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf>
6. Guidance for Industry, Standards for clinical trial imaging endpoints. Food and Drug Administration August 2011, <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm268555.pdf>
7. Ford R *et al*, Lessons learned from independent central review, *European Journal of Cancer* 45(2): pp268-274, 2009
8. Tang PA *et al*, Influence of an independent review committee on assessment of response rate and progression-free survival in Phase III clinical trials, *Annals of Oncology* 21(1): pp19-26, 2010

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