Validation of e-clinical trial systems

E-trials are here to stay. **Rob King and Dr Michael Bowden** explain why the validation of such trials is a must-do job.

When the US Food & Drug Administration (FDA) posted regulations for electronic records and signatures in the Federal Register on 20 March 1997, the idea of a broad-based software solution for e-trial management was as elusive as wireless electronic data collection at the investigational site is today. The situation has changed rapidly. Open any industry publication and a glance at the myriad of advertisements promoting e-trial software confirms that we are in the midst of a revolution in the availability of software solutions for data capture and clinical data management tailored specifically to our industry. Of course, we still have to remind ourselves that more than 90% of trials are still conducted with first century support from stylus and paper. But we cannot ignore the fact that e-trials are here to stay and that they promise to deliver many of the efficiencies that we have all desired for so long.

If you have not yet participated in an e-trial, you soon will.

Background

As with any fundamental change in an industry or use of new technology, government agencies, professional associations and internal and external customers inevitably propose new regulations, guidance and expectations. Just in the last four months, eight countries have proposed or enacted new legislation concerning general use of electronic signatures and records.

In this whirl of electronic activity, the most common question related to e-trials is – is your system validated? In the USA, it all started for clinical trial professionals when the now infamous 'Part 11' took effect on 20 August 1997. The new regulation seemed harmless at first glance. The actual regulation is barely two pages long. A slight throbbing at

your temple starts to develop as you realise that the preceding 34 pages are comments on those two pages of regulation. The *coup-de-grâce* is a simple and direct statement in the regulation that reads '…such procedures and controls shall include the following: Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.'

Validation, verification and testing

Validation is commonly defined as 'does the system do what it was designed to do?' It sounds simple enough. But things are not always as they appear.

The FDA defines validation in their Glossary of Computerised System and Software Development Terminology as:

'Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes'.

The FDA also states in their guidance documents that validation is considered an umbrella term encompassing the processes of verification and testing (VV&T – validation, verification and testing).

The FDA's Glossary of Computerised System and Software Development Terminology lists several standards that the glossary references. These standards include IEEE (The Institute of Electrical and Electronics Engineers, Inc), Federal Information Processing Standards (FIPS), National Bureau of Standards (NSB), and International Electrotechnical Commission.

Let us, for a moment, step outside the FDA and look at the definition provided by the IEEE in their Standard Glossary of Software Engineering Terminology. Validation is defined as:

'The process of evaluating a system or component during or at the end of the development process to determine whether it satisfies specified requirements'.

Depending upon who assesses your system, it can be declared compliant or non-compliant.

The IEEE then notes that validation should be contrasted with verification. Verification is defined as:

'1. The process of evaluating a system or component to determine whether the products of a given development phase satisfy the conditions imposed at the start of that phase.
2. Formal proof of program correctness'.

These are then combined (verification and validation, V&V) and defined as:

'The process of determining whether the requirements for a system or component are complete and correct, the products of each development phase fulfil the requirements or conditions imposed by the previous phase, and the final system or component complies with specified requirements'.

Finally, testing is defined by IEEE as:

'1. The process of operating a system or component under specified conditions, observing or recording the results, and making an evaluation of some aspect of the system or component.
2. The process of analysing a software item to detect the differences between existing and required conditions, ie. bugs, and to evaluate the features of the software items'.

As you can see that simple statement in Part 11 and our simple definition of validation, 'does the system do what it was designed to do?', has taken on a level of complexity. The definition has now expanded based upon the attributes noted above to include:

- Validation must be documented;
- Validation requires pre-determined specifications and attributes;
- Validation as a process assumes that any development is also a formal process;
- Validation includes a formal verification process;
- Verification includes testing that documents expected and actual results;
- Validation assumes a system will not be released for use unless it has met the pre-determined specifications.

So back to the question – is your system validated? Unfortunately, the answer to that question is very similar to the concept that 'beauty is in the eye of the beholder'. Depending upon who assesses your system, it can be declared compliant or non-compliant. Professional organisations such as IEEE and ISO (International Organisation for Standardisation) and government agencies such as the United States Department of Defence have developed standards that can be referenced, but in our industry no 'gold standard' for validation has yet emerged.

Conduct the validation of your system in a manner similar to the conduct of a well-run clinical trial.

For those of us in the industry who are not engineers or information technology professionals, these standards may appear overwhelming and in some cases irrelevant to our particular system. With this in mind, the following advice is offered to assist you in your evolution to a validated e-trial system:

- Conduct the validation of your system in a manner similar to the conduct of a well-run clinical trial. First – document, document, document. The cardinal rule applies here also – if you do not have written documentation, then it was not done. As you would in designing a study, prepare a well-thought out plan for how you will validate, verify and test (VV&T) your system.
- Make the plan a formal document and consider it your 'protocol' for validation. In your protocol, define the background of the system and give detailed methodology for the VV&T, define your hypotheses (expectations/specifications) and

how you will test/analyse your hypotheses. Identify your validation team, their roles and the resources to conduct the validation. Do not proceed to the next step in your process without documented approval from responsible parties.

- During the validation process, have tools in place to measure and track your progress and whether the system is meeting your pre-defined specifications. If something is not working, fix it and document how you did it and that it now works. Just as you should have a clear audit trail of data in a clinical trial, the specifications in the system should be traceable as well.

At the end, you should have a history file of all the effort and results of your validation just as you would a study master file. Archive your history file and keep it for as long as you keep any study documentation for any trials conducted with the system.

If you are still worried that your system has not been fully validated and documented, draft a plan of how you will address it and improve your validation process. Due diligence goes a long way towards assuring others that you made your best effort.

As e-trials become more widespread, industry knowledge of validation will evolve and will be more widely disseminated in terms that we can all understand. The FDA is rumoured to publish guidance on validation any day now, followed by guidance on time stamps and audit trails.

So when the question is asked – is your system validated? Help is out there, more is on the way, and if you can design trials to test wondrous, new drugs and devices, you can utilise some of those same skills to successfully validate your e-trial systems.

Authors

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