Perfecting Practices

Workflow-based technology coupled with executive authoritative power, encourages process optimisation in the clinical trial continuum, helping to break down silos, enhance operational performance, and ensure quality in the electronic trial master file

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Over the past decade, the focus on technology as a driver of performance improvement in clinical trials has been intense (1-2). This is particularly true for study start-up, a widely recognised bottleneck encompassing the activities associated with site identification, feasibility assessment, selection, and activation required before the first patient can be enrolled in a study.

Practices intended to streamline study start-up timelines include the use of technology investments to expedite the collection of clinical data and to help sponsors/CROs better monitor clinical trial performance, but, despite many attempts at improvement within organisations, gains in end-to-end cycle time have not been made (3).

A comprehensive survey conducted by the Tufts Center for the Study of Drug Development determined that a mere 8% of sponsors and 14% of CROs are extremely satisfied with their study start-up processes (4). By comparison, approximately 40% are either somewhat or completely unsatisfied with those methods. Respondents reporting that they are extremely satisfied have cycle times 57.5% shorter than those claiming to be completely unsatisfied.

Unsurprisingly, CROs investment in technology is outpacing that of sponsors, as the outsourcing of clinical trials continues to gain steam (5). Overall, 80% of organisations that have invested in technology report time savings, with respondents reporting 30% shorter cycle times over those with inadequate technologies.

However, despite technology remaining critical, it may be only part of the solution as emphasis shifts to process optimisation. Stakeholders have learned that point solutions can hinder the flow of data across the continuum, causing already entrenched silos to dig in further. The need to focus on the overall process – instead of marginal improvements – should resonate with stakeholders responsible for study start-up management.

Fortunately, technology provides more than just an opportunity to automate processes, but a chance to rethink the inefficiencies of silos. Some stakeholders want to move away from vertical silos and think horizontally. This method uses automation and workflows to integrate operational data across all functions, making extracting meaningful insights from those data easier, and, more importantly, offers significant reductions in overall study cycle times.

An end-to-end solution with workflows that aggregate data from disparate sources can draft documents in the correct format from the start and release them downstream into the electronic trial master file (eTMF). This approach can break down silos that have long-performed in isolation with little understanding of what the next department needs to fulfil its regulatory obligations and achieve targets measured by performance metrics.

The importance of this change being driven by upper management cannot be overstated. Executive buy-in provides the critical impetus and strategic insight to align with the organisation's goals for quicker development of better therapies. Without this direction, efforts to jump-start overall performance optimisation tend to flounder as departments retreat to their silos.

In short, tools, although essential, do not create a master craftsman. This comes from combining experience with the authority and talent to influence how studies are conducted from an operational perspective. Research suggests that organisational issues become strategic and of interest to upper management once they believe it has relevance to performance (6).

Specifically, purpose-built workflow-based study start-up solutions can identify the documents needed to conform to downstream regulatory requirements and can also signal bottlenecks or breakdowns in study execution. This approach helps to avoid rework, delays, and cost overruns; improves cycle times; and facilitates audit-readiness.

A seminal report from the Institute of Medicine confronted the need to improve the clinical trial process head on by encouraging process transformation through quality improvement efforts, stating that process change rooted in technology should be embraced through the following suggestions (7-8):

- Undertake 'creative destruction' of old clinical trial business models in favour of newer business models that complement advances in technology
- Apply technologies, such as web-based clinical trials and smartphones, in place of outmoded mechanisms
- Engage in more strategic planning and consider new organisational structures for entities conducting clinical trials

Since this report, process improvement has emerged as a hot button issue as evidenced by the expanding volume of literature. For example, some articles confirm the widely acknowledged

challenges linked to contract and budget negotiations as a particularly rate-limiting step in study start-up. Martinez *et al* found those tasks to be the most time-consuming part of the study activation process and widely variable in duration due to lack of standardised processes (9). Using a simulation model, they determined that increasing the efficiency of contract and budget development would reduce activation time by 28%. Other articles describe the need for an organised six sigma approach to better study start-up processes, whereby steps are carefully defined and continuous improvement becomes standard practice (10).

While the industry tries to actively implement processes that improve study start-up quality, regulatory efforts may be the necessary driving force.

The ICH-GCP E6 (R2) guideline, the first renewed Good Clinical Practice guideline in 20 years, includes a new section focussed exclusively on risk-based quality management (11). It states that the sponsor should implement a system to manage quality from the start and throughout all stages of the trial process. This section addresses topics such as critical process and data identification followed by sub-sections focussed on risk factors, namely risk identification, risk evaluation, and risk control.

In essence, the guideline acknowledges that technology has advanced to the point that it can support processes and generate data that provide actionable insights into risks and study bottlenecks. One example is the use of an application programme interface, which makes integrating cloud-based solutions possible, such as electronic data capture and the clinical trial management system, optimising the flow of data across the clinical trial continuum, eventually releasing them into the eTMF. Unfortunately, entrenched siloes have long stymied these efforts, resulting in various stakeholders having minimal understanding of what is needed downstream, leading to an inefficient assembly-line process from one department to the next.

This awkward management style is one of the root causes of problems with the eTMF. Typically, information about the standardised taxonomy and metadata provided in the TMF Reference Model is not shared with study start-up team members, leaving them frequently unaware of which documents are needed or the required format for release into the eTMF (12). This creates challenges for the regulatory group tasked with mapping documents to the eTMF, as well as indexing the metadata, as start-up generates almost half of the TMF artefacts.

Fortunately, with the help of technology, the opportunity to rethink the inefficiencies of siloes is garnering attention. This refers to using automation and workflows to integrate operational data across all functions, making extracting meaningful insights from those data easier (13). Some believe that bringing interdependent functions together with the help of technology and critical teams will help navigate the highly complicated global regulatory maze.

Optimising study conduct starts with embracing a workflow-based process that defines the documents needed for study start-up. This method boosts quality by preparing documents that are accurate, complete, and conform to the eTMF format established by a sponsor's or CRO's regulatory team, enhancing audit readiness.

The START 2 study on start-up process highlights how sponsors and CROs profess a strong need for improvement. Both had lengthy site start-up cycle times in the range of four months for CROs for repeat investigative sites as compared to five months for sponsors, with new sites having even longer times.

Numerous factors can adversely impact study start-up and its efficiency in an industry plagued by rising development costs and increasing complexities (15). Complex protocols (leading to increased difficulty in finding patients who meet the inclusion/exclusion criteria); protocol amendments; competition for sites, contract, and budget negotiations; regulatory changes; and compliance for global studies, IRB approvals, PI, and CRA turnover, among others, contribute to significant trial delays (16-20).

Given these statistics and inherent bottlenecks, a workflow-based tool that facilitates quality efforts is a sensible option. The tools integrated data from several eClinical solutions provides an end-to-end continuum that allows properly formatted documents and structured artefacts to flow into the eTMF. With the help of this tool, documents eventually needed for the eTMF can be defined upfront, during study start-up. This is a major advantage because, within those documents, often more than 400 draft and supporting artefacts can be structured, resulting in a final set of approximated 60 artefacts that will be released into the eTMF.

As clinical trial stakeholders ramp up efforts to optimise the study start-up process and begin the arduous task of dismantling siloes, recognition is growing that technology is a critical component. Without it, sponsors and CROs will continue to experience the measurable ramifications of poor quality, namely delays, cost overruns, poor communication among study teams, and lack of preparedness for audits. These problems can be avoided with the expanded use of workflow-based tools and performance metrics. For example, despite the presence of many point solutions, eight months remains the average timeframe for moving from pre-visit to site initiation (21).

With proactive planning supported by integration of information from disparate data sources, issues will be identified earlier, rather than when they reach the eTMF. Currently, regulatory metrics derived from documents arriving in the eTMF are developed too late to provide proactive insight and allow for timely interventions in study execution. In contrast, with a real-time workflow tool, insight from performance metrics can offer the transparency needed to take action in real time. By embracing this approach, complemented by support from key

decision makers, it is possible to move the needle on process change and increase the likelihood of more predictable cycle times, better adherence to study budgets, and audit readiness.

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About the author

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