WHITE PAPER

Optimizing Study Startup: How Technology Enables Evidence-based Decision Making

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Study startup accounts for the majority of delays in the conduct of clinical trials, driving up research costs and increasing time to market. New technologies now offer drug sponsors unprecedented opportunities to leverage data in more meaningful ways to improve the efficiency and quality of study startup activities. These advanced technology platforms standardize and integrate multiple data streams that were previously siloed, providing access to an expanding pool of data that can better inform decision-making. Application of sophisticated analytics offers access to more meaningful intelligence, and real-time data supports timely action to address issues and prevent delays. In this paper, the authors profile startup metrics and discuss how PPD's integrated, real-time technology platform has harnessed multisource data to optimize site selection, site activation and patient enrollment. Using this new methodology, PPD-conducted studies achieved a 15 percent reduction in startup cycle times for the critical startup measure of final protocol to first patient in.

INTRODUCTION

Inefficient study startup is a well-recognized cause of major delays and unplanned expenditures in clinical drug development. As many as 70 percent of trials experience startup delays[1,2] and 85 percent to 95 percent of days lost in clinical trials are due to delays in site recruitment.[3] With the cost of managing an active site estimated between $1,500 and $2,500 per month, strategies that improve startup efficiencies can have major impact on reducing overall research costs and time to market.[4]

Assessment of startup time and cost has been hampered by lack of access to uniform data, lack of consistent measurement and terminology, and siloed startup operations. Recent analyses provide evidence that underscore the need to methodize the selection of investigative sites, simplify workflow and seamlessly integrate processes, which drive follow-on efficiencies in site activation and subject enrollment.

This paper discusses startup improvements that can be achieved by applying expanded, multisource data resources using an integrated, real-time technology platform. The authors share PPD's experience using such an integrated technology and reporting solution to enhance data transparency and meaning, and to optimize operational efficiencies. Since adopting this approach in 2012, rapid study startup of top investigators has contributed to a significant cycle time reduction in PPD-conducted studies.

PERFORMANCE BENCHMARKS: IDENTIFYING STARTUP BOTTLENECKS

The three principle startup functions—site selection, site activation and subject recruitment—each involve a constellation of activities coordinated among multiple stakeholders and conducted in overlapping timeframes. In light of increasing competition for research subjects and ever-increasing clinical trial costs, there is an urgent need to re-examine key trial metrics, identify process bottlenecks and adopt strategies aimed at reducing cycle times.

Cycle Times. One of the most rigorous analyses to date is the 2012 "START" (Startup Time and Readiness Tracking) study conducted by the Tufts Center for the Study of Drug Development (CSDD).[4] Eleven biopharmaceutical companies provided startup data from 105 global trials involving 5,296 sites and 774 country level regulatory submissions.

In the START study, the most common sequence of activities following receipt of the final protocol was: pre-study visit; site selection; contract/budget execution; regulatory submissions/approvals; and first patient in (FPI). Measured from pre-study visit to first patient in, cycle times averaged 6.5 months for Phase I and 10.4 months for Phase II/IV (Table 1).[4]

Table 1. Startup Activities; 2012 "START" Timelines

Site Selection

- Feasibility: Review protocol requirements
- Identification: Potential investigator contact

Site Activation

- Pre-study site visit
- Budget and contract negotiation
- Regulatory document collection
- IRB/EC submission and approval
- Regulatory/GCP submission/approval
- Clinical supplies delivery
- Site training

Subject Recruitment/Enrollment

- Promotional activities
- Enrollment: First Patient In (FPI)

Tufts CSDD 2012 START Cycle Times
(Pre-study visit to FPI)

Phase I average: 6.5 months

Phase II/IV average: 10.4 months

Source: Tufts CSDD 2012 START Cycle Times in Lamberti M, Brothers C, Manak D, Getz K, Benchmarking the Study Initiation Process, Therapeutic Innovation & Regulatory Science, 2013.

Compared to this Tufts benchmark, PPD's new technology-enabled approach significantly outpaces this performance average, also notably reducing PPD's own startup operations timeline by approximately 15 percent in 250 trials conducted over 18 months.

PPD is leveraging wider resources of multisource data to improve study startup using an integrated, real-time technology platform.

Major Bottlenecks. The Tufts CSDD study confirmed previous reports, citing the most common causes of study delays as: poor site selection; lengthy contract and budget processes; slow gathering of regulatory documents; and ineffective subject recruitment strategies. In a 2011 CenterWatch survey of global investigative sites, for example, more than 40 percent of site respondents said the three greatest causes of delays are contract and budget negotiations, ethical committee review and approval, and patient recruitment/enrollment.[5]

Poor site selection is the root cause of follow-on delays, introducing higher risk for delays in budgeting processes, regulatory submissions and subject enrollment. Mitigating risk in site selection is pivotal to the entire clinical trial process. Identification and recruitment of high-quality, engaged investigative sites drives follow-on efficiencies in patient recruitment, regulatory approvals and data quality. In 2007, a major pharma company reported that, over a six-year period, 26 percent of contracted investigator sites recruited 80 percent of trial subjects, while 11 percent recruited only one subject.[1] The Tufts CSDD analysis found that study timelines typically double in order to meet desired enrollment levels. Only half of investigative sites meet enrollment targets, while 37 percent under-enroll and 11 percent fail to enroll a single patient.[6]

METHODIZING STARTUP USING NEW TECHNOLOGY

Drug developers participating in the Tufts CSDD benchmarking analysis agreed strongly that reducing study initiation cycle times is critical to improving overall research efficiencies.[4] They identified the following factors as most likely to reduce startup delays:

+ Streamlined, data-driven site selection
+ Electronic document/workflows
+ Visibility, with clearly integrated sponsor/CRO processes

Integrated, real-time electronic data capabilities now enable these requirements. Developed in the 2010s, these technology platforms combine real-time data reporting and quantitative analytics to methodize selection of the best sites, streamline electronic data workflows, increase transparency in trial operations and simplify communications between sponsors and CROs. This technology-induced shift toward a new standard brings sponsors closer to trial data and is enabling major advances in clinical research, from adaptive trial design to risk-based monitoring.

In addition to operational efficiencies, these platforms give sponsors new capabilities to integrate and apply multisource data to the drug development process. Researchers have ever greater access to vast health databases: DNA and tissue biobanks, drug surveillance, disease registries, historical study data, prescribing data and electronic health records, health claims and outcomes data. Access to expanded and integrated pools of data are advancing evidence- based decision-making and enhancing efficiencies across the drug development spectrum.

PPD is leveraging wider resources of multisource data to improve study startup using an integrated, real-time technology platform. Early experience is demonstrating the value of this evidence-based model over current industry approaches to site selection, site activation and patient recruitment.

PPD'S DATA-DRIVEN MODEL: PRECLARUS™ TECHNOLOGY

In study startup, multisource data—harnessed by methodologies including quantitative analytics, and modeling and simulation—is driving progress in:

+ More effective use of historical site performance data
+ Comparative monitoring of site activation timelines
+ Increased accuracy of recruitment forecasts
+ Faster, more efficient communication among sponsors, CROs and sites during regulatory submissions and contract negotiations

PPD's evidence-based approach harnesses multisource data using its Preclarus technology platform. PPD teams leverage this analytics platform and expanded data pool during early startup phases to optimize protocol and study design and, during later phases, to optimize site selection and accelerate startup activities.

Preclarus consolidates and standardizes data from numerous, diverse sources. An industry tool, Tibco® Spotfire™, "sits" atop this data warehouse in a customized PPD architecture that generates standard views and outputs across departments with near real-time access. Data are presented on dashboards that provide interactive visualizations and analytics—accessible to sponsor and PPD teams—that can be used to investigate single data points, or data in aggregate, to identify study trends. Live, real-time views of patient data and operational metrics give research teams a shared platform for detailed analysis, strategizing and decision-making.

Efficiency improvements result from the technology's increased speed and accuracy, and by enabling research teams to identify issues and act earlier to mitigate delays and risks to data quality. Business logic can be developed within databases and tracking capabilities facilitate process optimization and continuous improvement. Transparency improves communication and fosters collaboration among cross-functional teams. Functional silos are broken down, allowing experts to partner in sharing intelligence and improving business relevance.

As an operational platform for startup activities, Preclarus underpins new data-driven approaches that improve cycle times and data quality.

ADVANCING THE SITE SELECTION PROCESS

Poor site selection results in costly delays due to slow or insufficient subject enrollment and potentially selecting sites with historically slow startup timelines. In their discussion of the impact of startup activities on research time and budget, Manak and coworkers cite industry reports that only 7 percent of sites meet enrollment timelines. They note the severe impact on budget, given estimates that sponsors risk losing between $600,000 and $8 million each day a product is delayed to market.[1]

According to a recent Industry Standard Research (ISR) survey, "leading edge" site selection practices focused primarily on database searches (used by 22 percent of industry respondents) and on relationships and networking (10 percent). ISR concluded that sponsors do not dedicate significant resources to advancing site selection processes.[7]

Better methodologies to identify optimal investigational sites have been hampered by various constraints, such as cost and the time pressures that result from urgent medical needs to quickly evaluate new therapies. Time and cost pressures preclude broad, time-consuming searches and on-site investigator evaluation. Traditional approaches rely on sponsor and CRO investigator lists, referrals and, more recently, agreements with site management organizations, academic medical centers and large hospitals. Listings often

depend on subjective evaluations retrieved from survey databases. New technology and wider data resources now provide capabilities to optimize selection methodologies.

Evidence-Based Site Differentiation. PPD's data-driven approach uses multiple data sources to expand identification of potential investigators. Preclarus analytics then provide rigorous, objective evaluations based on site performance history and investigator demographics and capabilities to select the optimal sites for a specific study. By generating quantitative assessments of site enrollment capabilities and startup engagement, this approach avoids the loss of time and research dollars that results from activating low-performing, unmotivated sites. Sponsors are better able to predict data quality, timelines, costs and how to allocate study resources.

Using Preclarus technology, PPD is able to expand its investigator database to sources beyond its organizational experience. This comprehensive listing is refined by our ability to match study qualifiers to the countries and sites best able to access the target subject population. In addition to exports from internal and shared databases, we are able to connect to industry data and open sources to accumulate a substantial collection of sites with proven track records. Sites are considered for PPD studies based on the investigator's specialty and therapeutic area experience, geographic region and the site's physical capabilities to perform the study.

The initial list is quickly refined using industry data that confirm locations of appropriate patient populations and identify sites that are conducting competing studies. PPD historical investigator data then facilitates prescriptive site selection based on actual performance in subject recruitment and site activation in previous studies. These data also contain key site quality indicators that can be used during the study for operational review and performance tracking of startup activities.

Based on the risk-mitigation strategies embedded in site selection process, PPD is able to better predict the enrollment timeline amongst this cohort of prescribed sites.

Objectivity, Speed and Data Standardization. PPD's evidence-based methodology reduces subjective judgments common in site selection and delivers the speed critical to meet research timelines. This level of rigorous site evaluation and data mining was challenging in the past, because it was too time- and labor-intensive to pursue manually during the fast-paced site identification period. The Preclarus solution accelerates the process, as PPD is able to prepare an initial prescriptive site list in a matter of minutes. The third critical factor is data standardization. The ability to leverage multiple data sources requires an "apple-to-apple" comparison. The PPD solution uses Master Data Management (MDM) methodologies to standardize terminology and measurement points and establish the logic and conventions that underpin data integration and analysis.

Leveraging Business Intelligence. While most site selection is based on the ability of investigators to recruit subjects for a given therapeutic indication, Preclarus data and analytics allow for deeper levels of performance evaluation to match high-performing sites to specific research requirements. Preclarus enables PPD teams to access principle investigator profiles by unique or unusual study circumstances and to generate intelligence as well as lists and reports. This and other intelligence can be applied to meet future challenges.

PPD teams can identify regional disparities in site performance—for example, disparities that might be due natural disaster or social, political or economic events. PPD is able to build profiles of regions with unique populations for therapeutic indications. That allows teams to dig deeper into historical data to uncover unique aspects, such as experience with various technologies or special patient populations. When faced with aggressive enrollment timelines, data on startup cycle times of candidate sites can be reviewed to make recommendations and decisions about selecting sites that have the potential to become active before the end of enrollment.

ADVANCING SITE ACTIVATION AND PATIENT ENROLLMENT

In study startup, patient enrollment and site activation are conducted in overlapping timelines. Sites frequently overestimate the number of patients they will be able to enroll. This and other subjective performance information leads to enrollment delays when it becomes clear—late in the site activation process or early in the recruitment phase—that additional sites must be activated in order to meet enrollment targets. One analyst poses that if industry-sponsored trials activate 65,000 sites per year at a cost of $20,000 per site, a mere one-percent reduction in non-enrolling sites would save $13 million.[8] Integrated, real-time technology solutions bring new capabilities to speed enrollment and reduce costs.

Tracking Activation in Real Time: Managing by Outliers. Near real-time delivery of site, patient and study data through Preclarus dashboards boosts site management efficiencies and reduces chances of error. Joint sponsor-CRO views of operational trial data reduce miscommunications and omissions across research teams about the status of a trial. It eliminates traditional reporting functions: static monthly reports, line-item study review calls and the need for managers to collate report data from multiple groups. The same dashboard views inform each functional group of current status, fostering accountability and allowing teams to use call and meeting time for problem-solving and proactive planning.

The conduct of site activation and management through the PPD technology solution is in dramatic contrast to current industry practice. A 2012 survey of global investigator site methods of document exchange found that 77 percent of respondents use traditional channels: email, fax and courier; 66 percent of respondents spend two hours per week searching for documents; 78 percent send documents to sponsors or CROs at least once a week, and in some cases more than five times a week.[9]

As a result of advances in speed and accuracy, near real-time Preclarus data allow research teams to quickly manage startup operations in a just-in-time manner. Data analytics and dashboard displays provide a holistic view of an individual site in the context of all sites and rapidly identify metrics that serve as risk indicators. Teams can view the critical path elements to full site activation and 100 percent enrollment. In these custom visualizations, teams can monitor the predicted timeframes for ethics approvals and quantify the number of personnel needed each week to perform initiation training visits. The critical path spotlights discrepancies between targets and actual performance, enabling analysis of discrepancies to guide decisions for remedial action. Teams can quickly identify the cycles of contract negotiations and regulatory approvals, and more precisely estimate the rate of site activation and enrollment.

Tracking and Optimizing Enrollment. Enrollment optimization begins with feasibility assessment of protocol requirements. Accruing data managed by Preclarus allows research teams to adjust feasibility strategies to optimize enrollment based on actual site performance. Using Preclarus, PPD teams identify enrollment trends early and act quickly to address delays before research budgets are negatively affected. Enrollment is tracked by site, based on indicators, such as screen failure and withdrawal rates. Actual enrollment is compared to contractual obligations to determine whether sites are enrolling as projected.

Failure points are identified early. PPD teams can quickly activate support mechanisms for slow-enrolling sites, such as centralized recruitment programs; determine whether activated sites can enroll additional patients; and decide whether additional sites will be needed to meet goals. Preclarus real-time data speeds tracking of inclusion/exclusion criteria to learn whether a particular criterion is causing enrollment issues and should be reassessed by the sponsor.

The Tufts CSDD survey noted that 32 percent of sites do not receive centralized recruitment support.[7] Traditionally, recruitment is viewed as a site responsibility and most recruitment programs still rely on accepted strategies, such as physician referrals and print/broadcast ads. Only 11 percent of trials use social media for patient recruitment. PPD supports sites with centralized, tailored recruitment and retention plans that incorporate promotions, including use of social media, designed to reach potential research participants.

FUTURE IMPLICATIONS

PPD's early experience of startup reductions demonstrates that integrated, real-time technology platforms can deliver dramatic advances within sponsor and CRO organizations. As a business intelligence tool, PPD's Preclarus solution allows us to quantify PPD performance across projects and individual functions. As an embedded Business Process Management (BPM) technology, Preclarus gives PPD the ability to gain efficiencies within and across operations while embedding best practices and achieving constant process improvement. PPD's development and application of standardized data and benchmarks will support future industry growth in the electronic age.

In addition to improving operational efficiencies, more profound research advances are possible, as electronic platforms enable more applications of multisource data and establish an explorative environment for new, data-driven insights. In the immediate future, PPD is working to implement further data integrations and visualizations through the use of internal and external data sources. Significant changes are anticipated in light of increasing industry access to health data and to advancing methodologies, such as those emerging from the TransCelerate initiative, a collaboration among pharmaceutical and biotechnology companies to create research process improvements to advance efficiencies.[10] PPD contributed to this effort and is poised to serve as a frontrunner in applications of these new approaches. Use of portal technologies, industry-leading data repositories and collaborations among sponsors and service providers will drive access to more robust data sets, support better decision-making and increase the efficiency and understanding of clinical evaluation.

Moving forward, the application of expanding, multisource data implemented on these new platforms promises to become foundational in the design and conduct of clinical trials.

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