OUTSOURCED PHARMA

The Need For Speed In Clinical Study Startup

09**JUL**2015
By Craig Morgan

The status of clinical trials continues to stymie industry stakeholders anxious to rein in the cost of product development and adhere to tighter timelines. Despite intense pressure to speed development, mounting evidence documents ongoing inefficiencies tied to complicated protocols, globalization, and old-school paper-based processes, driving clinical stakeholders to embrace technologies that are finally moving the needle. Cloud-based solutions such as clinical trial management systems (CTMS), electronic data capture (EDC), and the electronic trial master file (eTMF) are all quantum leaps, but their adoption rates vary. And significantly, they do not address one of the most inefficient and costly bottlenecks of clinical trial conduct – study startup (SSU). A study conducted by the Tufts Center for the Study of Drug Development (CSDD) determined that it takes eight months, on average, to move from pre-visit through site initiation. The cost of initiating a site has been estimated at $20,000 to $30,000, followed by the cost of maintaining a site, which is approximated at $1,500 per month.

The *New York Times* recently published two articles focused on heightened pressures to pick up the pace so new therapies can become available sooner to seriously ill patients across the globe. One story highlights rising consumer demand for access to promising treatments before the drugs are approved or even before their clinical trials have been completed. To address this issue of compassionate use, Johnson & Johnson is named as working with a bioethicist who will oversee a panel of independent decision makers to review these requests. The other article details the various programs from the Food and Drug Administration (FDA) that create special pathways for speedier drug approval. According to the article, one-third of recently approved drugs qualify for at least two of the special programs.

Given society's growing insistence on faster drug development, this article explains how an improved SSU process, enabled by cloud-based technology, aligns with that goal by significantly impacting cycle times in clinical trials. This leads to greater cost savings and faster market entry, making valuable therapies available to patients sooner.

A Look at Study Startup (SSU)

It is widely acknowledged that the clinical trials process is highly complex, and the revenue lost daily due to a drug not yet available on the market has been estimated by Cutting Edge Information to be in the range of $1 million - $8 million. Data from the Tufts CSDD indicate that mean clinical development time is 6.7 years. To confront these issues of cost and time, the industry has been emerging from its slow-moving paper-based roots as technology has evolved toward cloud-based solutions. The emphasis has first focused on study conduct, with little attention paid to SSU, but as stakeholders are gaining a greater awareness that better SSU processes are tied to shorter clinical timelines, interest in this opportunity is growing.

There is no standard definition of SSU, but a thoughtful 2013 piece by Lamberti et al lists activities such as country selection, pre-study visits, site selection and initiation, regulatory document submission, contract and budget execution, and enrolling the first patient as typical SSU fare. They note that each step has multiple components, making study delay highly probable from the beginning. Moreover, they point to poor case report form design, lack of recruitment planning, and not initiating sites in a timely fashion as contributing to delays. A 2014 report funded by the United States Department of Health and Human Services provides additional insight. It names sponsor-imposed barriers to SSU such as overly complex internal review methods and highly restrictive inclusion/exclusion criteria as factors adding to a stalled SSU process.

To tackle the multitude of SSU issues in a way that gains traction with clinical trial stakeholders, a collaborative approach has been deemed essential. One of the early efforts was funded by FDA, awarded to Duke University, and undertaken by the Clinical Trial Transformation Initiative (CTTI), a public-private partnership representing academic institutions, biopharmaceutical sponsors, government liaisons, contract research organizations (CROs), and IRBs. As a starting point, some of these entities participated in a retrospective research project, with results published in 2013. They were asked to provide data from 2009 for all Phase III studies in SSU mode across all therapeutic areas. The collected data served two purposes: to use a collaborative approach to establish the current level of SSU efficiency in the US; and to create effective approaches for improving it, including the development of standard terms and time points to be used as benchmarks. The main conclusion of the research was that in the US, many stakeholders in the clinical trial enterprise fail to routinely collect standardized measures of SSU cycle times, a practice that is common in many other industries.

Key SSU Cycle Times

Type of Cycle	Definition
Site cycle	Number of days between the date protocol was received at the site and date of protocol submission to the IRB
Site to IRB cycle	Number of days between the date protocol was received at the site and the date of final IRB decision on the protocol
Site to contract cycle	Number of days between the date protocol was received at the site and the date of contract execution
Site to patient cycle	Number of days between the date protocol was received at the site and the date of first patient enrollment
IRB cycle	Number of days between IRB submission and IRB final decision
Post-IRB to patient cycle	Number of days between IRB final decision and the date of first patient enrollment
Post-contract to patient cycle	Number of days between the date of contract execution and the date of first patient enrollment

Chart 1

Source: *Cycle Time Metrics for Multisite Clinical Trials in the United States, 2013*

Seven cycle times of interest were identified (Chart 1), and despite small sample size and a large amount of missing data, there were several meaningful findings. Site type was significantly associated with the site to contract cycle ($P < 0.001$), with private practice sites (median of 35 days) significantly differing from all other site types (median of 57, 74, 102, and 104 days for independent, academic, VA, and hospital-based sites, respectively). Furthermore, a clear association between IRB type and cycle time metrics emerged, whereby for six of the seven cycle times investigated, central IRBs had significantly shorter cycle times than local IRBs. Specifically, central IRBs took an average of seven days to reach a decision on protocols submitted for final review, as compared to 35 days for local IRBs.

Building on this work, the clinical trials industry has been expanding the volume of literature on SSU and hosting workshops and seminars on the subject. A recent webinar entitled *How to cut clinical trial timelines in half* touts the importance of embracing teamwork as key to mitigating issues that hinder SSU and derail timelines. Tenley Koepnick, Director Global Development Operations for Allergan explains that teams should focus on:

- Proper planning and preparation
- Better protocol management to avoid having to add amendments
- Smart site selection
- Strategic global considerations

In particular, Koepnick comments that the issue of protocol amendments is costly and adds to SSU timelines. According to research from the Tufts CSDD, the various phases of clinical research have, on average, anywhere between two and 3.6 amendments per protocol, with 37% of them deemed avoidable. Furthermore, a substantial number of protocols have an amendment before the first patient is even enrolled. This practice is most frequent in Phase I, where 52% of amendments occur during SSU—prior to the start of patient enrollment. Later-stage clinical trials had a smaller percentage of amendments prior to patient enrollment, but it was still substantial, in the range of 30% - 38% for the various phases. On average, the direct cost per amendment totaled $497,500, and the median total cycle time for full implementation was two months.

Streamlining SSU

The clinical trial landscape is ripe for bringing substantial improvements to the SSU process. As discussed, there are challenges posed by the many steps involved in SSU coupled with the industry's overall lack of rigorous data collection needed to calculate performance metrics. Much of the information used to launch clinical trials often resides in multiple databases, and SSU tends to be conducted using Excel spreadsheets, e-mail, e-rooms and shared file drives. As a result, time is wasted in status meetings, as the desired information is not readily available. Fortunately, these meetings can be eliminated or reduced as current technology allows for efficiencies using cloud-based systems that automate processes, increase visibility and improve collaboration with sponsors, CROs, sites, regulators, and review boards.

A purpose-built SSU solution is the missing piece in a world of electronic tools that are widely adopted for more efficient study conduct, such as CTMS, eTMF, EDC, and more recently, eSource. According to the 2013 Clinical Trial Management Systems Survey by eCliniqua and BioClinica, approximately 60% of respondents use digital software, such as CTMS, to manage clinical trials. A 2014 survey conducted by Veeva Systems found that 21% of CROs and 15% of sponsors use an eTMF application, and a content management system is used by roughly one-third of sponsors and CROs.

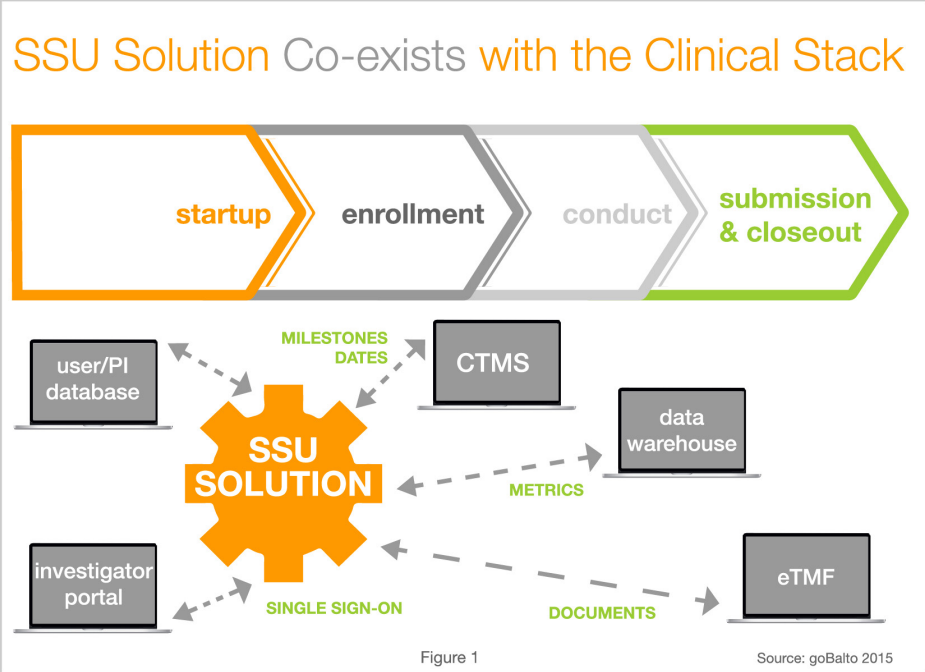

Figure 1 Source: goBalto 2015

Speeding SSU sets the stage for bringing much needed process efficiencies across the entire lifecycle, starting with allowing users to be proactive by viewing information in real-time. With the advent of a purpose-built SSU solution, real-time viewing becomes possible through smart workflows that standardize processes. This type of solution also guides study teams to complete and track study-related documents and tasks required for any site, country, or study based on company-specific standard operating procedures or internal processes. If study requirements change, workflows can be updated accordingly. Also, this application functions as a single repository for in-progress documents, and information only needs to be entered once.

An application program interface (API) is used to integrate with the other eClinical operations—the "clinical stack"—to optimize the clinical trial continuum by allowing information to flow among the various integrated components (Figure 1). It is also designed to provide better collaboration with sites and improve business processes (Chart 2). Moreover, documents from the principal investigator's (PI) database and the investigator portal can be accessed via a single logon. Together, these benefits function as major timesavers in site activation.

Benefits of a Cloud-Based Solution That Speed SSU

- Regularly collaborate with sites
- Improve business processes
- Exchange documents
- Identify bottlenecks
- Avoid redundant processes
- Review and normalize processes (to enable global metrics)
- Consolidate information in one place
- Predict progress more accurately
- Drive data-based business decisions
- Set global milestones
- Access study data anytime, anywhere
- View global study status

A case study from a major pharmaceutical company describes the value of using an SSU application in all of its US sites that conduct oncology trials. Prior to the implementation, the company reported having no manual spreadsheets for progress reports, no view of work in progress or real-time study startup status, and no mechanism for identifying bottlenecks. After an eight-month implementation, the company experienced a 32% reduction (in weeks) in SSU. This included receiving essential documents from sites in 17 weeks instead of 30, and completing contracts and budgets in 3.5 weeks instead of 4.2 weeks.

A Better Process

Many of the steps involved in SSU create delays, but with the advent of purpose-built cloud-based technology, electronic solutions can make a disruptive impact by shortening clinical trial cycle time. Research from the Tufts CSDD indicates that a 10% improvement in the clinical trials process may be tied to a $250 million savings from reduced cycle time. Even a more modest 5% improvement may be associated with $102 million in savings tied to shorter cycle time.

With better SSU processes, the focus can shift from monitoring to better collaboration with sites. Through automation, all of the documents reside in a central location, allowing sites to be easily and gently reminded of outstanding tasks that need to be fulfilled. This approach helps to improve the relationship between sites and CROs, as sites are not constantly being called or e-mailed in pursuit of specific documents. As for sponsors, an electronic SSU solution allows them to focus on true market differentiation as they have real-time access to status updates, enabling faster action, instead of waiting to hear from the CRO for this information.

Importantly, the data contained in a robust SSU application addresses the industry's longstanding problem of not collecting sufficient metrics to document the status of how a study is starting to unfold. It is also a critical addition to the ongoing clinical trial automation through integration with eTMF and CTMS systems. It is the last piece of the clinical trial continuum to be automated, and the one with a promising ability to cut costs by shortening timeframes to development of therapies needed by patients worldwide.

Craig Morgan *is a technology and life sciences management professional with more than 15 years experience in the application of informatics and bioinformatics to drug discovery. He currently heads up the marketing and brand development functions at goBalto, working with sponsors, CROs and sites to reduce cycle times and improve collaboration and oversight in clinical trials.*

Craig Morgan
Head of Marketing | goBalto