The Quintessential Guide to Planning a Successful Clinical Trial

Navigating the "Sticking Points" that Lead to Missed Milestones

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The route from bench to bedside is not for the faint of heart. It's a long, expensive, and complicated process that rarely results in drug approval. Finding a promising drug candidate and getting into the clinical phases of research is hard enough; getting it through trials is even harder. Our discovery that >30% of clinical trials are also failing to meet timelines for major study milestones – such as last subject in – seems to add insult to injury. And the single biggest reason for the high failure rate in these intricate, often multi-national trials is simply a failure to plan.

A proper planning process is crucial to the operational success of a study. Not only should it focus on ideal scenarios, but it should also incorporate risk-mitigation strategies and well-defined contingency plans that can correct issues before a trial completely derails. To expand upon our recent white paper, 'Rescue' is Not a Dirty Word, we want to tackle the complex study planning process. In this white paper, we will cover the multiple strategies, tactics, and considerations that should be given attention at the beginning of every clinical study.

Establishing Timeline & Budget Expectations

The three basic constraints of any project are universal: time, money, and quality. The same holds true for clinical trials (Figure 1). Because so few drugs ever reach the market, and because the drug development process is so costly and time-consuming, most pharmaceutical companies and CROs agree that high-quality data is a must. As a result, the two constraints playing tug-of-war become time and money, leaving sponsors with the question: is it more important to operate within a given budget, or is it imperative to beat a close competitor to market? These are the types of questions that need to be addressed very early on and will inherently influence decisions that are made throughout the life of a project.

Establishing Timelines

The desire to complete a clinical trial as quickly as possible will inevitably be tempered by cost constraints. Establishing reasonable timelines will also take into consideration the challenges of the target patient population (i.e. inclusion/exclusion criteria), the prevalence of the disease in countries seeking drug approval, regulatory nuances between these countries or site types, the availability of site and subject resources, and, of course, the need to produce quality data in a world where standards are constantly rising.

Timelines should then be optimized to accommodate the primary needs of the sponsor and major study stakeholders, while still being realistic in terms of cost and risk (e.g. risk to the quality of the data, or risk to meeting the timeline itself). Identify the total trial length and establish goals for meeting your major milestones which are appropriate for the countries selected in terms of importation requirements, regulatory approval, and enrollment rates. Some good milestones to plan around include: kick-off, finalizing the protocol, submission to regulatory authorities and local ethics committees, commencing site activation, first subject in, first subject out, last subject in, last subject out, database lock, completion of statistical analyses, site closeouts, and CSR completion.

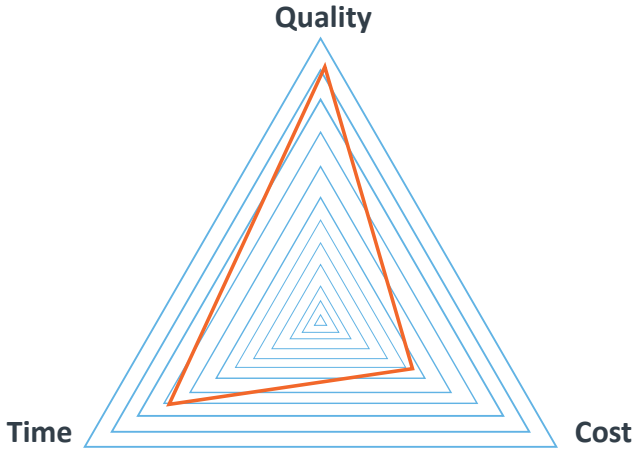

Figure 1. Time-Cost-Quality Trade-off Analysis. An ideal clinical trial is one that is low-cost and high-quality data with a short timeline. In studies, data integrity is a must, anchoring the Quality corner of the triangle. Therefore, during the planning stage, the trade-off between Time and Cost should be carefully considered.

Financial Expectations and Budget Planning

Everyone's favorite topic: money. If you're in the pharmaceutical industry, you understand the financial reins that keep budgets tight. In our recent rescue white paper, we briefly addressed how this pressure often leads to overly optimistic budgetary planning and cost-cutting wherever possible. The problem is, if you see a budget that seems too-good-to-be-true, it probably is. When cost are cut too low, it often results in reduced man-power to solve problems quickly, reduced monitoring, and ultimately reduced data integrity. In some cases, the result is a slow-moving study with poor quality data, unsuitable for drug approval. Successful sponsors and CROs have a good grasp on what it takes to provide good-quality data with an understanding that there's a delicate balance between cost, time, and quality.

Feasibility

Subject Availability and Country Selection

Determining subject availability in a given venue is arguably one of the most important variables to consider during the planning process. In large international studies, this question becomes even more complex as disease prevalence, the number of competing studies, varying standards of care, access to reference drug, and, sometimes, even various political environments can indictate how feasible it is to enroll your ideal subject in a specific country or region. These and additional considerations for venue selection with regards to clinical and regulatory environments are outlined in Table 1.

When developing an overarching country and site strategy, one of the best things you can do is talk to the pros. Key opinion leaders, principal investigators and site staff are invaluable relationship resources to turn to when designing a venue/site strategy. They can usually tell you fairly quickly how feasible it will be to find the patient population in their region, and sometimes, will even provide protocol feedback, such as tips for increasing patient compliance or reducing unnecessary complexities. A rigorous country selection process will delineate and rank all the variables at play which could interfere with access to patients. For example, the non-availability of a required concomitant medication in the country of interest may be a deal-breaker, whereas a slight difference in the standard of care for diagnosing the disease of interest may not be. Every study should be subjected to the same meticulous process for patient targeting so that overlooked factors don't manifest months into the study, when it is too late to make easy changes.

Reliable Sites

Inadvertent selection of high-promising, low-performing sites is a real concern in clinical study execution. There are several indicators that can help you select the right sites. The best sites will have a reliable access to the target patient populations with high ROI recruitment strategies. This includes investigators with strong networks and sites with established patient databases. In the beginning of a study, sites can recruit with a low-cost internal recruitment plan by digging into these databases and contacting eligible subjects via phone, email, post-cards, and social media. As the study progresses, however, sites may need to employ other tactics to continue to meet enrollment goals. When possible, use sites that you know… and when all else fails and you must use a new site that you haven't worked with before, be conservative – divide their enrollment estimates by half or more when developing timelines.

Table 1. Key Factors in Venue Selection. Selecting the right venue(s) in which to conduct a clinical trial and/or to gain approval for a drug is a multifaceted process. The various clinical and regulatory environments which differ between countries should be considered when selecting a venue.

The Clinical Environment	The Regulatory Environment
• Prevalence of the disease or indication in the venue • Patient population that meets the i/e criteria and their distribution relative to research sites • Access to appropriate standards of care • The number, size, and capability of available sites in the venue • Availability of sites with high quality standards, sufficient resources for oversight, recruitment processes, and tracking/reporting capabilities • Availability of necessary equipment/diagnostics • Competing studies which can affect enrollment rates • Availability of reference drug and concomitant medications • Site costs and startup/contracting timelines • Local healthcare environments • Patient protection, transparency, and data integrity	• The regulatory approval timelines and requirements • Whether the data produced in that venue would likely be acceptable for regulators in the countries where the marketing authorization is intended • The requirements and timelines for import/export licenses to be obtained • Validation and translation requirements for any of the clinical outcome assessments, such as scales • Acceptable data privacy protection and safe transfer to the country where the data is analyzed • Requirements for additional data to be supplied prior study authorization • Political events or level of scrutiny for developing global/ex-regional data

Furthermore, locational logistics are becoming ever-more important in the feasibility of using even the highest-enrolling sites. With time-sensitive drugs and biological samples, it's extremely important to take into consideration where the site is located with regards to drug depots and central labs, otherwise one runs the risk of a headache working around logistical issues when there are critical samples at risk. The best sites will not only have reliable access to the target patient population, but will also meet all logistical requirements.

Resources

In addition to optimizing the clinical environment to ensure enrollment performance, it's also important to ensure all needed resources are going to be available for first patient in. One seemingly obvious needed resource is drug supply. Plans need to be in place for not only drug manufacturing and stability testing, but time should also be allocated for packaging and distribution of the drug product. Another resource that needs to be heavily considered and thoroughly planned prior to signing contracts are the technological resources that may be required for the study. Various technologies have the potential to reduce complexities, streamline communication, and provide real-time data to sponsors. However, choosing the right technologies (e.g. IXRS, remote data entry systems, EDC, etc.) that can be easily integrated to one communicative network can take time early into a study and should be planned for. If done correctly, integration technology can simplify a study and minimize the number of unexpected issues associated with software communication. However, failing to implement a technology to "save a buck" or including a new technology without considering how implementation will affect co-dependencies in the study timeline can lead to missed milestones. These intra-study communication strategies require proper attention early on.

Work Planning Process

Accountability

Well before a trial begins, the program management hierarchy needs to be clearly defined. Ask, who is going to be held responsible for what? This process starts with developing a Project Planning Process (yes, a plan to plan). Identify who is going to be responsible for developing timelines, central filing plans, communication plans, etc.

Once this Project Planning Process is in place and the project team is assigned, every task needs to be assigned to either the sponsor or the corresponding CRO. These tasks include everything from the development of investigator brochures, to trainings, to investigator meeting materials and attendance, to TMF housing and maintenance, to CSR completion, and everything in-between. This is especially important when implementing a functional outsourcing strategy with multiple vendors covering different functional areas. Without a clear definition of deliverables from each vendor, important tasks may be inadvertently left out. For example, if using a different CRO for data management and statistical analysis (which is not uncommon), ensure that important tasks like SDTM mapping are including as a line item deliverable. Properly outlining tasks and responsibilities takes time up-front, but in the long run saves on time by reducing the number of dropped balls and change-orders down the road.

Study Plans

When developing your study plans, the challenge is to create efficient processes that meet the specific needs of the program directors, meet the requirements of the ICH/GCP guidelines and corresponding regulations, but at the same time don't exceed the capabilities of your team. This exercise is not cookie-cutter; every plan should be tailored to the project at hand. Many teams make the mistake of simply rolling over project plans from a prior study, without much care or thought. This practice is the best way to ensure that your study plans are neither efficient nor effective, and at times, following such a plan may work to the detriment of the study. For this section, we want to highlight a few important plans that are often mishandled: Communication, Data Sciences, and Monitoring.

Communication Plan

A key element that is often overlooked in study startup is the development of a solid communication plan. Once the structure of the project team is well-established, there should also be a method in which the project team, vendors, investigators, ethics committees, and regulatory authorities should communicate throughout the duration of the study. Expectations of communication methods (e.g. email, teleconference, face-to-face) as well as meeting frequency are best outlined before or during study kick-off. A strong communication plan established early into a program puts your team in the best position to handle

problems and queries both quickly and efficiently. Not to mention, it saves the team a ton of unnecessary emails trying to figure out the "who's who" during the study.

Data Sciences Plan

Well thought out procedures associated with data management, integration, standardization, and analytics influence much more than just how reliable your study results are. Forward-thinking data science strategies with full integration of electronic data capturing systems can boost the efficiency of your study team, drive the focus of monitoring efforts, increase the odds of hitting milestones early, and ultimately reduce study costs by trimming down timelines and man-power to resolve issues.

Getting data integrated into one centralized location allows for timely analysis of key efficacy, safety, and quality variables. With a powerful Electronic Data Capture (EDC) system, all data collected during the study will be captured in one place, where a rolling data-cleaning system can be implemented for patient data to be reconciled on a continuous basis. This approach focuses monitoring efforts on patients, and as a result, sites, which are going to complete first. Continuous cleaning not only ensures that the data is clean and of high-quality, but it also decreases time on the study back-end for data-base lock. This can be especially valuable for studies operating under extremely aggressive timelines.

An additional benefit of a fully integrated EDC system is the ability to set up a single conversion process for putting the data into a standardized format, as opposed to multiple conversion processes over different timepoints of the study. The FDA now requires all studies to be put into CDSIC format upon submission, however many companies postpone CDISC standardization until the end of the study to save on upfront costs, particularly when they lack funding or confidence in the outcome of their study. Sponsors and CROs have their preferences. However, when formatting is done early in the study, powerful SAS® data analytics programs can be taken advantage of to make the data work for you.

One of the most valuable assets of a proper Data Sciences Planning process is data analytics, which can close a feedback loop to drive other elements of a study, including monitoring, project management, and safety. It replaces former contingency planning with informed, data-driven responses to various events that arise during a clinical trial. A modern-day contingency plan is based on the facts, and a sponsor/CRO should have several contingency plans in place for any potential pitfall that presents itself. The benefits of utilizing data analytics are vast, but can give valuable insight into the key metrics of study design, including the number of late visit reports, percent SOVs, protocol deviations, etc. Records of ongoing and historical performance, safety, and efficacy trends throughout a clinical program shape response, and can drastically reduce the risks associated with operational issues that cause so many clinical trials to fall behind schedule and exceed their expected budget.

Monitoring Plan

A comprehensive monitoring plan is a priority for all studies and is intended to establish guidelines for a clinical team to monitor and provide overall management for sites. When done correctly, the monitoring plan supports the successful clinical execution and completion of a project per study timelines with the highest quality.

When it comes to meeting major milestones, such as Last Subject In, defined recruitment (or rather, lack thereof) escalation strategies can prove extremely useful (Table 2). These strategies should outline reactive measures to be taken as a lack of recruitment is experienced over time. That is, if a site is failing to enroll, follow-up triggers (number of patients screened and/or enrolled), follow-up formats (e.g. email, phone calls, letters, on-site visits), and executors and recipients of the follow-up should be clearly outlined during multiple time intervals following site activation. For example, if zero patients are enrolled or even screened at a site two to four weeks after site activation, it might be sufficient for a CRA to send a follow-up email to the study coordinator and cc the PI. However, if a site has failed to screen or enroll patients after 8 weeks, it might warrant an on-site visit by the CRA or Sponsor as a 'booster' visit to help motivate site staff and resolve any issues that may be impacting site success. These types of escalation strategies should be defined early on, so that if a site starts slipping behind their enrollment projections, appropriate action can be taken immediately without any lag-time.

Table 2. Non-recruitment Escalation Example. If a site begins failing to meet screening and enrollment projections, it is important for a sponsor/CRO to have well-established escalation procedures in place. A non-recruitment escalation plan facilitates communication with respect to pre-screeening, enrollment, and prioitization.

Timeframe	Follow-up Triggers	Follow-up Format	Follow-up Contact by CRO/Sponsor	Follow-up Contact at Site
2 Weeks	0 Screened	E-mail	CRA	Study Coordinator
4 Weeks	0 Screened	Phone	CRA and CTM	Study Coordinator
8 Weeks	0 Screened	On-site booster visits determined by PM	CRA and Sponsor (as needed)	Study Coordinator and PI
10 Weeks	0 Enrolled	Letter to site (follow-up and inquire)	PM and Sponsor	Study Coordinator and PI
12 Weeks	0 Enrolled	Phone	PM/PD and Sponsor	Study Coordinator and PI
16 Weeks	0 Enrolled	Letter to site (consider closure)	PD (after Sponsor consultation)	Study Coordinator and PI

Another key topic of the monitoring plan that can directly impact study milestones, such as database lock, is source document verification (SDV). The plan should define the frequency of monitoring visits, decided based on the amount of data, visit length, and in some cases, data cleaning schedules. In some instances, a site may enroll more than expected, which may affect the CRA's ability to complete SDV in the originally allotted timeframe and given the number of days spent on-site. A monitoring plan should be flexible to allow for increased number of visits to perform SDV when needed, or to reduce these visits if the SDV can be accomplished by remote means without sacrificing needed face time. This type of flexibility can be critical meeting objectives without blowing the budget as the study enters the later phases of database lock and site close-out.

In addition to timeline, a monitoring plan should strive to ensure that quality standards are met. This includes clear definition of quality of parameters, tracking, and having cross-functional review meetings at defined intervals during the study. For example, for a 12-month enrollment period, managerial review meetings should be held at least once per quarter in order to ensure proper actions are met. These quality parameters encapsulate various topics, such as under- or over-reporting of adverse events, open action items, open queries, and late data entries.

Finally, we would like to further highlight some of the benefits of using the aforementioned data-driven monitoring strategy. Sometimes sponsors hire CROs for different study scopes (e.g. CRO 'A' gets contracted for Monitoring and Safety, while CRO 'B' will handle Data and Safety). This approach is very common and can sometimes work quite well. However, we warn sponsors not to make this decision lightly – you may be missing out on some key study optimization strategies!

Data analytics allows for analysis of quality metrics that can assist CRA's in making the most out of their time. If data is programmed to be standardized early on, a big data approach can be taken to look for anomalies in the data that may have not previously been identified or only get noticed at the end of the study when all sites are closed out. If anomalies are identified early, the site can be retrained or placed on hold before major data integrity issues arise. In another scenario, this approach may allow the team to identify some new drug effect that the sponsor wasn't aware of previously, which can then be flagged for tracking for the remainder of the study. By implementing these "smart monitoring" strategies, you can make on-site visits more meaningful by directing CRAs to possible problem-areas in the data and potentially reduce the number of on-site visits required. This not only saves money and time wasted on unnecessary CRA travel, but it also increases overall study efficiency by freeing up CRA time and allowing them to focus on the most important tasks.

While a "smart monitoring" approach will naturally increase site communication with the monitoring team by making the visits more meaningful and query resolution more effective, site communication shouldn't stop there. When it comes to site relationships, the key is consistency. Sites should consistently be communicated with to discuss enrollment efforts and strategies or to relay information on study findings to facilitate screening.

For example, perhaps you've seen in your study that a PI has pre-screened a patient and deemed them ineligible mistakenly (i.e. they noticed that a patient had once used a drug that is exclusionary, but perhaps overlooked the fine-print that indicated that patient should have only been excluded if the drug was used as a first-line treatment for a specific indication), it may be valuable to discuss this with the site. Setting up routine communications, such as newsletters or tips-of-the-month, will build study relationships, reiterate protocol specifications, and reduce mistakes at the site level.

A Proper Planning Process

If one thing is evident in our overview of the clinical trial process, it's that even key aspects like resource allocation, enrollment, and monitoring take a back seat to planning. Planning that covers the full breadth of a clinical program from inception to market, and that dives deep into every aspect of a trial. In fact, the planning stage plays such a crucial role that its successful execution alludes to the success or failure of a clinical trial.

Moreover, this planning needs to account for, and even expect, that the trial will at some point be in trouble. In our previous white paper, we found that over >30% of all currently active clinical trials were significantly behind on meeting milestone goals – and ultimately at risk of operational failure. If anything, that is a conservative figure. Many trials fail "silently" – a brief look at clinicaltrials.gov shows numerous trials that haven't been updated in months or years, indicating that the real number of failing trials is likely much higher than what we could determine using available data. Rigorous planning becomes even more important when you realize that there are really very few levers that can be used to change the course of a trial. Quality is non-negotiable – the data generated has to be good enough to pass strict regulatory review. That leaves only time and money, and both come in limited supplies. Proper planning in advance can account for limited resources and create timelines and budgets that are resistant, or at least accommodating, of unplanned issues. Poor planning can stretch both to the point of breaking – as we've seen with some recent blockbuster programs that have been unceremoniously cut loose. In the words of Benjamin Franklin, "By failing to prepare, you are preparing to fail."

We will be expanding on planning, contingencies, and trial rescue in future white papers, ebooks, and blog posts. If you have concerns about planning to succeed in your clinical trial, contact us for a trial assessment.

About the Author

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Dr. Michelle Bousquet is a leading clinical trial rescue consultant with a goal of bringing safe and effective drugs to patients in need as quickly as possible. Michelle joins Biorasi after a career as a pre-clinical research fellow at both the University of Florida and Singapore's Agency for Science, Technology, and Research (A*STAR). Her research focused on small molecule drug discovery and gene editing techniques to study the prevention and treatment of cancer. Her passion for optimizing the route to drug approval began with the development of a drug-screening platform to raise the bar for drugs entering Phase 1 clinical trials. After transitioning into the clinical space, Michelle developed a proprietary clinical trial assessment and rescue process. With this expertise, Michelle works in project management and has rescued large, multi-national clinical trials in complex indications.

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