

## Medical Imaging Core Laboratories

Colin G. Miller

Technological advances have lead to an increasingly important role for centralized imaging laboratories.

**M**edical imaging has developed extensively over the last 30 years. It now plays an ever-increasing role in the development of new therapeutics, either as a surrogate endpoint or an endpoint in its own right. Recent years have also witnessed the development of the so-called “core lab” or imaging laboratory for the centralized quality control and assessment of images. The so-called imaging core labs (ICLs) were formally defined in 2003<sup>1</sup> and are shown in Figure 1. Central processing vendors have become a major part of the clinical trial process, to the point that at the Partnering with Central Labs, ECG and Imaging Labs Conference in 2004 and again in 2005, several speakers commented that 80% of the data going to the FDA passes through the vendors in this category.

The development of the ICL has been driven to a great extent by Food and Drug Administration (FDA) requirements. The first noticeable direct statement to this effect was in the draft FDA guidelines issued in 1983 for the Development of Drugs in the Field of Osteoporosis.<sup>2</sup> These draft guidelines still provide the basis for trial design in osteoporosis and clearly state that the data for assessing bone mineral density (BMD) from dual energy X-ray absorptiometry (DXA/DEXA) instruments should be centrally evaluated and reviewed. The European guidelines on postmenopausal osteoporosis follow a similar pattern.<sup>3</sup> The Clinton-Kessler Oncology Initiative of March 1996<sup>4</sup> gave pharmaceutical companies an opportunity to use tumor shrinkage as evidence of therapeutic efficacy in clinical trials, although the usage of imaging had already been used with Betaseron.<sup>4</sup> The FDA Guidance of March 13, 1997<sup>5</sup> provides an opportunity for biotechnology and pharmaceutical companies to expedite their respective clinical development by executing a single clinical trial with judiciously selected multiple endpoints in lieu of several separate clinical trials, each with its own endpoint. This FDA Guidance cites the approval of Berlex’s Betaseron for multiple sclerosis, where clinical efficacy and magnetic resonance imaging (MRI) were the combined endpoints.

The acceptance of multiple endpoints within a single trial

places medical imaging in a more central role within clinical trial development. The most recent guidance was issued jointly with the Center for Biologic Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER), focusing on the image data requirements for submissions of medical imaging (contrast) agents and biological products.<sup>6</sup> Furthermore, there are now a series of presentations available discussing the role of medical imaging with respect to the Critical Path Initiative.

### A change in attitude

This change in the agency’s attitude toward medical imaging is evidenced by the focus on the rigor and attention to detail that will be required when including an imaging endpoint in a clinical trial. The advances in technology have paved the way for regulatory agencies to now review medical imaging data and audit the procedures performed at the clinical sites without leaving their desk. Furthermore, in oncology, there are new draft guidelines provided by the FDA for the submission of therapeutics in the treatment of cancer<sup>7</sup> that reference the imaging guidelines for medical imaging and biological products. Therefore, it can be assumed that these imaging guidelines pertain to all drugs in the oncology arena, which is supported by the recent creation of the Division of Medical Imaging and Radiopharmaceutical Drugs within the Center for Drug Evaluation and Research (CDER). This division is headed up by Dr. George Mills, the principal author of the imaging guidelines.

ICLs now form an integral part of the clinical trial arena in all therapeutic areas where medical images have to be collected. The need for an ICL is therefore predicated on regulatory issues to standardize the data and to remove bias from site evaluation (ICLs fall into the heading “Central Processing Vendors” area in Figure 1.)

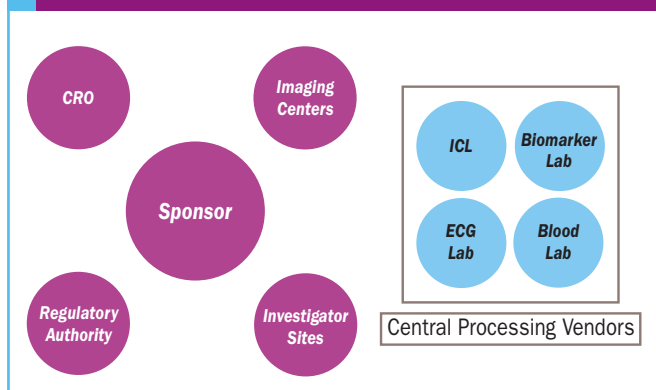
### Imaging’s increasing role

Medical imaging is gaining an increasingly important role in clinical trials. This is due to three major driving forces in the industry. First, there are the improvements in medical imaging technology

and image quality, such as 3D Computerized Tomography (multi-slice CT) and standardized fast acquisition modes in MRI. Ultrasound has also seen major strides in improvement in imaging quality and increased use in cardiovascular applications. New ultrasound contrast agents have also contributed to improvements in image quality and diagnostic efficacy. In addition, nuclear medicine has also made major strides in PET and SPECT technology, due in no small way to the Centers for Medicare and Medicaid Services' (CMS) approval of PET for lung cancer and, more recently, other oncology and neurology applications. Other improvements in imaging technology include the combination PET/CT scanner and 3-Tesla magnet MR systems. Newly approved imaging contrast agents will also improve our ability to gain functional assessment of organ and tissue function and provide more direct measure of therapeutic effect within the target tissue. Even within the standard acquisitions, there is a constant development of new analysis techniques that provide more information from imaging than had initially thought possible.

The continuing need to shorten the drug and biologics development time continues to provide an impetus to use imaging endpoints in clinical trials—particularly in early phases of clinical development—and this will only be enhanced with the development of the new Pre-IND or so-called Phase 0 studies being suggested by the FDA. Early assessment of safety and efficacy can also be accomplished with many imaging applications. There is excitement about the impact that imaging will have on genomics and the search for disease-targeted therapy. The development of molecular imaging contrast agents and markers, particularly for PET and functional MRI, will be valuable tools in development of pharmacogenomic therapeutics. As imaging methodologies become more useful surrogate markers of disease, the ICL will play a key role in the design and execution of therapeutic clinical trials.

**Figure 1.** Schema of the Central Processing Vendors in relationship to other key clinical trial participants. (ICL = imaging core lab.)



## The need to shorten the drug development time continues to provide an impetus to use imaging endpoints in clinical trials.

As with the selection of all central vendors, sponsors must now carefully evaluate who they want to handle their central processing data and how these are going to be integrated into the overall trial management. Even if only 50% of the data going to the FDA (and not the 80% that has been claimed) passes through this box of service providers, it is imperative that sponsors ensure that the data is handled by companies with the experience that can ensure success in getting their data through the FDA review process expeditiously.

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