

A Contract Research Organization's Challenge: Validating Cutting-edge Software for Imaging in Clinical Studies

Brenda K. Young, BA, CRA

Senior Director, Clinical Operations, ACR Image Metrix, Philadelphia, Pennsylvania

Dena Flamini, RT(R)(MR)(M)

Imaging Technologist, American College of Radiology Imaging Core Laboratory, Philadelphia, Pennsylvania

James Gimpel, RT(R)(MR)

Image Analyst, American College of Radiology Imaging Core Laboratory, Philadelphia, Pennsylvania

Conducting imaging in clinical trials often involves the use of cutting-edge computer software. The computer systems featured in the medical imaging workstations used in clinical investigations must be validated prior to data collection in support of a regulatory submission. Good clinical practice (GCP) guidelines, derived from international standards adopted by the US FDA, are the benchmarks for drug and device clinical trials that may involve imaging data. Computer systems used in all FDA-regulated clinical research must be validated according to GCP standards.

The ACR Image Metrix approach to the challenge of computer system validation in two different clinical trials is described in case study format. By following strict work processes, we achieved installation qualification and performance qualification. Although we did not fully understand the complex mathematics and physics underlying the software and imaging workstations, we executed system validation by consistently focusing on standard operating procedures with the computerized system.

Key Words

Computer system validation; Imaging clinical trials; Software validation; GCP guidelines; Imaging workstation validation

Correspondence Address

Brenda K. Young, ACR Image Metrix, 1818 Market St, Suite 1600, Philadelphia, PA 19103 (email: byoung@acr-imagemetrix.net).

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INTRODUCTION

A wide array of imaging technology is incorporated into contract research organization (CRO) projects. The use of imaging as a predictive biomarker has applications in all stages of drug development. Many clinical trials rely on imaging results as an endpoint or outcome measurement. There is a role for both well-established and emerging radiologic modalities in ongoing clinical studies in several therapeutic areas (eg, oncology, cardiovascular, orthopedics, neurology). Some of the imaging studies used in clinical trials include computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography, and magnetic resonance spectroscopy (MRS). There is a need for precise imaging studies that can be tailored to evaluate specific anatomical, physiological or biochemical features of interest in a clinical research trial.

Both the FDA and the European Medicines Agency (EMA) have issued regulations and published guidance documents pertaining to the need to validate computer systems used in clinical research (1–3). Computer systems are often involved in data generation (including image

acquisition) and document management. This article describes ACR Image Metrix's experience with the validation process for two different computer systems used in clinical studies performed for pharmaceutical companies.

BACKGROUND

"Guidance for Industry: Computerized Systems Used in Clinical Investigations" is an FDA publication that applies to electronic systems containing any data used to support a marketing application (3). Essentially, electronic source data must meet the same fundamental elements of quality as paper data. Thus, it must be attributable, legible, contemporaneous, original, and accurate (4). All computerized data used to support a marketing application are subject to strict regulatory criteria prior to acceptance. The particular requirements that apply to imaging workstations used in clinical studies are as follows(5):

- The system design satisfies its assigned processes in the study protocol.
- Standard operating procedures (SOPs) and procedural controls are in place.

- The system maintains accurate source documentation.
- Internal security measures are activated.
- External security (eg, access restrictions and cyberprotection) tools are activated.
- System and access controls are functional.
- The system is available for audit or inspection.
- Personnel who use the system have been adequately trained.

The *Code of Federal Regulations*, 21 CFR 11, stipulates that good clinical practice (GCP) principles require independent review of a computerized system. The extent of validation necessary is based upon the system's risk of compromising data integrity, authenticity, or confidentiality (4). Hence, systems with higher risk require more validation than systems with lower risk. When dealing with medical imaging workstations, the preservation of data integrity mandates that the original images are unaffected (in no way altered or enhanced) throughout the imaging process. An imaging CRO can greatly increase the likelihood of data authenticity through real-time image transmission from the acquisition site to the imaging core laboratory for centralized image collection.

A computerized system is composed of hardware, software, and SOPs. The system must satisfy the processes it has been assigned. For example, in an imaging clinical study, the software must display image data and manipulate (ie, reorient) images without altering them.

Guided by quality system regulations (21 CFR 820), device manufacturers must meet FDA software development validation requirements (6,7). The literature contains numerous examples of computer system validation for clinical or laboratory data management, adverse event reporting, and safety programs. However, little has been written about validating imaging applications and workstations used to generate data for a clinical trial.

Commercial off-the-shelf software (COTS) requires validation to meet GCP requirements. While testing and verification of COTS is the software vendor's responsibility, the CRO industry standard is to ensure validation for each

clinical trial. Hence, COTS must be installed on appropriate hardware, featuring access controls and adequate system security. This is known as installation qualification. The computerized system must also accommodate the work process involved at a particular workstation. This is known as performance qualification. The following two case studies describe our experience in the validation process for two different computer systems subsequently utilized in clinical studies:

- NUTS: Commercial software program that uses cutting-edge imaging technology to quantify tissue chemical composition and plot the data as a line graph (Acorn NMR, Livermore, CA).
- Computer-aided detection (CAD): An imaging workstation used in virtual reconstruction of the colon with integrated CAD software that highlights a region of interest.

METHODS AND RESULTS FOR NUTS

The FDA helped delineate a role for MRS in a clinical trial for a lipid-lowering agent with the potential adverse effect of increasing liver fat levels. At the pre-Investigational New Drug meeting, the FDA cited an article from the *American Journal of Physiology, Endocrinology, and Metabolism* in which MRS was used to measure hepatic fat via NUTS nuclear magnetic resonance (NMR) data analysis software (8). The sponsor thus agreed to measure hepatic fat in trial participants with MRS using NUTS for processing and displaying NMR data.

Providing a measure of organ biochemistry, MRS data is plotted as a line graph. MRS capabilities range from display of a basic biochemical spectrum with integration and peak listing to complete structural analysis and interpretation. The most commonly used nuclei are ^1H (proton), but ^{31}P , ^{19}F , and ^{13}C can also be studied. ^1H -MRS is easier to perform than other spectroscopic techniques and provides high signal-to-noise ratio. In the imaging core laboratory, ^1H -MRS follows conventional MRI.

NUTS graphically shows the prevalence of chemical compounds resonated by MRI, which emits radio waves directed at protons in the

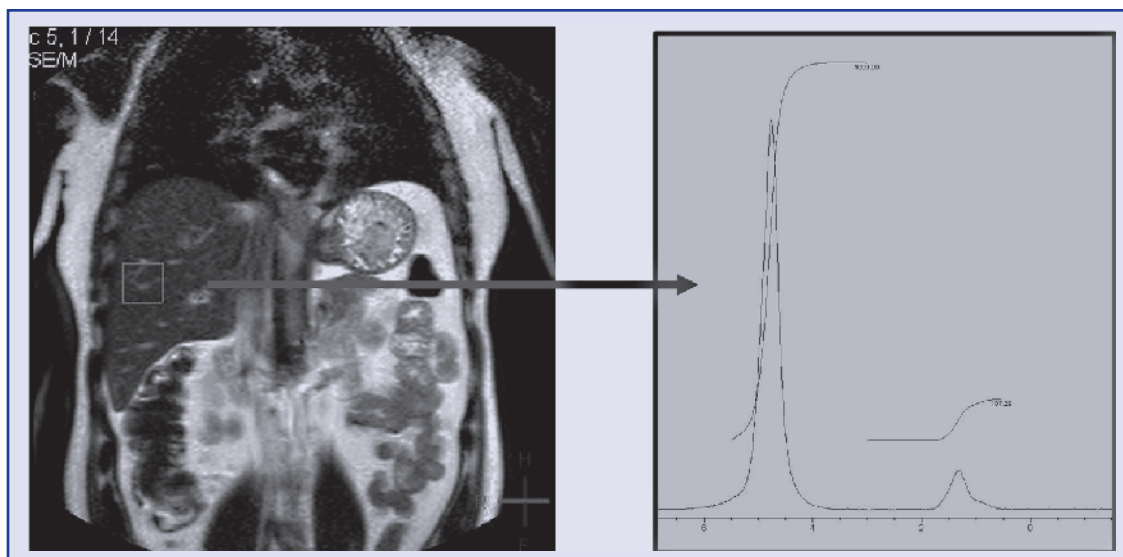


FIGURE 1

Hepatic water and fat composition quantified by NUTS.

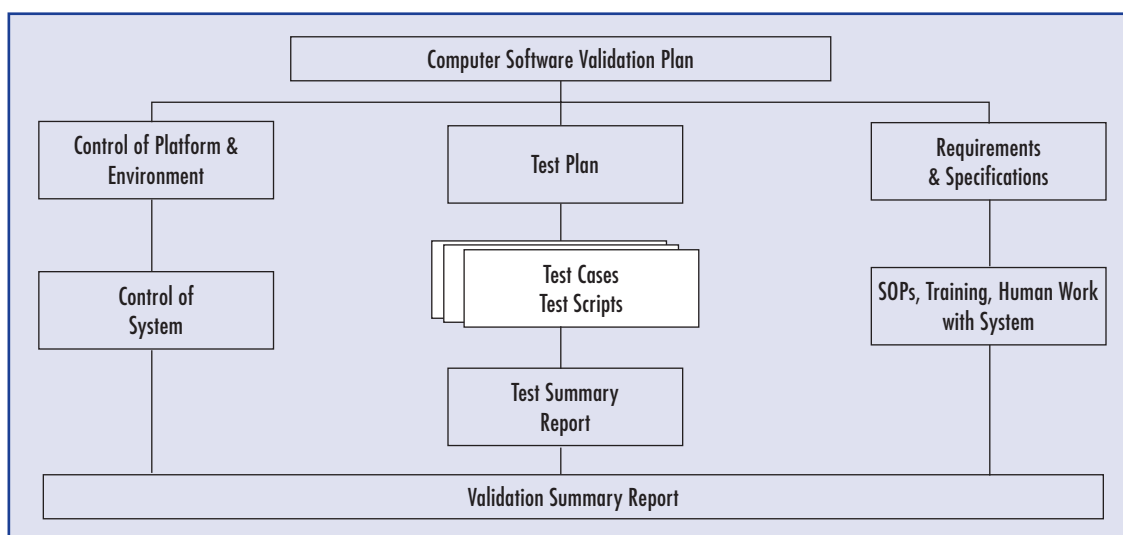


FIGURE 2

Computer system validation schematic.

body area under study. Because protons are most abundant in water molecules, MRI reveals differences in water content between various body tissues. MRS uses spectral graphs to show the prevalence of chemical compounds in tissue. In this trial, MRS was used to measure liver fat relative to water. NUTS software converts MRS data into a spectral display (Figure 1).

Our challenge was how to validate NUTS, an example of a COTS. To meet that challenge, we developed a computer system validation plan (CSVP), which encompassed three primary divisions: workstation and environmental control, software testing, and work process requirements (Figure 2). The CSVP also outlined team roles, SOPs, and a validation timeline.

When COTS is installed on appropriate hardware, featuring access controls and adequate system security, installation qualification is achieved. NUTS software was installed on a Windows PC workstation with restricted access and appropriate cyberprotection in our imaging core laboratory. By controlling the system (hardware), platform (workstation), and environment (imaging core laboratory), we met the federal requirements for installation qualification.

Similarly, we followed the CSVP to achieve performance qualification. When a computer system satisfies the work process involved at a particular workstation, performance qualification is met. We ensured performance qualification by conducting numerous test cases and

FIGURE 3

General example of NUTS performance qualification.

Instrumentation Software Functionality
TC2.TS1 – Import data from the magnetic resonance spectroscopy raw data file.
TC2.TS2 – Execute spectral processing commands.
TC2.TS3 – Perform quantification from the processed spectrum.

test scripts and making process adjustments whenever necessary. While emulating normal tasks expected of the system, these trial runs evaluated the functionality of both the workstation (platform) and the software.

For performance qualification, we also developed and outlined expectations (ie, requirements and specifications) for the system. These included SOPs featuring instructions on how to utilize MRS and NUTS to measure liver fat percentage. We relied on the methodology of Szczepaniak and colleagues (8) to quantify hepatic fat based on MRS data and NUTS. We outlined user requirements to conduct the test cases and test scripts. The *NUTS Data Analysis Software User Manual* provided additional information.

After validating the NUTS software, we quantified the hepatic fat percentage for each participant at five different time points during the clinical trial. Our functional process (Figure 3) can be summarized as follows:

- Test data are imported from the MRI.
- MRI images are processed using NUTS software.
- NUTS test data results are compared to the same data from a SIEMENS Syngo MRS device.
- The difference in test data between the two machines is calculated.
- A $\pm 4\%$ margin of error is acceptable, due to potential human error (ie, physical interaction with the software).

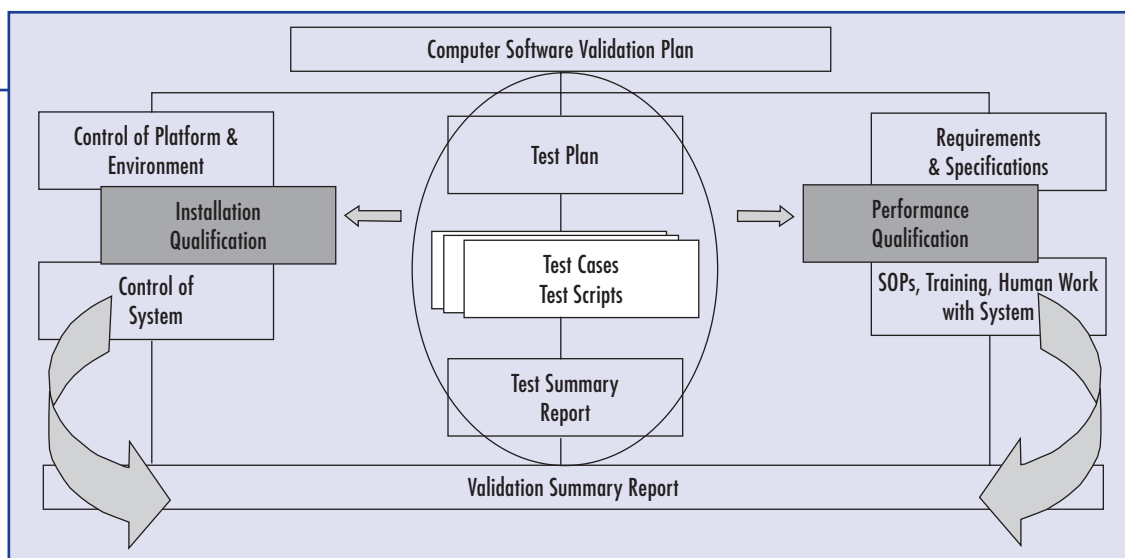
By following the CSVP, we met GCP regulatory requirements for both installation qualification and performance qualification (Figure 4). Once the CSVP was fulfilled, we produced a validation summary report, detailing the steps taken to achieve qualification of both system installation and performance. Per federal guidelines, this report was approved by management prior to using the system to obtain data in support of a regulated clinical trial.

METHODS AND RESULTS FOR CAD

In this case, the CAD algorithm was integrated into a CT virtual colonography workstation. Working in concert with advanced visualization hardware and software, CAD technology incorporates image processing, pattern recognition, and artificial intelligence. We were charged with running a large multicenter, multireader study evaluating over 200 virtual colonography cases. The interpretations of several radiologists

FIGURE 4

Schematic of an executed validation plan.



were compared to the “truth,” as determined by an expert panel, and analyzed statistically.

CAD devices incorporate pattern recognition and data analysis to direct the reader’s attention to suspicious areas. CAD technology relies on algorithms that combine values, measurements, or anatomical features extracted from the radiological images. Based on these algorithms, CAD devices highlight potentially abnormal findings (eg, colonic polyps in our study) warranting further evaluation by a radiologist (9). As computerized systems, CAD devices must undergo the aforementioned validation process. Similar to our experience with NUTS, we developed a CSVP for the CAD system.

As previously discussed, federal guidelines for computer system validation encompass qualification of both installation and performance. Installation qualification requires reliable hardware, featuring adequate access controls and system security. With the CAD software, we presumed that appropriate development practices, per FDA guidelines for device manufacturers, had been followed. Hence, our validation concerns began with other aspects of installation qualification (ie, control of the platform and environment). The reading workstations resided in our imaging core laboratory. By controlling the system (hardware), platform (workstations), and environment (imaging core laboratory), we achieved installation qualification.

Next, we addressed the challenge of performance qualification. To this end, our CSVP included a test plan, requirements, specifications, and SOPs (ie, a work process). The main challenge was developing SOPs for radiological interpretation using CAD software. This work process had to address reader interaction with three elements: the workstation, the workstation software, and the CAD software. We created a reader study guide, which also served as an instruction manual for performance qualification testing.

The test plan included a dedicated training workstation that enabled simulation of the work process for participating technicians and radiologists (Figure 5). The test cases and test

scripts endured a simulated work process, which included image interpretation by participating radiologists.

The CSVP for this study had several requirements and specifications. The requirements included functions the workstation and CAD software executed at the radiologist’s discretion. The command icons were tested to ensure they worked as expected. The reader study guide delineated the step-by-step process necessary to navigate through both the workstation software and CAD software. The radiologists (readers) measured the polyps they found and captured a screen shot of the findings. Ensuring the reliability and reproducibility of this step was a critical aspect of our performance qualification testing.

Workstation specifications included configurable viewing between various anatomical views (ie, 2D/3D, prone/supine, and axial/coronal/sagittal). Additionally, the virtual colon was presented in both prone and supine views.

Furthermore, the CAD function had to meet several specifications. When performing properly, CAD highlighted suspicious findings in blue (Figure 6). The radiologist’s paradigm required image interpretation both with and without CAD. Thus, manual engagement of CAD (ie, the ability to turn it on and off) required verification.

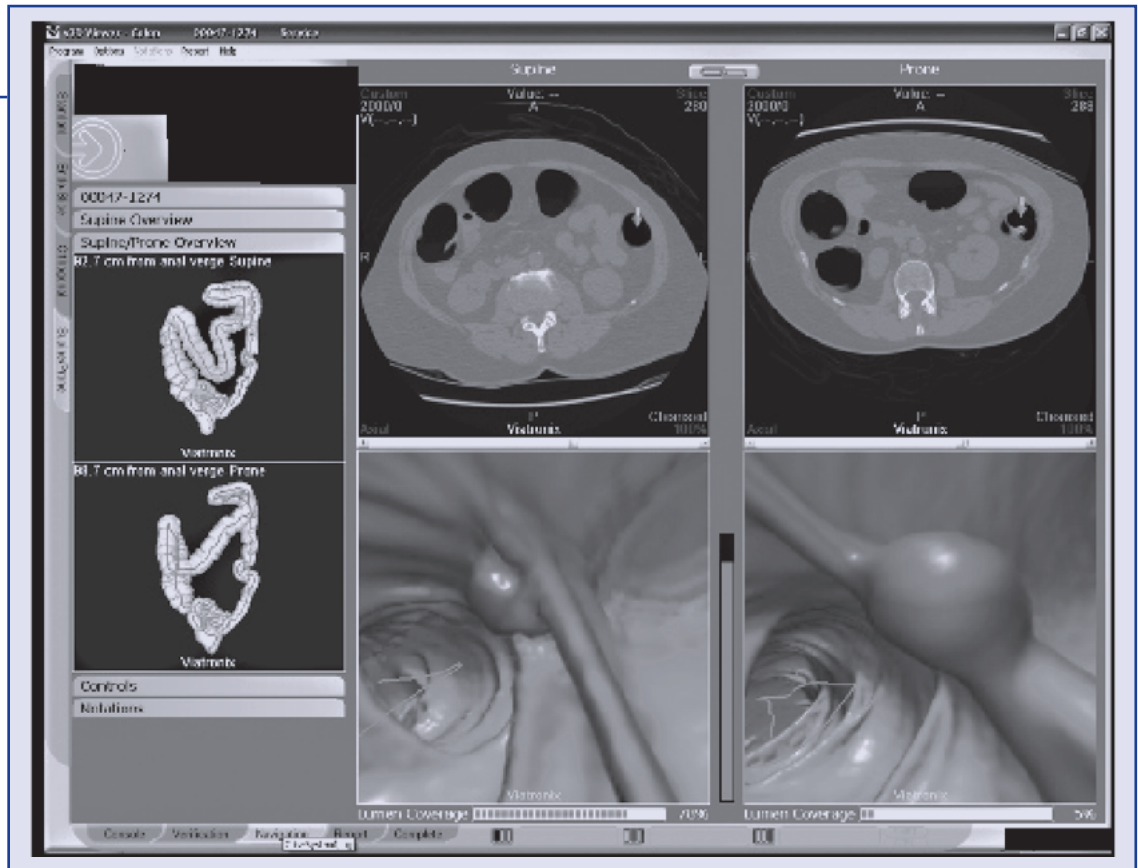
Once all of these issues were addressed, we obtained the necessary testing documentation and executed the performance qualification of the CAD software and workstation. By following the CSVP, we met GCP regulatory requirements for computer system validation. Once the CSVP was fulfilled, a validation summary report was produced and approved by management. Thereafter, the system was approved to obtain data in support of the CAD/CT colonography clinical trial.

DISCUSSION

Software validation can start with output from an approved device only when using specific output measures approved (validated) by the FDA. If we assume that MRS hepatic fat measurement was not validated by the FDA, then we

FIGURE 5

Representative view of a CAD virtual colonography workstation.



relied on an unapproved output from the device in our validation of NUTS software. This would mean that our experience with NUTS cannot be universally applied to any device or software validation.

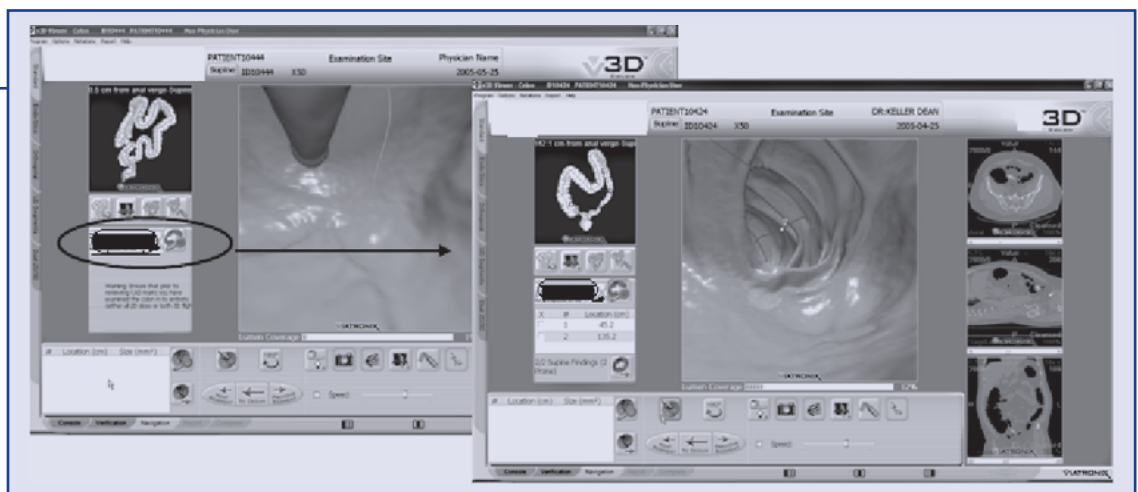
However, the study performed by Szczepaniak et al. (8) proved that MRS was a reliable instrument for measuring hepatic fat content. This large study (>2,000 patients) validated the re-

producibility of hepatic MRS, found to have highly correlated duplicate measurements with a low coefficient of variation. Such findings would suggest our validation of NUTS software did not depend on an unreliable output measure.

Regarding the CAD software, we assumed that it had been developed per FDA guidelines for appropriate software development practices (21

FIGURE 6

CAD highlights region of interest in blue.



CFR Part 820 Quality System Regulation). Hence, we overlooked primary validation of the CAD software, jumping ahead to other aspects of installation qualification (ie, control of the platform and environment).

CONCLUSION

As practitioners involved directly in clinical operations in the imaging core laboratory, we often assume our responsibility for reliable data starts once we receive the image. On a day-to-day basis, we rarely think about the rigorous process involved in validating the computerized systems we rely on for data acquisition, analysis, and archiving. However, a strict adherence to SOPs enabled us to achieve validation in these two case studies.

Overcoming numerous challenges, we achieved computer system validation for two novel imaging software programs used in clinical studies: NUTS and CAD. We followed a methodical CSVP in pursuit of installation qualification and performance qualification, the two key aspects of validation.

In our experience, performance qualification was more difficult to achieve than installation qualification. Understanding the work process that testing simulates was integral to executing performance qualification. While we did not fully comprehend the complex mathematics and physics underlying the software and workstation, we understood the SOPs involved with the computerized system. Ultimately, computer system validation in clinical trials is possible only when a standardized work process has been used to test the technology.

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The authors report no relevant relationships to disclose.

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