STUDY START-UP TIMES: ONE SITE’S ANALYSIS OF THE PROCESS, THE PROBLEM, AND THE PLAN TO SHORTEN TIMES.

A Capstone Paper Submitted to the Krieger School of Arts and Sciences Advanced Academic Programs in Partial Fulfillment of the Degree of Master of Science in Research Administration

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May 2018
Abstract

Some of the greatest technological advances in medicine have come from clinical trials. These trials provide cutting edge technology to patients suffering from acute and chronic illnesses. Getting these trials started expeditiously saves money, time, and more importantly benefits patients in need of relief. Unfortunately, many trials do not get started as quickly as the industry and institutions had planned. Very few publications address delayed study startups.

The author’s institution conducted a retrospective analysis of ten clinical studies (5 drug and 5 device) at their local institution to determine where the delays were in the study startup process. Utilizing 7 metric cycle times developed in 2010 at the Clinical Trials Transformation Initiative, time points were collected and analyzed. Most of delays came from the IRB process as well as budgeting and contracting. Once the study startup delays were identified, a plan for the author’s institution was developed to reduce those times.
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Glossary

**IRB Cycle.** The number of days between IRB submission and IRB final decision.\(^1\)

**Site cycle.** The number of days between the date the protocol was received at the site and the date of protocol submission to the IRB.\(^2\)

**Site to contract cycle.** The number of days between the date the protocol was received at the site and the date of contract execution.\(^3\)

**Site to IRB cycle.** The number of days between the date the protocol was received at the site and the date of final IRB decision on the protocol.\(^4\)

**Site to patient cycle.** The number of days between the date the protocol was received at the site and the date of first patient enrollment.\(^5\)

**Postcontract to patient cycle.** The number of days between the date of contract execution and the date of first patient enrollment.\(^6\)

**Post-IRB to patient cycle.** The number of days between IRB final decision and the date of first patient enrollment.\(^7\)

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**Abbreviations**

CMS – Centers for Medicare and Medicaid Services

CRO – Contract Research Organization

CTTI – Clinical Trials Transformation Initiative

FDA – Food and Drug Administration

IRB – Institutional Review Board

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\(^2\) Ibid

\(^3\) Ibid

\(^4\) Ibid

\(^5\) Ibid

\(^6\) Ibid

\(^7\) Ibid
Chapter 1. Introduction

1.1 Background

Ralph Waldo Emerson once said, “Men love to wonder, and that is the seed of science.” Human curiosity has yielded some of the greatest scientific innovations of all times. Of these innovations, cardiovascular clinical trials have provided cutting edge technology and drugs to patients in need of relief from their acute and chronic diseases.

Many examples come to mind. The Da Vinci, a machine that is replacing traditional open-heart surgeries in favor of a more minimally invasive way of heart surgery.\textsuperscript{8} The Jarvik 7, the first artificial heart, used to help bridge patients to heart transplantation.\textsuperscript{9} Other inventions include CardioMems, an implantable device used to help doctors monitor patients with heart failure from a distance with the hope that constant surveillance will decrease their hospitalizations.\textsuperscript{10} Transfemoral Aortic Valve Repair (TAVR) provides a minimally invasive approach to aortic valve repair and that allow a patient to go home the next day vice an open heart approach and lengthy recovery.\textsuperscript{11}

Devices aren’t the only innovations that have changed the cardiovascular world. Drugs such as Opsumit and Remodulin were created to help treat patients with pulmonary arterial hypertension while drugs such as Crestor have helped patients reduce their cholesterol levels.\textsuperscript{12}

\textsuperscript{8} This year's top 10 advances in cardiovascular diseases, (2014). Retrieved from https://www.health.harvard.edu/press_releases/this-years-top-10-advances-in-cardiovascular-disease
\textsuperscript{9} Ibid
\textsuperscript{10} Ibid
\textsuperscript{11} Ibid
Scientific breakthroughs don’t happen overnight, they are tested over and over again in clinical trials before being submitted to the Federal Drug Administration (FDA) for approval to market and sell to patients. Clinical trials are conducted to test a product or drug’s safety and efficacy in the people they are intended to help. Industries that engage in clinical trials want to begin these studies as expeditiously and efficiently as possible.

1.2 Statement of the Problem

Prolonged study startup times prevent clinical trials from beginning in a timely manner. There are no clear industry standards on how long a study startup should take. What is clear is that delays cost money and time for the institution as well as prolong care for the patients who are dependent on these new technological advances. There has been speculation as to why these delays occur. Some blame the sponsor while others place the blame on the institutions conducting the studies.

The author’s institution decided to analyze study startup times to find out where the delays were occurring and implement a plan to reduce those times. The author’s institution is a physician-owned cardiovascular hospital which is part of the largest healthcare system in the state. The cardiovascular research office employees 23 staff, 4 of which hold administrative roles. It currently has over 100 active clinical studies which enrolls approximately 83 patients per month. Currently, study startup times are not closely followed or analyzed at this institution nor is there a standard time goal for the startup process. Also, no one knows where in the startup process delays occur or why.
1.3 Research Questions

What are the average study startup times and are there ways in which an institution can reduce this process? Where are the delays coming from? What changes can be made to reduce these times?

1.4 Objectives

1. To establish the average study startup times for both drug and device studies at one institution.
2. To determine the causes of slow study startup times.
3. To identify areas of improvement.
4. To establish a more effective system to track study startup times.
5. To put a plan into place that streamlines the process and reduce study startup times to 120 days.
Chapter 2. Review of the Literature

There are very few publications that focus on study startup times and the implication of their delays. In 2010, the Clinical Trials Transformation Initiative (CTTI), funded by the FDA, organized a retrospective analysis of study start up times across 19 organizations in the United States.\(^{13}\) Out of this initiative came seven key cycle times needed to create an accurate analysis of study startup times.\(^{14}\)

1. **Site Cycle** - the number of days between the date the protocol was received at the site and the date of protocol submission to the IRB.
2. **Site to IRB cycle** - the number of days between the date the protocol was received at the site and the date of final IRB decision on the protocol.
3. **Site to contract cycle** - the number of days between the date the protocol was received at the site and the date of contract execution.
4. **Site to patient cycle** - the number of days between the date the protocol was received at the site and the date of first patient enrollment.
5. **IRB cycle** - the number of days between IRB submission and the IRB final decision.
6. **Post-IRB to patient cycle** - the number of days between IRB final decision and the date of first patient enrollment.
7. **Postcontract to patient cycle** - the number of days between the date of contract execution and the date of first patient enrollment”\(^{15}\) (Abbott et al., 2013, p. 154). These key cycles will be the basis for the retrospective analysis in this paper.


\(^{14}\) Ibid.
Chapter 3. Project Description

Once an industry sponsor selects sites to conduct their clinical trials, the study startup process begins. First, a Confidentiality Disclosure Agreement (CDA) is signed by the Principal Investigator (PI). In most cases, once the CDA is signed, the sponsor will send a file containing regulatory documents to the site. That file contains the study protocol, the investigator’s brochure, the sponsor’s budget, the informed consent (ICF) template, and the FDA and Centers for Medicare and Medicaid (CMS) approval letters. Some sponsors will send regulatory documents prior to receiving FDA and CMS approval which significantly slows down the startup process. Without FDA or CMS approval, Coverage Analysis can’t begin. Since, regulatory documents that arrive are not time-stamped upon arrival so there is no way to gauge exactly when the startup process began.

The current process has regulatory documents arriving via email to whomever the sponsor or Contract Research Organization (CRO) has a working relationship with (either supervisor or Research Coordinator). A CRO is a company that is hired by the sponsor of a clinical study to manage all research related activities. A site survey completed by CenterWatch in 2011 revealed that 73% of respondents still used either email, fax, or courier to deliver their regulatory documents.\textsuperscript{15} There is not one designated email address where all regulatory documents are received. Without an efficient log in system there in no way to track where documents are at any given time. This form of document delivery has resulted in lost emails.

\textsuperscript{15} Intralinks global investigator site survey: Results highlight need for the adoption of web-based clinical trial document exchange tools to drive efficiencies and increase productivity. (2011). Retrieved from http://ir.intralinks.com/External.File?f=2&item=g7rqBLVLuv81UAmrh20Mp/7aRom76rKfZir7ayBElbDMFbSYYuqo1DiO7r mYng4Ob7Pj43uvhXwMkElmmjjg==
forcing the CRO to resend them to the institution.\textsuperscript{16} The end result is a delay in startup of the clinical trial.

It is only when all regulatory documents have been received that a staff member posts and disperses the documents to staff in legal, contracting, and IRB so they may begin their part of the process. After this posting, another staff member, either a coordinator or data analyst with experience in the startup process, assumes the responsibility of the startup process and begins their part by completing a study feasibility tool which is then presented to the research team in their weekly meetings.

The research meetings are composed of physicians, research nurses and coordinators, data analysts, finance and regulatory specialists. It is during this time that new studies are discussed. A feasibility tool is utilized to determine if conducting a clinical trial at the institution is feasible. Feasibility tools are used to aid researchers in deciding whether or not to start a study at their site. It also helps them determine if they have an adequate patient population to conduct the study. Feasibility tools help an institution decide if the patient population and budget are adequate to garner profitability for the institution. If a site does not have the population to conduct the study then time, effort, and money will be wasted. A feasibility tool was implemented at the author’s institution, that focuses solely on three key points: patient population, budget, and scientific merit. This tool was designed to ensure that a new clinical study would yield good science as well as be profitable at the institution. If a study is approved by the physicians and management, then the Coverage Analysis is started.

The Coverage Analysis is “a systematic review of all procedures listed in the study protocol’s schedule of events to determine which ones are ‘billable’ and where the services

\textsuperscript{16} Ibid.
should be billed.”17 The coverage analysis is used in conjunction with the Center for Medicare and Medicaid’s (CMS) Current Procedural Terminology (CPT) codes to determine the amount of money a healthcare provider is reimbursed for a procedure or test.18 The coverage analysis lets the study start up team know what will be billed as research and what will be billed to the patient’s insurance. The coverage analysis is completed at the local level and then sent to Administration for their review and approval. If there are any changes, Administration will return it for corrections. The Coordinator or Analyst then must correct it, resubmit it and then wait for approval. This constant back and forth creates delays in the process because a study cannot move forward with the budget until a coverage analysis is approved. The CPT codes also let the startup team know which ones to use when calculating the internal budget. Once approved, the internal budgeting process begins.

Internal budgets, at the author’s institution, are done at the local level and, and like the Coverage Analysis, are sent for approval from Administration. They have traditionally been done on Excel spreadsheets which have been shown to prolong study start up time. According to goBalto, sites that were still using Excel spreadsheets to do their internal budgets “reported that the review and revision cycle for a single study was taking more than five weeks.”19 Figure 1 identifies the most common types of technology utilized in the management of study startups. Spreadsheets, such as Excel, are the most frequently used. Due to the complexity of clinical trials, the internal budget can be a long and tedious process. After approval by Administration, the contract and budget negotiations begin.

Budgeting and Contracting are traditionally considered two separate pieces of the startup process. One cannot be completed without the other and so for this analysis the author combined these into one cycle. The Association of Clinical Research Professionals (ACRP) found that 49% (Figure 2) of study startup delays were caused by contracting and budget negotiations.\textsuperscript{21} The average time to fully execute a Clinical Trial Agreement (CTA), in the United States, averaged around two months.\textsuperscript{22} There are many reasons why contract negotiations get delayed but four main issues have been identified.


\textsuperscript{22} D.S. Araujo. (2017). 4 villains that can delay your clinical trial agreement (CTA) and how to defeat them. Retrieved from https://www.clinicalleader.com/doc/villains-that-can-delay-your-clinical-trial-agreement-cta-and-how-to-defeat-them-0001
First, limited negotiation parameters on the sponsor side can cause delays. Many sponsors create one budget for all sites without taking into consideration “geographical locations, institution size, and other pertinent information.” Healthcare costs will vary depending on geographical location.

The second reason for budget and contracting delays rests upon on the individual sites. When local institutions create their own internal budgets, they need to make sure they are done using fair market value of the tests and procedures in their geographical area. Internal budgets should be accurate, fair and have the ability to be justified if asked.

Also, many sites have Master Service Agreements with sponsors they work with frequently. Master Service Agreements are documents that have already been agreed upon between both parties so the language doesn’t need to be re-negotiated each time they start another clinical trial. At the author’s institution, Master Service Agreements are used frequently but budget negotiations still cause major delays in the startup process.

Third, each local institution (either nationally or globally) will have their own specific requirements that need to be included in the final contract. Knowing what these are can decrease delays.

Fourth, internal bureaucratic requirements, on either the sponsor or site side, can result in contract negotiation delays. Legal reviews also add to this delay. According to the CenterWatch Survey (Figure 2), legal reviews contribute to 26% of study startup delays.

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23 Ibid.
24 Ibid.
25 Ibid.
26 Ibid.
27 Ibid.
28 Ibid.
29 Ibid.
At the author’s institution, the Clinical Trial Agreement (CTA) and budget are handled by a team of lawyers and contract negotiators. The CTA focuses on six main areas: intellectual property, study data, indemnification, subject injury, confidentiality, and publication rights. The contracting team also acts as an intermediary between the CRO and local institution during budget negotiations. Budget negotiations are stalled when there is a breakdown in communication with the CRO, contract negotiators, and the local institution. While this is ongoing on, the Institutional Review Board (IRB) is working to review and approve the study.

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**Figure 2. Factors that cause Study Delays**

According to a CenterWatch Survey, the factors most often causing study delays are:

- **Contract & Budget Negotiation & Approval**: 49%
- **Patient Recruitment & Enrollment**: 41%
- **Protocol Design & Refinement**: 26%
- **Legal Review**: 26%
- **IRB Review & Approval**: 25%

![Source: CenterWatch Survey 2009](image)
IRBs were implemented after numerous cases of inhumane experiments on human subjects were discovered. Examples include, the abuse of Jewish prisoners during World War II, the Thalidomide tragedy, and the Tuskegee experiments.\textsuperscript{32} Atrocities such as these led to the Beecher Report and the Declaration of Helsinki that established the IRB as well as set ethical guidelines for researchers.\textsuperscript{33} Acting under federal oversight, the IRB has evolved over the years to include their growing number of responsibilities.\textsuperscript{34}

Due to increasing amount of IRB responsibilities, at the author’s institution, the IRB process accounts for much of the startup delays\textsuperscript{35} Collapsing under the enormous weight of regulatory documentation, IRBs can no longer simply focus solely on protecting the well-being of human subjects.\textsuperscript{36} They are also tasked, among other duties, with certifying that investigators do not have conflicts of interest with sponsors and that research staff are current on their regulatory training.

When regulatory documents are received at the author’s institution, the Regulatory Coordinator reviews the protocol, investigator’s brochure, ICF template, as well as any recruitment tools. The author’s institution utilizes a local IRB and requires all sponsor ICF’s to be transferred onto their ICF template. This process can be time consuming and with recent changes, the local IRB updated their current template to include additional confidentiality and Health Insurance Portability and Accountability Act (HIPAA) language which has increased the time needed to revise the ICF templates. Once changes are made, the regulatory coordinator returns it to the sponsor for approval. This must take place before the regulatory coordinator can

\textsuperscript{33} Ibid. \\
\textsuperscript{34} Ibid. \\
\textsuperscript{36} Ibid.
submit it to the IRB for initial review. Unfortunately, while sponsor review and approval is needed, this can delay a startup even more, especially if the sponsor requires changes.

The local IRB consists of three boards that oversee all clinical studies across the health care system. Two boards conduct full reviews while the third one conducts expedited reviews. Each one meets monthly and has one IRB coordinator assigned to it. Altogether, over 1,000 active studies, institution wide, not including the ones currently in the startup process are reviewed by the IRB.

Once the ICF template is sponsor approved, the regulatory coordinator submits the study to the IRB for initial review. Upon receipt, a study is assigned to one of two IRB Boards unless it’s considered a low risk study, in which case it will be assigned to the expedited review board. The IRB coordinator does the pre-review of the study and returns it if there are stipulations that need to be addressed prior to a review by the full board.

After pre-review stipulations are met, the study is submitted to two Physicians on the IRB for review. Again, any stipulations from them must be met prior to the full board review. Unfortunately, many of the stipulations are vague causing the Regulatory Coordinator at the site to exchange numerous emails in order to get clarification. This could be rectified by making a phone call to eliminate the back and forth that ensues.

In summation, the IRB will not release an outcome letter until finance, contracting, and statistical review are complete. This can lead to a 30-day delay in releasing the outcome letter after the IRB has reviewed and approved a study. Once the board has approved a study it must be sent for signatures from IRB members, finance, budgeting, and contracting to ensure their part of the process is complete.
Another factor affecting the process is staff turnover. At the local IRB, staff turnover significantly slows down the IRB part of the startup process because of additional workload and responsibilities that the remaining coordinators must endure until new coordinators are hired and trained, which can take months.
Chapter 4. Needs Assessment

In order to establish a realistic study startup timeline, the author had to determine current timelines that were being used by the institution. This was difficult because there was no process in place to track when clinical trials arrived at the institution or as they make their way to contract execution. There is much speculation by Administration as to what those times are and what they should be. Many believe that current study startup times are greater than 180 days but should be less than 90 days.

In this Capstone Project the author conducted a retrospective analysis of 10 clinical studies (both device and drug) looking at the following:

1. when the regulatory documents arrived on site,
2. how long it took to submit the regulatory documents to the IRB,
3. how long the study was in the IRB cycle,
4. how long the study was in the contract cycle, and,
5. how long it took to enroll the first patient.

Once these dates and times were established then the author could identify areas for improvement.
Chapter 5. Methodology

5.1 Methodology Design

A retrospective analysis was done on ten clinical studies at the author’s institution selected at random. The studies that were analyzed included five device studies and five drug studies. Using the key cycle points discussed during the Clinical Trials Transformation Initiative and the use of Smartsheets, dates were collected and analyzed. Since documents were not time stamped upon arrival and staff that received some of the documents may have left the organization, the only dates that could be used as site arrival date were those that had been saved to the Institution’s shared drive (which may or may not have been the day they arrived). Smartsheets was utilized to track the dates and compile a total time in each of the cycles as well as a total cycle time (arrival of regulatory documents to when the first patient is enrolled).

5.2 Research Retreat

While data was being collected, a research retreat was held at the local institution which included a discussion on study startup times and ways in which administration could help to reduce these times. Discussions were held with Administrative officials regarding Coverage Analysis, IRB, and contracting on how to reduce study start up time. It was determined that parts of the startup process that were being conducted at the local level were not being done efficiently. Participants in the retreat designed a plan that included taking those parts and centralizing them in a way that would streamline the process, save money, and reduce time. The retreat gave the author’s institution take away actions that were put into effect.
Chapter 6. Results and Discussion

6.1 Results

Once the number of days in each cycle were collected for both the drug and device studies, the amount of time was analyzed to determine where the greatest delay occurred in the study startup process. Correlations were noted between both the device and drug studies. The average cycle times for the drug studies are summarized in Table 1 while the device studies are summarized in Table 2.

6.1.1 Drug Study Results

The largest delays in the drug studies were found in the Site to Patient Cycle with an average of 271.8 days. The two other cycles that had the greatest average time was the Site to Contract and the Site to IRB cycles. The average Site to Contract cycle for the drug studies was 149.4 days. This was the time from when the regulatory documents were received at the site until the fully executed contract. The Site to IRB cycle is the amount it took from when regulatory documents were received until the date that the IRB approved the study. The average days for this cycle was 150.4 days. The Post Contract to Patient Cycle was 123.4 days and The Post IRB to Patient Cycle was 122.4 days. The average time in the IRB Cycle for the five drug studies was 111.4 days. The shortest cycle in the drug studies was the Site Cycle with an average of 40 days.

6.1.2 Device Study Results

The largest delay in the device studies was the Site to Patient Cycle with an average of 274.4 days. The other two cycles with the greatest average times was the Site to Contract Cycle
and Site to IRB Cycle. The Site to Contract Cycle had an average of 193.2 days while the Site to IRB Cycle averaged 208.6 days. The entire IRB cycle for the device studies averaged 152.4 days. The Post Contract to Patient Cycle was 82.2 days. The two shortest cycles in the device analysis was the Post IRB to Patient Cycle and the Site Cycle. The Post IRB to Patient Cycle had an average 66.8 days while the Site Cycle for device cycles averaged 57.2 days.

### 6.1.3 Comparison and Contrast Between Drug Study and Device Study Results

There were many correlations between the drug and devices studies. The longest cycle for both drug and device studies was the Site to Patient Cycle. Drug studies averaged 271.8 days while the device studies averaged 274.4 days. The second longest cycle for both drug and device studies was the Site to IRB cycle. The drug studies averaged 150.4 days while the device studies averaged 208.6 days. The third longest cycle for both sets of studies was the Site to Contract Cycle. Drug studies averaged 149.4 days while the device studies averaged 193.2 days. The shortest cycle for both drug and device studies was the Site Cycle. Drug studies averaged 40 days while the device studies averaged 57.2 days.

In Contrast, there were notable differences between three of the cycles. The largest difference between the drug and device studies was found in the IRB Cycle. Drug studies averaged 111.4 days while the device studies 152.4 days. Next, the Post IRB to Patient cycle was the second contrast in both drug and devices. The drug studies averaged 122.4 days in this cycle while the device studies 66.8 days. Finally, the Post Contract to Patient Cycle had the smallest difference. The drug studies in this cycle averaged 123.4 days while the device studies averaged 82.2 days.
Table 1. Summary of Drug Studies

![Drug Studies Chart]

Table 2. Summary of Device Studies

![Device Studies Chart]
6.2 Discussion

Tables 3 and 4 below represent the data that was collected during the Clinical Trials Transformation Initiative in 2010. This information was collected from a survey of cycle times across 19 organizations between January 1, 2009 through January 1, 2010. Table 5 represents a comparison of the CTTI data for hospital-based sites and the average cycle times for both drug and device studies at the author’s local institution. The Site Cycle averaged 68 days in the Initiative while at the author’s local institution, the average number of days was 48.6. The author’s institution never tracked when regulatory documents were received nor was there one central email address or portal where these documents arrived. There is no way to accurately determine when these documents were received other than when they were posted on a shared drive.
Table 3. CTTI cycle time metrics, part I

<table>
<thead>
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<th>By Category</th>
<th>Site Cycle</th>
<th>Site to IRB Cycle</th>
<th>Site to Contract Cycle</th>
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<td>Median (IQR)^a d</td>
<td>Nonmissing</td>
<td>Median (IQR)^a d</td>
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<td>3383 (62.7)</td>
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<td></td>
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</tbody>
</table>

IRB, institutional review board; IQR, interquartile range; ARO/CRO, academic research organization/clinical research organization; NA, not applicable.

*The IQR is reported for each cycle. Although this measure specifically compensates for the effect of outliers, the range of values for this measure even within a given site type illustrates the likelihood of the interplay of several factors on cycle times.

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The Site to Contract Cycle, averaged 104 days at the Initiative and 171.3 days at the local institution. An analysis of this data brings up a few possible reasons. First, the complexity of some the studies could cause an extended delay. Also, the local institution does not have a standardized process for the internal budget based on the complexity of said studies and because of this, budget negotiations hinder the progress of the contract execution. Finally, the contracting and budgeting cycle are handled by both the local institution and Administration. Due to both

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Table 4. CTTI cycle time metrics, part II

<table>
<thead>
<tr>
<th></th>
<th>IRB Cycle</th>
<th>Post-IRB to Patient Cycle</th>
<th>Postcontract to Patient Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonmissing, n (%)</td>
<td>Median (IQR)</td>
<td>Nonmissing, n (%)</td>
</tr>
<tr>
<td>All data</td>
<td>2585 (47.9)</td>
<td>9 (0-403)</td>
<td>3136 (58.2)</td>
</tr>
<tr>
<td>IRB type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>1537 (55.3)</td>
<td>7 (0-403)</td>
<td>1823 (65.6)</td>
</tr>
<tr>
<td>Local</td>
<td>602 (32.9)</td>
<td>35 (0-392)</td>
<td>812 (44.4)</td>
</tr>
<tr>
<td>Missing</td>
<td>446 (56.7)</td>
<td>7 (0-290)</td>
<td>503 (64.0)</td>
</tr>
<tr>
<td>Organization type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic</td>
<td>15 (2.7)</td>
<td>52 (14-118)</td>
<td>196 (35.1)</td>
</tr>
<tr>
<td>ARO/CRO</td>
<td>375 (53.3)</td>
<td>8 (0-225)</td>
<td>317 (45.1)</td>
</tr>
<tr>
<td>Biotechnology</td>
<td>273 (53.3)</td>
<td>5 (0-392)</td>
<td>151 (29.5)</td>
</tr>
<tr>
<td>Device</td>
<td>24 (30.4)</td>
<td>30.5 (7-117)</td>
<td>40 (60.8)</td>
</tr>
<tr>
<td>Government</td>
<td>0 (0)</td>
<td>NA</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Investigators</td>
<td>21 (48.8)</td>
<td>20 (0-202)</td>
<td>34 (79.1)</td>
</tr>
<tr>
<td>Pharmaceutical</td>
<td>1877 (54.4)</td>
<td>10 (0-403)</td>
<td>2392 (69.4)</td>
</tr>
</tbody>
</table>

IRB, institutional review board; IQR, interquartile range; ARO/CRO, academic research organization; NA, not applicable.
*The IQR is reported for each cycle. Although this measure specifically compensates for the effect of outliers, the range of values for this measure even within a given site type illustrates the likelihood of the interplay of several factors on cycle times.

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being in different geographical locations, direct communication is limited and email is the main mode of communication.

The Site to IRB cycle average time for other hospital-based sites is 109 days while at the author’s institution, it averaged 179.5 days. Some possible reasons for this, at the local institution, include stipulations that are vague thus requiring various emails between the local Regulatory Coordinators and the IRB Coordinator to clarify the problems. This cycle also includes the time in which the Regulatory Coordinator at the local institution must transfer the Sponsor’s Informed Consent to the local IRB Template, return it to the Sponsor and wait for approval. Most Sponsors have additional changes that must be made and reviewed (again) before it can be submitted to the IRB. Once the IRB approves a study, it must go through various checks to ensure that contracting, budgeting, and statistical review is complete prior to releasing the outcome letter.

The IRB cycle time in other hospital-based sites, averaged 33.5 days while at the local institution the average number of days was 131.9 days. This is almost four times the average of other hospital-based sites. Like the Site to IRB cycle, this time includes various stipulations that must be addressed. Also, if any of the investigators on the study don’t have current regulatory training such as Human Subject Protection, Biomedical Researcher, or Good Clinical Practice on file, this could delay the study being reviewed.

Conflict of Interest is another issue that has been found to halt a study from being reviewed. If the IRB finds that a Principal Investigator has a Conflict of Interest and depending on how large of a conflict, he or she may have to recuse themselves as Principal Investigator and assign another to fill that position. If this occurs, the Sponsor must be informed and approve any new changes. This would require that all regulatory documents, including the ICF and Contract
be corrected with the new Principal Investigator’s name. Situations such as these create an extended delay in this cycle.

The Site to Patient Cycle time averaged 222 days in other hospital-based sites while at the local institution, the average number of days in this cycle was 273.1. This cycle caused the greatest delay for the local institution as well as other hospital-based sites. One possible reason for this is that some studies don’t enroll as well as the investigator or site had anticipated. This is where a strong feasibility tool is imperative at the beginning of the study startup process.

The Post-IRB to Patient Cycle time averaged 102 days for the hospital-based sites while the local institution averaged 94.6 days. This is the only cycle in which the local institution had a shorter average time than other hospital-based sites. When the device and drug studies were analyzed it was noted that the device studies had the shortest amount of time in this cycle. As stated before, the IRB won’t release the outcome letter which essentially gives the institution the “green light” to begin enrollment. Upon further analysis of the device studies, it was noted that coordinators and investigators will “pre-screen” potential upcoming patients for these studies and as soon they are “green-lighted” they enroll these patients quickly prior to their procedure or surgery.

Drug studies at the local institution averaged 122.4 days in this cycle. At the author’s institution, there were a couple of possible reasons for this. There was staff turnover that caused screening and enrollment to cease. Also, some studies had extensive inclusion/exclusion criteria that made enrollment difficult.

While drug studies tend to run for a long period of time, sometimes years, device studies at the author’s institution typically last less than a year. In addition, follow-up appointments for
the device studies occur simultaneously as the patient’s regularly scheduled appointments. This eliminates the need for additional visits.

Post-Contract to patient cycle for hospital-based sites averages 95 days while the author’s institution averaged 102.8 days. Occasionally, a study can receive IRB approval (minus receiving the outcome letter) before a contract is fully executed.

Table 5. Comparison of CTTI date and Local Institution Cycle Times

<table>
<thead>
<tr>
<th>Comparison of CTTI and Local Institution Cycle Times</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="chart.jpg" alt="Chart showing cycle times comparison" /></td>
</tr>
</tbody>
</table>

- **Avg for Hospital-based Sites**
- **Avg for both drug and device studies at local institution**
Chapter 7. Recommendations and Conclusions

7.1 Recommendations

Based on the analysis of ten studies at the author’s institution and the input received from the research retreat, a list of recommendations was created by the author. The author believes that the recommendations below will help to reduce clinical trial startup times.

**Recommendation 1.** A centralized email address needs to be created so that Sponsors and CROs have one area to send their regulatory documents. This recommendation will help alleviate emails getting buried or startups being delayed due to vacations or illnesses. Also, this gives the startup team an exact date of when documents are received on site without having to rely on shared drives or memory to retrieve these possible inaccurate dates.

**Recommendation 2.** The feasibility tool, which focuses on scientific merit, population, and budget, should continue to be utilized before a study is approved at the institution. For this recommendation, new changes that should be maintained include pulling three years of population history for a study. This would accurately depict if the institution has adequate patient population for the study.

**Recommendation 3.** A Feasibility Committee was formed during this project and should continue. It was created to properly vet potential clinical studies. This new committee was formed and implemented to take the feasibility review out of the weekly research meetings and put it into a more controlled and unbiased environment where the potential studies are closely analyzed.

**Recommendation 4.** The Coverage Analysis should be centralized and only done by the Administrative Coverage Analysis team. The Administrative Coverage Analysis team are experts
in their field and have a wealth of experience with Center for Medicare and Medicaid Services coding and billing. Coverage Analysis’ are only done once per study and having the administrative team conduct these, will cut down on study startup times.

**Recommendation 5.** Allow the local institution to conduct their own budget negotiations. Currently, a contracting team in administration conducts these negotiations but rely heavily on local institution input. The local institution has a copy of the Sponsor’s budget and they know what is needed to start a study, financially, as well as the manpower needed to conduct the study in its entirety. Having the local institution control their own budget negotiations cuts down on the current back and forth with the administrative team acting as the liaison between the local institution and the CRO or Sponsor.

**Recommendation 6.** Standardize the study startup costs based on the complexity of the clinical trial. The internal budget is composed of study startup costs, labor, and laboratory tests and procedures. Study startup costs include the time to prepare IRB paperwork, obtain signatures, and train staff on the study. The study startup costs have traditionally caused the most disagreements in the budget negotiations. Every study, regardless of whether a master service agreement exists or not, have differing study startup costs. Standardizing them alleviates these disagreements. For smaller, less complex or risky clinical trials startups should be $10,000. Mid-size trials $15,000 and large and complex trials $20,000.

**Recommendation 7.** The institution needs to purchase an electronic system or software that can accurately track startup times. Currently, Smartsheets tracks cycle times but requires a staff member to manually input dates which can lead to errors. The research community has numerous platforms available that can help facilitate study startup and accurately track when cycle times begin by electronically timestamping them when they are received.
7.2 Conclusion

Study startup delays costs money and time for both the Sponsor of a clinical trial as well as the local institutions. Most importantly, patients miss the opportunity to participate in trials that could possible benefit their health and wellbeing. The author’s institution analyzed 10 clinical trials (five devices and five drug) to establish a baseline study startup time at their organization. During the analysis, delays were discovered in different time metric cycles. Those delays were analyzed for ways in which the institution could work to reduce them. Recommendations were made based on the findings and actions were taken. Continued progress will help the local institution establish a more efficient study startup process.
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Appendix 1

Local Institution Data Findings

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Drug Study #1</th>
<th>Drug Study #2</th>
<th>Drug Study #3</th>
<th>Drug Study #4</th>
<th>Drug Study #5</th>
<th>Avg Days</th>
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<tr>
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</tr>
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<table>
<thead>
<tr>
<th>Cycle</th>
<th>Device Study #1</th>
<th>Device Study #2</th>
<th>Device Study #3</th>
<th>Device Study #4</th>
<th>Device Study #5</th>
<th>Avg days</th>
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</tr>
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<td>37</td>
<td>83</td>
<td>5</td>
<td>129</td>
<td>82.2</td>
</tr>
</tbody>
</table>
Alexandria Biberstein received her Bachelor’s Degree in Nursing from Georgia Southwestern State University in May 2006. She worked in critical care for 10 years before becoming a Research Nurse in 2015 specializing in cardiovascular research. Her research experience includes conducting drug and device trials as well as participating in study startups, budget and contracting, and regulatory.