

Core Strength

Oliver Bohnsack of Perceptive Informatics reviews the expanding use of core imaging laboratories in Phase I clinical trials

The core imaging laboratory is expanding imaging in Phase I clinical trials by offering standardised approaches to image acquisition, interpretation and analysis. A host of regulatory guidelines is encouraging the use of imaging in clinical trials, including Phase I. When imaging is incorporated into studies from the beginning, results of those efforts allow sponsors to make better and faster go/no go decisions about the fate of investigational compounds.

Core imaging laboratories have a valuable role to play in expanding the use of imaging in early phase clinical trials. With the need to characterise the pharmacokinetic and pharmacodynamic (PK/PD) profiles of investigational compounds as quickly as possible, sponsors are considering the core lab as an effective choice for incorporating imaging into Phase I studies. Its purpose is to develop consistent methodologies for acquiring images and to offer non-biased centralised interpretation, audit trails and archiving services – key benefits for sponsors in search of imaging biomarkers that hint at a compound's safety and efficacy from the beginning. Imaging biomarkers assessed by core labs hold the promise of helping sponsors make better, faster and more cost effective go/no go decisions about the future of an investigational compound.

This article focuses on how core imaging labs can improve quality in the imaging process through its infrastructure and by leveraging regulatory guidelines to bring a level of

harmonisation to image acquisition and interpretation. The infrastructure enables core labs to improve image quality through implementation of standardised practices at participating imaging sites. Regulations and recommended guidelines are the driving force behind how core labs operate and develop their practice of independent, blinded and unbiased reading and interpretation of images.

By offering services for early phase development, core imaging labs can provide a significant cost advantage to sponsors who might otherwise wait until the start of pivotal studies to use imaging. At that late stage, discovering that a compound is either ineffective or unsafe at effective doses is quite costly. Studying that compound earlier on might have resulted in its discontinuation, saving time and financial resources that could have been diverted to more promising candidates. Research suggests that a 10 per cent improvement in predicting failures before clinical trials could save \$100 million in development costs per drug (1).

Figure 1: Multiple liver metastases from colo-rectal cancer

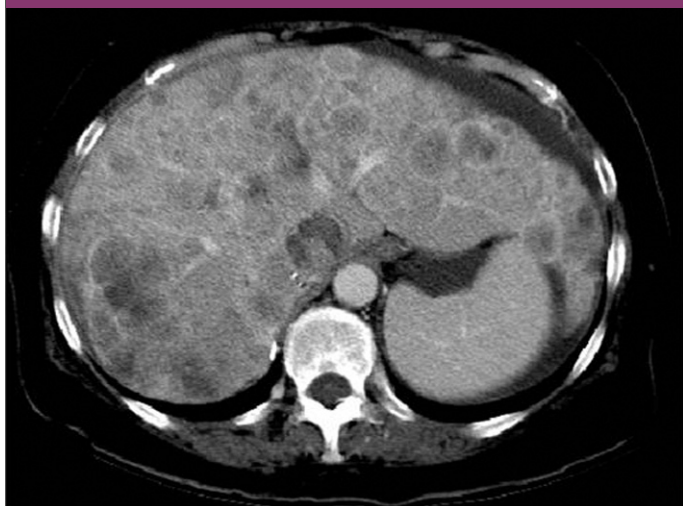
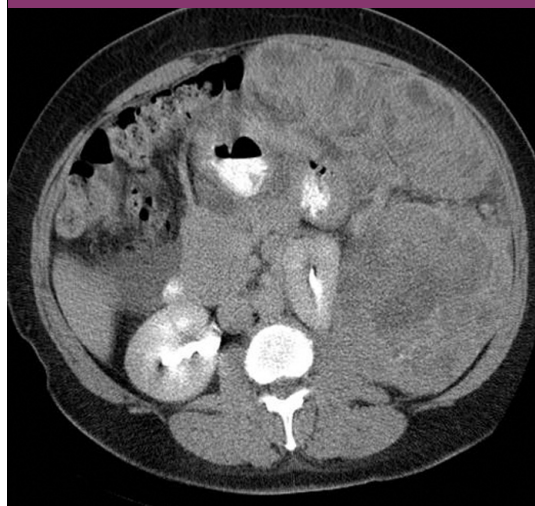


Figure 2: Large tumour mass from gastro intestinal stroma tumour





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CORE IMAGING LAB OVERVIEW

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Standardised imaging requires more than establishing a protocol to produce consistent high quality images. It entails a comprehensive practice that offers a transparent process and training in how images should be taken at investigative sites (see Table 1). The images are then collected from all of the imaging sites through hard copy film, CD-ROM or via a secure FTP file sent directly from server to server and interpreted at a central location. A key advantage of this organised approach is that fewer comparable subjects and fewer standardised imaging sites are needed to generate useful data, further reducing costs.

The core lab does not house image review expertise internally, so it contracts with unbiased experts and thought leaders for

blinded interpretation of the images and multiple iterations of analysis for the various imaging methodologies. These independent imaging specialists evaluate images for all phases of clinical trials. Typically, in early studies, they are evaluating images acquired through nuclear medicine techniques such as positron emission tomography (PET), single-photon emission computed tomography (SPECT) or functional magnetic resonance imaging (fMRI). For later-phase multi-centre trials, more traditional methods such as x-ray, magnetic resonance imaging (MRI) and multislice computerised tomography (CT) are generally employed. The combination of core lab competency, coupled with input from top tier investigators and key opinion leaders, is designed to yield best-of-both-worlds unbiased results.

The standardised method offered by the core imaging lab is in stark contrast to the typical Phase I imaging scenario. Generally, early phase imaging takes place at a handful of academic medical centres, each with its own set of imaging guidelines. Images gathered in this fashion tend to be non-combinable and difficult to interpret; they would not stand up to multiple iteration of analysis, and do little to maximise the use of imaging effectively in Phase I clinical trials.

Besides inconsistent styles of imaging among academic medical centres, there are also significant issues of bias in interpreting the images. In single site studies conducted at medical centres, it is often the same investigators who see patients who also perform the image analysis on those patients. This means that the investigators are not blinded to the results, and if they do not see outcomes in an image, such as tumour changes, in the way they expect to see it, they may continue to change the imaging method and parameters until they see what they set out to see.

Such a biased approach – intentionally or unintentionally – may provide just the expected results to merit a journal publication. Bias may even be acceptable initially, because in the early exploratory stages of testing a new compound in humans, sponsors and investigators are not yet certain of what they are seeking. There are no regulatory restrictions against the use of imaging biomarkers to seek signals for early

Table 1: Services offered by core imaging laboratories

- Standardisation of imaging and image management at investigative sites
- Image collection at a central location and management of the blinding process
- Developing independent review charters for review and approval by regulatory authorities
- Subcontracting independent reviewers and training them on the assessment criteria and reviewer roles and responsibilities
- Managing the logistical processes involved in the independent review
- No intellectual property issues

Source: *Perceptive Informatics (2009)*

decision making, but once a study advances beyond the realm of a single academic site, sponsors cannot use this biased approach and must move to a blinded, unbiased method of evaluating a compound if results are to have statistical validity. This is a regulatory requirement, and it creates the opportunity for the independent, unbiased imaging core laboratory (2).

REGULATORY FRAMEWORK

The use of imaging in clinical trials, particularly in later phases, is an established practice, and has a growing presence due to advances in technology and a host of regulatory guidance from the FDA and EMEA (see Table 2). Because the guidances do not restrict use of imaging to late-phase studies, guidelines can also be applied to early-phase studies. This section provides an overview of some of the major regulatory influences, highlighting an emphasis on Phase I, where applicable.

In the US, imaging in clinical trials has been gaining traction since 1996, when statements were put forth by the FDA about detection of tumour shrinkage as a way to accelerate approval of oncology drugs (3). A year later, the 1997 FDA Modernization Act was enacted (4). This law states that applications may be approved upon determination that a product has an effect on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit. Surrogate endpoints can be detected by imaging, and an imaging-based finding itself can be a surrogate endpoint, so this statement implies that imaging is an acceptable method for making a determination about a compound's profile. Imaging-based endpoints are typically associated with later phase studies, but they can also be considered imaging biomarkers, which tend to be linked to early studies.

The Modernization Act was followed by numerous imaging guidances, most notably the three-part series entitled *Developing Medical Imaging Drug and Biological Products*

Table 2: Some imaging-related guidances, guidelines and regulatory documents in the US and EU

- 1997 FDA Modernization Act
- Developing Medical Imaging Drug and Biological Products
 - Part 1: Conducting Safety Assessments
 - Part 2: Clinical Indications
 - Part 3: Design, Analysis, and Interpretation of Clinical Studies
- Guidance for Industry, Investigators, and Reviewers – Exploratory IND Studies
- PET Drug Products – Current Good Manufacturing Practice
- National Cancer Institute Guidelines
- Draft Guidance on Clinical Evaluation of Diagnostic Agents
- Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics
- Guidelines on Good Radiopharmacy Practice (GRPP)
- The future of pharmaceuticals for human use in the EU
 - The specific case of radiopharmaceuticals

Source: *Perceptive Informatics*

(2,5,6). The guidances are intended to assist developers in planning their clinical trials for medical imaging agents such as contrast agents and diagnostic radiopharmaceuticals. Part 3, *Design, Analysis, and Interpretation of Clinical Studies*, contains a section on how to conduct blinded imaging evaluations. The guidance states that protocols should clearly specify when readers of images should be blinded to patient identifiers and when readers should be fully independent. It recommends that a fully blinded image evaluation by independent readers serve as the principal image evaluation for demonstration of efficacy.

The National Cancer Institute has established imaging guidelines for methodologies including fluorodeoxyglucose (¹⁸F-FDG) PET imaging (7). One of the guidelines, based on an article by Shankar *et al*, makes the point that there were no widely accepted standardised protocols for using ¹⁸F-FDG as a PET tool for assessing response to therapy (8). Following deliberations within the industry, a recommended set of procedures has been outlined. The procedures are intended to standardise how PET images are acquired and interpreted to enable Phase I assessment of therapeutic response.

Also targeting Phase I is the Guidance on the Exploratory Investigational New Drug (IND) application (9). The purpose of the Exploratory IND is to increase efficiency of drug development by defining ways to accelerate Phase I clinical trials. According to the guidance, this method involves minimal human exposure and has no therapeutic or diagnostic intent. It can, however, yield information on pharmacokinetic and pharmacodynamic properties of a compound, which is knowledge that sponsors can use to develop intellectual property and craft Phase I studies.

In Europe, there are several guidelines that address imaging in early clinical trials. The recent Draft Guideline on Clinical Evaluation of Diagnostic Agents discusses the use of imaging to obtain pharmacokinetic and first-in-human safety assessments with single mass dose and increasing mass doses of a diagnostic agent (10). It also mentions that Phase I studies involving imaging may be performed in healthy volunteers or in patients. The Appendix to the draft states that images should be a blind read with the use of appropriate reading grids that allow for a degree of consistency among several readers of the images. Bias among readers is to be kept to a minimum (11).

The Radiopharmacy Committee of the European Association of Nuclear Medicine (EANM) issued Guidelines on current Good Radiopharmacy Practice (cGRPP) in 2007 (12). These non-binding guidelines describe how to handle radiopharmaceuticals in clinical practice and in clinical trials. The Association also crafted a position paper: *The future of pharmaceuticals for human use in the EU – The specific case of radiopharmaceuticals* (13). In this document, the Association comments that performing quality imaging in early studies should be encouraged through an emphasis on education and other factors (see Table 3).

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CORE LAB FOCUS ON GUIDELINES

With this litany of US- and EU-based guidelines and regulations, it behoves sponsors and academic institutions to become familiar with their intent and to consider incorporating the standardised, non-biased imaging requirements and recommendations into clinical trials, including Phase I studies. But sponsors are focused increasingly on their core competencies, so it may not make strategic sense for them to invest in the internal regulatory expertise needed to implement and monitor all aspects of imaging for early and late phase studies involving sites around the globe. In general, through their academic connections, sponsors have access to highly skilled radiologists with extensive experience in producing good exploratory results, but they devote modest resources to conforming to the multitude of regulatory guidelines meant to yield consistent outcomes that will improve their go/no go decision making and accelerate regulatory submissions.

From this perspective, outsourcing this function to a dedicated core lab for all phases of clinical trials might be a smart move. Operationally, core labs provide an infrastructure that is generally not found at academic medical centres and would be quite costly to reproduce. This entails independent review and blinding as required by regulations, plus image processing capability, extensive software applications and image data quality control. Core labs also provide archiving services, audit trails, support and site training.

Part of the infrastructure includes development of an independent review charter (see Table 4), a document sometimes 80 pages in length that details all the steps, from scanning the patient through to an independent read, including the assessment criteria used. It functions as an imaging protocol for a study, and because of its depth of detail, it is a separate document from a regular study protocol. Typically, the charter is tailored for exploratory early phase studies and then scaled up to be more rigorous and regulatory compliant for later phase studies.

There are also image acquisition guidelines, sometimes known as an imaging manual. This document outlines how sites are to scan the patients, so that all images from all patients and all sites are somewhat standardised, allowing the

independent reviewer to see comparable images. To be effective, the guidelines are written so that they can be implemented by the imaging technologist and are as stringent or flexible as needed. They are anatomy-, scanner- and protocol-specific. Once trials involve multi-centre sites in later phase studies, the harmonised practices across all sites are meant to reduce the chances of reviewers making incorrect assessments due to inconsistent image quality.

ADDING VALUE

Imaging has become a mainstay in later phase clinical studies, but with the ramping up of the core laboratory and its promise of standardising early phase imaging practices, imaging is being introduced into more Phase I studies. In an industry

Table 3: In support of imaging in early studies

- Facilitation in the endorsement, diffusion and availability of results from early clinical trials and pilot studies should be fostered
- In order to support the conduct of early phase clinical trials with radiopharmaceuticals (RP), the following are particularly important:
 1. Promoting education
 2. Quality requirements for precursors for RP
 3. Toxicological information of RP
 4. Dosimetry information of RP

Source: The future of pharmaceuticals for human use in the EU (2007)

Table 4: Independent Review Charter

- Receipt and storage of image archive
- Assessment of technical adequacy
- Image archive submitted for independent review
- Deviations list
- Blinding and labelling – how and by whom?
- Methodology for image presentation – Random? Sequential?
- Sequence of independent review
- Required interpretations – Radiologists? Oncologists?
- Locking of independent assessments
- Explanatory comments
- Assessment criteria – Rationale or justification for changes?
- Selection criteria for the independent reviewer

Source: Dr George Mills, 2003 (FDA)

anxious to accelerate the clinical development process, waiting to begin imaging until Phase IIb or III is too late and too costly.

Throughout the clinical trial process, from early Phase I through to Phase III, the core imaging lab can play a vital part in helping sponsors discover the characteristics and potential of investigational compounds. Not only does the lab provide services that help sponsors comply with regulatory guidelines about standardisation and blinding of results, it also brings an infrastructure that can yield an economic impact. In early studies, the core lab can develop protocols for CT, fMRI, PET and SPECT imaging meant to uncover signals that will determine whether a compound continues in development or is set aside in favour of more promising ones. When switching to larger studies, sponsors working with a core lab can take the cost-effective step of studying fewer non-evaluable patients in a smaller number of imaging sites because the protocols established by the core lab result in those sites acquiring images in a more consistent way. This allows for more accurate interpretation and more actionable information. Overall, embracing early imaging techniques that speed up and improve clinical development by generating unbiased results will serve to improve decision making around the future of compounds and generate better data that may eventually lead to more timely regulatory submissions.

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