Advanced Clinical

WHITE PAPER

Defining the Computer Systems Validation (CSV) Lifecycle: Four Foundational Components Supporting Your Clinical Trials

Introduction

Today's technology continues to accelerate. The proliferation of handhelds, wearables and cloud-based services permeate our lives and places of business. As the affordability and adaptability of electronic means of communication, data sharing and distribution become ubiquitous, individuals and businesses often forget about the ramifications of data integrity and privacy in the name of speed and access.

For the life sciences industry, the embrace of electronic solutions is nothing new. Electronic systems that create, house and report data as it relates to clinical trials have been around for over 20 years. In fact, biopharmaceutical companies in the business of designing and managing clinical trials to prove the safety and efficacy of a new, investigational product would prefer to operate in a paperless environment, as these systems are easily available, paperless, scalable, and enable streamlined New Drug Applications to the FDA.

The rationale behind this is warranted by the simple fact that electronic means by which a clinical trial is managed provide limiting human intervention and therefore fewer mistakes. In theory, this rationale makes sense. Why trust every step of a clinical trial to an error-prone human when you can operate an agnostic, repetitive, electronic system that can scale to handle thousands of data points and users? We then begin to assume that if we use electronic systems to replace humans in managing clinical trial data, risk or error is removed. Surely an electronic system will not lose or alter data or rarely miscalculate outcomes? Hardly. Remember these systems are built and maintained by humans themselves. Their seemingly agnostic aura is not so agnostic. Human personnel operating within a clinical trial must be qualified and trained to perform their job. This is managed through a company's Quality Management System: a methodical, rational, logical, and prescriptive set of procedures and instructions that force the operator to perform tasks in a repetitive fashion, often with "quality" built into the process(es).

Since software systems are not humans, a similar set of expectations are applied to systems. Luckily, regulatory authorities like the FDA and international standards groups like ISO have created codified sets of rules and laws that form the baseline for how companies will use systems. Risk, intended use, validation and change control are among the key attributes of systems that lay out the foundation for validating, maintaining, and controlling systems that support clinical trials.

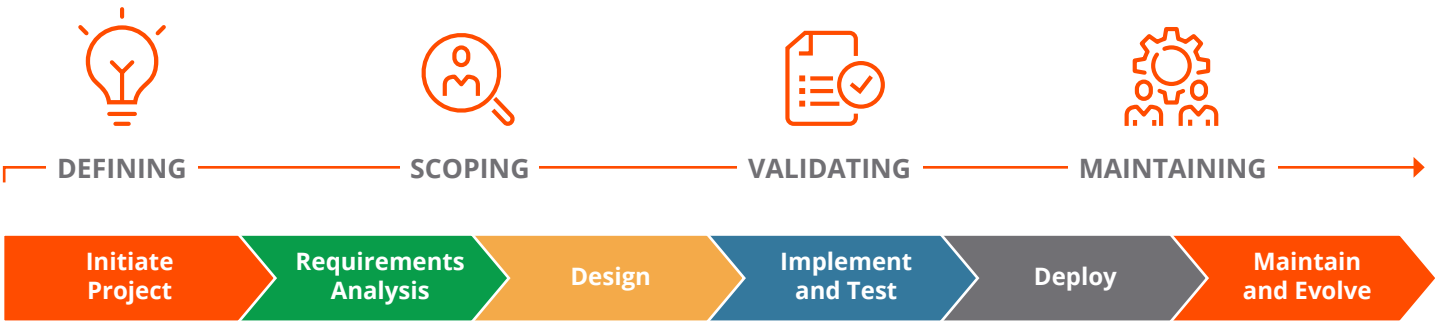
The collative sphere in which these things live and operate supports Computer Systems Validation (CSV) activities. This is a holistic lifecycle that provides controls and evidence that systems in use during clinical trials are working as intended, as demonstrated through documented validation and management processes. Validation of computer systems ensures accuracy, reliability, consistent intended performance, the ability to discern invalid or altered records, and a critical requirement of electronic record compliance, as described in the FDA 21 CFR 11.10(a) and EMA Annex 11, Section 4.

The four areas that encompass proper CSV include **DEFINING, SCOPING, VALIDATING,** and **MAINTAINING**. Let's take a closer look at how these four areas define the overall CSV lifecycle.

Part 1: Defining a Way to Validate Software

The first step in validation is foundational. CSV should be broken down into categories that answer the questions of *why, what, when, who* and *how*. Typically, having a set of controlled documents that will define and answer the questions noted above provides a lasting foundation that forces the business to be repetitive and maintain control over each and every system and its validation projects.

The FDA, EMA and other global regulatory agencies will audit companies that submit an NDA for approval and release to the marketplace. With this activity comes the responsibility of that company to demonstrate control over their systems and thus their data, and the safety of patients who were enrolled in their clinical trials. Having control of people, processes and the technology allows pharma and biotech companies to operate their business in a controlled and safe manner. As with anything else, nothing is perfect, but by defining and controlling the intent and execution of software validation, companies will minimize error, deviations and adulteration of data and product.



Part 2: Scoping the Level of Validation Needed

One-size-fits-all is not the way CSV should be administered for all systems. Depending on the size, complexity and intended use of that system, a certain scope or level of CSV rigor should be applied to the validation of that system. The FDA and industry standards organizations like ISO and ISPE endorse and describe the use of a risk-based methodology that drives the scope of validation and intended use for any system inclusive of Standard 13485 and GAMP 5 respectively. Couple that with the need to assess the system for applicability of 21 CFR Part 11, Annex 11, HIPAA, etc. Additionally, identification of the type of system will be required, which also drives the scope of validation rigor. Most systems are either Off the Shelf (OTS), Configured Off the Shelf (COTS), or Bespoke. One may end up with a highly complex and regulated system that must be thoroughly validated. Activities inclusive of requirements gathering, project, validation and test planning are common processes that manifest themselves in documents that provide objective proof that a system has been validated for its intended use. Conversely, OTS systems that operate in a plug-and-play fashion may require a minimum set of documentation and validation, since there are no customizations or major configurations that add to the complexity and risk of the system. A multifaceted, repeatable scoping exercise must be done for all new systems. The outcome of those assessments will ultimately dictate the type and rigor of validation needed.

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Part 3: Validating a Solution

The validation of a solution requires a stable, repeatable process driven by a solid risk and system assessment. The validation of a solution then requires that a prescribed Software Development Lifecycle (SDLC) be followed. This is the “how” part of software validation. By having a documented SDLC that is tailored to the outcome of the risk and system assessment, organizations can cleanly build and execute a documented validation strategy with trained staff and value-added tools. At this stage, the organization will determine who will drive and complete the validation project.

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It is imperative that organizations leverage trained staff to execute all activities within the SDLC. Creating minimum deliverables like a Validation Plan (roadmap), Installation Plans (IQs), Functional coding and Testing Plans/artifacts (OQs), Test Plans and Protocols (PQs) and finally a Trace Matrix and Validation Report (attestation of built, functions and performs as intended by the organization).

Other documents, case-dependent, may be created. Of course, these documents serve two purposes:

- First, they are manifestations of actions and processes demonstrating due diligence for a software system from an "as intended" perspective.
- These are "audit-ready" deliverables that should be reviewed, approved, and controlled in a logical fashion.

These sets of documents should serve as stand-alone artifacts that can "tell the tale" of validation with minimal support from operational staff.

Part 4: Maintaining a Validated State

One of the most difficult aspects of CSV is maintaining a validated state. Systems Validation may be a finite activity as it occurs "per release," but is perpetual in its nature to preserve the system's validated state so long as an organization actively uses it to support clinical trials. However, a solution can have dozens of releases within one calendar year. Something as simple as adding a field in a database to capturing additional patient information like age or gender can kick off dozens of hours of operations work to update specifications, verify, validate, confirm, and document the change. This may also include testing and training by and of end users, the need for new hardware, and potentially increased IT Helpdesk-type support. Organizations should have processes in place to handle changes to their systems via bug fixes or upgrades. The SLDC process should guide the organization through all the necessary workflow changes that take the system from its existing state to its new state. Operational work and processes should once again manifest themselves in stand-alone, audit-ready documentation that demonstrates control over people, processes and technology.

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Conclusion

Building a Solid Csv Foundation Will Improve Execution and Efficiency

Do you think your organization is ready for an inspection? Are you comfortable with your IT people, processes and documentation? Here are some key questions you should consider when assessing your organization from a CSV perspective:

- Does your organization's Quality Management System define an SDLC and/or CSV process?
- Do you have trained, capable IT staff that can not only validate a system based on its intended use but maintain it as well?
- Does your organization have a controlled, repeatable SDLC process?
- When validating software, does your organization logically collect approved CSV deliverables that are audit ready?
- Does your organization consistently consider existing and new regulations and incorporate them into the SLDC process?
- Does your organization understand the need and value of Change Management? How well is it practiced and supported?
- If you have systems and processes in place, are you equipped to handle existing audit findings and Corrective and Preventative Action (CAPA)?

If you are unsure of the responses to any of the above statements, then it may be time to revisit your CSV strategy so that you are able to meet your business objectives using people, processes and technology that are fully compliant, risk-averse and efficient.