

Future Functions

James Conklin of ICON Medical Imaging charts the evolution of commercial imaging core laboratory technology systems

It is nearly 20 years since the first commercial imaging core laboratory was founded. Today, there are numerous commercial imaging core laboratories, numerous international imaging biomarker meetings and regulatory guidance documents to support the use of imaging in drug development. Many academic, government and commercial entities have contributed to the growth of this approach, which has become a mainstream tool for the development of numerous therapeutic drugs.

Medical imaging endpoints are accepted in many clinical trials, and when included in the study design, the FDA requires the implementation of a central, independent image review process. The proliferation of medical imaging endpoints and the resulting management, analysis and submission of medical imaging data has fostered the healthy growth of the medical imaging core lab industry, both for commercial and academic labs.

The increase in the number of labs and studies for which they provide services led to a somewhat varied set of documentation and implementation of various technology methods for what is a largely consistent undertaking. Pharmaceutical trial sponsors and the FDA initiated the desire for standardisation in these trials, and DIA has provided the leadership needed to obtain collaboration from all affected parties.

IMAGING CORE LABORATORY ACTIVITIES

Medical Imaging Data

Imaging core laboratories (ICLs) work directly with each investigational centre (site), the trial sponsor, and their associates to manage the collection of all subject image data through completion of this trial. Sites will acquire all images in accordance with the study protocol and will submit them to an ICL for quality assurance, standardisation, assignment of a random number and anonymisation (subject identification masking) for independent review. The ICL requires that each site deliver all original digital imaging data for each subject at each visit.

Imaging Site Technical Evaluations

Based on the investigational site list provided by the sponsor or their designee, the ICL distributes technical evaluation forms to each investigational centre to gather information about standard of care for the particular indication, imaging equipment, personnel, imaging data format and archival media. These are collected and used partly to ensure that sites can adhere to imaging protocol requirements.

Imaging Manual and Data Transmittal Forms

The ICL provides sites with a modality-specific *Imaging Manual* that includes: complete instructions for acquisition, documentation, query resolution, archival, and shipment of image data to ICL; imaging data transmittal forms (DTF); pre-addressed courier labels; study labels for the digital and film media and complete contact information – ICL provides site-training via teleconference covering all aspects of the imaging manual contents.

Image Acquisition

Patients enrolled in the study will undergo radiological or other imaging studies for disease assessment to include the anatomical areas of interest. The subject will be imaged at baseline and at other timepoints specified in the study protocol. Assessments will be performed in those areas where disease was found at baseline and any new areas of suspected disease.

Image Collection and Tracking

The ICL requires sites to submit subject image data promptly after image acquisition. Sites may deliver the images via secure FTP, via courier, or by direct collection by monitoring personnel.

Digital Image Data Translation

The ICL prefers to receive original digital data in native manufacturer format, archived in a non-compressed, unencrypted fashion. The ICL typically converts the manufacturer format into a standard non-proprietary DICOM 3.0 digital format, maintaining the original data integrity.

Film Digitisation and Quality Control

For those situations in which digital radiological or photographic data are not available, the ICL collects a complete original film set; if original films are unavailable, a complete set of high quality film copies is acceptable. The core lab digitises film data in accordance with the American College of Radiology (ACR) guidelines (1). The ICL creates calibrated, DICOM images from each digitised sheet of film. Films are digitally masked to anonymise subject and site information. Using the digital images and processed films, the ICL creates a standard, anonymous dataset digitally masking site and subject information.

Randomisation and Encoding Procedures

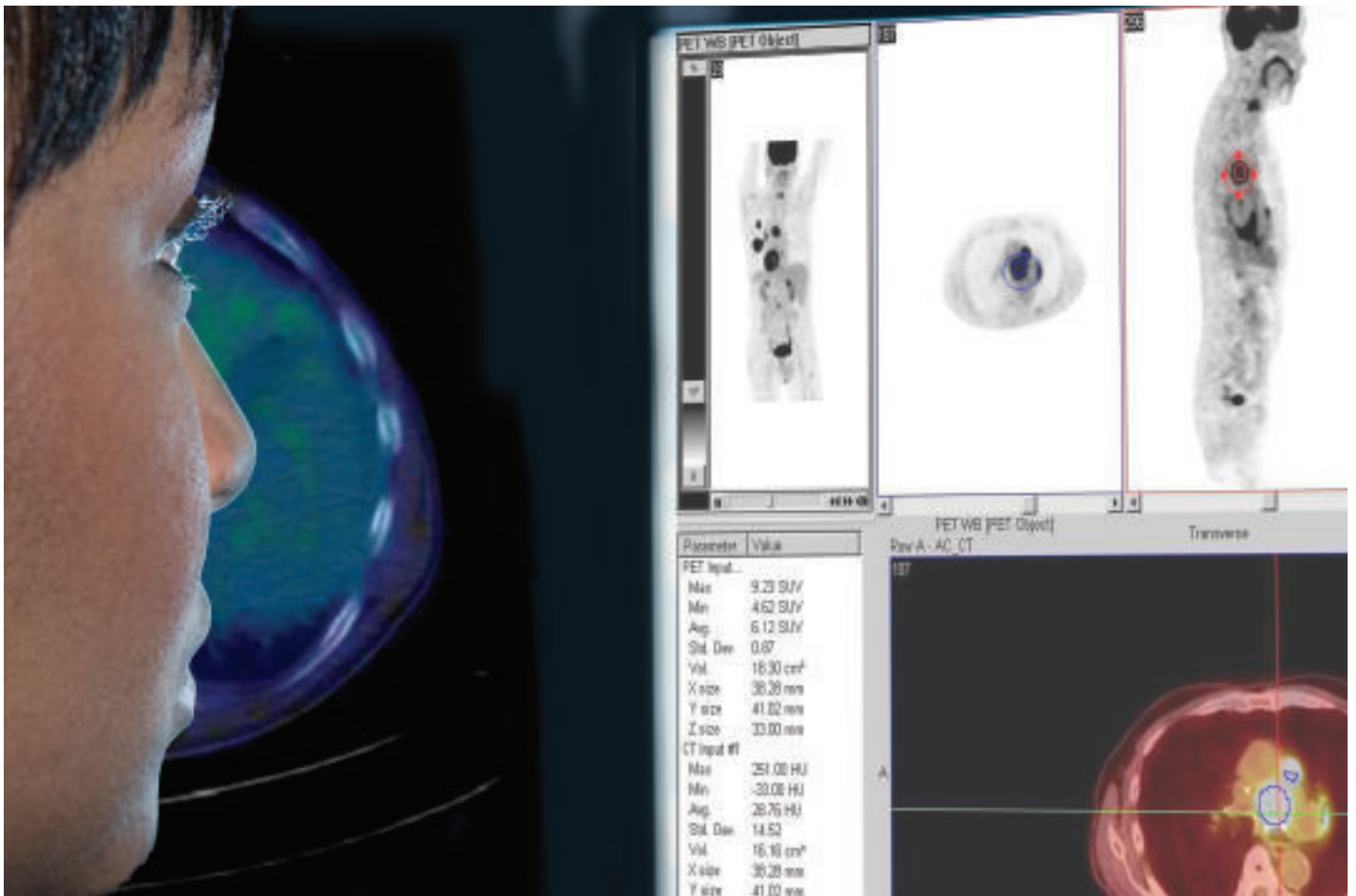
Once a dataset arrives at ICL, the core lab assigns a code generated from a randomisation schema that designates one unique random code number for each subject. All timepoint data for that subject receives a unique random code.

Digital Photography

Clinical trials are utilising digital photography more frequently with the easy and cheap availability of high quality digital cameras. When sites submit digital photography, the ICL maintains, archives and presents the images in a standard format. Calculations can be made with the aid of a size standard included in the view, on which the protocol, site, subject, anatomy and visit date are recorded. During independent review preparation, the ICL masks the site/patient information with the use of industry standard graphic software.

Image Quality Control

Qualified imaging specialists perform image quality control (QC), populating a QC form within the medical imaging review and analysis environment. The goals of QC are to verify patient



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identification, patient-image correlation, protocol-compliant image acquisition, image quality and proper documentation. QC is performed on digital data that has been de-identified. If image quality and/or protocol compliance issues are identified, the ICL initiates the query process.

Image Archival

The ICL archives all image data received for the study in a hierarchical format using a sponsor, protocol, site, patient, timepoint and modality structure. All original image data are maintained as source documents. Subsequent image manipulations such as encoding and region of interest (ROI) generation are also archived, creating a complete audit trail. The ICL implements strict limitations on electronic access to image data, and provides short- and long-term archival in facilities with stringent physical security measures.

Independent Review

The Independent Review Committee (IRC) will usually consist of two sequential components: 1) the independent radiology review; and 2) the independent clinical review. The independent radiology review will be conducted by two independent board-certified radiologists or other sub-specialty experts independently reviewing all individual subject data sequentially by timepoint so that each patient is reviewed twice. An additional board-certified specialist will adjudicate cases in which significant reader variability arises. Following the successful completion of training, reviewers will evaluate study subjects using the database that consists of baseline and all available follow-up timepoints. Once the assessment for a given patient is definitive, the independent clinical review will be conducted by one board-certified specialist assisted by an independent radiologist for consultation if required who will assess clinical data for each subject.

Clinical Data

The ICL can collect the clinical case report forms (CRF) and incorporate them into a database for transfer by the trial sponsor's designated contract research organisation (CRO). The clinical CRO will provide individual subject electronic listings of all relevant clinical data for the independent clinical review. Subject datasets are tabulated by date and presented in an electronic format to the haematologists or oncologists who are participating in the independent clinical review. Clinical datasets are to encompass all medical information relevant to the criteria.

Independent Clinical Review

Each subject's data will undergo an independent review separately by two board-certified specialists to determine the level of response or progression for each timepoint. The clinical consensus panel will be provided pertinent individual subject clinical information in a standard electronic format. The independent clinical review will assess both the clinical results and the radiologic findings to establish response and progression criteria.

Reviewer Selection and Training

The contracted reviewers for this study must be board-certified physicians with experience in the medical condition being evaluated and must be approved by the trial sponsor. Reviewers will not have participated in the study, nor shall they come from any of the study centres (sites). Contracted reviewers will be instructed as to the estimated time commitment and location of the review sessions, and shall agree to participate in a timely manner. Reviewers

are instructed that they are responsible for compliance with international conference on harmonisation (ICH) guidelines on good clinical practice (GCP) and food and drug administration (FDA) 21 Code of Federal Regulations (CFR) Part 11 (2).

EVOLVING REGULATORY ENVIRONMENT

On 16-17th October 2007 DIA sponsored the second meeting of the Medical Imaging Stakeholders Call for Action, which focused on the harmonisation of imaging review charters and integration of imaging in therapeutic development. The conference was attended by the pharmaceutical industry, CROs, the FDA and allied working groups. FDA divisions represented included arthritis, haematology, imaging, radiological health, and devices.

The first meeting of this consortium was in June 2007, and action items and working groups for the October meeting were established at this point. Each working group conducted teleconferences, and each team drafted sections of a common *Medical Imaging Standardization Technical Document* that was routed to the FDA in September 2007. The FDA provided comments and feedback on the draft submission in time for review and discussion at the October meeting.

There were four task areas: standardisation of imaging review charters, best review practices, site core lab interface, and data integrity and statistical analysis plan (SAP). The groups reached consensus with regard to protocol and SAP references in the charter, agreeing that including these documents in the charter appendix was an acceptable alternative to the common practice of including text via copy and paste in the charter body itself. The charter need only be versioned when the content of the protocol or the SAP is changed in a manner that affects the content charter.

ANOTHER MILESTONE – ELECTRONIC CLINICAL ENDPOINT COMMITTEES (eCEC)

Now that information technology systems have been developed for validating, managing and reviewing imaging and other associated clinical trial data, new opportunities inevitably become available. Many clinical trials incorporate evaluation of endpoints for either efficacy or safety, by independent adjudication committees. The CEC will review all relevant data in order to provide an independent, blinded determination of trial endpoints or events.

About the author



James Conklin is the Senior Vice President for medical and scientific affairs at ICON Medical Imaging. James is a John Hopkins-trained research physician with undergraduate and graduate training in electrical/computer engineering and a Masters degree in Management. He has been a Professor of Radiology at several

medical schools, published over 100 scientific papers and edited four books. One of the textbooks, *Imaging Techniques in Biology and Medicine*, published by Academic Press in 1987, provided the technical foundation for Bio-Imaging Technologies, Inc. He is board certified in both internal medicine and nuclear medicine.

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Historically, most adjudication work has been performed in the academic sector, in a paper-based environment. This setup relies on evaluation of paper CRFs, listings, videotapes, films and does not allow simultaneous project tracking or provide an optimal audit environment. Despite high level physician expertise, the conduct of the committee can be affected by a lack of real-time access to all data in an electronic manner and the ability to easily identify multiple data.

ICL Adjudication System

The ICL approach is based upon a database-driven information management system with the ability to distribute, view and interpret a variety of information objects. These systems also provide the ability to collect digital image data and convert the various image types into a standard digital format for inclusion in the adjudication database. They have complete workflows, tracking, reporting and controls specifically designed to meet part 11 requirements.

An electronic clinical endpoint system (eCES) offers a paperless and real-time adjudication solution for endpoint studies of data safety monitoring boards (DSMB) and CEC. This technology enables clinical data and related images to be posted and viewed by committee members online 24 hours a day in an electronic and fully 21 CFR part 11 compliant manner. The use of an eCES: eliminates the need for copying, overnight transportation and tracking of paper and film data; significantly reduces data loss; gives reliable, secure audit trails; enhances committee function due to superior organisation of data; improves your ability to track your study's progress and meet your strict guidelines; reduces costs with direct interface directly with various EDC systems as well as programmed SAS input; and provides secure remote access.

A typical eCES consists in the initial step of two independent physicians. Each independently completes an eCRF. These eCRFs are programmatically compared. If there is agreement, the outcome of the event is considered final and ready for transfer. If there is discord, there is a second step in which the event is reviewed by an additional group comprising one to three physicians who adjudicate in a further review. The complexity of this process and the amount of data reviewed provides a clear rationale for an ICL adjudication solution.

FUTURE APPLICATIONS

It is easy to foresee a continued integration of various facets of the electronic clinical development environment. One can envision that electronic data capture, interactive voice response, clinical databases and trial management systems will all be integrated in a simple system that enables the conduct of independent image reviews, clinical endpoint evaluations and electronic submission from one robust and secure system.

References

1. American College of Radiology, ACR Technical Standard for Digital Image Data Management, 1998 [Revised 2001, Amended 2006]
2. Food and Drug Administration, Guidance for Industry: Part 11, Electronic Records; Electronic Signatures – Scope and Application, Rockville, MD, August 2003



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