Insights to Accelerate Your Clinical Trial: How Proactive Planning in Study Startup Drives Efficiencies in Drug Development

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There is a compelling need to optimize operational efficiencies as pharmaceutical companies face escalating drug development costs, FDA scrutiny, and heightened competition to bring drugs to market. In the quest to accelerate the drug development process, it is broadly recognized that rapid study startup is a catalyst to propel overall project timelines. Yet, the study startup process continues to be a bottleneck at the outset that dramatically slows drug development.

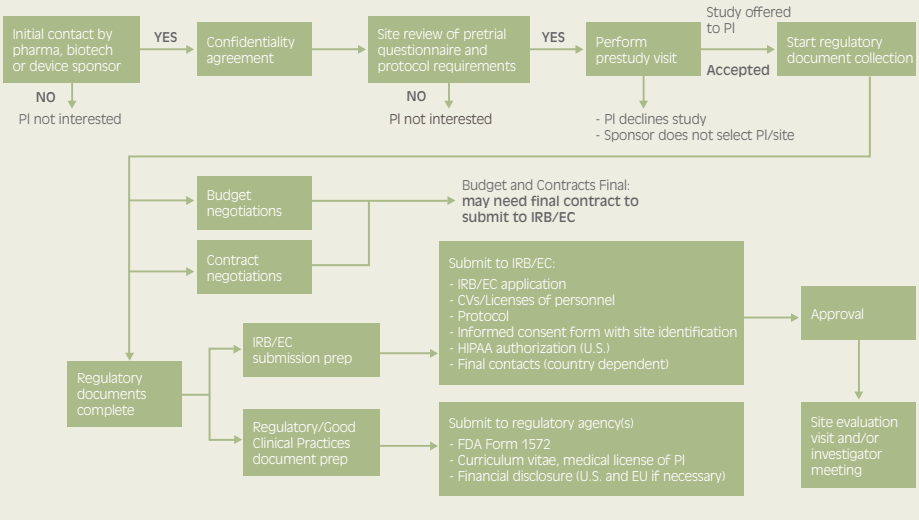

Figure 1
Study Startup Process – Study Startup 2.0 (*Monitor*, June 2011)

Study startup is equally complex in both drug and medical device trials. For effective startup, study leaders must be proactive in the development of a communication plan that allows for balanced collaboration between the multiple stakeholders responsible for driving the process. Establishing open and consistent communication across project teams is essential to rapid study startup as it sets the stage for efficient progress across the project's lifecycle.

Stakeholders who are key to the very complex activities involved in study startup at the site level, as outlined in Figure 1, include:

- sponsor
- principal investigator
- study site staff
- contracts and budgets administrators
- legal representatives
- institutional review boards or ethics committee members
- study vendors (laboratories, equipment, shipping)
- CRO cross-functional project team

Study startup at the site level is also a costly process. Some sites include startup costs within their budget while others, especially larger institutions, require pre-startup payments and occasionally separate contracts to encompass this initial phase of a trial. While the average site startup cost varies based on the complexity of the protocol, prices currently range from $8,000 - $15,000. According to the 2009 Investigative Site Survey conducted by Centerwatch[1], the five most common reasons for clinical trial delay (Figure 2) were:

- Contracts and budget negotiations and approval (49%)
- Patient recruitment and enrollment (41%)
- Protocol design and revision (26%)
- Legal review (26%)
- IRB review and approval (25%)

Understanding the complex challenges associated with drug development, it is clear that right from the start, standardized approaches in key areas are essential to driving efficiencies in the overall conduct of a trial. Thorough centralized planning, appropriate staffing resources, and methodical and timely execution of each study startup task can shorten the overall timeline and lead to faster site initiations. Ongoing evaluation and flexibility

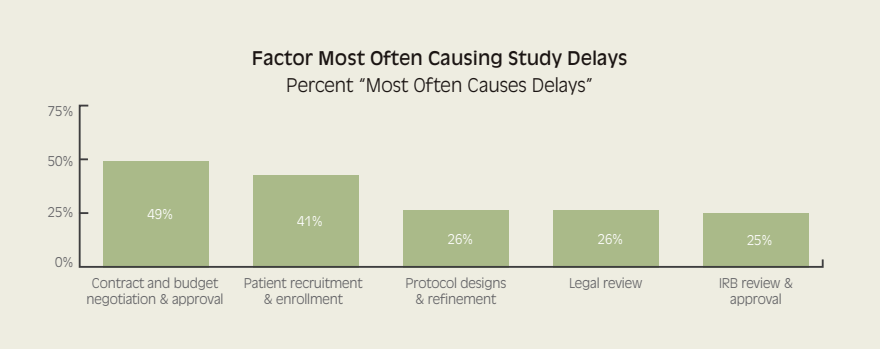

Figure 2
Factors Most Often Causing Study Delay (n=950), Centerwatch Survey of Investigative Sites in the U.S. 2009. Source: CenterWatch Survey of Investigative Sites in the U.S. 2009 (n=950)

to adapt the plan appropriately is important to maintain forward progress.

The following strategies are recommended to promote greater efficiency in the startup process.

Protocol Review

As the number of clinical trial investigators within the United States[2] has decreased, there is greater competition for experienced sites. Protocol considerations in pre-startup that support ease of execution and participation can help decrease costs, save on site startup time, and attract experienced clinical trial sites. A protocol that has undergone review by at least one experienced clinician can be the key to ensuring that the protocol is not only executable but is well received by investigative sites that are on the front lines of patient recruitment and retention.

A protocol that mirrors procedures within the site's existing clinical practice or workflow will allow for more efficient study completion and data collection (e.g. case report forms). A protocol that considers standard of care procedures does not generally require these same procedures to be repeated. This can be a significant time savings to both the site and the patient. Moreover, protocol procedures that are mapped to the standard of care are typically covered by insurance offering a cost savings to the sponsor.

Additionally, having an experienced statistician review the protocol at the start to identify the types of pertinent study data that should be collected for analysis eliminates the collection of extraneous data. This step makes it easier for the site to complete and document study procedures, decreasing the number of CRFs, queries and potential errors, thereby reducing monitoring and data management needs overall. The result is substantial cost savings and time efficiency for the sponsor.

Finally, it is important to develop a protocol that is flexible to change through interim analysis, adaptive design, and acceptable patient visit windows, thus avoiding non-critical amendments that may slow the progress of a trial. This helps to ensure a protocol is executable at the site level and therefore appealing to a site as a project is going through the site selection portion of a study.

Centralized Approach

Startup efficiencies can be realized through the use of centralized vendors, such as Institutional Review Boards (IRB)/Ethics Committees (EC), laboratory-testing facilities, and other key service providers. This approach supports consistent data reporting and startup documentation across all sites.

The use of a central IRB/EC allows the sponsor to prepare and submit the core study information to one entity for review. This ensures consistency in IRB/EC submission across sites and allows the sponsor to obtain approval of general study documents prior to site selection. Once sites are selected, this pre-planning can truncate the site-specific IRB/EC approval timeline since sites only need to complete and submit the site information versus completing a full study submission. In some cases, the use of a central IRB/EC at a large institution can reduce the traditional two month turnaround of IRB/EC submission to two weeks. This reduction in site effort and IRB/EC review time enables the site to focus sooner on other critical startup tasks, such as patient recruitment.

Another option to consider to streamline and centralize communication from multiple groups is the use of cloud computing. Especially in startup, cloud computing allows multiple users to perform centralized review, revision, and finalization of study documents in real time. This can drastically reduce traditional timelines related to the back and forth review and revision of documents such as contracts and budgets, regulatory document collection, and IRB/EC submission packets. For example, with the use of cloud computing and digital signatures, a National Cancer Institute 2010 pilot study reduced the standard 2.2 hours per signature in contracts and budgets to minutes. This resulted in a savings of about $500 per user[3].

For larger programs, which often incorporate multiple planned protocols, it may be beneficial to centralize the contracts and budget process by establishing a master service agreement with the site. This can shorten the negotiation timeline and startup hurdles for future protocols. In combination with a cloud-computing environment, documents previously collected can be transferred to future studies without requesting this same information from the sites.

Targeted Site Identification

Selecting sites with capabilities to fit a specific protocol greatly impacts efficient study startup. For example, it is important

to identify a site's experience with study-specific procedures, access to the target patient population, recruitment plans and supported screening, and enrollment projections. Twenty percent of sites in any given trial hold the majority of patient enrollment, while 50 percent fail to meet recruitment targets. In specialized patient populations like oncology, recruitment metrics decline further with about 50 percent of the sites not enrolling a single subject[4]. If it is important to include key opinion leader sites, careful consideration should also be taken to recruit a good mix of both independent and professional research sites to ensure enrollment of the appropriate patient population.

To shorten study startup, before undertaking a search for new sites, the qualifications and past performance of sites engaged in previous trials should be considered. CVs, medical licenses, GCP documentation, and appropriate laboratory documents collected for earlier trials can be applied to the new study. In addition, referrals from these trusted sites may help speed up the identification of additional qualified sites for a given trial.

The process of identifying a new site should include a thorough review of its capabilities using data available from industry websites such as clinicaltrials.gov or other internal or subscription-based feasibility databases. Sites should be carefully assessed, including the principal investigator or institution's qualifications, therapeutic area expertise, overall clinical trial experience, regulatory agency audit status, past accrual of the targeted population, available staff resources, and current and planned workload, and site capabilities.

For some studies, the use of research naïve sites may be needed to reach the target subject population. Without a doubt, more time and effort should be allotted for training, monitoring, and management of naïve sites. However, the time invested to develop and train a site new to conducting clinical trials may foster site loyalty to future research.

Web-Based Feasibility

Rapid and thorough site feasibility can help speed up and make study startup more efficient. A well-crafted, study-specific, web-based questionnaire is often easier for the site to use, and prompts quicker, more detailed responses, making it easier to manage the data collected from the site. The data from web-based questionnaires is easily compiled into spreadsheets or other electronic formats, with site information easier to search and organize. Less time is spent manually entering data received or correcting transcription errors from faxed or paper submissions.

The well-constructed questionnaire should ask for details pertaining to each site's specific startup procedures. While most sites allow contract, budget and IRB/EC review to occur in parallel, other sites may require a more controlled multi-step review process and the potential impact to startup timelines should be considered. In addition, using the questionnaire to identify whether a site can use a central IRB/EC or central laboratory is another important consideration. It is also recommended that along with the site questionnaire, the CV and medical license of the proposed principal investigator be collected for review, and stored centrally for future reference.

Startup performance is often a good indicator of the quality of site performance through the course of a study. A site that is responsive and organized in meeting startup timelines typically demonstrates a similar commitment to meeting enrollment of the first patient.

Study Specific Subject Recruitment / Retention Strategy

In order to achieve enrollment objectives for all studies listed on clinicaltrials.gov, it would be necessary for one in every 200 Americans to volunteer as a study participant[5]. However, volunteer study participation is not occurring at this rate, while competition for patient participation continues to rise. Therefore, pre-planning for startup activities becomes even more critical to mitigate the risk of slow enrollment. Before site recruitment begins, it is important to identify and clearly demonstrate how a given study differentiates itself from competing studies. Showing that patient recruitment and retention tools and support are in place is key to engaging, motivating and retaining experienced, top-enrolling sites.

When possible, submitting recruitment material templates to a central IRB/EC is a time saver that allows for consistency across sites and avoids the need for materials to be created and reviewed on a site-by-site basis. In addition, to support accurate enrollment forecasting and patient recruitment, ask sites to provide a de-identified (per HIPAA, or other data protection requirements) eligibility list for the target patient population, derived through patient registries, or an initial screening of patients from a clinical database. The extent of site involvement in a clinical research network may also be helpful as these networks can refer patients to participating sites.

Streamlined Regulatory Documentation Collection

Regulatory document collection can be streamlined to reduce the startup timeline by providing clear instructions and expectations on how to correctly complete documents and ensure a timely submission. Sites should be given sponsor and/or CRO contact information should questions arise. Pre-populating regulatory documents that allow for minimal input and verification from site personnel will save time, as well as eliminate iterations of the signature process and ensure accurate information is being collected the first time. With most licensing boards in the United States moving towards electronic renewals, the use of online medical license lookups can save sites in providing the documentation needed for startup; some laboratory certification lookups may also be conducted online.

Experienced CRO - Experienced Clinical Research Associates (CRAS)

Clinical operations is a critical component to any study. Working with a CRO that offers comprehensive clinical operations services can boost the pace of a trial. From study startup to study closeout, the right CRO can offer experienced clinical personnel to ensure proper planning and execution of a study with emphasis placed on patient safety and quality data. The right CRO can manage careful selection and retention of a monitoring team to ensure overall consistency through the course of a study.

Since the CRA is the intermediary to the investigative sites, it is important to educate the CRA upfront about trial expectations and objectives, including thorough knowledge of assigned sites and the study plan. CRA insights are valuable for site referrals that drive efficiencies. For larger study programs, alliance strategies with a CRO may also have significant cost benefits. As the CRO monitoring team's knowledge of a site develops with each succeeding study so does the reduction in cycle time improvements that can result in fewer contract delays[6].

Summary

Study startup in global drug development continues to increase in complexity; however there are many things that can be done to drive efficiencies in this phase. Productivity is driven by a rock-solid communication plan that aligns all stakeholders to efficiently operationalize a clinical trial.

Study startup delay can be mitigated through a combination of sound protocol design, the use of centralized vendors and tools to streamline processes, targeted site identification, use of appropriate patient recruitment and retention strategies, and applying the experience of a seasoned CRO and CRAs to proactively manage sites from startup through project completion. Putting these recommendations into action will significantly improve startup efficiency, and positively impact the overall project timeline.

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SynteractHCR is a full-service contract research organization with a successful 17-year track record supporting biotechnology, medical device and pharmaceutical companies in all phases of clinical development. With its "Shared Work – Shared Vision" philosophy SynteractHCR provides customized Phase I through IV services collaboratively and cost effectively to ensure on-time delivery of quality data so clients get to decision points faster.

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