MEDIDATA

WHITE PAPER

Picture This: Hassle-Free Imaging in Clinical Trials

The Ongoing Evolution of Image Management Technology

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Introduction

Over the past two decades, technology has changed virtually every aspect of health care – and the work surrounding capturing, storing, transmitting, and evaluating medical images in clinical trials is no exception. Medical images include for example DICOM images like MRI, CT scans, etc, and non-DICOM images including photos and videos.

The field of imaging has undergone a dramatic evolution. Today, the entire process is growing ever more efficient, compliant, and accurate with the help of Artificial Intelligence (AI), integrated systems, and unified solutions. These advances are optimizing workflows, reducing timelines, and improving visibility to, and control of, imaging activities.

And, perhaps most consequential, the use cases of imaging are expanding into new indications. This is due to the demonstrable value of imaging as a biomarker, new capabilities in the hands of patients, and a continuing trend toward decentralizing clinical trials.

The pace of this innovation is accelerating as technology promises to deliver a spate of innovation in the foreseeable future. Here, we pause to consider how far the field of imaging has recently come, discuss the latest innovations, and speculate what lies ahead.

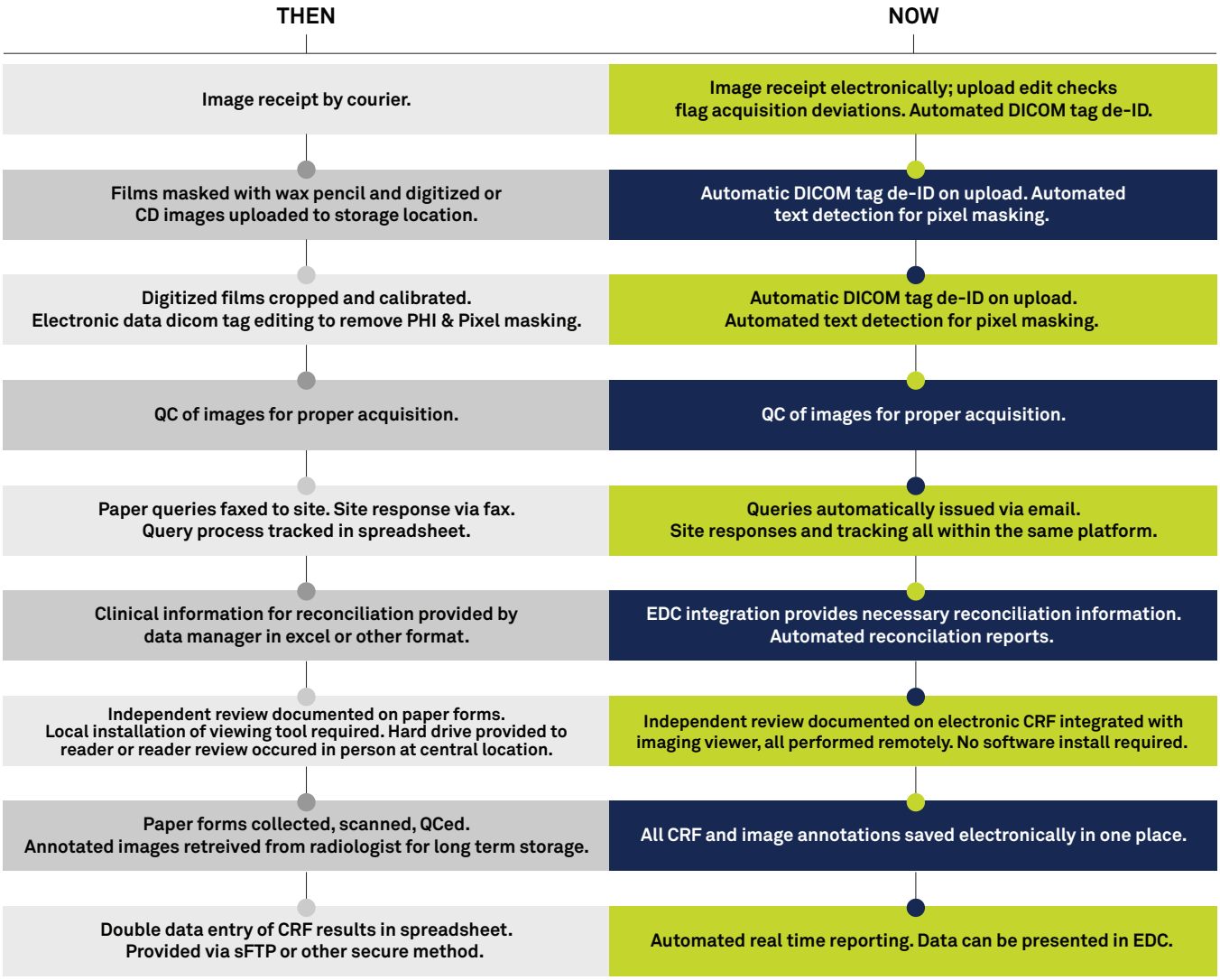
> "Automation is improving the speed and accuracy of many steps, including image submission, privacy protections, reconciliation, image assessment, and workflow management."

A Legacy of Silos and Inefficiencies

A look back at the way things used to be in the field of imaging does not elicit nostalgia, as even twenty years ago, using imaging in trials was, simply put, a hassle. The workflow by which images were taken, shared, and evaluated was a manual, disconnected process of disparate data sets/systems that led to double work, delays, errors, privacy issues, and rework.

The left-hand column of Figure 1 lists the basic steps once involved in sending, preparing, reading, and tracking images between clinical trial sites and core labs. Imaging core labs are specialized contract research organizations (CROs) dedicated to the collection, receipt and processing of medical images in support of clinical trials. In the past, hard copies of films needed to be mailed from sites to core labs, accompanied by a transmittal form; the review process was long, arduous, and error-prone; the paper trail was burdensome and the whole proposition was costly. Significant inefficiencies arise from having to mask out protected health information (PHI) manually, fax queries back and forth between the core lab and the site, reconcile the accompanying clinical information, document the review on paper, and record the case report form (CRF) results. Capping off all of these manual, disjointed steps was a lack of visibility and control over the whole process, which naturally led to delays and escalating study costs.

Figure 1: How Technology Has Changed Clinical Trial Imaging



An Interim Stage

While the right-hand column of Figure 1 represents the state of imaging technology today (discussed below), initial improvements to the process were made about 15 years ago (in 2007) when images could be transmitted electronically. However, the ability to do so required the use of special software and was limited to specific systems.

And while the introduction of electronic data capture (EDC) systems in the 1990's removed the need for paper CRFs and was a step in the right direction for trial sites, the use of EDCs did little to alleviate much of the manual work surrounding the use of images in trials. The EDC remained separate from the imaging tool in which images were uploaded and reviewed. Thus, sites had to devise a way to provide core labs with information contained within the EDC platform – typically via an Image Transmittal Form.

Then, the staff at the core lab had to compare the imaging information that the site had sent with the image itself to verify that the site had captured what was required. This usually meant manually comparing spreadsheets from two different systems. Inevitably, this led to queries back to sites for clarification of any discrepancies. It was not unusual for query rates to run as high as 35 percent or more!

The Era of Automated Image Management

Today, managing medical images is almost entirely automated, as highlighted in the right-hand column of Figure 1. Automation improves the speed and accuracy of many steps, including image submission, privacy protections, reconciliation, image assessment, and workflow management. The contrast to the days of manual image processing is most marked in secure image exchange, de-identification, and reconciliation.

SECURE IMAGE EXCHANGE

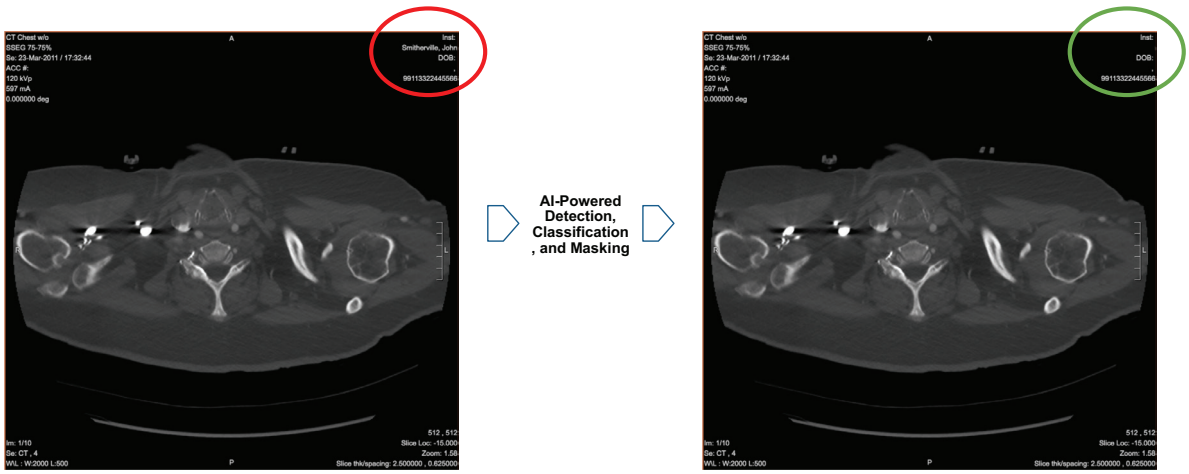
Image data is now captured electronically and transmitted between parties (sites, Sponsors, core labs, and CROs) securely and electronically using a structured submission process. Images can be uploaded from any type of computer, anywhere in the world, using any browser without installing any special software.

In the best systems, the interface is very easy for the site to use and requires minimal data entry. The system clearly identifies what is needed for the trial and provides on-screen instructions to "Click here to upload the CT" or "Click here to upload a photo of the lesion." Ideally, different features can be turned on or off depending on the Sponsor's requirements.

Some systems include a mobile capture feature for photos and videos that allows site staff to take a photo and upload it automatically. This means clinicians can carry their tablet into the exam room, take a photo, and then scan a QR Code that will initiate the uploading process.

DE-IDENTIFICATION

Now, an algorithm can automatically detect potential PHI burned into an image and present it to the user for a decision. The user can then mask the information permanently with the click of a button. (Previously, as listed in Figure 1, the user had to examine the image for any PHI and then manually either mask it (in hard copy) or draw a box around it (on screen) to redact it.)



The software can redact such information in bulk, eliminating manual steps and saving time. In removing any opportunity for human error, this automated step helps ensure compliance with all data privacy regulations.

RECONCILIATION

The burden of reconciliation is greatly reduced because the EDC system and the imaging platform can now be fully integrated. Staff at the core lab no longer must compare spreadsheets or toggle back and forth between two screens in different systems to compare what was sent to what was required. The most sophisticated imaging platforms also have built-in query capabilities and the ability to track the status of queries.

A World of Innovation Awaits

At this writing, work is being done to automate and improve many other aspects of imaging in clinical trials, often relying on AI and Machine Learning (ML) algorithms. Innovations that can be expected in the foreseeable future include:

Expanded Uses of Medical Imaging

For years, imaging was used to provide endpoints in clinical trials within just a few indications – primarily oncology and orthopedics. The technology exists, however, to capture images directly from patients to document symptoms and patient milestones, opening up potential applications in a number of different therapy areas. These include:

Movement disorders

- Sit/stand test
- Speech
- Dermatology
- Rash/eczema
- Injection site reactions
- Bruising
- Cosmetic effects
- Wound care
- Post incision/surgery recovery

Musculoskeletal/inflammatory diseases

- Joint swelling
- External inflammation

Pediatrics

- Developmental milestones (crawling, walking, first words, laugh)

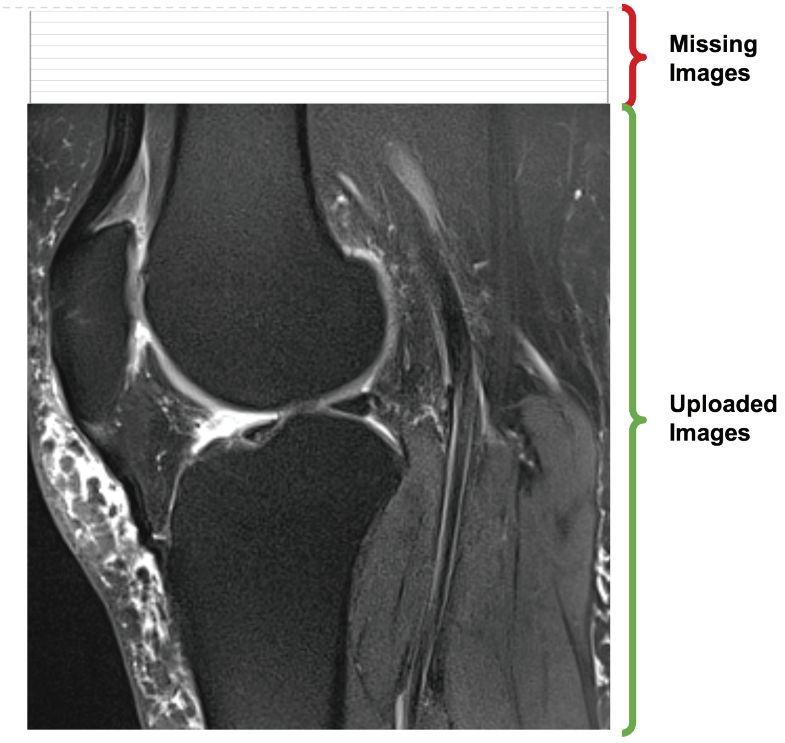
And, across the board, imaging can now be used to ensure patient compliance with their treatment regimen, providing:

- Proof of medication use
- Confirmation of appropriate placement of wearable devices
- Checks on wound care application

Note: The types of photos that are usable must support endpoints that are standardized.

AI-ASSISTED QUALITY CONTROL

Because the parameters set for images in trials are so often different than those applied in providing the standard of care (SOC), sites' conformance to the trial parameters is not a given, and imaging is prone to error. Thus, it is customary for medical images generated in a clinical trial to be checked at the core lab against a variety of quality parameters. For example, in a standard oncology trial, the following parameters are typically confirmed: anatomical coverage, contrast enhancement, scan parameters, field of view, and patient consistency over time. This quality control check is crucial to ensuring that the subsequent assessment by a radiologist is accurate, which, in turn, is essential to collecting valid trial endpoints. However, it is a manual, subjective, and time-consuming step that only adds to the cost and quality challenges of conducting clinical trials.



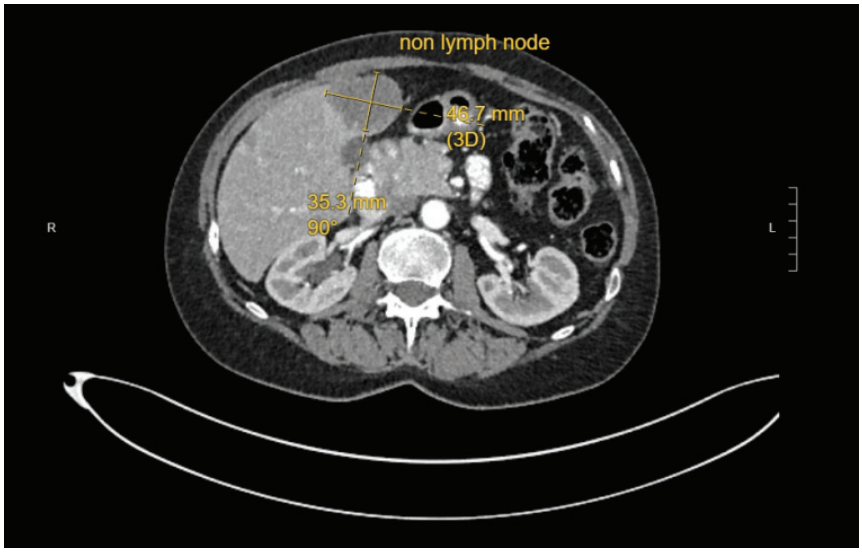
To help remove the subjectivity and reduce the amount of time that core labs need to spend performing manual quality control (QC) checks, AI algorithms can be created to automatically verify critical quality parameters. These could even be applied in the clinic when the image is taken so that issues could be flagged at once, before the patient leaves the clinic.

> "These advances are designed to improve the drug development cycle by enhancing image and data quality, supporting patient centricity, reducing overall costs, and speeding time to market."

RADIOLOGIST ASSESSMENT

Imaging assessments are, of course, critical to supporting endpoints, particularly in oncology trials. However, reviewer assessments can be expensive, time-consuming, and prone to variability among readers.

Currently, algorithms are being developed and perfected to aid radiologists in their assessments by performing automated measurements according to the relevant assessment criteria. For oncology trials, such algorithms will be capable of identifying, premeasuring, and categorizing lesions for presentation to the radiologist. The radiologist would then review the algorithm's work and approve it or modify it. This would save both time and money, as radiologists are usually one of the trial's most expensive resources.



READER PERFORMANCE MONITORING

In the future, technology will also be used to monitor reader performance as a means of ensuring that radiologists are accurately applying the chosen criteria. Algorithms can be developed to automatically identify patterns in reader assessments that suggest a deviation from the imaging criteria or to check for consistency across radiologists. Such analyses could be used to identify readers who may not be applying the criteria consistently and who may need more training. For example, RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) is the gold standard assessment for solid tumor trials. For this criteria, identification of new lesions at a followup visit drives an assessment of disease progression. Often two radiologists are assessing each visit independently, and the pool of radiologists can be even larger. An algorithm could automatically assess variations in radiologists selection of new lesions early in the process, so that action can be taken to mitigate any errors in the review, especially for assessments that have such a direct impact on the endpoint.

SEARCHABLE IMAGE LIBRARIES

By now, many Sponsors have amassed 20+ years of medical images that represent a trove of information that could be used to advance research and development, provided they are properly aggregated and archived. Specifically, they must be tagged, searchable, and tied to safety and endpoint data as well as pertinent medical history.

Once aggregated in a library, algorithms could be applied to these datasets to discern meaningful correlations between clinical and imaging data, giving Sponsors the ability to identify correlations that they may have otherwise missed. As an example, Sponsors could spot clinical similarities in patient subsets to explore why some cohorts did – or did not- respond to treatment. Conceivably, such an image library could also be used to find patients who would potentially be eligible for a trial.

PATIENT-SUBMITTED IMAGES

Imaging technology – as with other digitized trial components – will be able to support decentralized trials. It is entirely plausible that images will be collected directly from patients using smart phones, tablets or other devices to support use cases like monitoring of wound healing, etc. (See “Expanded Uses of Medical Imaging” for indications and applications where patient-submitted images would be suitable and advantageous.) Patients may even be able to submit images of past assessments to qualify for a trial. For example, if proof of an EKG in the past six months were needed to qualify for a trial, the patient could just upload a picture of it.

MORE SEAMLESS TRANSFERS/WORKFLOWS

Despite all of the progress mentioned, there remain some manual steps involved in preparing and sharing images. A site imaging technician, for instance, must burn a CD with the image and take it to the study coordinator who then uploads it into imaging software. This process will eventually be streamlined so that once technicians complete their scans, they simply press a button within the EDC platform to have the image automatically transferred and tagged with details of the trial, the subject, and the visit, etc. This is building toward the day when sites will be able to do all of their trial-related work within the EDC platform, removing the need to access a separate imaging tool.

Conclusion

These advances – whether newly available or still in development – are all designed to improve the drug development cycle by enhancing image and data quality, supporting patient centricity, reducing overall costs, and speeding time to market. Owing to the use of AI, the integration of systems, and the digitization of data collection, it might even be said that we're entering a golden age of imaging. Imaging assessments can be incorporated into clinical trials in a growing number of indications (often in ways that are patient-centric) as efficacy or safety endpoints without the delays and inconveniences long associated with the practice.