2020

Drivers of Start-Up Delays in Global Randomized Clinical Trials

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A doctoral project submitted to the faculty of the Medical University of South Carolina
in partial fulfillment of the requirements for the degree
Doctor of Health Administration
in the College of Health Professions

Acknowledgements

I would like to thank my committee members, Dr. Kit Simpson, Dr. Daniel Brinton, and Dr. Leila Forney for their expertise, perspective and guidance throughout my doctoral project. I would also like to thank my entire cohort for their camaraderie and encouragement throughout the DHA program. Their support, encouragement and humor made this a wonderful journey!

I also extend heartfelt thanks to my husband Francis and my daughter Gemma for their patience and support of as I pursued my dream of earning a doctoral degree. Finally, thanks to my parents for their support and for emphasizing the values of hard-work and education.

Abstract of Dissertation Presented to the
Medical University of South Carolina
In Partial Fulfillment of the Requirements for the
Degree of Doctor of Health Administration

EXAMINING STUDY START-UP DELAYS IN GLOBAL RANDOMIZED CLINICAL TRIALS

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Background: Global, randomized clinical trials are extremely complex. Trial start-up is a critical phase and has many opportunities for delay which adversely impact the study timelines and budget. Understanding factors that contribute to delay may help clinical trial managers to work more efficiently, hastening patient access to potential new therapies. **Methods:** We reviewed the available literature related to start-up of global, Phase III clinical trials and then created a fishbone diagram detailing drivers contributing to start-up delays. The issues identified were used to craft a checklist to assist clinical trial managers in more efficient trial start-up. **Results:** We identified key drivers for start-up delays in the following categories: regulatory, contracts and budgets, insurance, clinical supplies, site identification and selection, and site activation. **Conclusion:** Initiating global randomized clinical trials is a complex endeavor, and reasons for delay are well-documented in the literature. By using a checklist, clinical trial managers may mitigate some delays and get clinical studies set-up as soon as possible.

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1 CHAPTER I INTRODUCTION

1.1 Background and Need

Multisite, randomized, controlled trials (RCT) are considered the gold-standard to assess the safety and efficacy of potential medications (Sullivan, 2011). FDA regulated trials increasingly engage sites outside the United States, including sites in developing nations, in order to hasten patient enrollment and reduce costs (da Silva, Amato, Guilheim and Novaes, 2016).A 2016 review found that the number of institutions outside the United States participating in clinical trials doubled from 2006 to 2016, while the proportion in the United States and Western Europe decreased (da Silva et al, 2016). Including sites outside the US is especially important when there are many competitive trials for the disease under study or when the condition is a rare disease. In addition to faster enrollment and reduced costs, benefits to international trials include promoting a global standard of care and expanding the market for new treatments (Crow et al, 2018; Glickman et al, 2009). Clinical trials conducted across multiple countries have many challenges due to incongruity of laws, regulations governing the conduct of research, infrastructure (or lack of infrastructure) and local standards of care (Crow et al, 2018).

Clinical study start up is critical as it must occur before patients can be enrolled and patient recruitment is a key determinant of success in a clinical trial (Huang et al, 2018). Cheng, Dietrich and Dilts suggest that the time required to activate a trial is inversely related to its enrollment (2010).The critical study start-up period consists of many tasks, and any delays have a cumulative impact, crippling the progress of the study. While study start-up is always complex, it is much more complex when multiple countries are involved.

In order to achieve recruitment, sites need to be qualified, gain regulatory approval, negotiate and execute clinical trial agreements and receive training (in addition to many other study level tasks). Delaying start-up often means extending the overall study timelines which not only can incur significant additional cost, but can threaten the feasibility of the trial (Atassi et al, 2013; Kantarjian, Stewart and Zwellig, 2013; Kurzrock et al, 2009). RCT typically compare the proposed treatment to the current standard of care; however, as times goes on there is increasing chance that the standard of care might change. As Giffin et al point out, the experimental treatment may be deemed irrelevant before the trial is completed if the standard of care has moved on; if nothing else, this can make enrollment slow significantly (2010).

Examples of other adverse trial outcomes due to start-up delays include wasted drug or drug shortages due to expiry, loss of clinical sites due to lack of interest or competing studies and loss of ability to enroll patients due to a change in the local standard of care. Perhaps most importantly, delays in study start-up lead to delay in access to treatment for patients, as well as lost opportunity costs.

Prolonged timelines increase trial cost therefore diminishing future revenue or return on investment (Giffin et al, 2010). Estimates indicate that it costs up to $2 billion dollars to bring a new drug to market (Treweek et al, 2018). A Phase III, randomized, trial may cost anywhere between $11.5 million to $52.9 million depending upon the therapeutic area and complexity of the study (Morgan, 2019). Bentley et al performed a scoping review of the literature, examining the costs associated with clinical trials in 288 papers published from 2001 – 2015 (2019). 37% of the papers reviewed pertained to multinational clinical trials (Bentley et al, 2019). Many of the articles (88%) provided recommendations to reduce trial costs, including improving operational efficiency (Bentley et al, 2019).

To address the issues that may arise during study start-up, each step of the start-up process must be critically assessed. Incremental improvements in each task may add up to significant efficiency (Treweek et al, 2015). To optimize enrollment in a clinical trial, it is best to have sites initiated and open for enrollment as early as possible during the finite recruitment period. "An ounce of prevention is worth a pound of cure", e.g. preventing delays in sites being open for enrollment is much better than trying to correct issues with enrollment downstream in the trial timeline.

Setting a trial up for success starts with a well-written protocol, detailing the key aspects of the trial (Al-Jundi and Sakka,2016). It is important to ensure that the protocol adequately answers the research question, and provides informationabout how the study will be conducted that is sufficiently detailed to allowconsistent interpretation across multiple research sites (Al-JundiandSakka,2016). Getting early buy in on the protocol design from stakeholders is important. An amendment to the study protocol has a marked impact on study start-up timelines (Lamberti, Chakravarthy and Getz, 2017). Amendments create substantial re-work in terms of study documentation, regulatory and ethics submissions and contracts/budgets depending upon the nature of the amendment. If regulatory approval is dependent upon implementation of a protocol amendment, sites in that jurisdiction may be on-hold; unable to enroll and contribute to the study until the amendment is processed. Lamberti et al found that a substantial protocol amendment can add an average of 3 months to study timelines; amendments also incur significant cost not only in time, but in re-work and driving up vendor fees (Lamberti, Wilkinson, Harper, Morgan and Getz, 2018). For the purposes of this study, start-up will be triggered from final protocol to first patient enrolled.

1.2 Problem Statement

Global, randomized clinical trials are extremely complex projects that require substantial resources to execute.It is important that trials be as efficient as possible, as they may delay effective therapies from being available to patients/consumers and are extremely costly to run.The start-up phase of a clinical trial (from a protocol or study concept to enrollment) is crucial to the outcome of the study.Delays in start-up may have significant adverse effects on the outcome of the study. There is substantial variation in start-up timelines and also ample opportunity for improvement (Lamberti et al, 2017).

1.3 Research Question

The objective of this study is to systematically examine and document factors affecting start-up time for multinational clinical trials using quality improvement tools. The study is innovative in that little information on study start-up delays from a sponsor perspective is available in the published literature. Results will be importantfor informing stakeholders planning multinational clinical trials about potential administrative challenges inherent in study start-up. The fact that we use well accepted quality improvement tools to identify key "driver" of start-up delay will make it easy for others to apply our findings to improve study start-up practices in global clinical trials. The study findings will be used to develop a checklist to help users navigate the study start-up process efficiently. This qualitative integrative analysis will have three components: 1) Review the available literature related to the start-up of clinical trials; 2)Apply quality improvement tools to experience on a recent global Phase III clinical trial, summarizing driving factors in a fishbone diagram; and 3) Usethe issues identified and opportunities for improvement found to construct a checklist for trial planning. The following areas will be considered in-scope for this review: regulatory approvals, site contracts and

budgets, insurance, clinical supplies, site identification and selection and inefficient processes/pitfalls.

2 CHAPTER II SCOPING LITERATURE REVIEW

Previous studies examining trial start-up have largely focused on the perspective of a single clinical site or a group of clinical sites. In these studies, IRB/ethics approvals and site contract/budget negotiations were often cited as the prime contributors to start-up delay (Atassi et al, 2013; Choi et al, 2015; Crow et al, 2018; Dilts and Sandler, 2006; Kenyon et al, 2011; Krafcik et al, 2017 and Ravina, 2010).Atassi et al reviewedover 50 clinical trials in amyotrophic lateral sclerosis (ALS) and found IRB review was the primary contributor to start-up delay and that sites with more experienced staff were able to negotiate these timelines faster (2013). Dilts and Sandler, however, studied the impact of process, structural, and infrastructural barriers to opening an oncology clinical trials (2006) and found that improving the IRB process would not help unless other inefficiencies, specifically the contracting process, were not also improved (Dilts and Sandler, 2006). Abbott et al performed a retrospective analysis including data from over 5000 clinical sites (2013). They also found that the use of a central IRB was associated with shorter cycle times when compared to a local IRB (Abbott et al, 2013).

Kenyon et al shared lessons learned from an ongoing multicenter, randomized controlled trial (STICH II), conducted at over 80 centers across 20 countries (2011). They noted that key administrative barriers in the study site activation included gaining ethics approval, executing site contracts, and getting everything in place needed for a site to be considered activated or ready to enroll patients (Kenyon et al, 2011). Their findings related to slow ethics approval and CTA execution were consistent with the well-documented clinical site perspective previously detailed by Atassi et al, 2013; Choi et al, 2015; Crow et al, 2018; Dilts and Sandler, 2006;

Kenyon et al, 2011; Krafcik et al, 2017 and Ravina, 2010. The participating countries in the Kenyon et al (2011) trial demonstrated a wide variation in time to achieve ethics committee approvals; Kenyon et al note this could be for a wide variety of reasons (2011). These reasons may include poor quality submissions, review back-logs, clock-stops due to holidays, complex protocols, challenging regulations, and requirements for signed contracts and other rate limiting documents to be included in the submissions.

Regulatory Approvals

Regulatory approvals are a common source of delay in randomized, controlled clinical trials. In international trials, disparate regulations are another source of delay in achieving regulatory approval (Crow et al, 2018; Rodon et al, 2015). Each country has a different regulatory approval pathway involving a sequence of reviews by the country competent authority and site ethics boards, each with their own idiosyncrasies and timelines (Crow et al, 2018). In some countries, regulatory submissions require difficult to obtain documents like executed site contracts or insurance policies, which significantly slows the approval process. After regulatory approval is granted, there may be subsequent steps before trial medication can be imported, i.e. an import license may be required. A detailed understanding of regulations and requirements in each participating country helps to predict start-up timelines.

Regulatory delays on a site level are dependent on whether a site uses a local IRB or ethics committee or participates in a central review. Evidence suggests the use of a centralized Institutional Review Board (IRB) that governs multiple sites, rather than a local IRB overseeing each site, significantly reduces time to IRB approval (Abbott et al, 2013; Krafcik, et al, 2017).Some countries (e.g. Finland, England) centralize ethics review either regionally or nationally, while US and Canadian sites often use local institutional review boards (Eapen et al,

2013; Hemminki et al, 2016). In the United States, private practice and independent sites are more likely to utilize a central IRB than academic, hospital-based and VA sites (Abbott et al, 2013). Ravina et al studied the impact of local IRB review of the consent and protocol in a multicenter clinical trial in Parkinson's disease (2010). They found 76% of the local IRB mandated changes were requested to align with standard institutional language and were not substantive changes to the protocol (Ravina, 2010). While US Federal Regulations support and encourage the use of cooperative IRB review arrangements, few institutions use them because of concerns about liability/oversight and a perception that local IRBs will provide local context (Ravina, 2010). Centralized review of the consent and protocol may free overburdened local IRBs and site study personnel to engage in more oversight of local conduct, enhancing protections to research participants (Ravina, 2010). Additionally, the use of a central IRB may reduce cost. A 2002 assessment of 63 academic medical centers estimated a median cost of $741, 920 (range $171,014 – $4,705,333) per year to support a local IRB (Sugarman et al, 2005). The majority of these costs were due to staff salary (Sugarman et al, 2005). Central IRBs may also improve trial efficiency as they meet frequently and the meeting calendar is well documented. IRBs within the United States and ethics committees abroad have varying schedules for conducting review and issuing approval (Kenyon, et al, 2011). The frequency of ethics meetings varies greatly across trials and can be as frequent as weekly to monthly or quarterly or perhaps even twice per year (Kenyon et al, 2011). In a retrospective study, central IRBs were associated with significantly shorter cycle times, including conducting protocol review within an average of 7 days as compared to 35 days for local IRBs (Abbott et al, 2013).

Site Contracts and Budgets

The process of negotiating site contracts (clinical trial agreements) and investigator grants (the study budget for an investigative site) is another key barrier in opening clinical trials (Araujo, 2018; Dilts and Sandler, 2006; Choi et al, 2015). Contract and budget negotiations between clinical sites and sponsors can take months to negotiate and execute (Dilts and Sandler, 2006). Kiriakis et al measured final negotiation and full-execution times for 467 contracts across 29 clinical sites participating in a multi-site study (2013). Across the participating sites, mean time to final contract negotiation was 55 days or 1.8 months and mean time to final execution was 103 days or approximately 3.4 months (Kiriakis et al, 2013). In another global trial conducted at 57 centers in 16 countries, contract executions spanned an average of 7.9 months for US sites (range = 2.5-17.2 months) and 8.7 months for sites outside the US (range = 2.5 – 24.9 months) (Minisman et al, 2012).

Start-up activities, including negotiation of clinical trial agreements (CTAs), are often conducted on behalf of sponsor companies by clinical research organizations (CROs) (Choi et al, 2015).CRO-managed negotiations require significant sponsor oversight and failure to do so may result in weeks of delay as well as cause damage to the relationship with the study site (Araujo, 2018). Negotiation in these cases can be delayed for reasons including inexperienced staff, inadequate budget templates, limited negotiation parameters and prolonged legal reviews (Araujo, 2018). Site requests that cannot be approved by the CRO go from site to CRO to Sponsor for approval, then back to the site. It is important to provide sites with a sponsor contact for escalation of negotiation issues as needed (Araujo, 2018). Establishing a master CTA and/or budget with the study site is an investiment in efficiency for future clinical trials (Araujo, 2018; Kiriakis et al, 2013). In a study by Kiriakis et al, sites using master agreements and previously

negotiated contract language enjoyed significantly reduced negotiation times (mean = 33 days) (Kiriakis et al, 2013).

Once contracts are in place, sites may require pre-payments before they will officially initiate the trial. These pre-payments are another source of delay, as it takes time for the payer to set-up the site in their systems and generate the payment. Lamberti, Zuckerman, Howe, Shapiro and Getz confirmed that sites are particularly sensitive to payment issues and that making sure that sites receive timely payments is a means to strengthen the relationship between sponsors and sites (Lamberti, Zuckerman, Howe, Shapiro and Getz, 2011). Unfortunately, issuing timely payments is made more complicated when a clinical research organization is administering sites payments on behalf of the sponsor. CROs may have procedures in place that limit the frequency of site payments.

Insurance

Liability insurance is a critical aspect of clinical trial start-up, yet an area that is complex and often misunderstood (Goudsmit, 2013). Insurance procurement is an area of start-up often overlooked by clinical trial managers (Brettler, 2018). It has the potential to add significant cost to the study and delay to the start-up process as proof of insurance is part of the regulatory document submission and approval in some countries (Bretler, 2018).As with other aspects of multi-national clinical trials, each country has their own set of rules governing indemnity insurance (Chingarande and Moodley, 2018; Crow et al, 2018; Tang et al, 2019). Multinational studies include a combination of different policies to mitigate risk to the sponsor in the event a participant is injured and is awarded financial compensation (Goudsmit, 2013). The sponsor company generally holds a global master liability policy that is sufficient to cover some countries including the United States, Canada and New Zealand (Crow et al, 2018; Goudsmit, 2013). The

global policy is renewed annually (Goudsmit, 2013). Other countries require local policies, issued by a locally licensed insurance company (Goudsmit, 2013). Local policies have varying requirements and typically cover the duration of the study; they would not require renewal unless the study runs longer than the initial term covered (Goudsmit, 2013). Depending upon the information required on the insurance certificate, policies may require update if the number of sites, estimated patients to be screened or randomized in that country changes. A change to an insurance policy can take weeks and hold up start-up in the country so it is important to get this right. A case study examined the insurance requirements across the 5 BRICS countries: Brazil, Russia, India, China and South Africa (Chingarande and Moodley, 2018). Within the regulations in these countries, they found a spectrum of different requirements; India had the strictest requirements, requiring compulsory insurance for all research participants, while regulations for China do not mention research related injuries at all (Chingarande and Moodley, 2018). South Africa and Russia both required varying levels of liability insurance. Brazilian law does have provisions for compensation due to research related injuries; however, it does not explicitly require sponsors to procure country specific insurance prior to the start of a clinical trial (Chingarande and Moodley, 2018).

Clinical Supplies

Clinical supplies represent another area with the potential for substantial impediment to initiation of international clinical trials, as clinical supplies must be shipped to countries across the globe (Lamberti, Hsia, Mahon, Milligan and Getz, 2016; Rodon et al, 2015). If sites do not have clinical supplies, they are unable to enroll and treat patients. Preparing and delivering clinical supplies to remote regions around the world is especially challenging as each country has their own particular language and regulatory requirements (Bielmeier and Crauwels, 2012;

Lamberti, Costello and Getz, 2012). The study medication for a clinical trial is also referred to as investigational medicinal product (IMP). In a trial including multiple countries, labeling IMP can be particularly challenging. Each country has their own combination of required data elements on the drug label, which must be translated into local language (Smith-Gick et al, 2018). Smith-Gick et al documented 19 data elements (e.g. drug name, storage conditions, for "clinical trial use" phrase) that may be required on the label depending upon the country (2018). Additionally lead time for packaging and labeling can be quite long. Smith-Gick et al report a timeframe of approximately 30 weeks from design and approval of conventional booklet labels to shipping kits to sites (2018). Incorporating the use of electronic labels (eLabels) presents an opportunity to reduce this timeline to 16 weeks (Smith-Gick et al, 2018).

Multinational studies require the clinical supply manager to keep apprised of local import and export regulations and shipping timelines (Lamberti et al, 2012). Lamberti et al examined logistics data for 73 clinical trials in a variety of therapeutic areas and across all phases (2016). They found shipping clinical supplies to clinical sites took 3.4 days on average, although there was a wide variation in shipping times depending upon the region and supply strategy (e.g. use of central depot, local or regional depot for distribution). (Lamberti et al, 2016). Obtaining import licenses for clinical supplies is another start-up activity that needs to be considered. Requirements for import licenses are variable depending upon the country and can be especially challenging and time-consuming to procure in Argentina, Russia, China, Columbia and India (Lamberti et al, 2016). Shipment of clinical supplies may be the last step before a site can screen and eventually enroll a study patient. Delays of even a few days made add up across sites, resulting in significant deficits to the enrollment period.

The majority of studies use interactive response technology (IRT) to manage screening, patient enrollment, randomize patients, manage clinical supplies including ordering and dispatch and tracking (Lamberti et al, 2016; Schiavon, 2019a). The IRT system build is a resource intensive activity that may take weeks or months during the study start-up and must be validated and in place before sites can be activated in the study. This can be a challenging activity for study teams, especially if they have limited experience with IRT system configurations (Schiavon, 2019a).

In addition to managing the investigational agent, many trials use comparator drugs and co-therapies that must be sourced and provided as part of the study. Sourcing and managing these additional drugs is difficult, adds significant cost to the study and often is a source of delay and increased study cycle time (Lamberti, Walsh and Getz, 2013). It is difficult for study sponsors to obtain comparator drug directly from the manufacture and often a 3rd party supplier must be employed (Lamberti et al, 2013). The primary cause for delay is obtaining the requisite paperwork that is needed to support the regulatory submissions and trial operations; these documents include certificates of analysis and stability data to support decisions around temperature excursions (Lamberti et al, 2013). Once comparator products are procured, they may need to be re-packaged or re-re-labeled depending upon county specific regulations (Lamberti et al, 2012).

Site Identification and Selection

The performance of study sites is both variable and unpredictable (Getz, 2009). Each study has unique characteristics that determine whether a site may be well-suited to participate (Potter et al, 2011). Many sites do not meet the enrollment goals set forth at the beginning of a study and others fail to enroll at all (Getz, 2009). A review of 151 global clinical studies

indicated that more than 10% of selected sites do not contribute to study enrollment (Lamberti, 2018).

Increased competition for good, experienced clinical sites is a significant challenge (Lamberti et al, 2017). In general, the more complex a study, the more difficulty CROs and Sponsors will have selecting the right sites. When stakeholders (sponsors and designees) select sites for a clinical study, they carefully evaluate key site qualifications to determine whether the site will be selected to participate in the study. Criteria for assessment include experience with research and the therapeutic area being studied, access to patients that meet eligibility criteria, appropriate staff, facilities, training and equipment and interest in participating in the study (Hurtado-Chong, Joeris, Hess and Blauth, 2017; Lamberti et al, 2017). While site selection is critically important to the downstream success of the trial (time to site activation and eventually enrollment and collection of quality data), the process for doing is not standardized and may be sub-optimal (Getz, 2008, Hurtado-Chong et al, 2017).

Generally, Sponsors and CROs reach out to potential sites to determine interest and then require interested sites to sign a confidentiality agreement (CDA). There is opportunity for delay here as legal terms are negotiated between the parties. Employing a master CDA that has a term of several years is one opportunity to increase efficiency across multiple studies (Kurzrock et al, 2009). Once a CDA is in place, a protocol synopsis and detailed feasibility questionnaire are issued to the site to complete.

Feasibility questionnaires are intended to collect information to help sponsors/CROs select the best sites for their study; however, they are often designed in a hurry, as sites need to be selected quickly. The sooner sites are selected, the sooner regulatory submissions can be prepared and submitted, capturing as many valuable enrollment months as possible. Because of

compressed start-up timelines, the timelines for sites to complete feasibility assessments are often short and as a result yield inaccurate or incomplete information and possibly overly-optimistic enrollment projections (Getz, 2008), Sponsors frequently take the site prediction of enrollment and discount the patient numbers that they provide, yet the results rarely align to the site's actual performance (Getz, 2008).

While the sponsor/CRO are assessing the site, the site is also evaluating whether the study would be a good fit for their business (Harper & Christison, 2012). In order to do so, they may utilize the feasibility questionnaire and also may request other study documentation including the full protocol, CRFs, lab manual, budget, etc. (Getz, 2008); Harper & Christison, 2012). Often, these documents are not fully developed at the time of site selection (Getz, 2008). After sites complete and return the feasibility questionnaire, the data is assessed and a subset of eligible sites are selected to move on to a pre-study visit.

In an effort to get site evaluation visits done quickly, often before resources are fully assigned, site evaluation visits may be conducted by CRAs assigned for this purpose aka SWAT CRAs. These CRAs may not be able to answer basic questions about the study, another significant source of frustration for clinical sites (Robert, Kantarjian and Steensma, 2016). The feasibility assessment is a critical part of site selection and should include thoughtful, well-structured surveys with confirmatory assessments on site (Sampalis et al, 2017).

Hurtado-Chong et al, representing the AOClinical Investigation and Documentation (AOCID), AO Foundation in Dübendorf, Switzerland, tested a systematic process to improve site selection for a clinical study (2017). The authors noted that previously, their institution selected sites primarily based on investigator interest, with studies yielded low recruitment, resulting in prolonged timelines and added cost (Hurtado-Chong et al, 2017). In this study, 266 interested

sites were screened and reduced to a short list of 24. This smaller pool was evaluated via telephone interview and 12 sites (in 6 countries) were then selected to participate in the study (Hurtado-Chong et al, 2017). Despite a lengthy 30-45 minutes telephone interview discussing the study, two sites in one country had to be replaced due to contracting issues (Hurtado-Chong et al, 2017). Nevertheless, the sites selected met recruitment and data quality goals, indicating that the method applied has promise (Hurtado-Chong et al, 2017). It is resource intensive to conduct 30-45 minutes phone interviews with sites across the globe, but perhaps it will save time and money in the long-run if sites that would not enroll patients are eliminated during the process.

A recommendation by the Clinical Trials Transformation Initiative (CTTI) suggests that obtaining evidence-based information from clinical sites may be required to obtain reliable recruitment targets and that querying electronic health records may be a helpful source of such information (Huang et al, 2018).

Selecting "repeat" sites, or sites that have worked with a sponsor or CRO on a previous study, is an opportunity to reduce cycle times (Lamberti et al, 2018). Cycle times for repeat sites were 28% shorter than cycle times for newly selected sites (Lamberti et al, 2018). However, after participating in a clinical study, many sites do no elect to participate in a subsequent one. A survey of over 200 investigators yielded key barriers to continued participation in clinical trials were primarily related to lack of opportunity, time and finance (Corneli et al, 2017). Over ½ of the survey respondents participated in a single clinical trial, with some citing lack of opportunity as the reason that they did not participate in subsequent studies (Corneli et al, 2017). Key challenges faced by investigators include workload balance, time and financial requirements,

complex regulations and contracts, lack of infrastructure, inadequate training and data collection challenges (Corneli et al, 2017; IOM, 2010).

Bruhn et al investigated methods to identify trial sites that will meet recruitment targets (2019). In an exploratory study, 10 trial mangers were asked to predict site performance for 56 sites across 8 clinical trials (Bruhn et al, 2019). While this was a small sample, trial managers did not predict the sites that would fail to meet recruitment with enough certainty to support decision making (Bruhn et al, 2019). However, the study yielded a list of 8 red-flags that may signal a site will not meet recruitment goals: 1) poor performance on previous trials, 2) a slow approval process, 3) strong staff beliefs/preferences about recruitment to the study 4) recruitment target (both unrealistically high or too low), 5) challenging protocol to execute, 6) lack of staff engagement (especially Principal Investigator), 7) lack of staff experience, 8) overly busy site staff (Bruhn et al, 2019). In a subsequent study, these red-flags will be tested to help streamline site identification and start-up.

Site Activation

Dilts and Sandler examined the study start-up process at two types of research sites, a National Cancer Institute comprehensive cancer center and a community oncology practices (2006). Their team developed process flows for all major activities that occur during start-up at the site level (Dilts and Sandler, 2006). They found that there were more than 110 steps required to start-up a study at the academic medical center, with 50% deemed non-value added (Dilts and Sandler, 2006). Study approvals required 27 groups, and it took a median of 171 days to get a trial open (Dilts and Sandler 2006). Each site undergoes a complex start-up process before they are able to enroll patients on a clinical study. In a multicenter global trial, this is magnified by the number of sites that are participating and compounded by the study level

activities that are required to start a trial (e.g. building databases, etc). Opening a multicenter cooperative group trial required more than 769 processing steps (Dilts, Cheng, Crites, Sandler and Doroshow, 2010).

Before opening a site to enrollment, Sponsors/CROs have a checklist of required documents that must be in place including IRB/ethics approval, a signed contract, budget, an FDA 1572 form or equivalent statement of investigator, CVs, medical licenses and financial disclosure forms from the principal investigator and all sub-investigators. Documents required before the start of a clinical study are detailed in ICH E6 (R2) in Section 8.2 (FDA, 2018). It is imperative that site start-up tasks are completed quickly and correctly, to avoid set-backs and additional cycles of regulatory review (Abbott, 2013). ICH E6 (R2), section 5.14.2 states that the sponsor should not supply a clinical site with study drug until all required documentation is in place including a favorable opinion from the IRB/EC and regulatory authorities (FDA, 2018). A minor error on a critical document such as an informed consent form, insurance policy or import license can present a significant set-back as the site may not be able to enroll patients until the error is corrected.

Abbott et al noted that cycle times are not consistently collected across studies/sponsors/CROs and suggested that the industry measure key intervals in the site start-up cycle to assess performance in multisite trials (2013). These include (1) the date the final protocol was sent to a clinical site, (2) the date of IRB decision, the date the contract (initial draft/template) was sent to the site, (3) the date that the site contract was signed, (4) the date the site was activated (open to enrollment) and (5) the date for the first patient's consent (Abbott et al, 2013). Employing standard metrics will allow clinical trial managers to identify areas for improvement and assess whether improvement initiatives are working (Abbott et al, 2013).

Inefficient Processes

The Institute of Medicine (National Academies of Sciences, Engineering and Medicine) conducted a workshop entitled "Transforming Clinical Research in the United States" (IOM, 2010). Attendees indicated that many studies are conducted without leveraging resources that may already be in place, essentially re-inventing the wheel for each trial (IOM, 2010). For example, a CDA or contract template may be sent to a site that a sponsor has worked with before, without incorporating previously negotiated and approved legal language prompting a new cycle of negotiations. Additionally, CVs and medical licenses may be requested from each site for every site without regard if the documents are on file for another study and could be cross-referenced. The Mayo clinic formed a cross-functional team to examine their start-up process for industry sponsored trials (Watters et al, 2018). They implemented improvements across 3 locations in Minnesota, Florida and Arizona (Watters et al, 2018). A few key changes including concurrent review of IRB, contract and budget and assignment of a project manager to each study conferred a significant reduction in start-up timelines (Watters et al, 2018).

Study start-up requires choreography of many interwoven steps and processes. Inefficiency at any step along the way can have a cumulative negative impact on study timelines. Traditionally, many start-up processes have been managed via manual tracking. The introduction of technology has the potential to increase efficiency greatly; however, processes must also evolve to ensure data is integrated (Schimanski and Kieronski, 2013).

Contract Research Organizations (CROs)

While the use of CROs continues to increase, the interface between study sites and CROs is not always efficient, resulting in site frustration (Kantarajian et al, 2013; Robert, Kantarjian and Steensma, 2016). There is conflicting data on whether CROs save time or introduce

unnecessary bureaucracy, costing more time during study start-up. One site assessed the study start-up across 38 of their clinical trials and found that CROs may expedite start-up in some areas, but cause delays in others (Krafcik, Doros and Malikova, 2017). Benefits of CROs include substantial human resources that can easily flex up and down depending upon the needs of a project (Robert, Kantarjian and Steensma, 2016). CROs also typically have well-established procedures and templates to facilitate work done in accordance with good clinical practice. Experienced staff at both the site and the CRO was attributed to increased shortened start-up timelines (Krafcik, Doros and Malikova, 2017; Kurzrock et al, 2009). CROs have teams in each country that can communicate in local language and are familiar with local customs. Attempting to manage countries without local personnel may lead to difficulty due to language and time zone issues (Crow et al, 2018). Further, experienced CRAs can help guide and train inexperienced site personnel (Robert, Kantarjian and Steensma, 2016). Lamberti et al found that CROs completed their work 6 – 11 weeks faster than Sponsor companies (2018).

While CROs can add considerable value to the clinical trial process, they may also add complications. Kantarjian et al associate the increase in per patient costs (well exceeding inflation) each year to the growth of the CRO industry and its associated bureaucracy(2013).CROs have particularly high turn-over, especially in the CRA role that typically interfaces with clinical sites (Robert, Kantarjian and Steensma, 2016). This is a source of frustration with investigators and their staff as the CRA is often the primary contact (representing the CRO and also the Sponsor) that liaises with a site on a clinical trial. It is disruptive for the site to establish a relationship with a new CRA and may cause re-work as the new CRA gets acclimated to the study and the sites processes/procedures and patient data. While Sponsors can delegate almost any task to a CRO, they are ultimately responsible and must provide

oversight. It is important for CROs to provide a direct line of contact with the Sponsor when the site feels they need it/are not getting a satisfactory response from the CRO to facilitate efficiency and maintain a good working relationship with the site (Robert, Kantarjian and Steensma, 2016).

Other outsourcing

Trial data is collected using case report forms, which may be paper forms or administered through an electronic data capture (EDC) system (Sampalis et al, 2017). Case report forms are developed before the onset of a clinical study and in some countries draft CRFs may even be a component of the regulatory submission. Further, some clinical sites may request a draft CRF to confirm the data that they will be required to collect.

The next step in examining study-start up delays in global, randomized clinical trials is to examine the issue under the lens of a study sponsor and apply quality improvement tools to elucidate the factors resulting in delay of clinical trial start-up.

Translations

There are a number of translations that will be required for a multi-national study, and these requirements vary from country to country (Crow et al, 2018). Patient facing materials including informed consent forms are translated into local language(s), sometimes many different languages for countries like India where patients may speak one of many dialects. Study staff in countries may have a working knowledge of English but prefer technical documents in local language for improved comprehension. Some countries may require that the documents comprising the regulatory submission be translated into local language. When approvals are received, the approval letter may be in local language and require translation for a US sponsor. Translations may be slow and costly and should be factored in to study start-up timelines as they have the potential to cause delay to site activation.

3 CHAPTER III METHODOLOGY

The objective of this study is to systematically examine and document factors affecting start-up time for multinational clinical trials using quality improvement tools. This quality integrative analysis will have three components: 1) Review the available literature related to the start-up of clinical trials; 2) Apply quality improvement tools to experience on a recent global Phase III clinical trial, summarizing driving factors in a fishbone diagram; 3) Use the issues identified and offer opportunities for improvement found to construct a checklist for trial planning.

Previous studies examining study start-up timelines and benchmarks have conducted surveys or used retrospective data from previous trials to identify factors that contribute to slow study-start-up. Studies using fishbone diagrams to analyze start-up issues have been performed from an investigative site perspective in King Fahad Medical City, Riyadh (2016-2017) and at a site in the US (Boston University, 2017). In those studies, the authors examined cycle time metrics and factors contributing to delays at their sites. Other studies used retrospective analysis to identify metrics that may help manage start-up. A study site in Korea examined hundreds of clinical trial agreements, with a focus on CTA negotiation cycle times (Choi et al, 2015). Dilts and Sandler mapped the study start-up processes at Vanderbilt-Ingram Cancer Center, and also analyzed the historic timing of these processes (2006). One paper was generated when a clinical operations team in India brainstormed from their experience (Bhagat et al, 2016).

3.1 Research Design or Method

In this qualitative study, a fishbone diagram will be used to explore reasons for start-up delay and identify possible causes. Subsequently, a check-list will be prepared to help proactively plan for and avoid causes for start-up delay, which will yield a cumulative positive effect on study enrollment.

3.2 Sample Selection

A comprehensive review of the literature was performed using the key words "study start-up delays" with investigation into the key areas

3.3 Instrumentation

The fishbone diagram is a visual tool that helps identify root causes contributing to an issue. Antony, Palsuk, Gupta, Mishra and Barach performed a systemic review of the use of six sigma tools in healthcare (2018). Benefits included cost savings, speed/timeliness, and process flow improvement (Antony et al, 2018). Tools were examined for use across the "Define, Measure, Analyze, Improve, Control" or DMAIC roadmap and the fishbone diagram was identified as a tool commonly used during the analyze phase (Antony et al, 2018).

3.4 Protection of Human Subjects

This study was exempt from the MUSC institutional review process for protecting human subjects in research.

4 CHAPTER IV JOURNAL MANUSCRIPT

Title: Drivers of Start-up Delays in Global Randomized Clinical Trials

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Keywords: global clinical trials, study start-up, best practices, performance, process optimization, trial efficiency

Abstract

Background: Global, randomized clinical trials are extremely complex. Trial start-up is a critical phase and has many opportunities for delay which adversely impact the study timelines and budget. Understanding factors that contribute to delay may help clinical trial managers to work more efficiently, hastening patient access to potential new therapies. **Methods:** We reviewed the available literature related to start-up of global, Phase III clinical trials and then created a fishbone diagram detailing drivers contributing to start-up delays. The issues identified were used to craft a checklist to assist clinical trial managers in more efficient trial start-up. **Results:** We identified key drivers for start-up delays in the following categories: regulatory, contracts and budgets, insurance, clinical supplies, site identification and selection, and site activation. **Conclusion:** Initiating global randomized clinical trials is a complex endeavor, and reasons for delay are well-documented in the literature. By using a checklist, clinical trial managers may mitigate some delays and get clinical studies set-up as soon as possible.

Introduction/Background

This study was conducted prior to the outbreak of the COVID-19 pandemic. After the onset of the pandemic, many planned clinical trials were delayed due to widespread lockdowns and to conserve resources for front-line healthcare workers. Trials in many indications including life-threatening illnesses like cancer and cystic fibrosis have been delayed by the pandemic (BioWorld, 2020). Once initiation of delayed studies does resume, it will be essential to conduct start-up activities as efficiently as possible to expeditiously bring new medications and treatments to patients.

Randomized, controlled trials (RCT) are considered the gold-standard to assess the safety and efficacy of potential medications (Sullivan, 2011; Umscheid, Margolis & Grossman, 2011). FDA-regulated trials increasingly engage sites outside the United States, including sites in developing nations, in order to hasten patient enrollment and reduce costs (da Silva, Amato, Guilheim and Novaes, 2016). These studies are complex to start-up, especially when they include multinational sites subject to different laws, regulations governing the conduct of research, infrastructure (or lack of infrastructure) and local standards of care (Crow et al, 2018). Clinical study start-up is a key determinant of success in a clinical trial, and the time required to activate a trial may be inversely related to its enrollment rate (Huang et al, 2018; Cheng, Dietrich and Dilts, 2010). In order to begin recruitment, sites need to be qualified, gain regulatory approval, negotiate and execute clinical trial agreements and receive training (in addition to many other study level tasks). Delaying start-up often means extending the overall study timelines which can not only incur significant additional cost, but threaten the feasibility of the trial (Atassi et al, 2013; Kantarjian, Stewart and Zwelling, 2013; Kurzrock et al, 2009). Examples of other adverse trial outcomes due to start-up delays include wasted drug or drug

shortages due to expiry, loss of clinical sites due to lack of interest or competing studies and loss of ability to enroll patients due to a change in the local standard of care. Perhaps most importantly, delays in study start-up lead to delay in access to treatment for patients, as well as lost opportunity costs.

While it is important that all clinical trials run efficiently, Phase III trials are typically the largest and most complex studies prior leading to drug approval. A Phase III, randomized, trial may cost anywhere between $11.5 million to $52.9 million depending upon the therapeutic area and complexity of the study (Morgan, 2019). While clinical trial delays are well documented, this study offers a comprehensive start-up checklist as a useful resource for clinical trial managers seeking to improve trial efficiency.

Methods

This qualitative integrative analysis consists of three components: 1) a review of the available literature related to the start-up of clinical trials; 2) a fishbone diagram, created to summarize driving factors of start-up delays in Phase III global clinical trials; and 3) a study start-up checklist that clinical trial managers may use for trial planning. The following areas were considered in-scope for this review: regulatory approvals, site contracts and budgets, insurance, clinical supplies, site identification and selection and inefficient processes/pitfalls.

Protection of Human Subjects

This study was exempt from the MUSC institutional review process for protecting human subjects in research and does not contain any studies with human or animal subjects performed by any of the authors.

Results

The literature was reviewed using the phrases "clinical trial start-up and delays" and "study start-up and delays". The review included 89 peer reviewed journal articles as well as supplemental industry white papers and a book. Various reasons contributing to study start-up delay were well documented and key drivers for delay were detailed in a fishbone diagram (Figure 1). The major factors identified that contribute to start-up delay in RCTs relate to regulatory approvals, site contracts and budgets, insurance, clinical supplies, site activation, inefficient processes, CROs and translations. Key findings in each of these areas will be briefly discussed below.

Regulatory

Our literature review identified six key drivers contributing to regulatory delays: disparate regulations, submission delays, additional requirements subsequent to regulatory approval, use of a local ethics committee/IRB, infrequent ethics committee/IRB meetings and regulatory backlogs/clock-stops.

Disparate regulations and variation in start-up processes across countries has a significant impact on study start-up timelines (Crow et al, 2018; Rodon et al, 2015). Regulatory submission packages are complex and require a great deal of coordination, and when multiple countries are involved, the complexity and level of coordination needed is significantly increased, as the start-up team must carefully track the timeline and requirements of each country (Crow et al, 2018).

Additionally, regulatory submissions in some countries include difficult-to-obtain documents like executed site contracts or insurance policies, which significantly slows the time to submission of the regulatory package and consequently the approval is delayed. Negotiating and getting a site contract signed can take a considerable amount of time. Once regulatory

approval is received from the competent authority, some countries have additional regulatory requirements that must then be initiated before the country has full approval and sites can open for enrollment. For example, before trial medication can be imported an import license may be required that cannot; the application for these licenses cannot be submitted until country approval is granted and this may add weeks to study start-up.

Regulatory delays on a site level are dependent on whether a site uses a local Institutional Review Board (IRB)/ethics committee (EC) or is able to utilize a central IRB/EC. Evidence suggests the use of a centralized IRB that governs multiple sites, rather than a local IRB overseeing each site, significantly reduces time to IRB approval (Abbott et al, 2013; Krafcik, et al, 2017). In a retrospective study, central IRBs were associated with significantly shorter cycle times, including conducting protocol review within an average of 7 days as compared to 35 days for local IRBs (Abbott et al, 2013). Frequency of IRB/EC meetings also has an impact on start-up timelines. Meeting schedules can vary greatly across sites and may occur weekly, monthly, quarterly or as infrequently as twice per year (Kenyon et al, 2011).

Finally, regulatory review timelines may be delayed due to back-logs and clock-stops, at either a country or site level. For example, prior to reforming their regulatory review processes, China had a peak regulatory review backlog of more than 22,000 applications in 2015 (Xu, Gao, Kaitin, & Shao, 2018). Trial managers working with sites in China during this time would have to plan for very long regulatory review timelines and likely sites in China would join a global study long after other sites in other countries started enrolling patients.

Site Contracts and Budgets

Additional drivers of start-up delay are evident in the process of negotiating site contracts (clinical trial agreements) and investigator grants (the study budget for an investigative site)

(Araujo, 2018; Dilts & Sandler, 2006; Choi et al, 2015). Contract and budget negotiations between clinical sites and sponsors can take months to negotiate and execute. In a global trial conducted at 57 centers in 16 countries, contract executions spanned an average of 7.9 months for US sites (range = 2.5-17.2 months) and 8.7 months for sites outside the US (range = 2.5 – 24.9 months) (Minisman et al, 2012). Contributors to prolonged contract and budget cycle times include inexperienced staff, inadequate budget templates, limited negotiation parameters and prolonged legal reviews (Araujo, 2018). If a sponsor has worked with a site in the past, leveraging previously negotiated contract and budget terms may significantly reduce cycle times (Kiriakis et al, 2013).

Start-up activities, including negotiation of clinical trial agreements (CTAs), are often conducted on behalf of sponsor companies by clinical research organizations (CROs) (Choi et al, 2015). CRO-managed negotiations require significant sponsor oversight and failure to do so may result in weeks of delay as well as cause damage to the relationship with the study site (Araujo, 2018). It is important to provide sites with a sponsor contact for escalation of negotiation issues as needed (Araujo, 2018). Once contracts are in place, sites may require pre-payments before they will officially initiate the trial and initiate enrollment. Pre-payments can be another source of delay, as it takes time for the payer to set-up the site in their systems and generate the payment.

Insurance

Procurement of liability insurance is a complex and critical aspect of clinical trial start-up that may be underestimated by clinical trial managers (Brettler, 2012, Goudsmit, 2013). It has the potential to add significant cost to the study and delay to the start-up process as proof of insurance is part of the regulatory document submission and approval in some countries

(Brettler, 2012). As with other aspects of multi-national clinical trials, each country has their own set of rules governing indemnity insurance (Chingarande & Moodley, 2018; Crow et al, 2018; Tang et al, 2019). Multinational studies include a combination of different policies to mitigate risk to the sponsor in the event a participant is injured and is awarded financial compensation (Goudsmit, 2013). The sponsor company generally holds a global master liability policy, renewed annually, that is sufficient to cover some countries including the United States, Canada and New Zealand (Crow et al, 2018; Goudsmit, 2013). Other countries require local policies, issued by a locally licensed insurance company (Goudsmit, 2013). Local policies have varying requirements and typically cover the duration of the study unless the study runs longer than the initial term covered (Goudsmit, 2013). Depending upon the information required on the insurance certificate, policies may require update if the number of sites, estimated patients to be screened or randomized in that country changes. A change to an insurance policy can take weeks and hold up start-up in the country so it is important to get this right.

Clinical Supplies

Clinical supplies represent another area with the potential for substantial impediment to initiation of international clinical trials (Lamberti, Hsia, Mahon, Milligan and Getz, 2016; Rodon et al, 2015). Preparing and delivering clinical supplies to remote regions around the world is especially challenging as each country has their own particular language and regulatory requirements (Bielmeier and Crauwels, 2012; Lamberti, Costello and Getz, 2012). Additionally, each country has their own combination of required data elements on the drug label, which must be translated into local language (Smith-Gick et al, 2018). Smith-Gick et al documented 19 data elements (e.g. drug name, storage conditions, for "clinical trial use" phrase) that may be required on the label depending upon the country (2018). Packaging and labeling require approximately

30 weeks from design and approval of conventional booklet labels to shipping kits to sites (2018). Incorporating the use of electronic labels (eLabels) presents an opportunity to reduce this timeline to 16 weeks (Smith-Gick et al, 2018).

Multinational studies require the clinical supply manager to keep apprised of local import and export regulations and shipping timelines (Lamberti, Costello & Getz, 2012). Lamberti et al examined logistics data for 73 clinical trials in a variety of therapeutic areas and across all phases (2016). They found shipping clinical supplies to clinical sites took 3.4 days on average, although there was a wide variation in shipping times depending upon the region and supply strategy (e.g. use of central depot, local or regional depot for distribution) (Lamberti et al, 2016).

In addition to managing the investigational agent, many trials use comparator drugs and co-therapies that must be sourced and provided as part of the study. Sourcing and managing these additional drugs are difficult, adds significant cost to the study and often is a source of delay and increased study cycle time (Lamberti, Walsh and Getz, 2013). The primary cause for delay is obtaining the requisite paperwork that is needed to support the regulatory submissions and trial operations; these documents include certificates of analysis and stability data to support decisions around temperature excursions (Lamberti, Walsh and Getz, 2013). Once comparator products are procured, they may need to be re-packaged or re-re-labeled depending upon county specific regulations (Lamberti, Costello & Getz, 2012).

Site Identification and Selection

Increased competition for good, experienced clinical sites is a significant challenge for site selection (Lamberti, Chakravarthy & Getz, 2017). In general, the more complex a study, the more difficulty CROs and sponsors have selecting sites (Lamberti, Wilkinson, Harper, Morgan & Getz, 2018). When stakeholders select sites for a clinical study, they carefully evaluate key

site qualifications to determine whether the site will be selected to participate in the study. Criteria for assessment include experience with research and the therapeutic area being studied, access to patients that meet eligibility criteria, appropriate staff, facilities, training and equipment and interest in participating in the study (Hurtado-Chong, Joeris, Hess and Blauth, 2017; Lamberti, Chakravarthy & Getz, 2017).

Generally, Sponsors and CROs reach out to potential sites to determine interest and then require interested sites to sign a confidentiality agreement (CDA). There is opportunity for delay here as legal terms are negotiated between the parties. Once a CDA is in place, a detailed feasibility questionnaire is issued to the site to complete.

Feasibility questionnaires are often designed in a hurry, as sites need to be selected quickly so that regulatory submissions can be prepared and submitted, capturing as many valuable enrollment months as possible. Because of compressed start-up timelines, the time allotted for sites to complete feasibility assessments is often short and as a result questionnaires may yield inaccurate or incomplete information and possibly overly-optimistic enrollment projections (Getz, 2008), Sponsors frequently take the site prediction of enrollment and discount the patient numbers that they provide, yet the results rarely align to the site's actual performance (Getz, 2008). Often, key documents like the full protocol and budget are not available to sites at the time of feasibility (Getz, 2008). After sites complete and return the feasibility questionnaire, the data is assessed and a subset of interested and eligible sites are selected to move on to a pre-study visit.

Selecting "repeat" sites, or sites that have worked with a sponsor or CRO on a previous study, is an opportunity to reduce cycle times (Lamberti, Wilkinson, Harper, Morgan & Getz, 2018). Cycle times for repeat sites were 28% shorter than cycle times for newly selected sites

(Lamberti et al, 2018). However, after participating in a clinical study, many sites do no elect to participate in a subsequent one. Key challenges faced by investigators include workload balance, time and financial requirements, complex regulations and contracts, lack of infrastructure, inadequate training and data collection challenges (Corneli et al, 2017).

Site Activation

Before opening a site to enrollment, Sponsors/CROs have a checklist of required documents that must be in place including IRB/EC approval, a signed contract, budget, an FDA 1572 form or equivalent statement of investigator, CVs, medical licenses and financial disclosure forms from the principal investigator and all sub-investigators. Documents required before the start of a clinical study are detailed in ICH E6 (R2) in Section 8.2 (FDA, 2018). It is imperative that site start-up tasks are completed quickly and correctly, to avoid set-backs and additional cycles of regulatory review (Abbott, 2013). ICH E6 (R2), section 5.14.2 states that the sponsor should not supply a clinical site with study drug until all required documentation is in place including a favorable opinion from the IRB/EC and regulatory authorities (FDA, 2018). A minor error on a critical document such as an informed consent form, insurance policy or import license can present a significant set-back as the site may not be able to enroll patients until the error is corrected.

Abbott et al noted that cycle times are not consistently collected across studies/sponsors/CROs and suggested that the industry measure key intervals in the site start-up cycle to assess performance in multisite trials (2013). These include (1) the date the final protocol was sent to a clinical site, (2) the date of IRB decision, the date the contract (initial draft/template) was sent to the site, (3) the date that the site contract was signed, (4) the date the site was activated (open to enrollment) and (5) the date for the first patient's consent (Abbott et

al, 2013). Employing standard metrics will allow clinical trial managers to identify areas for improvement and assess whether improvement initiatives are working (Abbott et al, 2013).

Discussion:

The results of our analysis illustrate the need for increased efficiency in the start-up of global, multicenter randomized clinical trials. These projects are exceedingly complex and any delay in their execution has a significant financial impact and prolongs time to market for potentially life-saving therapies. In order to minimize delays due to all of the identified drivers, the study start-up team should include local experts with a detailed understanding of regulations and requirements in each participating country to accurately predict start-up timelines and help coordinate an efficient submission process. When countries with longer start-up timelines must be used, careful coordination of each step may help to optimize start-up.

The most surprising area of potential start-up delay was clinical trial insurance. This is not an area that is widely discussed, but due to varying country requirements and the need to transmit information from the clinical operations team/CRO to an insurance agent who then conveys to a local broker, there is a great deal of potential for delay. This is further complicated by the need for translations and for original documents with signatures in some regions.

Another surprising area for delay was that being too metric driven can actually be an area that contributes to start-up delay. For example, if a team is working toward a minimum benchmark, perhaps having a site initiation visit within 2 weeks of the executed contract and ethics approval, they may schedule all visits up to two weeks out and be meeting their metrics for success. However, on a large, global study with hundreds of sites, even a day lost when sites are not open for recruitment can add up and have a significant impact on study enrollment. While

metrics and benchmarks are important, the focus should also be on optimizing the start-up timeline for each site.

The Benjamin Franklin axiom "an ounce of prevention is worth a pound of cure" is relevant to clinical trial start-up in that it is far preferable to prevent start-up delays wherever possible rather than dealing with and resolving delays as they occur (Aguinis & Vandenburg, 2014). Seemingly small delays across various workstreams can add up significantly and yield substantial delays. While industry practice evolves to incorporate technology and implement evidence-based improvements, our checklist is intended to help clinical trial managers track study start-up activities and manage them as efficiently as possible.

Limitations

The data gathered in support of our fishbone diagram and the resulting checklist were primarily obtained through a literature review. We did not consult other clinical trial managers due to limitations in time and the scope of this project; however, this would be a valuable exercise in a future study.

As clinical trials require substantial financial resources to execute, evidence-based methods are needed to improve the efficiency of clinical operations. The Trial Forge initiative is an effort to increase the evidence base supporting clinical trial efficiency and quality (Treweek et al, 2015). One means to generate evidence regarding trial efficiency is conducting a study within a trial (SWAT), a study embedded within a clinical trial that examines a specific trial process (Treweek et al, 2018). Future research should generate evidence that demonstrates which clinical operations methodologies improve efficiency is important to avoid the waste of precious resources.

Conclusion

By following this checklist, clinical trial managers can trim effectively navigate the challenges of clinical trial start-up. With so many activities to coordinate, the start-up process will likely include delays; however, if this can be reduced, it will translate into more time for enrollment.

Funding Statement

No financial support of the research, authorship, and/or publication of this article was declared.

Declaration of conflicting interests

No potential conflicts were declared.

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Figure 1: Key Drivers for Study Start-up Delay in Global, Randomized Clinical Trials

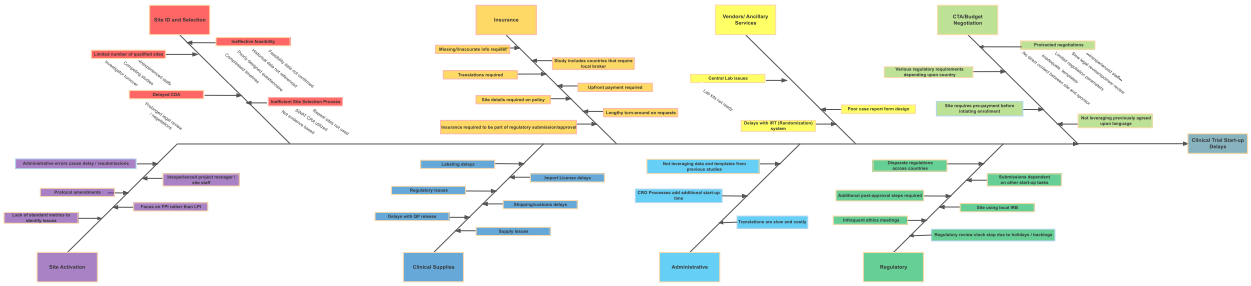

Figure 2: Sponsor Study Start-up Checklist for Global, Randomized Clinical Trials

Assumes a draft protocol (at least synopsis) is available and vendors have been selected

[ ] **Determine outsourcing strategy and select vendors**

Options may include performing the work in house, fully outsourced to a Clinical Research Organization (CRO) or a hybrid model that includes in-house and outsourced work.

[ ] Ensure that as much as possible all study requirements are adequately captured in vendor budgets to avoid delays that may result from approvals of out of scope work.

[ ] **Finalize Protocol**

If possible, protocol should not be finalized without input from sites. Best practice is to vet the protocol with stakeholders (including Principal Investigators (PIs) and study coordinators) before finalizing to avoid unnecessary protocol amendments, although country specific amendments may be unavoidable.

[ ] Budget for amendments that may arise as a result of regulatory review or unforeseen issues.

[ ] **Vendor Kick-off meeting with discussion of hand-offs**

Hold a kick-off meeting with the CRO and other vendors or internal groups to discuss who is responsible for what and any hand-offs that need to occur. For example, biostatistics may need to provide a randomization list to the Interactive Response Technology (IRT) vendor.

[ ] Ancillary service providers may require a review process with associated fee.

Factor in time and cost for this additional step if required.

[ ] **Country and Site Identification**

[ ] As early as possible, determine which countries will participate in the study so that a regulatory strategy and timeline can be established. Each country has their own procedures, timelines and regulatory submission requirements with interdependencies on other start-up tasks. Preparing a timeline for each country with the detailed steps including time for translations is extremely helpful.

[ ] Prepare a feasibility questionnaire; ensure that regulatory considerations are included (for example central IRB/EC, local IRB/EC, etc.)

[ ] Perform feasibility analysis and determine which countries/sites will move on to site feasibility and selection

[ ] **Regulatory**

[ ] Map out the timelines and document requirements for each country selected.

Most countries required signed Clinical Trial Agreement (CTA)/budget or insurance before issuing approval which may create a prolonged sequential process if not carefully managed.

[ ] Plan for the start-up cycle times for each country; may plan for a range (stretch goal vs. historical timelines)

Note: If your timeline allows, consider opening the study in one country or at select sites to work out the kinks before initiating all sites.

[ ] Prepare clinical trial applications for each country

[ ] Allow time for translation, notarization and apostillization of documents (if applicable)

[ ] Complete EU Application Form to secure **E**uropean **U**nion **D**rug **R**egulating

Authorities **C**linical **T**rials (EudraCT) number (required if trial includes sites in the European Union)

[ ] Create record in clinicaltrials.gov and other registries as applicable (must be complete within 21 days of first patient enrolled)

[ ] **Site Feasibility and selection (for each site)**

[ ] Confidentiality agreement **Note – this must be signed before **any** study specific documentation is shared with the sites**

[ ] Feasibility questionnaire – this will help evaluate if the site is a good fit for the study, access to the target patient pool and how many patients the site expects to enroll.

[ ] Confirm both site and sponsor/designee interested in moving forward

Note: providing sites with incomplete documents will make it difficult for sites to determine feasibility and interest

[ ] Perform site qualification visit (if selected to move forward)

[ ] Collect start-up documents including financial disclosure forms, medical licenses CVs for key site personnel

[ ] Provide "selected" sites with the following key documents:

[ ] Protocol (may be a synopsis, draft or final depending upon stage of protocol development).

[ ] Investigational Brochure/package insert for study treatments

[ ] Informed Consent form - country level template or site specific document including previously negotiated language if working with a "repeat" site

[ ] Case Report Forms/lab manual (when available)

[ ] Study specific documents including patient facing materials and questionnaires

[ ] Country specific contract templates or site specific document including previously negotiated language if working with a "repeat" site

[ ] Country specific budget templates or site specific document including previously negotiated language if working with a "repeat" site

[ ] Perform investigator due diligence check

[ ] Negotiate and finalize site contract/budget

[ ] Prepare and submit central and local EC submissions for review

[ ] Obtain requisite IRB/EC approvals

[ ] Site specific laboratory reference ranges if applicable

[ ] Collect and analyze key cycle time metrics for each site. Consider the following (Abbott et al, 2013):

- Date final protocol was sent to site
- Date of IRB decision (both local and central IRB)
- Date initial contract template was sent to site (includes budget)
- Date site contract executed
- Date of site activation (all contractual, regulatory and pre-study start requirements met)
- Date of first patient consent

[ ] **Informed Consent Form**

[ ] Draft a master Informed Consent form (ICF) template

[ ] Draft a country specific master ICF template modified to include required and customary language for each country

[ ] Ensure the template ICFs are reviewed and vetted by legal; material changes to the document after legal review may require legal approval

[ ] From country specific ICF, negotiate a final ICF for each site.

[ ] For "repeat" sites (sites that have participated in previous studies); consider incorporating previously agreed upon language into the master before sending to avoid unnecessary rounds of review

[ ] Once ICF has been approved by both site and sponsor/designee then submit for EC approval

[ ] **Site Contract**

[ ] Draft a master clinical trial agreement (CTA) template for the study; Consider incorporating language from the Common Language Evaluation and Reconciliation a.k.a. CLEAR initiative (from the Society of Clinical Research Sites)

[ ] Draft a country specific CTA template for the study modified to include required and customary language for each country. In some countries multiple templates will be needed (investigator, institution, etc.).

[ ] For institutions that will participate in multiple studies with the same sponsor, consider having a master CTA and/or budget agreement in place that can be used for a defined term without having to re-negotiate each study.

[ ] For repeat sites, incorporate previously agreed upon language to avoid multiple rounds of review.

[ ] Some sites may require a letter of intent (to cover start-up costs)

[ ] Some sites may require or an indemnity letter or separate indemnity agreement

[ ] Allow time for translation, notarization and apostillization of documents (if applicable)

[ ] **Site Budget**

[ ] Draft an itemized master budget template, detailing the cost of each procedure; provide as early as possible to allow time for negotiations

[ ] Draft a country specific budget templates modified for the country and type of institution as appropriate.

[ ] For repeat sites, incorporate previously agreed upon costs to avoid multiple rounds of review.

[ ] For sites that require a start-up payment in order to initiate the study, promptly release start-up payments

[ ] It is in the best interest of the sponsor to closely manage negotiations to avoid significant and to maintain good working relationship with study sites; select most experienced negotiators available

[ ] **Insurance**

[ ] Select a vendor with vast experience securing insurance for clinical trials requesting references if possible. Insurance can have prolonged timelines; a vendor may quote turn-around times of 48 hours when in reality it takes weeks to get the actual documentation needed for regulatory submission.

[ ] Determine the insurance requirements for each country to be included in the

study. Many countries require translations of the study title and other documents into local language.

[ ] Request translations and site lists for each country as required (often at least the protocol title must be translated into local language).

[ ] Create an insurance worksheet that details the start date/end date of coverage, # of screened patients (planned), # of randomized patients (planned) and any other details required for each country. This will be a helpful reference, especially if changes need to be made during the study. Some countries cannot exceed the # of patients screened/randomized on the policy without an amendment and regulatory approval so it is best to overestimate.

[ ] Initiate request for insurance as soon as possible, as this may be the last document needed for a regulatory submission.

[ ] Work closely with insurance broker to minimize any delays and expedite turn-around of policies.

[ ] Track metrics for turn-around time (initial request to receipt of final policy, time for amendments).

[ ] **Case Report Form Design and testing**

Best practice is to have the CRF in place before the 1st patient is enrolled to avoid data entry delays and back-log. If possible, include stakeholders in user acceptance testing to vet the CRFs before they are finalized to optimize design and avoid amendments. Consider technology that allows data to be transferred directly from the electronic source into the eCRF to minimize data entry and source data verification.

[ ] Develop and test screens and reports

[ ] Develop and test edit checks

[ ] Create Case Report Form (CRF) completion guidelines (aka data manual). This may need to be translated into local language, depending upon the participating countries.

[ ] Prepare data management plan or equivalent

[ ] **Pharmacovigilance**

[ ] Develop and test safety database for SAE reporting

[ ] Prepare safety monitoring plan

[ ] **IRT Development and testing**

IRT must be in place before the 1st patient is enrolled. If possible, include stakeholders in user acceptance testing to vet the system and reports before they are finalized to optimize design and avoid amendments. Technology should integrate well with the eCRF to avoid entering the same data in multiple places and with the drug supply vendor software to optimize the drug distribution to sites.

[ ] Allow time for the clinical supplies to be loaded into the IRT; ensure supplies are available at the regional depot before a patient is screened for study participation

[ ] **Central Laboratory (if applicable)**

[ ] Prepare and distribute lab manual; allow time for translation if required.

Note: lab manual should include explicit instructions for shipping lab materials, especially if shipping to another country.

[ ] Prepare sample requisition forms

[ ] Set up laboratory logistics

[ ] Assemble lab kits; ensuring that screening kits are on site in advance of first patient in. As many sites do not have room for bulk supplies; ensure that lab manual details what the initial supply will be and what the site will need to order in advance of subsequent patients visits including lead time.

[ ] Lab details (collection volume, genetic testing, duration of storage, etc.) need to be included in the informed consent form

[ ] **Clinical Supplies/Investigational Medicinal Product**

[ ] Create forecast

[ ] Procure comparator and other supplies as needed

[ ] Design master drug label and country specific drug labels; translated to local language as required

[ ] Work with drug supply vendor to get supplies packaged and labeled in accordance with regulations

[ ] Pharmacy Manual

Note: Best practice would be to have the pharmacy manual reviewed by a site pharmacist to ensure clarity.

[ ] Upon regulatory approval, procure requisite import and export licenses

[ ] Integrate material with IRT and supply depots/sites per planned study milestone (site activation, first patient screened, first patient randomized, etc.)

[ ] Make the requirements for clinical supplies clear up front (storage conditions, etc.). Consider that many sites do not have storage space for bulk supplies.

[ ] Provide clear direction on who will be providing which supplies and the required lead time. A cheat sheet with these details would be helpful for

site reference.

[ ] When evaluating countries, consider that study supplies that may be readily available or standard of care in the US may be difficult to procure in some countries and may need to be supplied by the sponsor.

[ ] **Site Activation**

[ ] Ensure that all requisite documentation and approvals are in place and that site meets criteria for activation.

[ ] Create a monitoring plan, detailing how the study will be monitored (needed before site initiation visits can take place).

[ ] Conduct site activation visit/training as appropriate.

[ ] Prior to activation, ensure site has appropriate access to all electronic systems needed for the study (EDC, IRT, etc.).

[ ] Allow time for site to complete coverage analysis for standard of care procedures, complete study specific trainings, and map study logistics across facilities

[ ] Ensure site has all supplies needed to begin screening (lab kits, etc.) and that it is clear who will be providing supplies/how they are ordered.

- Laboratory kits
- Study Drug (*may not be required to be onsite before site initiation)
- Regulatory binders including study specific forms, templates and manuals
- Other study specific clinical supplies

[ ] Administer any agreed upon start-up payments

[ ] Enable site to begin screening in the IWRS system

[ ] **Other**

[ ] Project management plan

[ ] Conduct study team trainings and arrange any additional site trainings

[ ] Plan investigator meeting/s (if applicable)

[ ] Set up central files (electronic trial master file/ eTMF)

[ ] Set-up regular calls with stakeholders to review study progress; consider regular calls with clinical sites in which PI participates to discuss AEs, enrollment issues, etc.

Note – this study start-up checklist is not meant to include all start-up tasks for all studies and should be adapted as necessary. Additionally, many of the items in this checklist are to be done concurrently, not necessarily in the order listed.

Helpful Links for more information:

Society of Clinical Research Sites (white papers including CLEAR contract language): https://myscrs.org/learning-campus/white-papers/

Trial Forge (trial efficiency, Study within a Trial or SWAT): https://www.trialforge.org/

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