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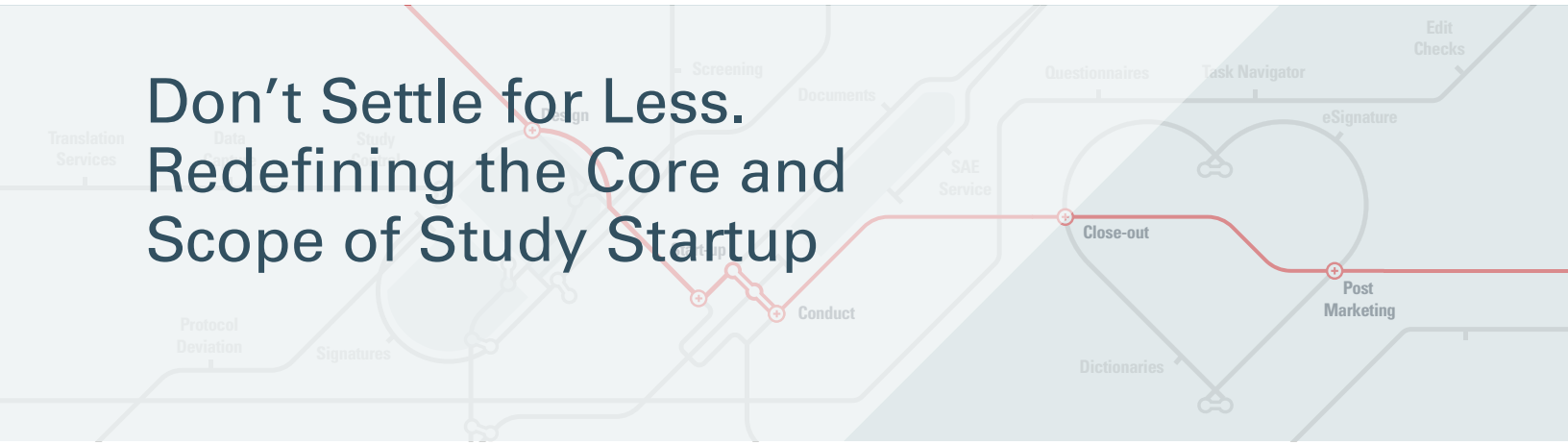
WHITE PAPER

Don’t Settle for Less. Redefining the Core and Scope of Study Startup



This white paper focuses on defining and expanding the definition of study startup, an element of clinical trials that is gaining attention because it offers the greatest opportunity to improve quality while compressing clinical trial timelines.

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Contents

Executive Summary

Technology designed to improve study startup is at the forefront of expanding this niche through initiatives that drill down to the granular level, which helps identify potential bottlenecks and other factors that could derail studies.

With nearly half of clinical trial costs unaccounted for, including known administrative costs, and much of those linked to study startup, it is telling that the industry is finally moving toward identifying those costs with the help of purpose-built tools that can determine, with a high degree of accuracy, when it is time to stop identifying sites.

This change in approach will continue to highlight how improving the study startup process is a great opportunity, yielding a major impact on quality, timeline and overall cost of clinical trials.

Purpose-built technology is expanding the definition of study startup

There are more than 281,000 clinical trials currently underway across the globe,[1] all having tackled the daunting task of study startup. It is surprising that this critical part of clinical trials lacks an industry-wide definition, especially since it is key to optimizing operational efficiencies and compressing timelines.

Study startup, as described by Lamberti et al, includes country selection, pre-study visits, site selection and initiation, regulatory document submission, contract and budget execution, and enrolling the first patient.[2] Each of these steps has multiple components, all of which must be tracked to reduce the likelihood of bottlenecks. Abbott et al,[3] published results of a survey that offered definitions of study startup benchmarks, such as "start time", and identified so-called "critical checkpoints" for this function. For the purposes of their survey, they described study startup as occurring between the time a protocol is submitted to the site for review and the time that the first study participant is enrolled, with various checkpoints along the way.

> "Fortunately, with the advent of purpose-built technology offering broad functionality, real changes are happening."

The importance of well-managed study startup is seen in data from various research initiatives. For example, a survey by the Tufts Center for the Study of Drug Development (CSDD) found that issues related to the budgeting and contracting portion of study startup are the major reason for site activation failure. This was true for 50.5% of sponsors and 54.3% of contract research organizations (CROs). Fortunately, with the advent of purpose-built technology offering broad functionality, real changes are happening to identify more accurately the best sites, steps causing delays, the associated costs, and why this is happening.

Best-in-class technology is workflow-based and enables input across the clinical trial continuum to generate data for the many study startup steps. With these customizable tools that enable transparency, collaboration, and better adherence to timelines, forward-thinking sponsors, CROs, and sites are recognizing the great potential of study startup to optimize clinical operations, boost quality, and track costs, many of which have long been unaccounted for. Moreover, stakeholders who value the data-driven insights offered by these solutions are understanding the opportunity cost of settling for technology that lacks a full suite of functionality.

Defining and Expanding the "Niche"

Sponsors, CROs, and sites that are serious about improving study startup and clinical trial operations overall are defining it and making proactive planning a top priority. This strategy reflects growing awareness of how upstream planning helps avoid serious downstream consequences, namely not having an audit-ready trial master file or having to engage in costly study rescue efforts due to lagging patient enrollment.[4] Given this reality, study startup can no longer be an afterthought limited to site activation, in its narrowest definition, and hoping for the best. Instead, as its definition expands, it is increasingly being viewed as the foundation of operational excellence.

The industry is taking this position as 40% of the artifacts that eventually flow into the trial master file (TMF) stem from study startup activities.[5] And since the TMF is the repository for completed essential documents that may be subject to regulatory audit, those documents must be accurate and easily accessible by stakeholders and auditors. Making this happen involves use of purpose-built technologies that offer a broad array of study startup workflows that are also linked to study conduct applications, namely electronic data capture (EDC), the clinical trial management system (CTMS), and the electronic TMF. This is possible with the integration of workflow-based tools by application programming interfaces (APIs), which allow two software programs to communicate with each other.[6] With this capability, it is possible to streamline operations, automate processes, increase visibility and improve collaboration among stakeholders.[7]

Of particular importance is the ability of this comprehensive approach to revamp upstream processes, such as protocol design, which leads to major downstream changes, such as fewer protocol amendments. To improve the protocol design process, TransCelerate BioPharma launched its Common Protocol Template (CPT) in 2016, which provides a common structure and endpoint definitions that are acceptable to regulators and is usable across protocols. It also facilitates downstream automation of clinical processes.[8] Next, TransCelerate aims to automate the reuse of selected protocol information to support statistical analysis planning and clinical study report authoring.[9]

With these current and anticipated improvements to protocol design, there could be a reduction in amendments, a costly practice that can seriously upset the study timeline. Research from Tufts CSDD found that 57% of all protocols, across all phases, have at least one substantial amendment, which leads to a study taking three months longer to complete, on average, as compared to studies without amendments. Furthermore, almost 40% of amendments take place prior to the first patient receiving the first dose in the clinical trial. The cost is hefty, with an amendment in a Phase II protocol costing an average of $141,000, and $535,000 for a Phase III protocol.

Perhaps the most concerning finding of this research was that one-third of all amendments were deemed avoidable. Problems such as undetected flaws in protocol design, errors in the protocol, and patient recruitment difficulties were among top reasons for amendments. This finding suggests the need for better upfront protocol planning. With this background, coupled with the right tools and a sharper definition, the study startup niche is growing. It has moved beyond site activation to include everything that occurs prior to enrolling the first patient closeout. (Figure 1).

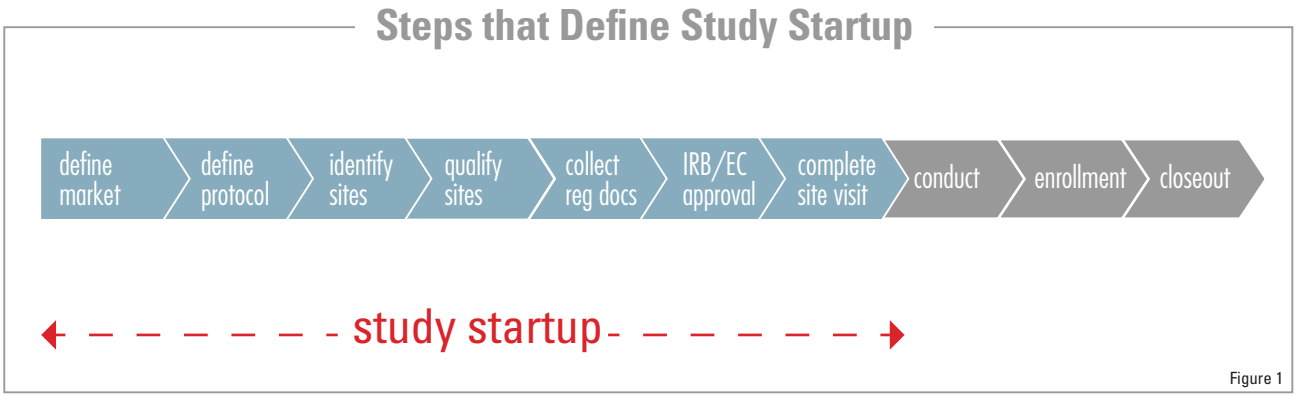

Figure 1

Source: goBalto 2018

To some degree, regulatory input is driving this expanded definition, as the Good Clinical Practice (GCP) guideline, updated in 2016, states that evolutions in technology are offering new opportunities to increase efficiency. Specifically, the guideline seeks "implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results." By starting with clinical trial design, the GCP guideline is encouraging stakeholders to improve processes from the very beginning.

Expansion of the study startup definition is particularly valuable because a published study from the Department of Health and Human Services illustrated that many of the costs associated with this function are unaccounted for. In Phase III, for example, which averages $19.89 million, 43% ($8.51 million) of total costs remain unaccounted for and are simply named "site overhead" and "all other costs".

Oftentimes, these unaccounted for costs reflect study startup functions that have not been clearly identified. For the most part, they have been overlooked or grouped into larger categories, such as the cost of IRB approvals, and site recruitment and retention costs. Other research substantiates this finding. Specifically, tasks ranging from pre-study visits through to contract or budget execution have relatively unknown costs, yet they represent upwards of 60% of study startup cycle time.[2]

For these reasons, definition is a big step forward. It allows for detailing the full spectrum of study startup and values technology that can improve processes, accelerate timelines, and generate detailed cost data.

The Right Technology

In the ongoing race to improve study startup, the right purpose-built technology plays a vital role. With the clinical trial sector transitioning away from Excel spreadsheets or limited point solutions in favor of workflow-based tools, study startup is making significant gains. That is no small feat, given its complexity.

As shown in (Figure 2), Oracle Health Sciences' study startup solutions, Oracle Health Sciences Select Cloud Service and Oracle Health Sciences Activate Cloud Service, trigger the workflows to be performed, and then track their accurate and timely completion. goBalto Select helps stakeholders avoid non-active and non-enrolling sites.

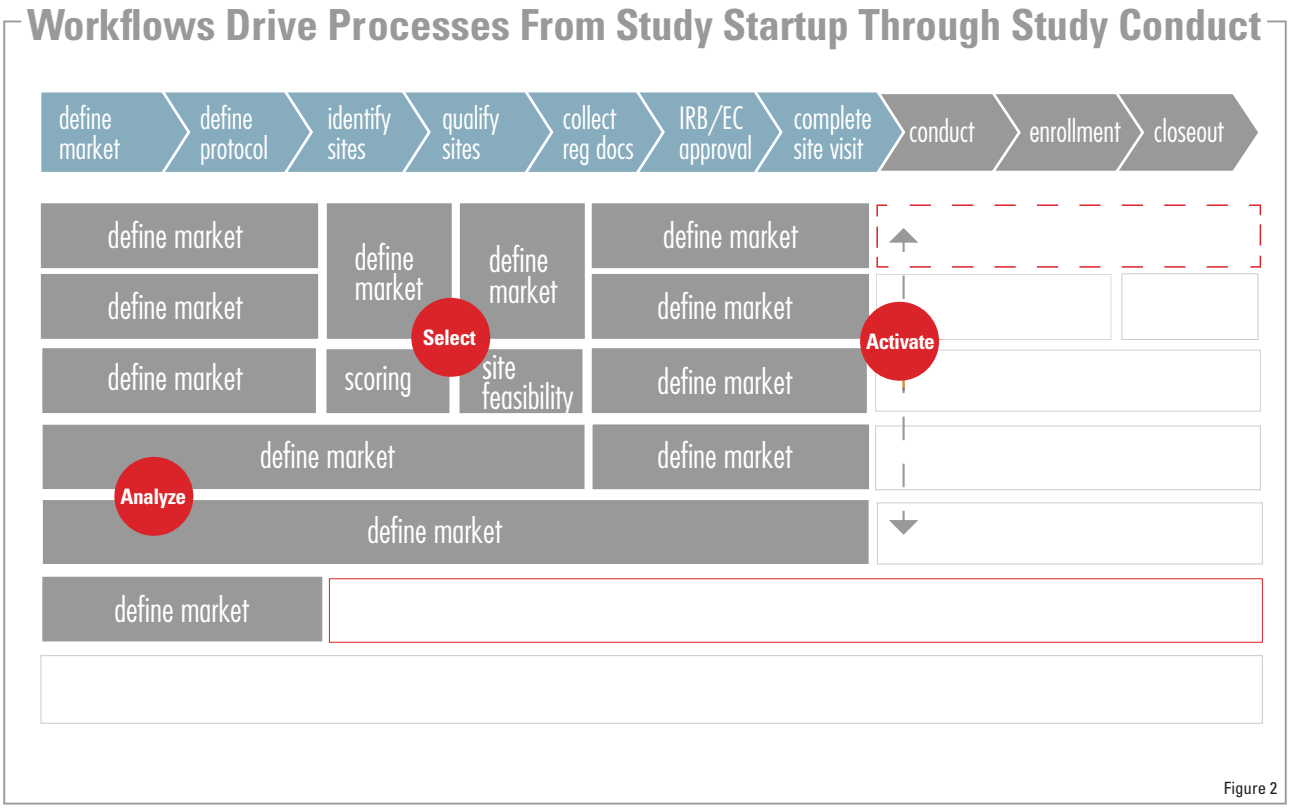

Figure 2

Source: goBalto 2018

To achieve this goal, goBalto Select combines internal and external data sources that allows researchers to create a master site profile from various data sources, such as investigator databases, CTMS, and feasibility surveys.

Together, they create a complete view of site performance. goBalto Activate, serves as the repository for in-progress documents and exports data that can be used for historical analysis and predictive analytics. Oracle Health Sciences Analyze Cloud Service, enables analytics by aggregating data and creating reports and other data visualizations.

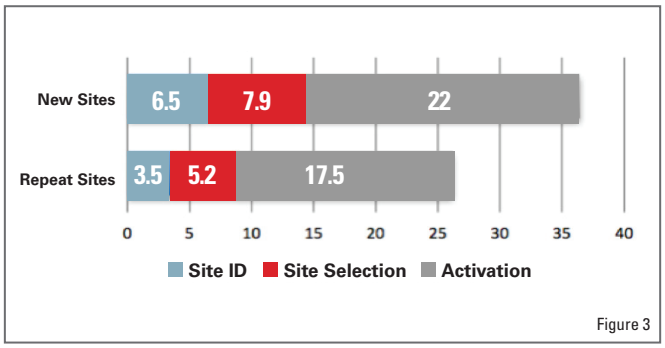

Figure 3

Source: goBalto 2017

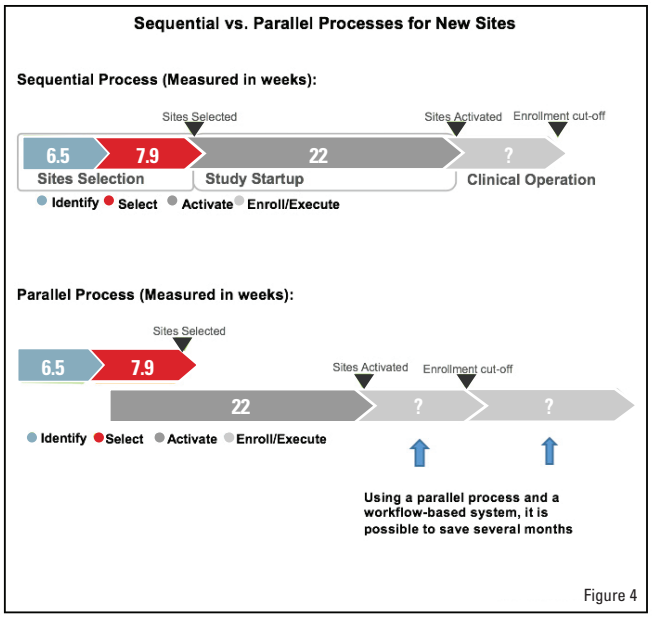

Figure 4

Source: goBalto 2017

With the help of this system, a sponsor or CRO can identify sites, and continue identifying them until analytics indicate with 90% – 95% probability that they will meet the enrollment target. In the meantime, those sites that are ready to activate can do so. This creates an environment in which sites can compete to be selected and compete to reach enrollment targets.

(Figure 5) depicts how this end-to-end workflow system works, using a parallel model.

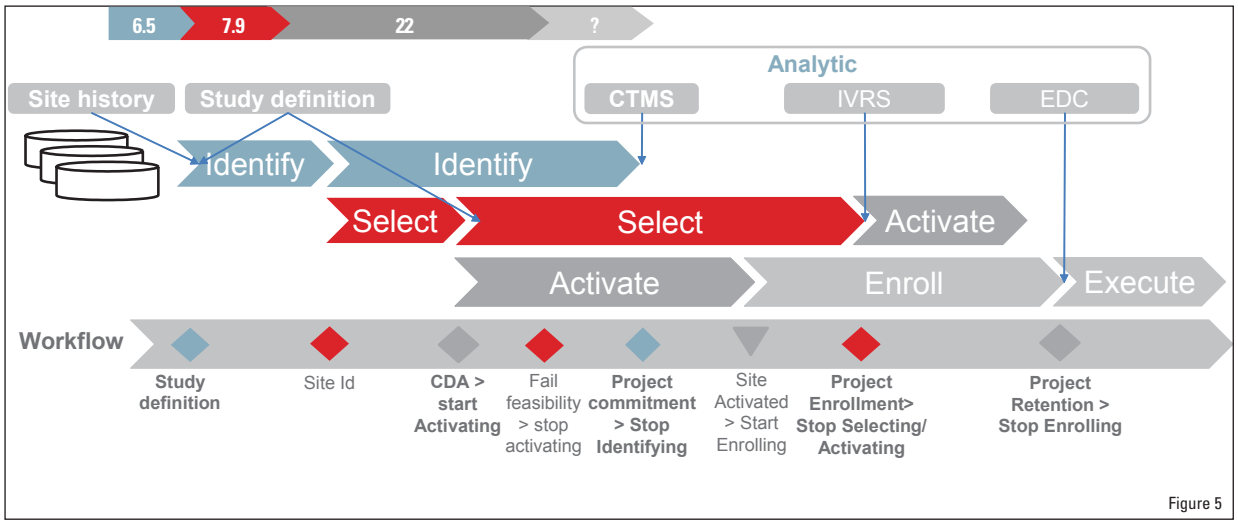

Figure 5

Source: goBalto 2017

This analytical approach is more exacting than defaulting to arbitrary milestones based on sequential methods that not only lack the data to find the best sites, but also cannot indicate when sponsors or CROs should stop identifying sites. There are available databases of site information, but those data do not necessarily lead to use of parallel process. A better approach for stakeholders looking to start a study is to review the protocol, and then use a parallel-based systemic approach to generate data and metadata specific to that study.

Better Data Means Better Understanding of Costs

With nearly half of clinical trial costs unaccounted for, including known administrative costs, and much of those linked to study startup, it is telling that the industry is finally moving toward identifying those costs with the help of purpose-built tools that can determine, with a high degree of accuracy, when it is time to stop identifying sites. The vast wealth of data that reside in technologies designed for study execution, such as EDC, CTMS, and more, can be integrated with workflow-driven solutions for study startup, allowing stakeholders to gain insight at a granular level into how a study process is unfolding and the associated costs.

With this forming of a system for entering data and applying data analytics, it is possible to move beyond milestones rooted in sequential processes and siloes in favor of a faster-moving parallel method that breaks down siloes and possibly shaves up to two months from the timeline. **This change in approach will continue to highlight how improving the study startup process is a great opportunity, yielding a major impact on quality, timeline and overall cost of clinical trials.**

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