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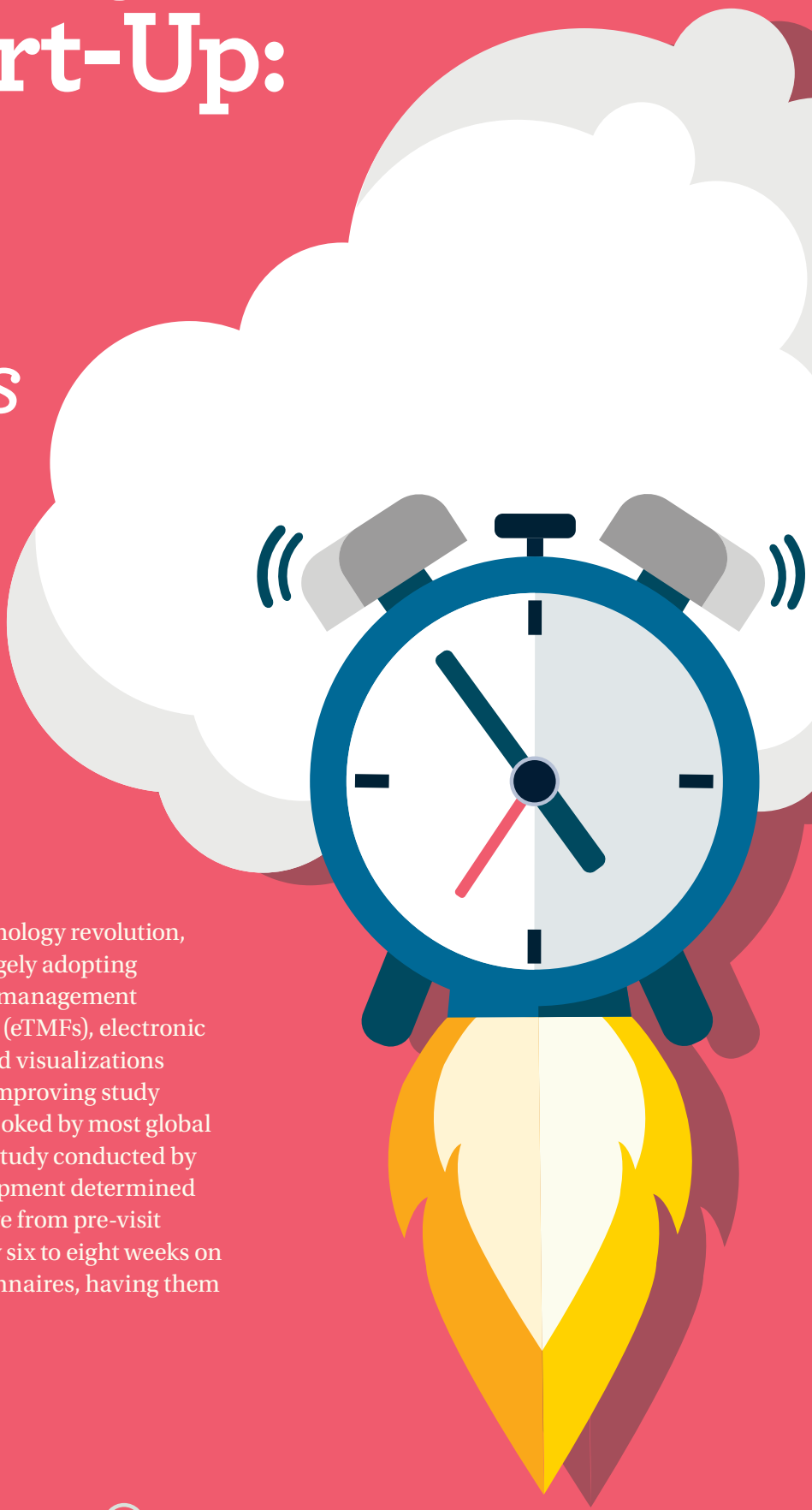
Accelerating Study Start-Up: *The Key to Avoiding Trial Delays*



PEER REVIEWED

Priya Temkar, MSc

In the midst of the current clinical trial technology revolution, although stakeholders in the industry are largely adopting various tools and platforms like clinical trial management systems (CTMSs), electronic trial master files (eTMFs), electronic data capture (EDC), and various analytics and visualizations to aid with ongoing trials, opportunities for improving study start-up (SSU) activities continue to be overlooked by most global pharmaceutical and biotechnology firms. A study conducted by the Tufts Center for the Study of Drug Development determined that it takes eight months, on average, to move from pre-visit through to site initiation,[1] out of which nearly six to eight weeks on an average are for sending feasibility questionnaires, having them completed, and receiving responses.[2]

72%

of studies run more than one month behind schedule

Quite often, the finalized site selection itself eventually becomes a rushed process, whereby hundreds of investigators/sites across the globe are selected over a short span in an attempt to hasten trial start-up. As a result, poor selection of trial sites becomes a problem during trial conduct, and reportedly increases the cost of clinical trials by at least 20%.[3]

In a typical Phase III study, this can translate into $2.25 million in expenses for non-active and under-enrolling sites. According to Cutting Edge Information, 72% of studies run more than one month behind schedule, and such delays can cost sponsors between $600,000 and $8 million for each day that a trial delays a product's development and launch.[4] The cost of initiating a site (which is the largest chunk of SSU cost) has been estimated at $20,000 to $30,000, and trial delays can add to this cost.[5]

A U.S. Department of Health and Human Services–sponsored report from 2014 cites key barriers to clinical trials, quite a few of which are related to SSU process, and highlights sponsor-imposed barriers, such as tedious multiple review methods and highly restrictive inclusion/exclusion criteria.[6] Meanwhile, a research effort funded by the U.S. Food and Drug Administration (FDA) and undertaken by the Clinical Trials Transformation Initiative identified seven SSU cycle times, and concluded that many stakeholders in the U.S. clinical trial enterprise routinely fail to collect standardized measures of SSU cycle times.[7] This highlights inefficiencies in SSU tracking process and demonstrates the need to implement measures to optimize the same.

The data on elements causing delays in SSU indicate that contract and budget negotiations and approval are responsible for 49% of study delays, followed by patient recruitment, which causes 41% of delays.[8] A global survey conducted by CenterWatch revealed that 73% of sites use traditional methods of e-mail, fax, and courier as a primary tool for exchanging clinical trial documents.[9]

Although the results may not be quite the same today, it is interesting to note that a 2005 report found that, despite decades of practice, sponsors underestimated the time required to complete 80% of studies, with the average Phase I study running over by 42%, Phase II study running over by 42%, and Phase III study running over by 30%. The report also found that the average Phase III study was completed more than six months behind schedule.[10]

Meanwhile, there are several therapeutic areas that pose particular challenges during the SSU phase. For instance, in oncology, with the emergence of molecular targeted therapy, the complexity of study protocols has increased, allowing for the inclusion of patients with a wide range of tumor types that share a common genetic mutation.[11]

SSU OVERVIEW AND THE TECHNOLOGY EDGE

The above facts and figures provided by various industry reports help us to put the spotlight on SSU, with an emphasis on the increasing need to accelerate steps in SSU process by utilizing suitable technology options to minimize manual intervention, reduce errors, prevent trial delays, and improve compliance.

If study timelines are not met in the SSU phase itself, this creates a cascading effect in terms of missing later study milestones. That is to say, delays in the determination of study feasibility, site selection, essential document collection, ethics committee submissions, and investigational product release impact site initiation visit timelines, making it tough to meet study conduct milestones and achieve recruitment targets as per the planned dates, which ultimately results in trial delays.

In the midst of the current clinical trial technology revolution, opportunities for improving study start-up activities continue to be overlooked by most global pharmaceutical and biotechnology firms.

FIGURE 1: Overview of Study Start-Up (SSU)

NOTE: The activities highlighted in yellow are areas in which technology can help to speed up SSU.

If study timelines are not met in the SSU phase itself, this creates a cascading effect in terms of missing later study milestones.

Figure 1 depicts a high-level SSU work flow, including the key stages and the respective activities performed under them.

SSU ACCELERATORS

Although appropriate site selection is the most challenging piece in SSU, a probable solution also lies within past site performance data. Lots of data may exist on a site's performance and experience in terms of patient populations, recruitment rates, audit compliance, and more, which could be valuable for gaining insights on site selection. Utilizing these past data of site performance and building predictive analytics tools can enable forecasting of a site's performance on new studies, and has proven to be a smart step toward addressing site selection issues.

To add to the above, use of an electronic feasibility system with a built-in "site scoring" tool for automatic analysis of feasibility responses and categorization of sites as medium, low, or high performers can benefit studies for years to come. Databases built from such online feasibility systems can provide a common platform for real-time feasibility study status across the globe, and can be utilized further for forecasting and identifying potentially suitable sites for future projects.

By adopting an online feasibility tool, pharmaceutical companies and contract research organizations can reduce the costs and effort devoted to e-mailing feasibility questionnaires, attending to follow-up reminders, and waiting to receive completed questionnaires. Manual tracking and analysis of feasibility responses will be eliminated, and the availability of standard and customizable feasibility status update reports and dashboards will benefit study management teams seeking to keep up with all the activities tied to global trials.

Another large chunk of start-up efforts is spent on coordinating the essential document compilation, review, and reconciliation steps required for various submission packages (e.g., for ethics committees, investigational product release, etc.). This is one of the crucial processes in SSU, and involves a lot of paper-based, manual intervention in many cases. However, a secure, web-based document exchange repository can serve as an effective coordination and communication tool whereby stakeholders from different parts of the globe can

By automating site feasibility studies, pharmaceutical companies can reduce the costs and effort devoted to e-mailing feasibility questionnaires, attending to follow-up reminders, and manual analysis of feasibility responses.

upload, view, and query documents within the tool based on their different access levels. This would enable study management teams to know the real-time status of the start-up documents collected and pending at different sites, along with built-in SSU milestone tracking and auto reminders to concerned stakeholders.

Industry surveys conducted on the use of web-based document exchange tools reveal that 41% of respondents consider time savings to be the biggest benefit, followed by 22% stating better organization of study-related information to be most valuable, and 22% believing easier communication with sponsors comes out ahead.[8] Implementation of such a document exchange repository will mainly reduce the turnaround time of handling essential documents during SSU (which are otherwise procured via e-mails or in hard copy and stored in various shared drives or online systems), along with reducing the pass-through costs associated with the same.

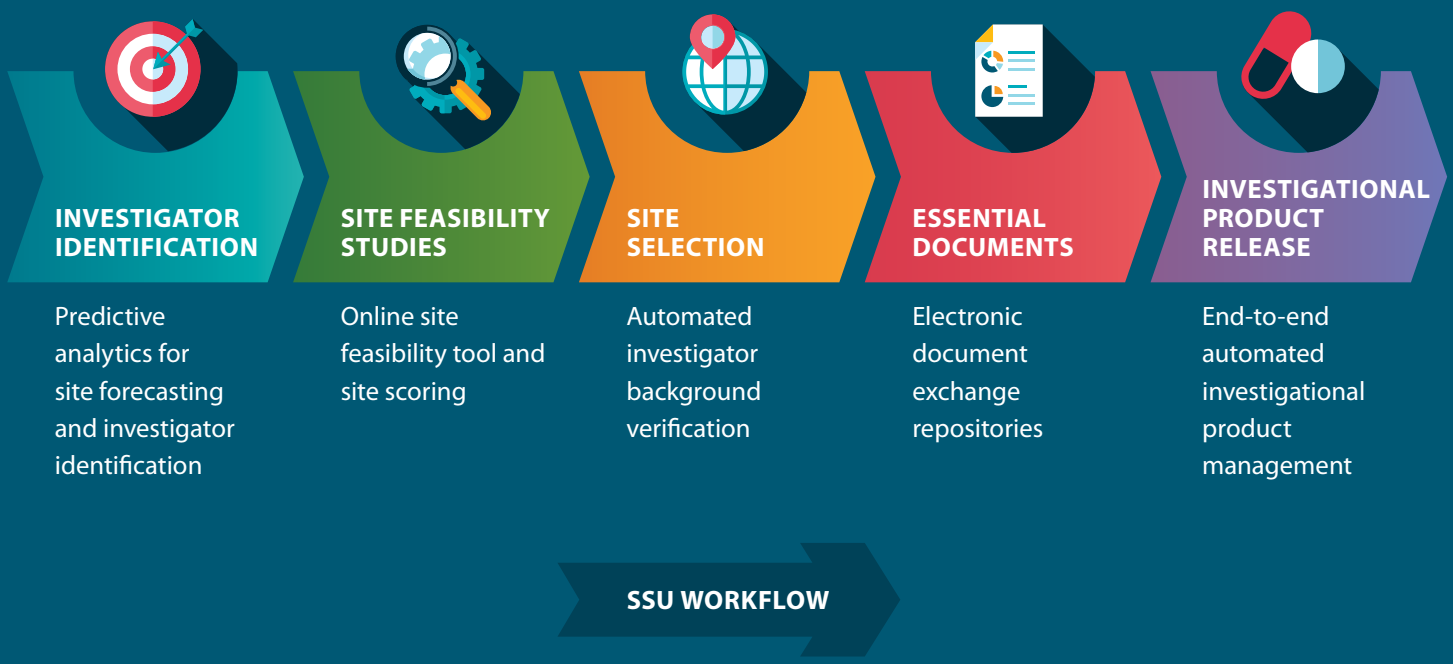
Data collected on use of web-based communication methods for centralized document exchange on four Phase II–III studies in which a combination of academic medical centers and private hospitals were used revealed up to 27% efficiency gains. In studies involving only private sites, up to 50% efficiency gains were noted (in terms of turnaround time reduction during the SSU document exchange).[8]

Meanwhile, investigational product release is another vital part of SSU that requires great precision in terms of managing the many details tied to product release packages, in order to meet specific timelines for drug release to the site and to ensure regulatory compliance in audits. An online document exchange portal can be used to help with package compilation and approval; however, a concept that is emerging in the industry is that of a completely automated investigational product management system. With such a system, an investigational product can be tracked from its arrival at the depot, to its delivery to sites (postapproval of its release package), to being dispensed to patients, to tracking each patient's compliance in terms of drug usage, and finally to the return or destruction of any unused product.

All of the above-mentioned data can be tracked on a single platform and monitored through an application in a smart phone; this can dramatically ease the process of investigational product management, not just in start-up, but also throughout the due course of the study. In fact, a recent case study from a major pharmaceutical company describes the value of deploying technology solutions in SSU at all of its U.S. sites that conduct oncology trials. Prior to implementation, the company reported having no automated task assignment and relying heavily on manual spreadsheets. After eight months of implementation, the company experienced a 32% reduction (in weeks) in the SSU stage.[12]

73% of sites use traditional methods of e-mail, fax, and courier as a primary tool for exchanging clinical trial documents

FIGURE 2: SSU Accelerators—The Technology Edge



In order to target the major SSU bottlenecks, carefully analyzing current processes and making a list of the key problematic areas are essential tasks, to be followed by implementing simple automations within existing processes.

Figure 2 continues the high-level SSU work flow, depicting the key stages and their respective SSU accelerators for giving study leaders the technological edge needed for optimizing their processes, including:

- Predictive analytics and site forecasting, to build efficiencies for investigator identification
- Automated online site feasibility and site scoring system, to facilitate faster turnaround time in feasibility
- Automated investigator background verification, to eliminate manual processes when checking for medical board sanctions and debarments in different states
- Electronic document exchange repositories to optimize and speed up SSU essential document collection
- e-2-e automated investigational product management systems, to gain real-time control of the drug supply and its accountability for greater quality compliance

Examples of initiatives launched by collaborative industry groups and aimed at accelerating SSU include an effort by Johnson & Johnson, Eli Lilly, and Merck,[13] as well as another by the nonprofit TransCelerate Biopharma Inc.[14]

WHERE TO BEGIN?

In order to target the major SSU bottlenecks, carefully analyzing current processes and making a list of the key problematic areas are essential tasks, to be followed by implementing simple automations within existing processes.

For instance, performing state-specific medical board sanction checks for hundreds of investigators in a global megatrial can be a massive manual activity, depending on the number of websites to be checked for each investigator. Automating this process by developing a tool to eliminate manual screening can reduce the time spent on this work and help with the compilation of data from different state board websites into a single file.

Similarly, developing macro solutions for certain manual tracking activities can be another alternative. For example, during the FDA debarment check of different investigators, data are usually checked from three links on the FDA website. Developing a macro solution for automatic comparison of data downloaded from the three links—to check if there have been any additions to the list of investigators from time to time during a study's conduct—is a useful solution for saving manual efforts that also increases compliance related to investigator background verification during the selection process for other studies.

50% efficiency gains were noted in private sites where data were collected using web-based communication methods for centralized document exchange

Once the problematic areas are addressed, study leaders can monitor the improvements in terms of turnaround time and process compliance, and further plan to implement major transformations with the help of customized tools and platforms suitable for their SSU process.

CONCLUSION

Any adoption of new technology brings with it various teething issues and challenges in terms of set-up, training, desired outcomes, and more; hence, progress has been slow in addressing the SSU issues described in this paper through technology solutions, but the trend has been in the right direction. Further, these solutions have proved to be beneficial investments for stakeholders in the clinical research enterprise as it evolves in an era of more powerful tools (CTMSs, eTMFs, EDC, etc.) for core trial conduct. Now it is time for the identification and implementation of the right tools in SSU.

As the staff at study sites and the members of overall clinical trial teams become more and more technologically savvy in their trial conduct, the learning curve necessary for handling new clinical trial systems becomes easier to manage. All stakeholders will need to welcome yet more upcoming technologies, and to make the switch from manual spread sheet–based processes and e-mail communication to secure systems with intelligence, thus enabling the full use of electronic data, automated processes, and dashboards along with a complete audit trail.

Implementing technology within SSU is indeed a challenging task, considering the expedited turnaround timelines to be met at each and every step. However, centralizing SSU via a trusted technology partner who can provide customized SSU solutions for standalone steps, as per the unique needs of each business can help to accelerate SSU.

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Priya Temkar, MSc, (priya.temkar@tcs.com) is a business consultant in the clinical operations services/life sciences area for Tata Consultancy Services Ltd in Mumbai, Maharashtra, India.