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DIA

ORIGINAL RESEARCH

# Drivers of Start-Up Delays in Global Randomized Clinical Trials

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## 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 and other stakeholders 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, site activation, and inefficient processes/pitfalls.

**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 initiated as soon as possible.

**Keywords** Global clinical trials · Study start-up · Best practices · Performance · Process optimization · Trial efficiency

## 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 [1]. Once initiation of delayed studies does resume, it will be essential to conduct start-up activities as efficiently as possible to expeditiously start clinical trials for the benefits of the clinical trial participants.

Randomized, controlled trials (RCT) are considered the gold-standard to assess the safety and efficacy of potential medications/therapies [2, 3]. FDA-regulated trials increasingly engage sites outside the United States, including sites in developing nations, in order to hasten patient enrollment, reduce costs and achieve market expansion by including participants for various geographies [4]. 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 [5]. 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 [6, 7]. In order to begin recruitment, sites need to be qualified, gain regulatory approval, including IRB/ethics committee approval, negotiate and execute clinical trial agreements, and receive training and clinical supplies (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 [8–10]. 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 clinical trial participants due to a change in the local standard of care rendering the control arm obsolete [11, 12]. Perhaps most importantly, delays in study start-up lead to delay in access to treatment for patients, as well as lost opportunity costs.

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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 [13]. 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, site activation, and inefficient processes/pitfalls.

## Protection of Human Clinical Trial Participants

This study was exempt from the Medical University of South Carolina (MUSC) institutional review process for protecting human clinical trial participants in research and does not contain any studies with human participants 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 (Fig. 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 have a significant impact on study start-up timelines [5, 14]. 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 are significantly increased, as the start-up team must carefully track the timeline and requirements of each country [5].

Additionally, regulatory submissions in some countries include difficult-to-obtain documents like executed site contracts or insurance policies, which significantly slow 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 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 [15, 16]. 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 [15]. 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 [17].

Finally, regulatory review timelines may be delayed due to backlogs 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 [18]. 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 participants.

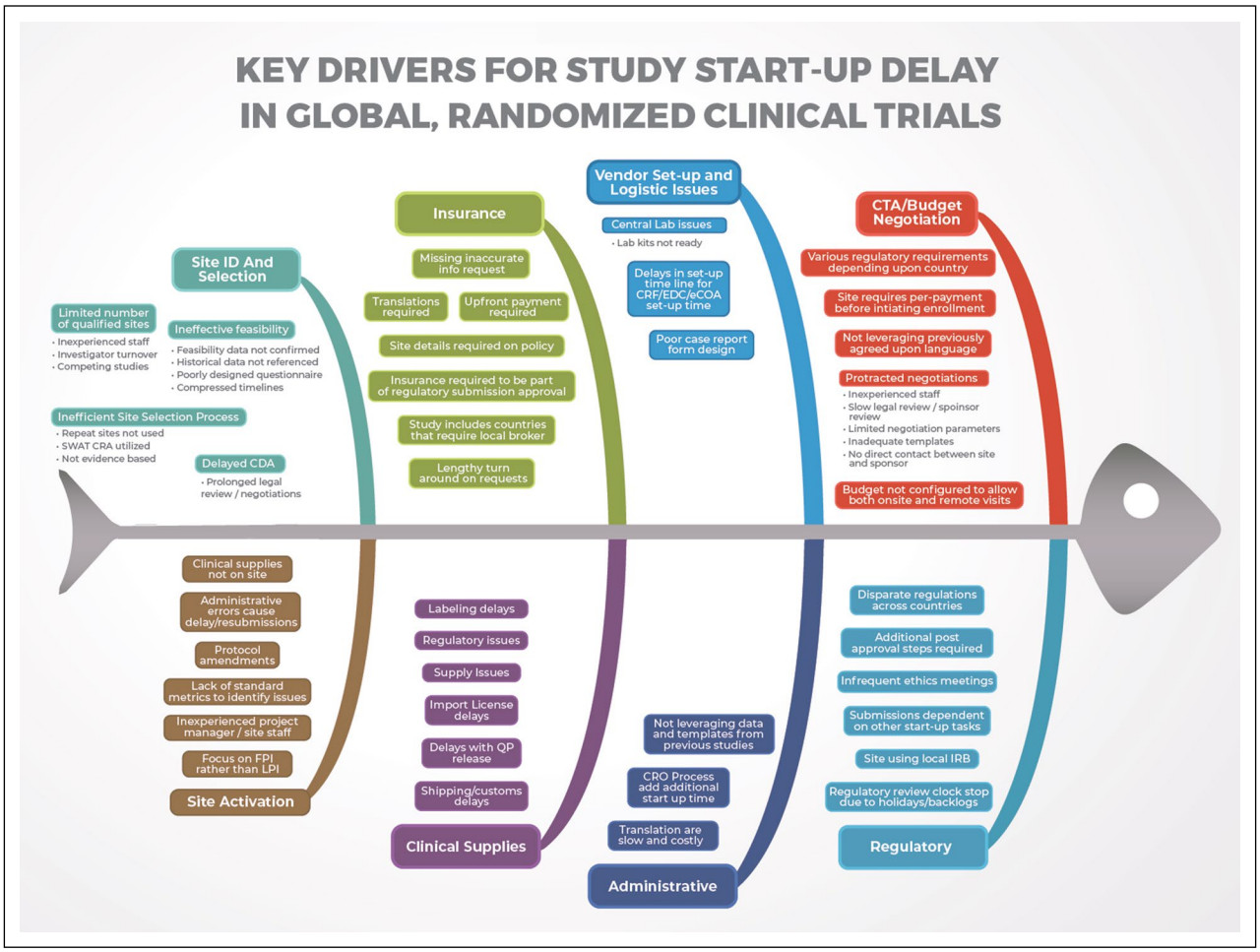


**Figure 1** Key Drivers for Study Start-up Delay in Global, Randomized Clinical Trials.

## 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) [19–21]. 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) [22]. Contributors to prolonged contract and budget cycle times include inexperienced staff, inadequate budget templates, limited negotiation parameters, and prolonged legal reviews [19]. If a sponsor has worked with a site in the past, leveraging previously negotiated contract and budget terms may significantly reduce cycle times [23].

Start-up activities, including negotiation of clinical trial agreements (CTAs), are often conducted on behalf of sponsor companies by clinical research organizations (CROs) [21]. 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 [19]. It is important to provide sites with a sponsor contact for escalation of negotiation issues as needed [19]. 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.

Clinical trials that incorporate decentralized visits (e.g., visits that occur in the patient's home) also have special contractual considerations. In such studies, it is important that the investigator fee structure allows for both in-office and remote patient visits. If this flexibility is not built in up-front, the contract will likely need to be revised, which is a costly and time-consuming process.

## Insurance

Procurement of liability insurance is a complex and critical aspect of clinical trial start-up that may be underestimated by clinical trial managers [24, 25]. 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 [24]. As with other aspects of multinational clinical trials, each country has their own set of rules governing indemnity insurance [5, 26, 27]. 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 [25]. 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 [5, 25]. Other countries require local policies, issued by a locally licensed insurance company [25]. Local policies have varying requirements and typically cover the duration of the study unless the study runs longer than the initial term covered [25]. Depending upon the information required on the insurance certificate, policies may require update if the number of sites, estimated participants 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 [14, 28]. 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 [29, 30]. Additionally, each country has their own combination of required data elements on the drug label, which must be translated into local language [31]. 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 [31]. Packaging and labeling require approximately 30 weeks from design and approval of conventional booklet labels to shipping kits to sites [31]. Incorporating the use of electronic labels (eLabels) presents an opportunity to reduce this timeline to 16 weeks [31].

Multinational studies require the clinical supply manager to keep apprised of local import and export regulations and shipping timelines [30]. Lamberti et al. examined logistics data for 73 clinical trials in a variety of therapeutic areas and across all phases [28]. 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) [28]. When trials include therapies that require refrigeration or frozen storage (e.g., biologics), the implementation of a good cold chain strategy is vital. Maintaining the cold chain is further complicated when multiple countries are involved and may include remote sites without ready access to couriers. In order to mitigate drug supply issues, stakeholders must keep apprised of import/export requirements and timelines for shipping and account for ample product overage when calculating drug supply requirements to ensure that local drug depots are well stocked. Finally, stakeholders must thoroughly vet site logistics to understand the flow of clinical supplies from supplier to pharmacy to patient and process temperature excursions quickly.

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, add significant cost to the study, and often are the source of delay and increased study cycle time [32]. 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 [32]. Once comparator products are procured, they may need to be repackaged or relabeled depending upon county-specific regulations [30].

## Site Identification and Selection

Increased competition for good, experienced clinical sites is a significant challenge for site selection [33]. In general, the more complex a study, the more difficulty CROs and sponsors have selecting sites [34]. 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 participants that meet eligibility criteria, appropriate staff, facilities, training and equipment, and interest in participating in the study [33, 35].

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 [36], 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 [36]. Often, key documents like the full protocol and budget are not available to sites at the time of feasibility [36]. After sites complete and return the feasibility questionnaire, the data are assessed and a subset of interested and eligible sites is selected to move on to a pre-study visit.

Site infrastructure should be assessed to ensure internet connectivity and ability to meet the technology requirements of the study. Sponsors may need to mitigate technology barriers by providing Internet access or supplying equipment as permitted by local regulations. Selecting "repeat" sites, or sites that have worked with a sponsor or CRO on a previous study, is an opportunity to reduce cycle times [34]. Cycle times for repeat sites were 28% shorter than cycle times for newly selected sites [34]. 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 [37].

### 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 subinvestigators. Documents required before the start of a clinical study are detailed in ICH E6 (R2) in Sect. 8.2 [38]. It is imperative that site start-up tasks are completed quickly and correctly, to avoid set-backs and additional cycles of regulatory review [15]. ICH E6 (R2), Sect. 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 [38]. 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 participants 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 [15]. These include (1) the date the final protocol was sent to a clinical site, (2) the date of IRB decision, (3) the date the contract (initial draft/template) was sent to the site, (4) the date that the site contract was signed, (5) the date the site was activated (open to enrollment), and (6) the date for the first patient's consent [13]. Employing standard metrics will allow clinical trial managers to identify areas for improvement and assess whether improvement initiatives are working [15].

## 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.

One way to increase quality and efficiency in clinical trials is through the incorporation of telemedicine and other technology to facilitate decentralized clinical trials (DCTs) or trials where at least a portion of the activities are conducted at the patient home. Benefits of DCTs include faster recruitment, improved retention of trial participants, increased comfort and convenience for trial participants, and increased access to trials [39]. However, start-up activities in decentralized clinical trials may need additional considerations including establishing new processes and training documents, procuring equipment, and assimilating regulations and legal requirements [40]. Components of DCTs that require special consideration include shipping clinical supplies directly to patients, electronic informed consent (eConsent), home health visits, telemedicine visits, remote site monitoring, and digital data collection tools [40]. To negotiate some of these challenges, study teams should proactively map data flow, data collection, data storage, and study procedures and develop robust training procedures for stakeholders [40].

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. A simple error on an insurance policy can significantly delay a regulatory submission or prevent a site from being activated when everything else is in place.

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.

[ ] Ensure that all activities that will be conducted by a CRO are detailed in a transfer of obligations document.

[ ] **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.

[ ] Identify and engage a key opinion leader (KOL) or panel of key opinion leaders

- When required, KOL input should be incorporated as part of protocol input/finalization. Additionally, a lead investigator may be required in some countries for regulatory submissions.

[ ] 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.

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

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 [41]. 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.

[ ] 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 **A**uthorities **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 participants the site expects to enroll.

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

**Figure 2** (continued)

## Limitations

The data gathered in support of our fishbone diagram and the resulting checklist (Fig. 2) 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. One means to generate

*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)

**Figure 2** (continued)

evidence regarding trial efficiency is conducting a study within a trial (SWAT) which examines a specific trial process [42]. Future research should generate evidence that demonstrates which clinical operations methodologies

- 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.

**Figure 2** (continued)

improve efficiency is important to avoid the waste of precious resources. Additionally, DCTs (which became a necessity during the COVID-19 pandemic) are an opportunity to greatly improve efficiency and quality in clinical research [39, 40]. The fishbone diagram and checklist do not detail start-up issues specific to DCTs; however, as they become more common, there is an opportunity to incorporate drivers of start-up delay specific to DCTs.

[ ] 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 participants (planned), # of randomized participants (planned) and

**Figure 2** (continued)

## 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 other high priority activities or contributions.

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 participants 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.

[ ] Determine whether a paper CRF or electronic data capture (EDC) system will be selected. If EDC, ensure site qualification covers technology readiness as well or offer alternative options, if possible.

[ ] 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**

**Figure 2** (continued)

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

[ ] Other 3rd party data sources (e.g. eCOA – electronic Clinical Observations Assessment)

[ ] Don't collect the same data in multiple places

[ ] **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 participants 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

**Figure 2** (continued)

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

**Figure 2** (continued)

- 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.

[ ] Additional considerations for decentralized clinical trials (DCTs)

[ ] Process map detailing data flow

[ ] Direct to patient shipping of clinical supplies

[ ] eConsent

[ ] Home health visits

[ ] Remote site monitoring plan

[ ] Procuring and validating digital data collection tools

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/

**Figure 2** (continued)

## Author Contributions

JL was the primary author of the work; this study was conducted for a doctoral project in the DHA program at MUSC. KS, DB, and LF all made revisions and approved the final product.

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## Compliance with Ethical Standards

## Conflict of interest

No potential conflicts were declared.

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