The Key to Successful Study Start-up: Right Path, Right Start, Right Patients

Quintiles Site Start-Up authors investigate the correlation between start-up organizations and on-site performance.

Despite efforts within the industry to finish trials on time, as many of 45% of clinical trials are completed late and approximately 80% of trials fail to meet their initial enrollment targets on time. As a result there is a significant influence on cash flow and resource allocation which can also impact other studies in a company's development plan.

Successful study start-up is an essential first step, and relies on overcoming a range of factors. These include country and site selection, streamlining and proactive planning, and patient recruitment strategy — all of which can influence decisions and have a dramatic and positive impact on the conduct of the entire study. These steps can also be expressed as setting the right path, getting off to the right start, and finding the right patients.

Figure 1 below illustrates a number of activities which present opportunities to positively influence start-up timelines and site performance. These opportunities focus on such items as early investment and engagement with sites (to gain difficult-to-obtain insights on factors such as treatment patterns and patient willingness to participate), document and workflow management, and data-driven country and site selection.

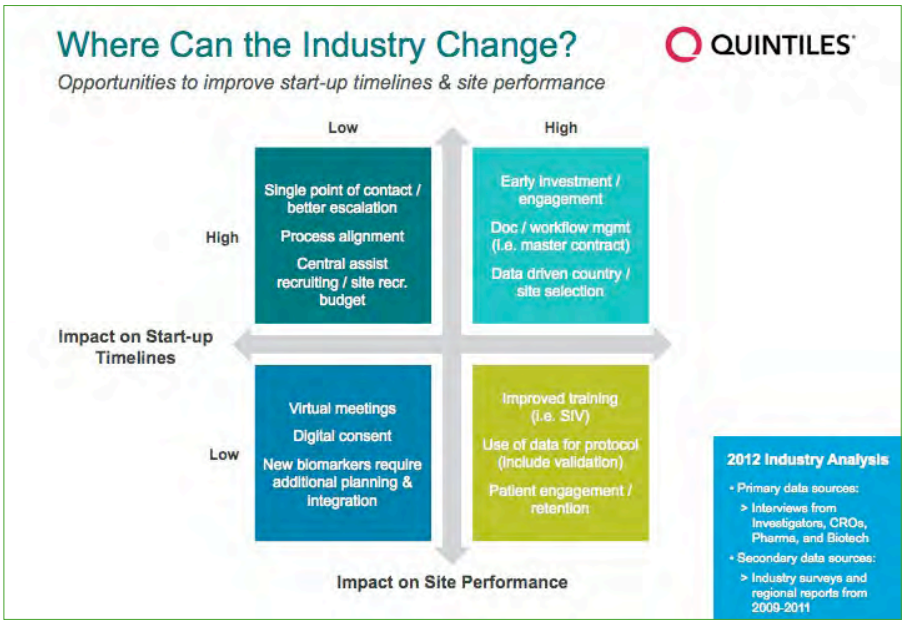

Figure 1: Where can the industry change?

Missteps during study start-up can interfere with overall success. One example is moving too rapidly into start-up, which may occur in response to pressures to get to market quickly, investor and senior management demands, competitive products coming to market, or patient needs. Although speed and efficiency is key, it is equally important to ensure that the team managing the study has enough time to confirm that key study variables are ready (for example, intellectual property, import/export considerations, vendors or electronic case report forms). Re-work in these areas can result in more significant delays later during study conduct.

To address this pressure, a framework is helpful, allowing for greater standardization and consistency, while also providing flexibility. This framework should integrate a set of tools and processes (such as analytics, performance data, and cycle timelines) to allow creation of an evidence-based site selection strategy customized to the particular needs of the trial. Experts from all fields — medical, feasibility, regulatory, product managers must then validate and tailor the strategy, with input based on strategic global relationships. An effective, high-level framework encompasses three stages — right path (an optimal approach based on critical groundwork), right start (with streamlined start-up and proactive planning), and right patients (identified using smarter recruitment methods) — with each being interrelated.

Selecting countries and sites

When making country, site and enrollment planning decisions, a common mistake is to rely on too little data or subjective information. This may include selecting countries and sites based on personal or corporate preferences, selecting countries because of short start-up timelines without considering overall impact to study performance, or predicting enrollment based on investigator enrollment estimates alone.

This approach often leads to the need to add countries or sites during the patient enrollment phase, to replace countries or sites that are failing to meet expectations, or to extend recruitment timelines due to slower-than-anticipated enrollment. Any of these can have a negative impact on efficiency, study budget, and timelines.

Feedback from investigators is a critical part of the study planning process; their insights into the feasibility of the study design, treatment pathway, patient population, and recruitment and retention planning allow for solid protocols and operational strategies to be developed. However, investigators may have difficulty quantifying their potential enrollment into a study at the feasibility stage due to a variety of reasons, including limited study information being shared with them, difficulty utilizing electronic medical record (EMR) databases to query for complex or very specific eligibility criteria, or changes to the protocol or indication landscape occurring after their estimates have been provided. Given these challenges, the industry standard is to reduce investigator enrollment estimates by approximately 50% before utilizing these rates for enrollment planning.

To evaluate this industry standard, a recent analysis compared investigator enrollment rate estimates received at the feasibility stage to those investigators' actual enrollment performance in the subsequent studies. Data from 11 studies across seven indications (major depressive disorder, rheumatoid arthritis and various oncology indications), and from 567 investigators globally, were included. These data confirmed investigators' tendency to overestimate enrollment rates, with 83% overestimating at the feasibility stage. A majority of investigators over-estimated their enrollment performance by 50% or more, and only 5% of investigators were able to estimate their enrollment performance to within 10% of the actual study performance. These findings emphasize how important a balanced, comprehensive feasibility approach is and how detrimental utilizing only one data source in isolation can be to operational planning (Figure 2).

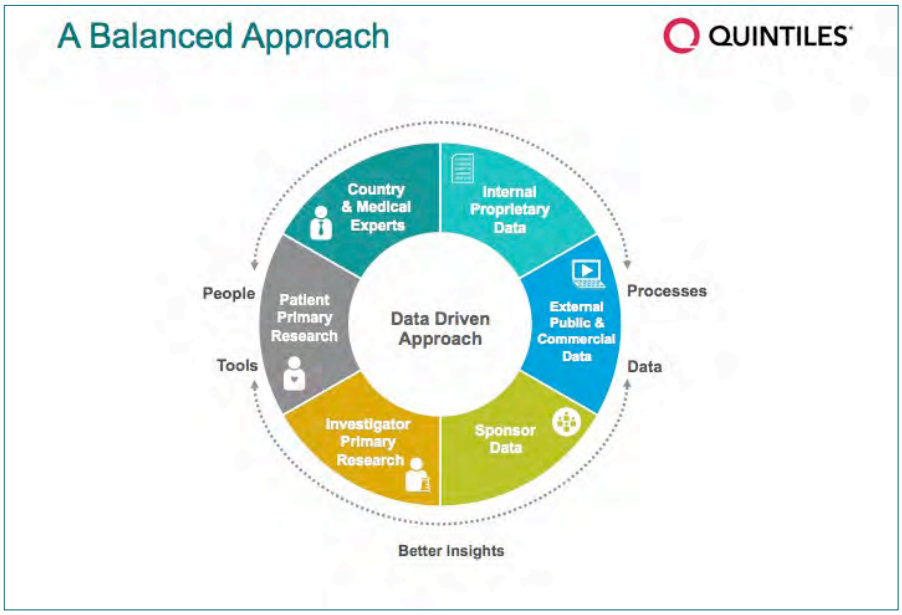

Figure 2: A balanced approach

We recommend leveraging data from six primary categories to help inform decisions, including internal proprietary data, external public and commercial data, sponsor data, investigator primary research, patient primary research, and country, regulatory and medical expert input. It is important that these categories are supported within an appropriate framework including the right set of people, processes and tools.

Not every data source will be appropriate for every study or objective, and some data sources may be weighted more heavily, depending on the opportunity. With the immense amount of data available it is critical to utilize the best tools to access the data, and the people and processes to manage, analyze, and implement the findings from this data in a balanced way so as to establish the right path.

Taking the guesswork out of start-up: streamlining and proactive planning

Building on this concept of a balanced approach, there is a need for efficient planning and an appropriate balance between being reactive versus proactive. A proactive start-up plan is effective in ensuring balance, especially when coupled with the use of standardized tools, templates, and processes. Study start-up is very complex, with multiple critical interdependencies and areas where elements can go off track. Aligning processes early in study planning to minimize decision-making and time delays can be particularly important and have a significant impact on timelines and productivity. Reducing the number of decision points for items such as site contracts, as an example, can have a positive influence on the start-up process as well as the overall relationship between the site, clinical research organization (CRO) and sponsor. When considering an appropriate start-up plan it is important to account for both real-world experience and performance data and regulatory interdependencies as part of the standard process. As such, countries and their start-up interdependencies can be classified by models, which drive the regional strategy within a proactive plan. These models include data, but allow for regional and country-specific experiences to be applied in a consistent and real time fashion. To support the proactive plan we recommend a real-time predictive intelligence system such as Quintiles Infosario® to monitor and analyze trends in start-up and study surveillance. Having access to this type of system not only helps identify and mitigate potential roadblocks, but serves to empower study teams to make proactive, informed decisions. Additionally, this system improves transparency and communication with all stakeholders.

A key challenge for industry and investigators is the number and variety of templates and forms that are required at start-up (Figure 3). In addition to process alignment, better alignment of templates and forms across the industry could yield a high return on investment and impact site performance and/or start-up timelines. For individual studies benefits of this kind of alignment for the sponsor include less time needed for CRO oversight and less time spent in negotiations. Sites benefit by not having to provide the same information trial after trial.

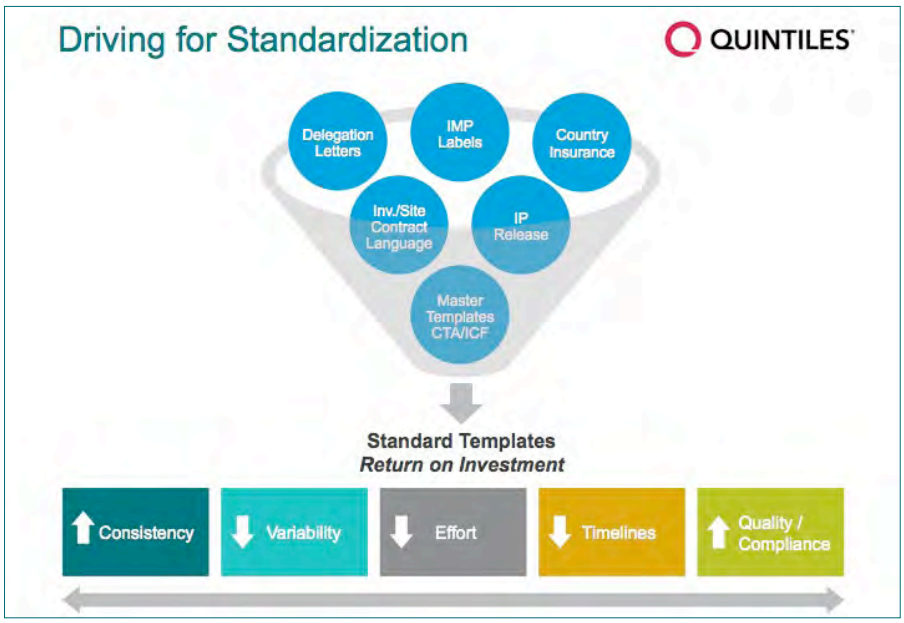

Figure 3: Driving for standardization

Overall, for intelligent study execution, study teams need the best, real-time information to make the right decision at the right time. To truly keep start-up on track, there is a need for access to real time data at a scalable level. One such system, Infosario (Figure 4) shows key performance indicators for a study in real time, giving access to important data as multiple levels (site, study, program, and portfolio). This enables the study team to review individual site performance metrics such as non-enrollers, start-up metrics as well as trend data for the study, program and portfolio. This makes it possible to closely track trends for a site or study (open queries, contract timelines, site selection visit/site initiation visit [SSV/SIV] cycle times, and enrollment factors). Data can then be compared to that from other studies in the program or portfolio, thus having a powerful impact on future studies and start-up planning.

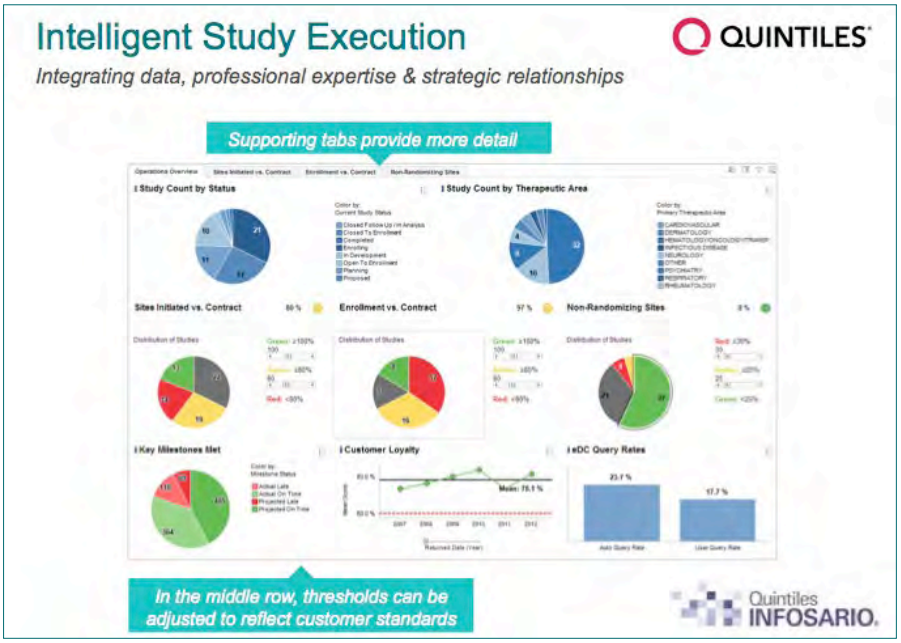

Figure 4: Intelligent study execution

Proactive, intelligent, patient recruitment strategies

Too often, patient recruitment is seen as a "nice to have," which is either not seriously considered up-front or is cut when finalizing the study budget. Study teams may plan to simply add a patient recruitment program later — if and when it is needed. Unfortunately, implementing a patient recruitment program for a study that is already behind in enrollment is more costly, less effective, and often just too late to help hit the target milestone dates.

Thinking about patient recruitment more proactively can pay off in shorter recruitment timelines and overall lower study costs. There are many recruitment and retention tactics which can be implemented on a given study, such as site toolkits and patient materials, investigator engagement activities, web-based tools, and direct-to-patient outreach, both traditional and digital, including social media. Through proactive planning, the needs of a specific study can be identified and a plan developed to address this in the simplest, most cost-effective way.

A tiered approach promotes steady enrollment and reduces the risk of costly slowdowns, enabling targets to be met or exceeded by enrolling the most qualified patients as cost effectively as possible. This approach aims to first maximize recruitment of existing patients at each site, then facilitate referral of patients identified by other physicians, and thirdly recruit and refer pre-screened patients from the community. A proactive plan also anticipates retention issues and ensures quality data collection by reducing risk of dropout, promotes protocol compliance by reducing patient burden, and keeps patients engaged by adding value to the study experience. A recent survey of more than 50,000 investigators globally about the best practices for patient recruitment and retention found that in the United States, where there is significant study competition, sites rely on advertising (predominantly) as well as referral partners to recruit additional patients. In countries outside the US, however, sites lean on their referral partners over the other options. Taking this data for individual countries, or by physician specialty, gives wide variations in findings. For example, in China and India, advertising was mentioned by only 6% of investigators, while 61% reported having enough patients at their sites. Also, nearly 90% of US sites and 80% in the rest of the world said they would be willing to accept pre-screened referrals from an outreach campaign — an important consideration for planning an intelligent, proactive recruitment strategy.

Taken together, these steps to successful study start-up have been proved to address key challenges and yield real results (Figure 5). Examples of this include on-time enrollment in 87% of trials, high customer satisfaction in 93% of trials, and high investigator loyalty in 87% of trials.

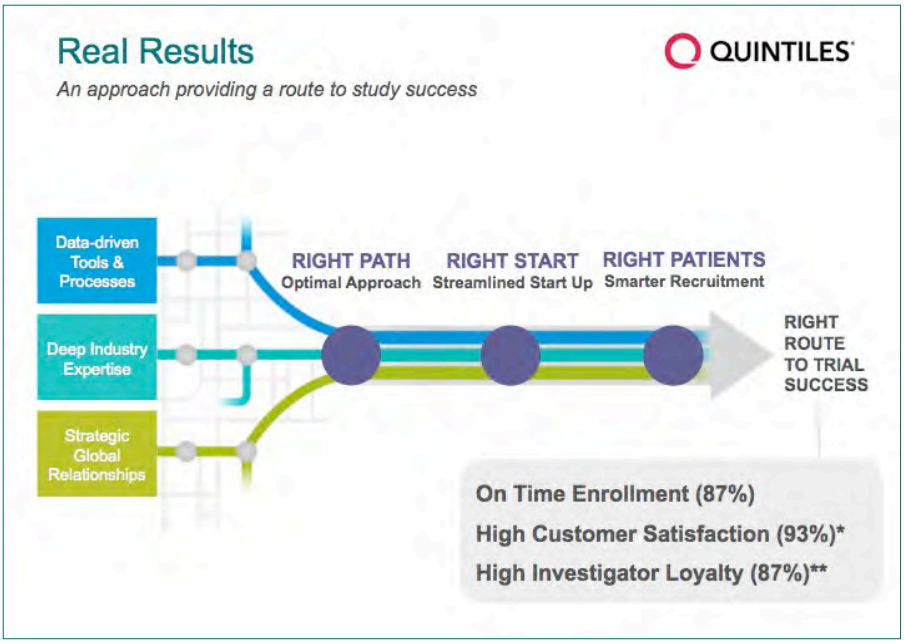

Figure 5: Real results

Summary

- As many of 45% of clinical trials are completed late
- Successful study start-up is an essential first step, relying on:
  - Appropriate country and site selection, based on a balanced and comprehensive feasibility approach, using internal proprietary data, external public and commercial data, sponsor data, investigator primary research, patient primary research, and country, regulatory and medical expert input.
  - Streamlining and proactive planning with an appropriate balance between reactive and proactive approaches. Proactive planning can be supported by a real-time predictive intelligence system such as Infosario to monitor and analyze trends in start-up and study surveillance.
  - Patient recruitment strategy should be seriously considered proactively, with the use of various recruitment and retention tactics to help shorten recruitment timelines and lower overall study costs.
- This framework of tools and processes allows for greater standardization and consistency in setting the right path, getting off to the right start, and finding the right patients.

Michelle Archibald, Senior Director, Site and Patient Strategies,
Quintiles

Michelle Archibald has an extensive and broad background in global drug development. She has worked in the CRO and Biotech industry for nearly 20 years in multiple management and leadership roles. As Senior Director of Site & Patient Strategies she is responsible for developing strategies for clinical trials and alliances with key customers, enhancing global collaboration and strategic planning for oncology activities between Integrated Site Services and Therapeutic Delivery Units.

Mark Brown, Vice President of Strategic Site Intelligence and Feasibility,
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Mark Brown has over 20 years' experience in clinical research in a multiple roles ranging from IT, Systems Validation, Data Management and most recently Investigator Site Management. Drawing on this broad experience, he currently manages the Integrated Patient and Site Strategies team at Quintiles. His team is focused on developing operational strategies for customer development programs. The scope of the team includes Protocol Feasibility, Strategic Site Intelligence, Patient Outreach, and Global Site Identification.

Julie Parmelee, Director, Patient Recruitment,
Quintiles

Julie Parmelee is a senior leader of the Patient Recruitment services team at Quintiles. She is responsible for developing patient strategies for clinical development programs across a wide range of indications, as well as driving innovative solutions to address recruitment and retention challenges. Patient strategy is a critical part of the clinical trial planning process at Quintiles. To craft an effective global recruitment strategy, she combines data-driven insights from patients, investigators, and in-country regulatory specialists together with the operational and therapeutic expertise across Quintiles.

Nicole Turner, Associate Director, Global Feasibility,
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Nicole Turner manages the North America Global Feasibility team at Quintiles. Her team is responsible for providing robust, comprehensive feasibility assessments that enable more effective planning at various stages of the clinical development continuum. Nicole works to combine and analyze relevant data from various primary and secondary sources to guide protocol development, evaluate potential study risks, and develop the most appropriate country and site strategies for clinical trials; this work spans all therapeutic areas and most indications, with more than 1500 feasibility assessments conducted over the past 5 years.