# THE IMPACT OF DELAY: ASSESSING THE EARLY INDICATORS OF DEVELOPMENT TIME AND ACCRUAL MILESTONES ON ONCOLOGY CLINICAL TRIAL SUCCESS

By

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To my 阿公, who taught me that continual pursuit of knowledge is a never-ending journey,

To my entire family, thank you for all the support and encouragement you have given me

and

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# CHAPTER I

# DISSERTATION OVERVIEW

## 1.1 INTRODUCTION & RESEARCH QUESTION

It is well-known that the majority of engineering, information technology, and construction projects either fail outright, or only achieve their goals at a significantly higher cost in terms of time and resources.[1, 2] Interestingly, there has been little investigation of the success or failure rates of health-related projects, most notably in the area of clinical trials. A clinical trial is a research study that tests how well new medical approaches work in people.[3] Clinical trials involving therapeutic drug agents proceed through a series of research experiments, or phases (I, II, and III), to gain scientifically supported insight prior to Food and Drug Administration (FDA) approval for such agents to be utilized by the general public.[4] Each clinical trial is regarded as a project in itself; for example, a phase III clinical trial in oncology requires approximately 784 calendar days to develop a single phase III clinical trial across 370 distinct processing steps involving more than 30 participants.[5, 6] If one considers the development of a drug as a "project", a potential therapeutic agent going through the series of phase I, II, and III trials translates to approximately $802 million (2003 USD).[7, 8]

The purpose of my research is to discover if there are early indicators of the eventual success of a clinical trial. Success, in the case of a clinical trial, will be measured from an operations perspective, i.e., a trial will be considered successful if it enrolls, or accrues, a sufficient number of patients such that a scientifically meaningful conclusion can be

drawn. This number of patients is typically identified in the trail design, or protocol, itself and is referred to as the accrual goal. Inversely, a failure of a clinical trial is the discontinuation of a trial before it achieves the minimum specified accrual goal.

Recent research has discovered that less than one in five cancer clinical trials conducted results in publication in peer-review journals, hence a large number of clinical trials are conducted without achieving their intended objective.[9] While the selective publication of clinical trials with negative results affects publication acceptance, a greater and often overlooked impact lies within the inability to achieve the adequate number of enrollments to demonstrate the scientific hypothesis.[10] In one setting, that of Comprehensive Cancer Centers, a sample from four major such institutions showed that greater than twenty-three (23%) of clinical trials selected to enter the portfolio (i.e. opened for accrual) did not even achieve the minimum patient accrual, hence no valid scientific outcomes could be observed.[11, 12] Obviously, there are substantial barriers to achieving clinical trial success, thus preventing the advancement of both scientific knowledge and the improvement of clinical practice.

Two primary aspects that may influence success of a clinical trial that will be investigated in this research are 1) factors that are related to the design and development stage of the trial and 2) factors that are observed once a trial is launched, or opened for patient accrual.

*Formally, the research questions posed for my dissertation are (Figure 1-1):*

1. *Does development time of a cancer clinical trial impact the likelihood of achieving success, i.e., achieving the minimum accrual goal?* *(Chapter 2)*
2. *Are there early indicators of a cancer clinical trial, once it is open to accrual that can be used to help predict the eventual success?* *(Chapter 3)*
3. *What characteristics of the design of the clinical trial impact the development time of a cancer clinical trial?* *(Chapter 4)*

The types of clinical trials investigated are oncology clinical trials supported through the National Cancer Institute (NCI). The primary focus of the research is to be able to assist the decision-makers within the NCI and clinical trials offices of academic and medical institutions during the development process in order to improve the likelihood that the trial will be successful with respect to accruals. Also, my research will provide guidance to such decision-makers during the conduct of a trial as to the likelihood of a trial successfully achieving its accrual goal once it has been activated or opened.

## 1.2 THEORETICAL FRAMEWORK AND LITERATURE REVIEW

### 1.2.1 Clinical Trials as a Healthcare Project

The development of a clinical trial is akin to the new product development process. A project is defined as a "complex effort made up of interrelated tasks, performed by various organizations, with a defined set of objectives, schedules, and budgets" [13]. For the purpose of my research, a project is a *clinical trial*. A clinical trial is a project that focuses on research to test how well new medical approaches work in people.[3] The development of a clinical trial is composed of various components such as

the protocol, forms, contracts and grants negotiation, as well as the many review functions. Each of these components is developed by specialized participants in the development process, such as physicians, research nurses, protocol editors, regulatory specialists, lawyers, and financial analysts. Each of these participants must coordinate with each other during the development processes to form the final resulting product of a clinical trial.

The intersection between portfolio planning through project selection and its application to healthcare is a ripe opportunity to improve the implementation of cancer clinical practices. Dimasi et al.[8] have documented the enormous costs and time associated with the new drug discovery process including the conduct of clinical trials. Previous research to uncover more descriptive detail of the clinical research process by Dilts et al[6, 14] has found that a significant amount of time and effort required to conduct a clinical trial is consumed in clinical trial setup from concept inception to study activation. Yet much of the research conducted on the productivity of clinical research is centered on the operations of post-activated clinical trials in the form of participation of patients in the available clinical trials.[15-19] Little research is available on the decisions and processes required to design and activate a study or on how factors known at concept design may predict eventual accrual performance. [6]

Noting the lack of published research in the area of clinical trial pre-activation activities (including clinical trial selection), a number of initiatives have been implemented which focus on improving the setup time by means of prioritizing clinical trials in order to accrue more patients to meaningful studies.[20, 21] These initiatives could

benefit from research that demonstrates the impact of the clinical trial selection decision on the overall performance of the portfolio.

### 1.2.2 Product Development Time vs. Clinical Trial Development Time

Fast cycle product development, or time-to-market, has been identified as a competitive advantage of a firm.[22, 23] For example, Japanese automobile manufactures were able to develop new models of vehicles and integrate innovations faster in order to meet the demands of the market.[24-26] Much like the new product development cycle, delays in the development cycle can drastically affect the resulting outcome of the performance of the clinical trial. In the automotive industry, it has been estimated that each day of delay in introducing a new car costs the organization about $1M loss in profit.[27] This is analogous to the pharmaceutical industry where each day of delay to market a new pharmaceutical product costs the manufacture about $1.3M.[28]

While the development time for other new-to-the-world products have decreased from 41.7 months to 24 months from 1995 to 2004 (a decrease of 42%), the time to develop a new drug has increased from 56.4 to 144months (increase of 155%) during the same time frame.[29, 30] Along with this increase in time are escalating costs for drug development, with costs reaching over $800 million per drug. Thus, pharmaceutical firms must rely on external partners, suppliers, and government agencies to aid in new drug development.[8, 29]

Comparing the success of a product or project and the outcomes of a clinical trial cannot be measured utilizing the same metrics. Specifically, new product success can be measured by profit or other monetary measurement while clinical trial success is

measured on scientific merit of the study outcome. While scientific merit is difficult to measure in a fungible manner, success of a clinical trial can be measured by whether or not the trial enrolled sufficient accruals in order to statistical support the trial's scientific objectives. Insight to this research will allow the comparison of the clinical trial development process to other new product or project development.

### 1.2.3 Measurement of Project Success

A substantial amount of literature has focused on the question of which projects an organization should pursue. One perspective into this decision is the assessment of individual project characteristics as they relate to project outcome (either success or failure). There have been several reviews on this subject that can be found in Balachandra and Friar[2], Dilts and Pence[1], Lilien and Yoon and Linton et al[31]. Research has focused on understanding project characteristics in order to improve the number of successful projects or to avoid project failure. Identifying the evaluative factors that lead to overall project success have been shown to yield an overall performance improvement in the project selection into the portfolio compared to actual portfolio performance.[32, 33] The justification behind research supporting the identification of characteristics of a study characteristics that correlate with outcomes is that decision makers make costly, ill-informed project selection decisions that could have been avoided with clearly defined up-front evaluative criteria.[34, 35]

Unfortunately, while there is an acknowledgement of the importance of clearly defining project characteristics that lead to success, a lack of convergence of project characteristics that correlate to outcome has resulted in little managerial impact and improvement to project selection decisions.[2, 22, 36] Balachandra and Friar have argued that

the lack of agreement among the identified project characteristics is a result of the uniqueness of characteristics dependent upon the type of project. [2] On the other hand, Krishnan and Ulrich[37] argue that past research has shown that there are only a handful of research studies supported by empirical evidence, with the majority of research founded on the opinions of surveyed participants. Table 1-1 presents a summary of the past studies and categorizes each by the study setting and the methodology used. The summary of literature supports the observation that there is little research that utilizes objective data to support the research findings. Furthermore, there is a lack of project success research that has incorporated the research of predicting project success in a health-care setting. My research will utilize objective data in a health-care setting, specifically in the development of oncology clinical trials sponsored by the NCI, to aid in predicting the success of such projects.

Research to understand how various project characteristics correlate to project success in a healthcare setting can provide insight into which factors are used to predict success. Furthermore, including objective data in the research will allow the comparison between quantitative factors that correlate to success.

## 1.3 RESEARCH SETTING

The Cancer Therapy Evaluation Program (CTEP) is involved in planning, reviewing, and coordinating clinical trials that are supported by the National Cancer Institute (NCI). CTEP is involved with investigational anticancer agents, novel therapeutic approaches to cancer treatment that are financially supported through the NCI. CTEP evaluates approximately 900 of the 1500 NCI-sponsored trials annually.[38] Each of the trials evaluated and approved by CTEP is supported by grants and

cooperative agreements from the NCI awarded to scientific institutions and individuals, and are conducted, at a minimum, by the faculty members and practitioners at those institutions who initiated the study idea. CTEP enrolls approximately 25,000 patients annually and conducts clinical trials at 1,958 institutions encompassing close to 10,000 investigators. Institutions that conduct CTEP-sponsored clinical trials included Cancer Centers, Comprehensive Cancer Centers, Cooperative Groups, Consortiums, US Government Agencies (such as NIH and NCI), and some international studies. Each of these intuitions is defined in Table 1-4.

A primary function of CTEP is to monitor and track the progress of clinical trials that are going through development, accruing patients, and are complete. This task is conducted by the Protocol Information Office (PIO) by means of supporting databases of past, ongoing, and future studies.

### 1.2.4 Sources of Data

Retrospective data for this research are gathered from the CTEP-PIO database, for clinical trial data between January 1, 2000 and December 31, 2007. A total of 5845 clinical trials are documented within this time frame which were either in development, accruing patients, completed, or had been disapproved. While each analysis in my dissertation utilizes the same database, samples drawn from this database are dependent upon the research question for that chapter. For example, to investigate the relationship between development time and accrual success in Chapter 2, the sample contains only trials that have both complete development time and have been closed to accrual.

Understanding early accrual indicators towards eventual accrual success will utilize trials that have been opened to accrual and completely closed to accrual in the sample collection period. Furthermore, only trials that have complete accrual information, that is, trials that have monthly records of accrual enrollment by patient through the Clinical Data Update System (CDUS) or Clinical Trial Management System (CTMS) are included in the analysis in Chapter 3.

Trials that have complete development time information are used to identifying characteristics that are related to development time as described in Chapter 4. Thus, trials included in this analysis must have complete trial characteristic information.

### 1.2.5 Measuring Trial Success

Project success is studied frequently, but the basic definition is rarely agreed upon. [39] Because the definition of success is attributed to the decision maker's perspective, past literature has simplified the definition of project success by equating it to meeting objectives of budget and schedule while achieving an acceptable level of performance.[40-42] A measure of success is then compiled based on these three factors using a scoring method such as the averaging of the three variables, weighted average, or processes such as analytical hierarchy process.[43-45] This issue tends to complicate the overall finding of the research and opens up the final outcomes to criticism.

For the purpose of my research, success is based on a single measure: trials achieving stated accrual objective. This greatly simplifies the ambiguity regarding the definition of a successful project. Clinical trials, like many scientific research endeavors, require a sufficient sample size (i.e., accruals) to arrive at statistically sound conclusions.

Once the sample size of the clinical trial is achieved, the primary questions defined in the clinical trial idea can be answered. Achieving sufficient accruals on a clinical trial is the minimum required objective that is necessary to achieve all other study objectives including scientific discovery, publication within academic journals, and development of new treatment options. It is important to note that success is not defined in terms of accepting or rejecting the stated scientific hypotheses in the trial; rather it is acquiring sufficient sample sizes (i.e., accruals) in order to test the trial hypotheses.

Based on our previous study, we have found a precipitous drop off of phase III cancer trials that achieve accrual goals of 80% of the maximum accrual goal and those that do not (Figures 1-2). Rather than utilizing the maximum accrual goal, I utilize a more liberal estimate of trial success by basing it on those trials achieving 100% of minimum accrual goal. I acknowledge that trial findings may be published without achieving adequate number of enrollments to demonstrate the scientific hypothesis, but it is noted that this is often observed only in trials with negative results.[10]

Because there is a clear distinction between trials that achieve stated accrual goals and those that do not, I use this dichotomous variable as the definition of clinical trial success throughout the research.

## 1.4 RESEARCH PROPOSITIONS

Three main propositions are addressed in this research. The propositions are interrelated and will build upon prior findings. A model illustrating the interaction of the propositions is shown in Figure 1-1.

### 1.4.1 Relationship Between Clinical Trial Development Time and Accrual Success

Most efforts to reduce barriers to patient accruals have been concentrated on post-activation efforts, that is, after a trial is open for patient enrollment or accrual.[46, 47] With recent findings that a large portion of time "conducting" a clinical trial is concentrated in the development and preparation, understanding of barriers during the pre-activation efforts must be uncovered.[48] A phase III clinical trial can take an estimated 26 months to develop requiring intricate collaboration among a diverse set of organizations.[5, 49-51] More importantly, understanding how the time required to develop a clinical trial impacts the likelihood of achieving accrual success will allow the identification of pre-activation barriers that significantly affect post-activation clinical trial performance. The proposition is addressed in chapter 2 and clarified in greater detail.

> *Proposition 1a: An increase in the time required to develop a clinical trial will have a negative impact on the likelihood of accrual success.*

### 1.4.2 Early Predictors in Accrual and Accrual Success

The projected accrual rates of those clinical trials conducted in the past have been found to be over-estimated compared with actual accrual rates, thus causing trials to be open to accrual longer than planned.[52] Uncovering the relationship between accrual performance at specific milestones, such as first patient enrollment and expected time to achieve accrual goal, with the eventual accrual success of the trial will allow for a greater understanding on the factors that help clinical trials success overall. Specifically, early indicators of accrual success can support early decisions to manage clinical trials during the accrual period. These results may provide the ability to intervene on trials with low

accrual and improve the likelihood of them achieving the scientific objective or, conversely, stopping resources from being invested in prolonging trials that have a low likelihood of accrual success. Regardless of decision, the ability to utilize predictors of accrual success in the conduct of the clinical trial will allow subjects (i.e., patients) enrolled on trials to have the greatest chance to contribute to the state of medical knowledge and improve the efficiency of resources and effort in conducting clinical trials.

> *Proposition 2a: Clinical trials with faster time to first enrollment will have a positive impact on the likelihood of accrual success.*

With a large number of clinical trials underestimating the time to achieve a specific accrual goal, an analysis of the actual accrual goal can be conducted relative to the expected time to achieve the accrual goal. Based on this analysis at the specified milestone, early assessment of the clinical trial is conducted in Chapter 3.

> *Proposition 2b: The accrual performance at the expected time to achieve the accrual goal is correlated to the eventual accrual success.*

Cancer incidence, or the occurrence of specific types of cancer in the population, as well as cancer mortality rate, or occurrence of death by a specific type of cancer in the population, may have a moderating affect on the relationship between time-to-first enrollment and accrual success. Therefore I test this relationship and control the outcomes of the analysis for this relationship. While approximately 2 – 7 % of the

population with cancer enroll on clinical trials, specific types of cancer have a higher incidence and therefore a greater number of patients available to enroll on such clinical trials. The cancer mortality rate may impact the accrual performances due to the severity of the disease and the demand to find additional treatment options.

> *Proposition 2c: Clinical trials directed towards cancers of greater incidences will have a shorter time-to-first enrollment then on those with lower incidences.*
>
> *Proposition 2d: Clinical trials directed towards cancers of greater mortality will have a shorter time-to-first enrollment on those with lower mortality.*

### 1.4.3 Characteristics Impacting Development Time

Understanding the clinical trial characteristics that are attributed to development times is important in order to be able to effectively manage clinical trial development. From the data of the available clinical trials recorded through the CTEP-PIO database, over 30 quantifiable characteristics have been recorded in either the NCI-concept sheets or NCI-protocol sheets.

From the perspective of the principal investigator who is designing the clinical trial, it is important to have a relative understanding the length of a specific clinical trial development and what the likelihood of completing accruals to the trial are. This is the focus of Chapter 4.

> *Proposition 3a: General clinical trial characteristics can be utilized as indicators to estimate clinical trial development times.*

## 1.5 ORGANIZATION OF DISSERTATION

The following chapters address the three sets of propositions in three chapters that are formatted based on the targeted peer-review journals. The findings related to proposition 1 are found in chapter II: "A Sense of Urgency – Evaluating the Link between Clinical Trial Development Time and Accrual Performance of CTEP-Sponsored Studies." Research findings related to proposition 2 are found in chapter III titled: "Predicting Accrual Success – Accrual performance of NCI CTEP-Sponsored Clinical Trials". Proposition 3 research and findings are found in chapter IV titled: "Impact of Clinical Trial Characteristics on Development Time of NCI CTEP-sponsored Clinical Trials." Finally, summary of the findings and proposed future studies are found in chapter V and VI.

References that are specific to the design and development of oncology clinical trials through CTEP are used throughout this dissertation. The definition of a clinical trial as well as the progressive phases that must be conducted prior to approving a therapeutic agent for market are outlined in Table 1-2. The various organizations and the scope of the main participants that are involved in conducting a clinical trial are defined in Table 1-3. Formal definitions from the National Cancer Institute Dictionary of Cancer Terms regarding the process required to develop a oncology clinical including the necessary protocol-specific items that need to be completed as well as the clinical trial development and accrual milestones are also provide in Table 1-4.[3]

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**TABLE 1-1: LITERATURE REVIEW OF RESEARCH ON PROJECT CHARACTERISTICS AS RELATED TO SUCCESS**

| Publication | Sample | Method | Objective / Subjective / Summary |
|---|---|---|---|
| Astebro,2003 | Canadian Inventors' Assessment Program | Historical Data | Objective |
| Baker et al 1986 | Steel, pesticides, food, and industrial chemical industries | Case Study | Subjective |
| Balachandra and Friar 1997 | n/a | Literature Review | Summary |
| Balachandra, 1984 | R&D Managers in Europe and US | survey | Subjective |
| Balachandra, 1996 | R&D Managers in Europe and US | survey | Subjective |
| Barczak, 1995 | Telecommunications | Survey | Subjective |
| Bard, Balachandra, et al 1988 | Peripheral Equipment Manufacturing | Case Study / Modeling | Subjective |
| Calantone and DiBenedetto, 1988 | Industrial Manufacturing | Survey | Subjective |
| Calantone et al | Industrial Manufacturing | Survey | Subjective |
| Cooper 1979a, 1979b, 1980a, 1980b | Canadian Industrial Companies | Survey | Subjective |
| Cooper 1983 | Canadian Industrial Companies | Survey | Subjective |
| Cooper 1984b,c,d, 1986 | Canadian Industrial Companies | Survey | Subjective |
| Cooper 1988, 1990 | Canadian Industrial Companies | Survey | Subjective |
| Cooper and Kleinschmidt 1987b, c | Canadian Industrial Companies | Survey | Subjective |
| Cooper and Kleinschmidt 1993,1994, 1995 | international chemical industry | Survey | Subjective |
| Cooper and Kleinschmidt 1995, 1996 | Industrial products in Canada, USA and Europe | Survey | Subjective |
| Cooper and Kleinschmidt, 1986 | Canadian Industrial Companies | Survey | Subjective |
| Cooper and Kleinschmidt, 1987a | Canadian Industrial Companies | Survey | Subjective |
| Dilts and Pence, 2003 | Government organizations and c | Survey | Subjective |
| Dvir et al 1998 | Defense projects in Israel | Survey and Interviews | Subjective |
| Ernst, 2002 | n/a | Literature Review | Summary |
| Griffin, 1997 | PDMA conference | Historical Data | Objective |
| Kumar, Persaud, and Kumar 1996 | High-Technology Firms | Survey | Subjective |
| Lilien and Yoon, 1989 | n/a | Literature Review | Summary |
| Maidique and Zirger, 1984 | US electronic industry | Survey | Subjective |
| Parry and Song, 1994 | Japanese Firms | Survey | Subjective |
| Pate-Cornell and Dillon, 2001 | NASA projects | Case Study | Subjective |
| Roberts and Burke, 1974 | Successful industrial laboratories | Case Study | Subjective |
| Utterback et al 1976 | Europeand and Japanese Industries | Case Study | Subjective |

**TABLE 1-2: TERMINOLOGY OF CLINICAL TRIAL AND PHASES OF CLINICAL TRIALS**

| Terminology | Definition |
|---|---|
| Clinical Trial | A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called a clinical study. |
| Phase I | The first step in testing a new treatment in humans. These studies test the best way to give a new treatment (for example, by mouth, intravenous infusion, or injection) and the best dose. The dose is usually increased a little at a time in order to find the highest dose that does not cause harmful side effects. Because little is known about the possible risks and benefits of the treatments being tested, phase I trials usually include only a small number of patients who have not been helped by other treatments. |
| Phase I/II | A trial to study the safety, dosage levels, and response to a new treatment. |
| Phase II | A study to test whether a new treatment has an anticancer effect (for example, whether it shrinks a tumor or improves blood test results) and whether it works against a certain type of cancer. |
| Phase III | A study to compare the results of people taking a new treatment with the results of people taking the standard treatment (for example, which group has better survival rates or fewer side effects). In most cases, studies move into phase III only after a treatment seems to work in phases I and II. Phase III trials may include hundreds of people. |

**TABLE 1-3: DEFINITIONS OF INSTITUTIONS AND ORGANIZATIONS**

| Terminology | Definition |
|---|---|
| Institutions | |
| National Cancer Institute (NCI) | NCI, part of the National Institutes of Health of the United States Department of Health and Human Services, is the Federal Government's principal agency for cancer research. It conducts, coordinates, and funds cancer research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer. Access the NCI Web site at http://www.cancer.gov. Also called National Cancer Institute. |
| Cancer Therapy Evaluation Program (CTEP) | CTEP plans, reviews, and coordinates clinical trials for investigational anticancer agents, from the inception of protocols through the preparation and submission of Investigational New Drug Applications (INDs) to the Food and Drug Administration (FDA). CTEP also serves as a liaison to the FDA for the extramural clinical research community and industry collaborators. Other CTEP functions include managing, tracking, and reviewing clinical protocols as well as monitoring, planning, and maintaining regulatory compliance of the clinical trials. In addition, CTEP coordinates the distribution of the investigational agents from industry collaborators for use in all NCI-sponsored clinical trials. |
| Cancer Centers and Comprehensive Cancer Centers | National Cancer Institute (NCI) designated Cancer Centers are recognized for their scientific excellence and extensive resources focused on cancer and cancer-related problems. All NCI-designated cancer centers receive substantial financial support from NCI grants and are reevaluated each time their cancer center support grant comes up for renewal (generally every 3 to 5 years). The NCI recognizes two types of centers: Cancer Centers and Comprehensive Cancer Centers, based on the type of grant received. In terms of patient care, there is no difference in the quality of care they each provide. |
| Cooperative Group | A group of researchers, cancer centers, and community doctors who are involved in studies of new cancer treatment, prevention, early detection, quality of life, and rehabilitation. Clinical trials carried out by cooperative groups are sponsored by the National Cancer Institute (NCI), and large numbers of patients take part in many locations. Examples include the Radiation Therapy Oncology Group (RTOG), Gynecologic Oncology Group (GOG), and Children's Oncology Group (COG). |
| Consortiums | Consortiums are formed by the National Cancer Institute (NCI) to address the need for large-scale collaborations across institutions. consortiums provide a coordinated, interdisciplinary approach to tackling important scientific questions, economies of scale, opportunities to quicken the pace of research, and a collaborative network of investigators. |
| Government Agencies | Many departments across the U.S. Department of Health and Human Services are involved in clinical research and can conduct research with collaboration with the National Cancer Institute |

## TABLE 1-4: DEFINITIONS OF CLINICAL TRIAL DEVELOPMENT TERMINOLOGY

| Terminology | Definition |
|---|---|
| Concept / Letter of Intent | Investigators wishing to carry out clinical trials with CTEP support must initially submit a concept (Phase III), or Letter of Intent (Phase I, I/II,II) outlining a plan for a new clinical study. |
| Protocol | An action plan for a clinical trial. The plan states what the study will do, how, and why. It explains how many people will be in it, who is eligible to participate, what study agents or other interventions they will be given, what tests they will receive and how often, and what information will be gathered. |
| Institutional Review Board | A group of scientists, doctors, clergy, and consumers that reviews and approves the action plan for every clinical trial. There is an IRB at every health care facility that does clinical research. IRBs are designed to protect the people who take part in a clinical trial. They check to see that the trial is well designed, legal, ethical, does not involve unneccesary risks, and includes safeguards for patients. Also called Institutional Review Board. |
| Centralized Institutional Review Board | The Central Institutional Review Board (CIRB) Initiative is sponsored by the National Cancer Institute (NCI) in consultation with the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP). The CIRB provides an innovative approach to human subject protection through a "facilitated review" process that can streamline local IRB reviews of adult and pediatric national multi-center cancer treatment trials. |
| NCI-Solicited Study | An idea for a clinical trial may be submitted in response to a solicitation for studies to carry out the CTEP development plan, which is formulated with input from the Investigational Drug Steering Committee and has the concurrence of the industry collaborator. |
| NCI-Expedited Study | NCI CTEP can identify studies of importance which require faster development time. When a study is expedited CTEP sets a tighter deadline on various clinical trial setup activities. |

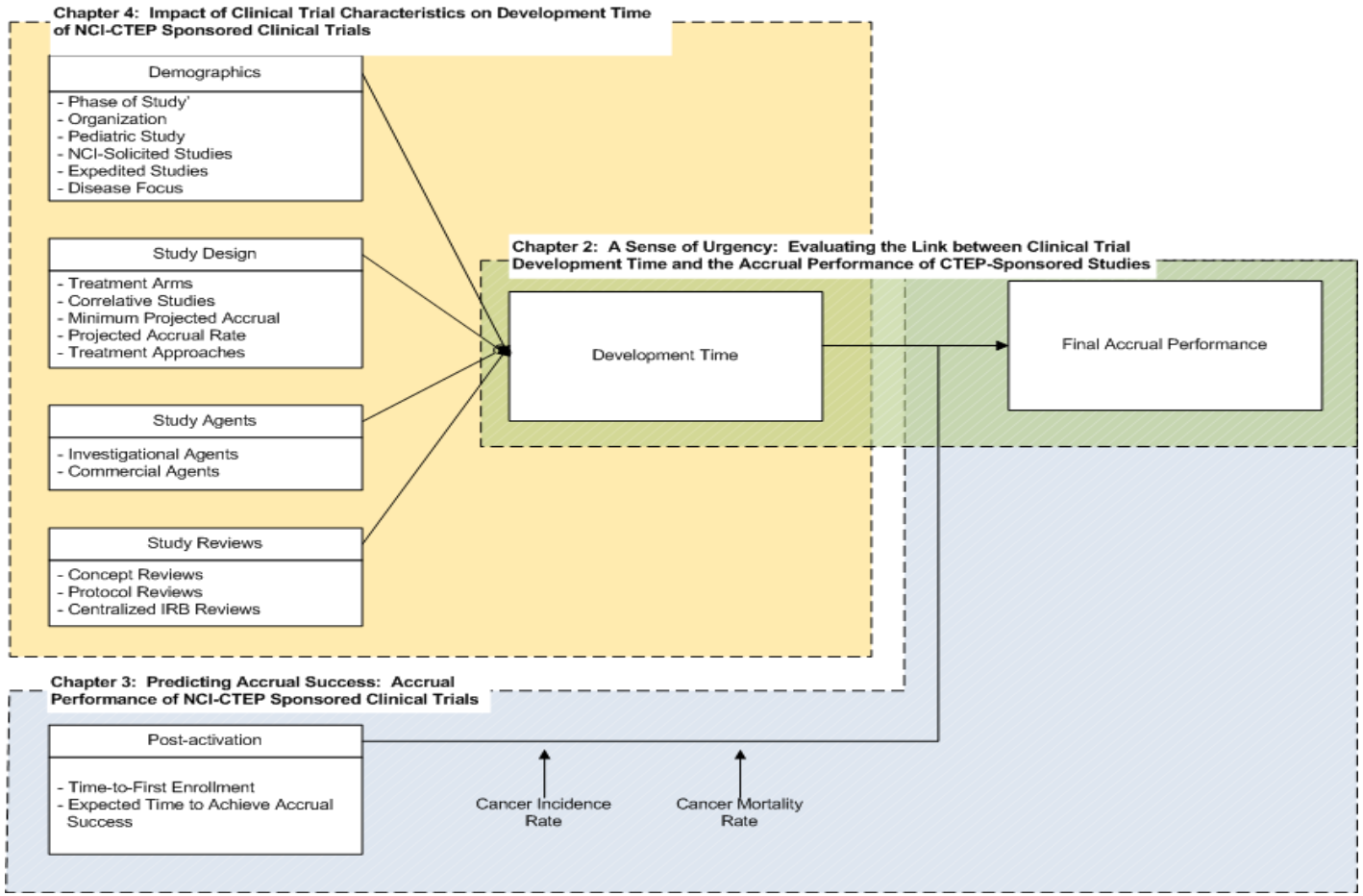
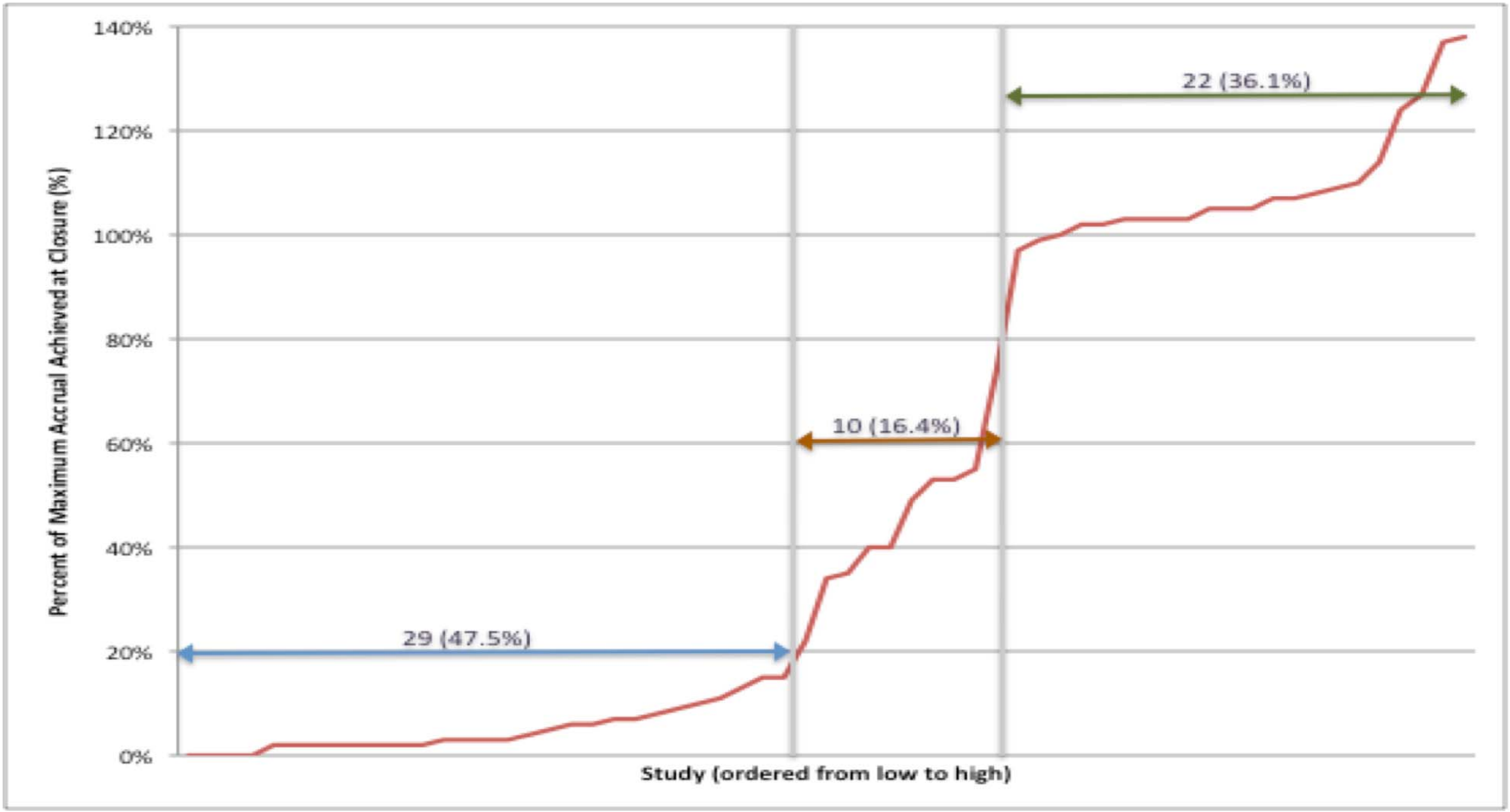



**FIGURE 1-1: RESEARCH MODEL**




***Note: Accrual goal based on maximum projected accrual goal**

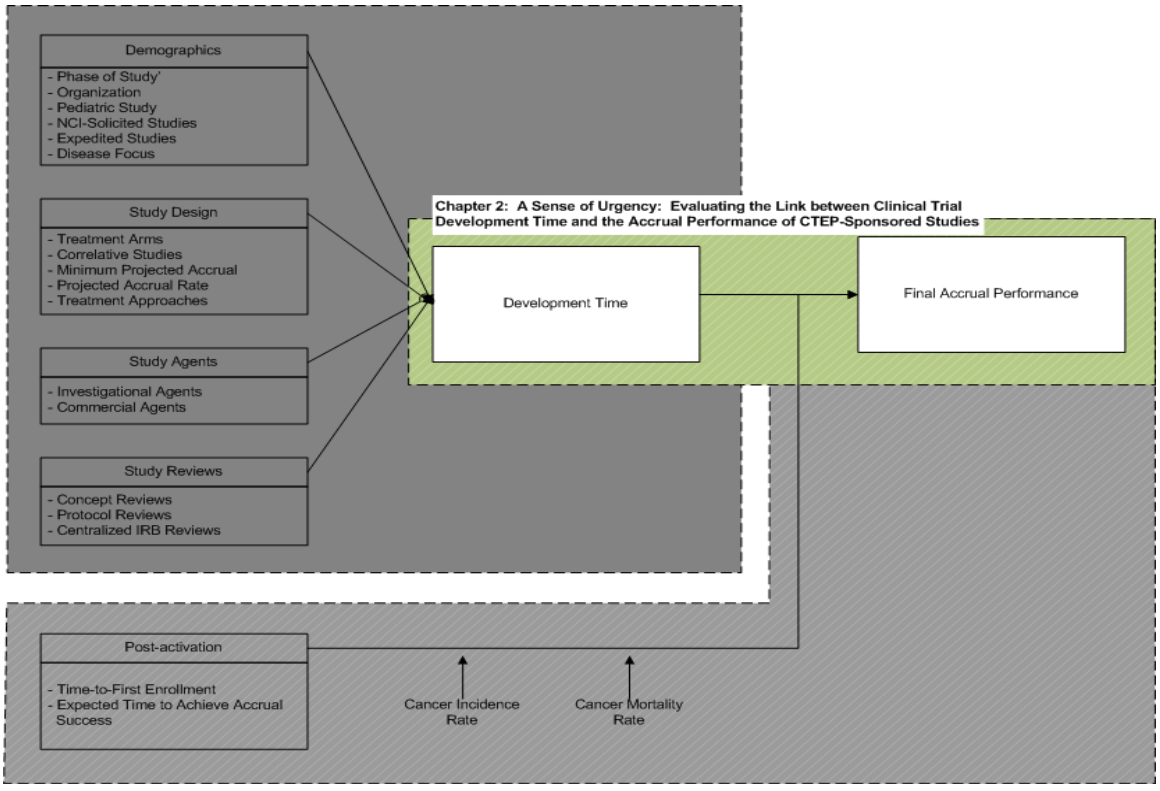
**FIGURE 1-2: PRELIMINARY DATA ON PHASE III THERAPEUTIC CLINICAL TRIAL ACCRUAL PERFORMANCE BASED ON MAXIMUM ACCRUAL PERFORMANCE**

# CHAPTER II

# A SENSE OF URGENCY: EVALUATING THE LINK BETWEEN CLINICAL TRIAL DEVELOPMENT TIME AND THE ACCRUAL PERFORMANCE OF CTEP-SPONSORED STUDIES

## 2.1 PREFACE AND RESEARCH MODEL

Little research has looked at barriers to clinical trials during the development period; No research has investigated the impact of development time of a clinical trial on the success of a clinical trial. Research in chapter delves into the relationship between of these two factors to understand whether studies with faster development time do in fact have a greater likelihood of success. We utilize a measure of clinical trial success based upon the achievement of projected accrual goals, as this is the minimum requirement necessary to statistically support the intended scientific objective.



## 2.2 ABSTRACT

***Background*** Post-activation barriers to oncology clinical trial accruals are well documented; however, potential barriers prior to trial opening are not. We investigate one such barrier: trial development time.

***Methods*** National Cancer Institute Cancer Therapy Evaluation Program (NCI-CTEP) sponsored trials for all therapeutic, non-pediatric phase I, I/II, II, and III studies activated in an eight year period (2000-2007) were investigated (n=553). Successful trials were those achieving 100% of minimum accrual goal. Time to open a study was the calendar time from initial CTEP submission to trial activation. Multivariable logistic regression analysis was used to calculate unadjusted and adjusted odds ratios, controlling for study phase and size of expected accruals.

***Results*** 40.0 percent (n=221) of CTEP-approved oncology trials failed to achieve minimum accrual goals, with 49.2 percent (n=30) of phase III trials failing to achieve at least 25 percent of accrual goals. A total of 8,723 patients (17.0% of accruals) accrued to those studies that were unable to achieve the projected minimum accrual goal. Trials requiring 9-12 months development were significantly more likely to achieve accrual goals (odds ratio, 1.94; 95% CI, 1.06 to 3.52, P=0.031) than trials requiring the median time (15-18 months); trials that exceeded 27 months of development time were significantly less likely of achieving accrual goals (odds ratio, 0.14; 95% CI, 0.04 to 0.54, P=0.004).

***Conclusions*** A large percentage of oncology clinical trials do not achieve minimum projected accruals. Trial development time appears to be one important predictor of the likelihood of successfully achieving the minimum accrual goals.

## 2.3 INTRODUCTION

In the United States, it is estimated that 1.4 million individuals will be diagnosed with cancer, and over half a million will die each year. Advances in therapeutic treatments have improved the 5-year survival rates over the past four decades,1 yet cancer continues to be the second leading cause of death in Americans, resulting in more deaths than the next five causes combined.2 New and innovative therapeutic approaches to improve the standard of care of cancer patients must be developed and then confirmed through a series of clinical trial phases to ensure both efficacy and safety.3 Phases I-III trials require sufficient patient enrollment so that the efficacy of the therapeutic agent(s) under investigation can be measured with a proper degree of statistical certainty.

Unfortunately, with only 2-7% of the adult cancer population participating in clinical trials, obtaining sufficient accrual is a known barrier to successful completion of clinical trials.[4, 5] Furthermore, it has been shown that the lack of appropriate trials represents a significant barrier to accruing oncology patients.[6] Hence, there should be a sense of urgency to develop properly safeguarded oncology trials such that treatments discovered at the bench can be translated effectively and rapidly into improved standard of care.

Understanding the reasons behind low accruing clinical trials is important. However, most of the efforts to reduce barriers to patient accruals have been concentrated on post-activation efforts, that is, after a trial is open for patient enrollment or accrual.[7, 8] It is our contention that there are factors involved during trial development that significantly impact accrual performance. We postulate that the calendar time required to transit from letter of intent (LOI) or concept through protocol development to final trial

activation is inversely related to successful accrual goal achievement. Research has shown that the time to develop a phase III oncology trial requires nearly 26 months with intricate collaboration among a diverse set of organizations. [9] While there are a host of other causes that may be attributed to low accruing clinical trials, development time has been shown to be a well-established and critical factor in the success of a new product across a host of other applications.[10]

To investigate the effect of trial development time on patient accruals to oncology trials, a retrospective evaluation was conducted on trial sponsored by the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP). CTEP evaluates approximately 900 out of the 1500 NCI-sponsored studies annually.[11] Each of the study evaluated by CTEP is supported by grants and cooperative agreements from the NCI awarded to scientific institutions and individuals and are conducted by the faculty members and practitioners at those institutions who initiated the study idea. This article uncovers the critical, yet often overlooked, barrier of lengthy trial development time as a major factor negatively impacting accrual performance in phases I-III oncology trials.

## 2.4 METHODS

All therapeutic, non-pediatric, phase I, I/II, II, and III oncology trials evaluated by CTEP that began trial development, opened to patient accrual, and subsequently closed to accruals between January 1, 2000 and December 31, 2007 in the United States were eligible. Data were supplied by the CTEP Protocol and Information Office (PIO), which maintains a tracking database of trial activities from concept submission to trial activation.[12]

The independent variable, development time, was the difference in calendar days between the date of initial CTEP receipt of LOI or concept and the date the trial was opened for accrual. For simplicity, calendar days were converted into months by dividing the total days by 30.33. When an activation time was missing (*n=14, 2.5%*), the date at which the institution activated or opened the study was used. It is important to note that this definition of development time does not include the days required to prepare the trial idea into a formal submission to CTEP. Previous studies of phase III trials have shown that this initial time can consume between 1 and 10 calendar months.[9]

The dependent variable, accrual-to-goal percent, was calculated using projected minimum accrual goal and actual final trial accrual. This provides a liberal estimate of trial success because it defines the minimum trial sample size needed to achieve desired scientific endpoint. If minimum patient accrual information was not available (n=5, 1.0%) the maximum patient accrual goal was used.

Final patient accrual was obtained from the CTEP-PIO database, with input from the Clinical Data Update System and the Clinical Trials Monitoring Service. Only trials permanently closed to accrual were analyzed, i.e., those temporarily closed to patient accrual and/or treatments for any other reason were excluded.

Accrual-to-goal percent was computed by dividing the actual trial final accrual by the projected minimum study accrual goal. Success was defined as a trial that achieved ≥100% of accrual-to-goal percent.

Clinical trials were divided among 6 groups based on accrual-to-goal percentages (0%, 1-24%, 25-49%, 50-74%, 75-99%, and ≥100%). Data were also analyzed and

segmented by trial development time at 3-month intervals to observe the impact of trial development time on achievement of minimum accrual goal in terms of odds ratios.

## 2.5 STATISTICAL ANALYSIS

Continuous variables were summarized by calculating medians and interquartile ranges (IQRs). A maximum 2-tailed alpha of 0.05 was maintained for determining statistical significance. Comparisons among trial types (i.e. phases I, I/II, II, III) were conducted using the Kruskal-Wallis test. Post-hoc comparisons of statistically significant overall tests used Mann-Whitney tests with a Bonferroni-adjusted alpha level of 0.008. Categorical and ordinal groups were summarized using univariate and cross-tabulated frequency distributions. Unadjusted and adjusted odds ratios, along with their respective 95% confidence intervals, were obtained using multivariable logistic regression analysis. Polynomial regression terms were used for overall patterns of trend. These results were compared with results using incident-rates from Poisson regressions. Statistical analyses were performed in either SPSS (version 15.0, descriptive and logistic regression) or Stata (version 10, logistic and Poisson regression).

## 2.6 RESULTS

A total of 553 CTEP-sponsored phase I, I/II, II, and III therapeutic, non-pediatric oncology trials that were initiated and closed to patient enrollment within the study period were eligible. Table 2-1 summarizes the development time and minimal accrual characteristics by phase of trial. Phase II trials accounted for the majority (58.6%, n=324); phase I trials composed 22.2% (n=123), followed by phase III (11.0%, n=61) and phase I/II (8.1%, n=45). Trials with incomplete timing data were excluded. No

statistically significant differences in accrual achievement between included and excluded studies were observed (P<0.001).

Overall median development time from initial CTEP submission to study activation for all types of trials was 15.0 months (interquartile range (IQR): 11.6– 19.4). Phase III trials had statistically longer development time than other types (P<0.008) with a median development time of 18.3 months (IQR: 14.2– 26.0). None of the differences in development time between the other types of trials were statistically significant.

Median minimum projected accrual goal for all types of trials was 22 subjects (IQR: 15-42)(Table 2-1). There were significant differences in projected minimum accrual goals between phase I trials compared with phase I/II, phase II, and phase III trials (P<0.008). Additionally, phase III trials had significantly greater projected minimum patient accruals when compared with trials of all other phases (P<0.008).

As shown in Table 2-1, 40.0% (n=221) of all trials did not achieve ≥100% of the projected minimum accrual goal. However, performance of the phase III trials was statistically significantly lower than that of the other types of trials, with 63.9% (n=39) failing to achieve this standard of performance (P<0.001). Particularly problematic in phase III studies, a large number of studies (n=30, 49.2%) failed to achieve ≥25% of their respective projected minimum accrual goals.

A total of 51197 individuals accrued to the oncology trials in the sample. The majority were enrolled in phase III trials (n=34361, 67.1%), followed by phase II (n=11718, 22.9%), phase I (n=3168, 6.2%), and phase I/II (n=1950, 3.8%). When comparing the proportion of patients enrolled on trials based on the achievement of the

projected minimum accrual, a total of 8723 participants (17.0%, min=16.2% phase I, max=18.1% phase II) were enrolled on clinical trials that closed with underperforming final accruals (Figure 2-1).

Visual inspection and statistical tests of the relationship between development time and probability of meeting minimum accrual goals indicated a statistically significant curvilinear component to the relationship (P=0.019 for the quadratic term) (Figure 2-2). The shape of this relationship held when adjusted for the size of the trials based on the projected minimum accrual (P=0.020 for the quadratic term). The results were very similar to those found using Poisson regression (P=0.033).

For ease of interpretation, development time was collapsed into 3-month time intervals. The rates for achieving minimum accrual goals tended to be highest within 3-6 months of the overall median development time (15-18 months), slightly higher at briefer times for phase I, I/II, and II trials. Rates of success decreased substantially as trial development time increased. Table 2-2 summarizes the likelihoods of achieving minimum accrual goals as the development time varied from the overall median development time.

Relative to trials with a median development time of 15-18 months, trials taking 9-12 months were statistical significant and more likely to achieve the minimum accrual goals compared to the remaining trials (OR=1.94; 95% CI, 1.24-4.57; CI=1.06-3.52; P=0.031). On the other hand, trials requiring 27-30 months or >30 months in development time were statistically significant and less likely to achieve projected minimum accrual goals than those studies taking the overall median development time

(OR 27-30 months: 0.14, 95% CI, 0.04 – 0.54, P=0.004; OR >30 months: 0.17, 95% CI, 0.07 – 0.41, P<0.001). Studies with development times between 18-27 months had a proportionally decreasing likelihood of achieving minimum accrual goals, but the odds ratio was not significant (Table 2-2).

Given the previously established differences in development time among the types of trial, the likelihood values adjusted for type of trial are also summarized. Additionally, raw projected minimum accrual numbers tend to be larger with phase III trials and given that those numbers provide a continuous (and thus more powerful) explanatory variable for whether or not accrual goals were met, thus the development time likelihood values adjusted for raw accrual projections are also displayed. Odds ratios adjusted for raw projected accrual numbers or adjusted for the effect of phase III trials resulted in similar findings when compared to the unadjusted values.

## 2.7 DISCUSSION

This study provides an in-depth analysis of the development time of CTEP-sponsored oncology clinical trials as it impacts study accrual performance during an eight-year period. The findings demonstrate that the time to bring forth an idea from concept to study activation has a significant inverse relationship to accrual performance.

The implications of identifying the correlation between development time and accrual performance are multiple. First, trials have a limited capacity to derive any scientific findings without the adequate accruals necessary for statistical support. Additionally, the scarce resource of patients is being underutilized if patients volunteer

for a study that never achieves its minimum accrual goal.[†] Data from this research show that approximately two of every five trials will fail to achieve sufficient accruals. For phase III trials, the rate increases to three failures out of every five trials conducted, where nearly one in every two fails to achieve at least 25% of stated minimum accrual goals. Along the same lines, 16-18% of participants were enrolled on a clinical trial that did not achieve minimum requirements in patient accruals. If we assume that minimum sample size goals were developed using statistical power analysis, failure to achieve such goals results in the limited ability to derive statistically valid conclusions, and therefore result in a less significant advancement of science than originally intended.

Unnecessary delays during the time required to develop a clinical trials can cause adverse implications in the likelihood of achieving the necessary accruals. The field of oncology clinical research evolves quickly which may cause interest in the original research question to wane.[13] Alternatively, long development times as well as poor accruals may be due to the lack of interest in the clinical trial from the origination of the idea. Regardless, pursuing clinical trials with a reduced likelihood of achieving accrual success limits the opportunity to conduct other clinical trials.

In an era of clinical research where resources limit the number of trials that can be pursued, as well as the limited availability of individuals willing to participate in clinical trials, it is essential to identify potential causes of low accrual likelihood before allocating significant resources to develop such trials. The retrospective analyses of phase I, I/II, II, and III trials suggest that there are opportunities to improve the number of successfully

[†] We acknowledge that many clinical trials closed due to adverse events both related to the clinical trial itself as well as derived from other similar study. Unfortunately we do not have the rational for study closing for the sample.

accruing trials. In particular, phase III clinical trial development times should be improved not only because of the potential importance of their findings on current standard of care, but also because such trials are most resource-consuming in terms of time, effort, and patient accruals.

Development time required for a trial is complicated by the many facets of scientific study design within the constraints of regulatory, ethical, and operational requirements.[14] Research delays during the development of a clinical trial are often attributed to the improvement of overall scientific merit or to ensure safety of the potential participants. However, opportunities to improve the development time arise when considering the number of non-value added (NVA) steps in the process flow, and the number of multiple, redundant, and overlapping steps that are involved in the opening of clinical trials. [9, 15] Findings from this research point to the fact that decisions that delay the deployment of clinical trials beyond the scope of scientific relevancy or ethical issues have negative repercussions on the likelihood of successful completion of the trial. Such issues must be acknowledged when considering modifying a trial to add an additional study arm, an additional correlative, or otherwise "tinkering" with a trial.

Finally, why is longer development time of interest beyond its ability to decreased likelihood of successful accruals? There are two other reasons: 1) patients will gain access to new therapies later (or not at all) than they otherwise would and 2) longer development times creates reduced innovation incentives as researchers concentrate on completing studies that have lower minimum patient accrual goals, which may result in fewer new therapies being developed. Indeed, in the data used in this analysis, Phase III studies accounted for only 11% of all studies. Academic researchers, who may be

struggling for tenure, are caught between Scylla and Charybdis[‡]: remain close to the lab and attempt only studies requiring minimal accrual goals or attempt a clinically significant translational trial but with the knowledge that a) there is a limited chance of achieving even minimum accrual goals due to circumstances beyond their control, and b) without achieving such goals, research will not be published, the state of knowledge will not be advanced, and the likelihood of tenure diminished. What should a rational untenured research decide? Clearly, this is not a choice that any institution wishes for its best and brightest oncology researchers to have to make. It is imperative that the systems and processes for clinical trial development be created to foster better and faster clinical trial development, with a minimum of administrative barriers.

A limitation of this analysis is that only the development time variable has been analyzed with regard to successful accrual. While there are hosts of other reasons for low accruals, this research has demonstrated that development time should be included in any investigation of low accrual causes as an important "barrier" to accrual. Continued research to uncover additional barriers within pre-activation efforts is imperative in order to foster the rapid access of clinical trials to patients and improve the likelihood of achieving the desired clinical trial objective.

[‡] Also known as between a rock and a hard place

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## TABLE 2-1: SUMMARY STATISTICS FOR CTEP-SPONSORED ONCOLOGY CLINICAL TRIALS BY DEVELOPMENT TIME AND ACCRUALS

| Percent of Project Minimum Accrual Met | | Type of Trial | | | | |
|---|---|---|---|---|---|---|
| | | **Phase I (n=123)** | **Phase I/II (n=45)** | **Phase II (n=324)** | **Phase III (n=61)** | **Overall (n=553)** |
| 0% | | | | | | |
| | No. (% by Type of Trial) | 8 (6.5) | 1 (2.2) | 13 (4.0) | 2 (3.3) | 24 (4.3) |
| | Development Time, months (Median, IQR) | 20.3 (16.4 - 34.4) | 31.6 (N/A) | 16.4 (12.0 - 22.7) | 12.7 (11.3 - 14.1) | 18.7 (12.5 - 26.9) |
| | Minimum Projected Accrual (Median, IQR) | 14 (12 - 25) | 90 (N/A) | 20 (12 - 34) | 396 (292 - 500) | 20 (12 - 33) |
| | Subjects Accrued | 0 | 0 | 0 | 0 | 0 |
| | Total Proposed | 132 | 90 | 331 | 792 | 1,345 |
| .1% - 24.9% | | | | | | |
| | No. (%) | 7 (5.7) | 7 (15.6) | 20 (6.2) | 28 (45.9) | 62 (11.2) |
| | Development Time, months (Median, IQR) | 17.9 (12.1 - 41.3) | 13.9 (12.7 - 16.4) | 19.4 (14.4 - 24.7) | 19.4 (15.8 - 31.0) | 18.5 (14.1 - 29.2) |
| | Minimum Projected Accrual (Median, IQR) | 18 (12 - 40) | 22 (20 - 66) | 26 (16 -43) | 545 (371 - 1,013) | 67 (22 - 480) |
| | Subjects Accrued | 15 | 28 | 82 | 1,546 | 1,671 |
| | Total Proposed | 167 | 243 | 634 | 26,147 | 27,191 |
| 25% - 49.9% | | | | | | |
| | No. (%) | 3 (2.4) | 3 (6.7) | 24 (7.4) | 4 (6.6) | 34 (6.1) |
| | Development Time, months (Median, IQR) | 16.0 (14.9 - 20.7) | 14.6 (14.1 - 19.1) | 16.8 (14.1 - 21.0) | 22.8 (17.3 - 48.7) | 16.8 (14.6 - 20.9) |
| | Minimum Projected Accrual (Median, IQR) | 25 (19 - 42) | 12 (8 - 18) | 33 (21 - 48) | 779 (406 - 1,196) | 33 (20 - 50) |
| | Subjects Accrued | 26 | 14 | 342 | 1,241 | 1,623 |
| | Total Proposed | 86 | 38 | 894 | 3,175 | 4,193 |
| 50% - 74.9% | | | | | | |
| | No. (%) | 13 (10.6) | 8 (17.8) | 33 (10.2) | 4 (6.6) | 58 (10.5) |
| | Development Time, months (Median, IQR) | 14.3 (11.9 - 17.9) | 18.1 (13.5 - 22.2) | 17.1 (12.5 - 22.6) | 19.7 (12.9 - 24.2) | 17.1 (12.6 - 21.7) |
| | Minimum Projected Accrual (Median, IQR) | 25 (6 - 33) | 30 (19 - 45) | 36 (24 - 42) | 586 (278 - 2,460) | 34 (21 - 44) |
| | Subjects Accrued | 207 | 201 | 877 | 2,540 | 3,825 |
| | Total Proposed | 324 | 313 | 1,403 | 4,432 | 6,472 |
| 75% - 99.9% | | | | | | |
| | No. (%) | 15 (12.2) | 3 (6.7) | 24 (7.4) | 1 (1.6) | 43 (7.8) |
| | Development Time, months (Median, IQR) | 16.8 (11.5 - 24.2) | 16.8 (12.0 - 20.0) | 13.9 (11.7 - 19.9) | 36.6 (N/A) | 15.6 (11.9 - 22.6) |
| | Minimum Projected Accrual (Median, IQR) | 18 (12 - 25) | 25 (24 - 36) | 30 (20 - 58) | 450 (N/A) | 25 (18 - 37) |
| | Subjects Accrued | 266 | 74 | 815 | 449 | 1,604 |
| | Total Proposed | 320 | 85 | 941 | 450 | 1,796 |
| ≥100.0% | | | | | | |
| | No. (%) | 77 (62.6) | 23 (51.1) | 210 (64.8) | 22 (36.1) | 332 (60.0) |
| | Development Time, months (Median, IQR) | 13.7 (10.6 - 17.9) | 13.5 (10.4 - 19.3) | 13.6 (11.3 - 17.0) | 17.4 (11.4 - 19.5) | 13.8 (11.0 - 17.6) |
| | Minimum Projected Accrual (Median, IQR) | 12 (6 - 21) | 18 (9 - 30) | 20 (16 - 32) | 535 (346 - 1,138) | 20 (14 - 35) |
| | Subjects Accrued | 2,654 | 1,633 | 9,602 | 28,585 | 42,474 |
| | Total Proposed | 1,262 | 577 | 6,104 | 22,600 | 30,543 |
| Total | | | | | | |
| | No. | 123 | 45 | 324 | 61 | 553 |
| | Development Time, months (Median, IQR) | 14.9 (11.0 - 19.6) | 14.6 (11.5 - 18.7) | 14.4 (11.6 - 19.0) | 18.3 (14.2 - 26.0)* | 15.0 (11.6 - 19.4) |
| | Minimum Projected Accrual (Median, IQR) | 15 (9 -25) | 21 (15 - 36) | 22 (17-39) | 500 (360 - 975)** | 22 (15 - 42) |
| | Subjects Accrued | 3,168 | 1,950 | 11,718 | 34,361 | 51,197 |
| | Total Proposed | 2,291 | 1,346 | 10,307 | 57,596 | 71,540 |

* Phase III > Phase I, I/II, II; P=.001,adjusted alpha <.008)
** Phase I <Phase I/II, II, III; P<.001, adjusted alpha <.008)
Phase III> Phase I,I/II,III; P<.001, adjusted alpha <.008)

**TABLE 2-2: UNADJUSTED ODDS RATIO FOR ACHIEVING MINIMUM ACCRUAL GOALS (WITH ADJUSTED VALUES FOR PROJECTED MINIMUM ACCRUAL AND TYPE OF TRIAL)**

| Development Time Intervals (months) | Unadjusted Analysis | | Adjusted Analysis Controlling for Projected Minimum Accrual | | Adjusted Analysis Controlling for Type of Trial | |
|---|---|---|---|---|---|---|
| | Odds Ratio (95% CI) | *P Value* | Odds Ratio (95% CI) | *P Value* | Odds Ratio (95% CI) | *P Value* |
| [0,9) | 1.20 (0.55 - 2.59) | 0.650 | 1.17 (0.54 - 2.54) | 0.686 | 1.13 (0.52 - 2.46) | 0.758 |
| [9,12) | 1.94 (1.06 - 3.52) | 0.010 | 1.96 (1.07 - 3.57) | 0.029 | 1.86 (1.02 - 3.40) | 0.044 |
| [12,15) | 1.01 (0.59 - 1.74) | 0.960 | 1.00 (0.59 -1.72) | 0.987 | 0.97 (0.56 - 1.67) | 0.906 |
| [15,18) (referent) | 1.0 | | 1.0 | | 1.0 | |
| [18,21) | 0.52 (0.27 - 1.00) | 0.051 | 0.54 (0.27 - 1.05) | 0.068 | 0.55 (0.28 - 1.07) | 0.078 |
| [21,24) | 0.78 (0.39 - 1.57) | 0.482 | 0.78 (0.38 - 1.57) | 0.478 | 0.75 (0.37 - 1.53) | 0.435 |
| [24,27) | 0.52 (0.20 - 1.35) | 0.179 | 0.54 (0.21 - 1.40) | 0.205 | 0.53 (0.20 - 1.37) | 0.191 |
| [27,30) | 0.14 (0.04 - 0.54) | 0.004 | 0.15 (0.04 - 0.58) | 0.006 | 0.16 (0.04 - 0.59) | 0.006 |
| [30, ) | 0.17 (0.07 - 0.41) | <0.001 | 0.18 (0.07 - 0.44) | <0.001 | 0.19 (0.08 - 0.46) | <0.001 |

* Referent indicates the median development time of all clinical trials in the sample

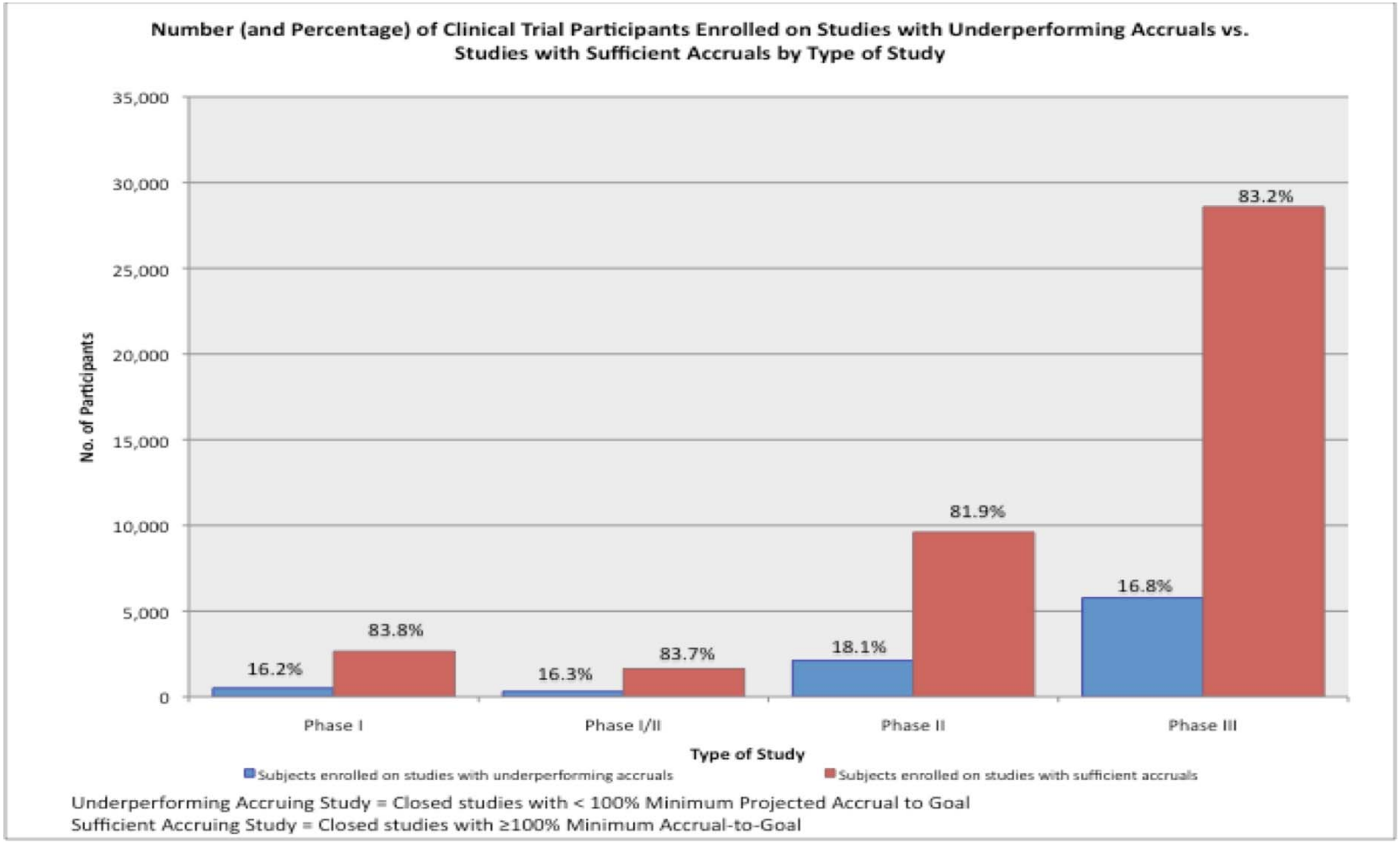
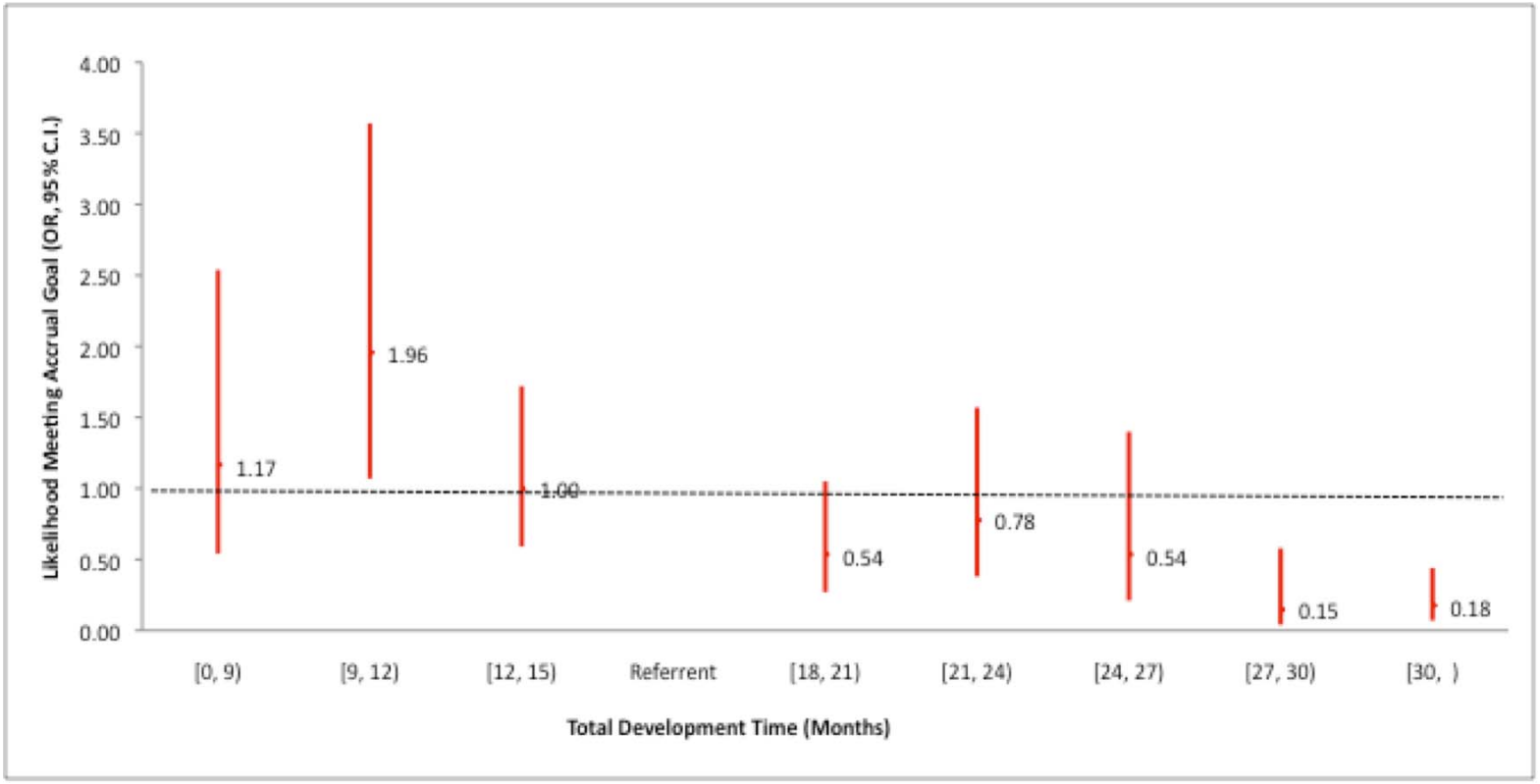



**FIGURE 2-1: UNDERPERFORMING VS. SUFFICIENT ACCRUING STUDIES BY PHASE**

**Likelihood of Achieving Sufficient Accruals as compared by the total development time for CTEP-sponsored therapeutic Clinical Trials, 2000 - 2007**




The bars indicate the calculated odds ratios with reference to the median development time. The vertical lines represent the 95% confidence intervals. The dotted line indicates the referent as defined by the median development time of the sample.

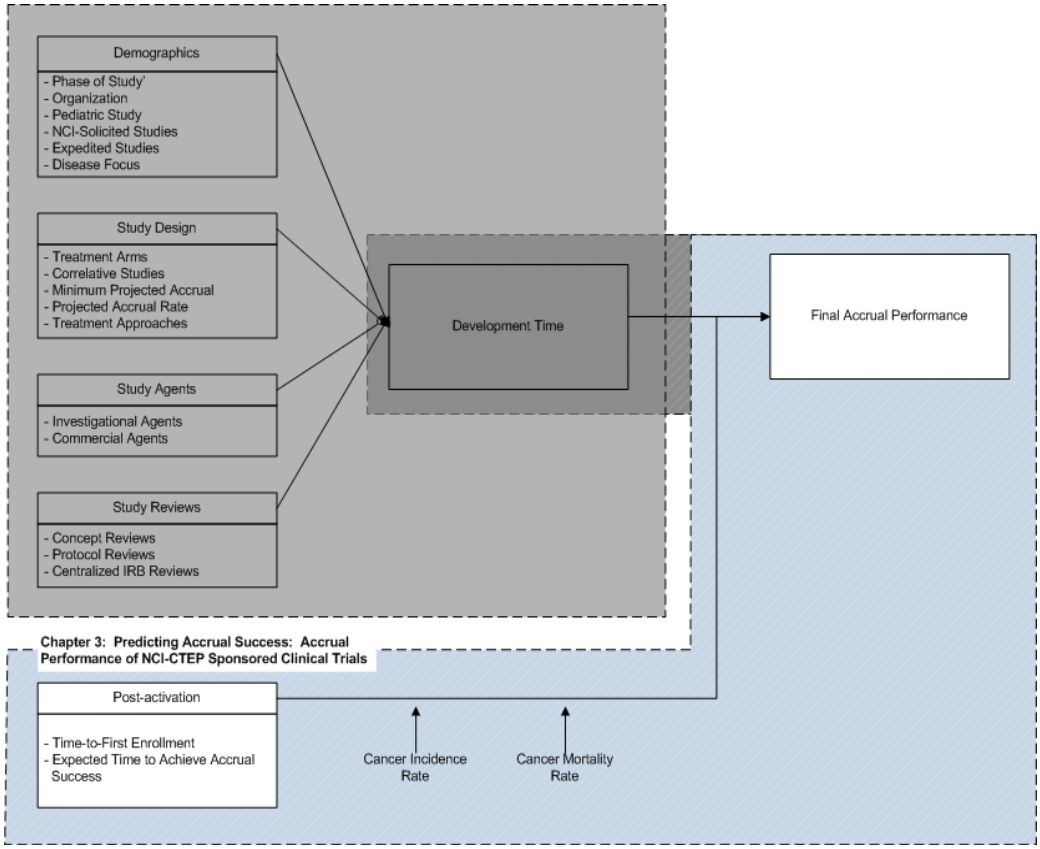
**FIGURE 2-2: ODDS RATIO OF ACCRUAL SUCCESS ACROSS DEVELOPMENT TIME**

# CHAPTER III

# PREDICTING ACCRUAL SUCCESS: ACCRUAL PERFORMANCE OF NCI-CTEP SPONSORED CLINICAL TRIALS

## 3.1 PREFACE AND RESEARCH MODEL

When comparing to the projected accrual performance, actual accrual period of studies are often under-estimated while the projected accrual are over-estimated. Research in this chapter investigates whether it is possible to forecast eventual clinical trial success in terms of achieving the desired accrual performance using early indicators of the accrual stage of a clinical trial. We use two specific accrual milestones: time-to-first enrollment and the expected period to achieve the accrual goal. We control for cancer incidences of the study to ensure that the analysis accounts for rarity of cancers.



## 3.2 ABSTRACT

***Background*** The need to increase the number of successfully completed oncology clinical trials is a well-known issue particularly for trials targeting therapeutic applications. As keeping under-accruing clinical trials open to accrual is expensive in terms of resources, research time, and use of volunteerism, it is important to understand if there are early predictors of eventual study accrual success.

***Methods*** Clinical trial records including accruals for all non-pediatric, phase I, I/II, II, and III therapeutic studies supported by the National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP) that were opened and closed to accrual between 2000 - 2007 (n=764) were gathered from multiple NCI databases. Successful clinical trials are defined as those achieving achieved 100% or more of the stated minimum accrual goal at the time of trial closure. Two observation points were analyzed per trial: 1) time-to-first patient enrollment, which measured the time from study activation to first patient on study, and 2) expected-time-to-accrual-goal as measured by the number of months from the date of first patient on study to the date the study would achieve its minimum accrual goal given the planned accrual rate. Pearson product moment correlations were used to investigate if cancer incidences or mortality related to either observation point. Multivariable logistic regression analysis was used to calculate the unadjusted and adjusted odds with respect to the likelihood of clinical trial accrual success at the two observation points. All calculations were adjusted for study phase, size of expected accrual, and time-to-first enrollment.

***Results*** A total of 81.5 percent (n=623) of the trials did not achieve projected accrual goals within the predicted accruing period. Furthermore, 37.2 percent (n=284) of trials failed to achieve the minimum projected accrual at study closure regardless of time the trial was open. Studies that achieved minimum projected accrual by study closure were 163.3 percent slower than the planned period to achieve the minimum projected accrual. Cancer incidences or mortality have no correlation to time-to-first enrollment (p=0.749 and p=0.152 respectively). Trials that accrue the first enrollment beyond two months (n=379, 49.6%) are statistically significantly less likely to achieve accrual performance than those trials that enroll patients under two months (odds ratio; 0. 637, 95% CI: 0.464 – 0.875, p=0.005). Of the studies that are open beyond the expected period to achieve the minimum projected accrual (n=603), those do not achieve at least 60.0% of the projected minimum accrual within the expected period (n=391, 64.8%) have a statistically significantly less likelihood of achieving final accruals by study closure (odds ratio; 0.190, 95% CI: 0.055 – 0.652, p=0.008).

**Conclusions** The time-to-first patient enrollment to a clinical trial as well as accrual performance by the expected period to achieve minimum projected accrual are shown to be a valid measure to evaluate likelihood of achieving minimum projected accrual. Identifying predictors of clinical trial success should be used in conjunction with scientific and other evaluations to aid in the decision to support or terminate trials with low accruals rates.

## 3.3 INTRODUCTION

It has been shown that less than one in five cancer clinical trials conducted have been published in peer-review journals.[1] While the selective publication of oncology clinical trials with negative results may affect publication rates, a greater and often overlooked impact lies with the inability to achieve the adequate accrual, or patient enrollment, to evaluate the proposed scientific hypotheses.[2] With approximately 3-5 percent of the adult cancer patients in the United States participating in clinical trials, individual clinical trials struggle to achieve the necessary accruals.[3] Under-accruing clinical trials can prolong the duration of the trial, delay realization of outcomes, or prevent scientific objectives from being achieved.[4] Unfortunately, it is typical that projected accrual rates to a trial are over-estimated, thus causing trials to remain open longer than planned.[5, 6] By prolonging the time is open, unanticipated costs of the clinical trial increase as they consume additional administrative and clinical resources.[7, 8]

Keeping a study open to accrual for longer periods does not guarantee the eventual accrual on a study. Previous observations of non-pediatric National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) sponsored clinical trials showed that approximately 40% of the trials did not achieve minimum projected accruals by study termination.[9] The ability to utilize predictors of eventual accrual to a trial will allow for better utilization of resources and increase the likelihood that subjects enrolled to trials will contribute to the state of medical knowledge. Therefore, we pose the following question: Are there early clinical trial predictors during the enrollment period that may be used to identify and assess the likelihood of a trial achieving accrual goals?

In an effort to understand the accrual patterns of oncology clinical trials, we conduct a retrospective study of CTEP-sponsored therapeutic trials between 2000 and 2007. Studies that are sponsored by National Cancer Institute (NCI) that involve collaborative efforts between Cancer Centers, Comprehensive Cancer Centers, Cooperative Groups, Consortiums, and industry sponsors must be evaluated through the Cancer Therapy Evaluation Program (CTEP). CTEP review and activate approximately 500 new clinical protocols annually and is the largest supporter of phase III clinical trials sponsored by NCI.[10, 11] We evaluate CTEP clinical trial accrual patterns throughout the entire enrollment period. Specifically we assess the likelihood that a trial will achieve accrual success at two observation points: at the time of first patient enrolment to the trial (time-to-first enrollment) and at the end of the expected enrolment time period, i.e., the length of time that a trial should have remained open given the projected accrual rate.

## 3.4 METHODS

### 3.4.1 Sample

All therapeutic, non-pediatric, phase I, I/II, II, and III oncology trials requiring CTEP evaluation that were activated and subsequently closed to accruals between May 1, 2000 and December 31, 2007 with complete accrual monitoring data (n=764) were eligible for this study. The CTEP Protocol and Information Office (PIO) provided clinical trial characteristics as well as accrual data via the Clinical Data Update System (CDUS) and the Clinical Trials Monitoring Service (CTMS), which monitors on a monthly basis all patient registrations to publicly sponsored cancer clinical trials. Projected accrual rates, projected minimum accrual goal, and activation dates of each trial are defined within the trial protocol and collected in the PIO database.

Studies that did not have information related to the projected accrual rates were excluded (n=24). If minimum projected accrual goals were not available, the maximum projected accrual goal was used (n=2). Studies that closed with zero accruals at the time of study closure were not included in the analysis, as they had no accrual rate (n=42). To investigate if incidence or morality rates impact accrual rates, data on the median age-adjusted cancer incidence and mortality rate between 2001 and 2005 was collected from the Surveillance Epidemiology and End Results (SEER) cancer registry.[12]

### 3.4.2 Variables

Figure 3-1 provides an illustrative description of key data points during the clinical trial accrual period as well as an example of one phase III clinical trial conducted by a cooperative oncology group through CTEP. As reviews for clinical trial performance can take place at monthly intervals, the unit of analysis for all time information is in months.

The date of trial activation is the date that CTEP receives notification that the study is ready to begin accruing patients from at least one institution that is participating in the trial. The date of activation is recorded in months for the purpose of calculations in this research and is approximated to the beginning of the month.

For each study, the date of the first patient enrollment was recorded to the nearest month. The time-to-first enrollment was calculated as the difference in months between the date of activation and the date of the first patient enrollment. For example, if a trial was opened on the 2nd of the month and the first patient enrolled occurs on the 25$^{th}$, the first enrolment would be shown to occur at the first trial review, or one month.

The minimum projected accrual of a study is defined within the protocol and is typically calculated from a combination of investigator consensus and statistical power requirements.

Rate of accrual in patients per month was specified within the protocol. The expected minimum projected accrual period is calculated by dividing the minimum projected accrual by the expected rate of accrual. It is assumed that the rate of accrual is linear.

Final accrual performance was dichotomous with those trials achieving 100% or more of minimum projected accrual enrolment at the time of complete study closure being defined as successful, and those trials not reaching this threshold as unsuccessful.[†] The accrual goal percentage was calculated by dividing the final accrual by the projected minimum accrual. Final accrual of a study was defined by the number of accruals on a study at the time the study was completely closed to accrual.

### 3.4.3 Observation Points

Two different observation points were utilized. First, time-to-first enrollment was recorded based on the number of months required from the month of study activation to the month of first enrollment. This point was evaluated in four groups depending upon the number of months to enroll the first patient (1-2 months, 2-6 months, 6-12 months, and >12 months). It was of interest to discover if "fast" enrolling trials (i.e., those within one or two months), were on a "fast" track for completion. The other periods were

[†] We acknowledge that studies can close due to a host of reasons, including adverse events, regulatory requirements, or other unforeseen situations. The specific reason for study closure was not available.

selected based upon the often-utilized 6-month and 12-month review cycles that institutions use to evaluate trial accrual performance. Analysis at the time-to-first enrollment was conducted against the eventual accrual success of a clinical trial at study closure.

Second, the accrual performance was observed at the estimated time to achieve minimum projected accrual. Studies were analyzed across six equally divided groups depending upon the actual accrual performance, as a percent of expected performance, at the expected period to achieve the minimum projected accrual (1-19%, 20-39%, 40-59%, 60-79%, 80-99%, and ≥100%). The accrual performance at the expected time to achieve the accrual goal is compared against the eventual accrual success of the clinical trial.

### 3.4.4 Example Trial

Figure 1 illustrates an example of a phase III clinical trial contained in the sample. The date of activation was on September 2002 with the first patient enrolled on the study on January 2003. Therefore, the time-to-first enrollment was calculated from these two dates to be 4 months.

The projected accrual rate for this study was 29 patients per month and the minimum projected accrual was 1058 patients. Using the time-to-first enrollment as a reference point for calculating the expected period to achieve the minimum accrual goal, the expected period was 37 months (rounded to the following month to ensure that all accruals were accounted for). Therefore the expected date that the study was to achieve the minimum accrual object was set at January 2006. On January 2006, the milestone at which the study was expected to achieve the minimum projected accrual; the number of accruals on the study was 195 patients. The actual accrual performance at the expected

period to achieve the minimum projected accrual was calculated by dividing the accrual (195) by the accrual goal (1058), which resulted in accrual performance of 18.43% of the expected accrual performance.

At study closure, the final accrual performance was calculated by dividing the final accrual of 357 patients by the minimum projected accrual of 1058 patients. This resulted in an accrual performance at study closure to be 33.74%. Because the final accrual performance is ≥100% of the minimum projected accrual, this study is classified as not success.

This methodology was conducted on the entire sample of 764 clinical trials and analyzed collectively.

### 3.4.5 Statistical Analysis

Descriptive statistics of medians and interquartile ranges (IQR) were used to summarize the continuous variables related to accrual characteristics of minimum projected accrual and expected period to achieve minimum projected accrual. A maximum 2-tailed alpha of 0.05 was maintained to determine statistical significance. Comparison among the trial types (i.e. phases I, I/II, II, and III) were conducted using the Kruskal-Wallis test with a post-hoc comparison of statistically significant overall tests using Mann-Whitney tests with a Bonferroni-adjusted alpha level of 0.008.

Categorical and ordinal groups were summarized using univariate and cross-tabulated frequency distributions. Unadjusted and adjusted odds ratios, along with their respective 95% confidence intervals, were obtained using multivariable logistic regression analysis. Adjusted odds ratios were calculated with the addition of adjusting

for both phase of the study and the size of the study measured by the minimum projected accrual to compensate for any interactive effects. Statistical analyses were performed in SPSS (version 16.0, descriptive and logistic regression).

## 3.5 RESULTS

A total of 764 oncology trials were identified as CTEP-evaluated, therapeutic, non-pediatric, phase I, I/II,II,III opened and completely closed to accrual between May 1, 2000 and December 30, 2007 (Table 3-1). The sample composed predominately of phase II trials (66.0%, n=504), followed by phase I (18.3%, n=140), phase I/II (8.2%, n=63), and phase III (7.5%, n=57).

The median minimum projected accrual goal for all types of trials was 25 subjects (IQR: 17-55). The estimated period to achieve the minimum projected accrual was 8 months (IQR: 5 – 15). Phase III trials has statistically significant and meaningful differences compared to the other types of trials for both the minimum projected accrual goal (25 patients for phase I, I/II, and II trials versus 530 patients for phase III trials; $p<0.001$) as well as the projected time to achieve the minimum projected accrual goal (7 patients/month for phase I, I/II, and II trials versus 40 patient/month for phase III trials; $p<0.001$).

Overall, 62.8% (n=480) of trials achieved at least 100% of the minimum projected accrual goals by closure. The number of the phase III trials that achieved the accrual goals by study closure was statistically significantly lower than non-phase III trials(38.6%, n=22; $p<0.001$). No statistically significant differences were observed

between the trials excluded (n=24) and the study sample with regard to final accrual performance (Spearman's Correlation: p=0.389).

Only 18.5% (n=141) of the trials achieved the minimum project accrual goal within the projected period of time. Phase III studies had the high proportion of studies that met the minimum goal within the expected period with 28.1% (n=16), followed by phase II studies with 21.6% (n=109), phase I/II trials with 7.9% (n=5) and phase I studies with 7.9% (n=11).

However, on average, trials achieving minimum projected accruals (n=480) were 163.3% slower than planned accrual period. Interestingly, Phase III studies that achieved the minimum projected accruals by study closure (38.6%, n=22) met the accrual goal within 73.9% of the projected period of time. This is significantly faster ($p<0.001$) than the other trial phases, where the period required to achieve the minimum projected accrual was 241.7%, 216.7%, and 142.9% of the projected period for phase I, phase I/II, and phase II trials respectively.

The trials that did not achieve the minimum projected accruals were open 127.9% longer than the expected period to achieve the minimum projected accrual. Phase III studies that did not achieve the minimum projected accrual on median closed prior to the expected period (47.2%). Phase I, I/II, and II trials opened beyond the expected period by 213.3%, 150.0%, and 130.8% respectively.

When comparing trials that achieved the accrual goal at closure to those that did not, phase I and II trials that closed without achieving the minimum projected accrual had a larger accrual requirement than those trials that did achieve the accrual goal (phase I:

p=0.009, phase II: p>0.001). Furthermore, studies that achieved accrual success had a significantly shorter projected accrual period compared to studies that did not achieve accrual success (phase I, p>0.001; phase I/II, p=0.017, phase II, p>0.001, phase II, p=0.003).

To investigate the relationship between time-to-first enrollment with the eventual accrual success of a study, multivariable logistic regression analysis was conducted to calculate the likelihood of achieving success. Clinical trials were stratified by the number of months required to accrue the first patient from study activation. The likelihood of achieving the accrual goal was highest for those studies that accrued the first patient with the first two months of enrollment (Table 3-2). All subsequent groups had a statistically significantly decreasing likelihood of achieving their goals compared to this referent group. Relative to trials that accrued the first participant within the first two months, trials taking between 2 and 6 months were statistically significantly less likely to achieve the minimum projected accrual (OR≤0.637; 95% CI, 0.464 – 0.875; p=0.005). Studies with the first accrual between 6 and 12 months as well as studies that had the first accrual beyond 12 months had an decreased and statistically significant likelihood of obtaining the minimum projected accrual at the time of study closure compared to the referent (OR≤0.208, 95% CI, 0.056 – 0.459; p=0.001).

The cancer incidences rate and the cancer mortality rate based on the disease focus of the clinical trial was collected from the SEER cancer registry and analyzed with respect to the time to first patient (Table 3-3). No statistical difference between cancer incidence or mortality and the time to enroll the first patient was observed (p=0.749 and p=0.152 respectively). The relationship between month to first patient and achieving

accrual successes held after adjusting for the minimum projected accrual of the trial, phase of the study, and cancer incidences by disease.

Of the studies that were open beyond the expected period to achieve the minimum projected accrual (n=603), the analysis of the actual accrual at the projected period required to achieve the minimum projected accrual was conducted with respect to accrual success (Table 3-4). Relative to studies that have achieved at least 80% of the minimum projected accrual within the projected period, trials with <60% of the minimum projected accrual have a statistically significant less likelihood of achieving the minimum accrual goals (OR 40% - 60% of minimum projected accrual: 0.190, 95% CI, 0.055 – 0.652, p=0.008, OR 20% - 40% of minimum projected accrual: 0.121, 95% CI, 0.036 – 0.409, p=0.002; OR 0% - 20% of minimum projected accrual: 0.065, 95% CI, 0.019 – 0.227, p>0.001). A total of 391 trials (64.8%) fell within the category of studies with <60% of the minimum projected accrual.

Given the previously established differences among phase, minimum projected accruals, and time-to-first enrollment on a study, the likelihood values were also then adjusted for these three variables. No statistically significant differences in the relationship between the percent of accrual achieved at the observation point were observed after adjusting for the additional factors.

## 3.6 DISCUSSION

The analysis of National Cancer Institute Cancer Therapy Evaluation Program oncology trials reveals that a small number of trials (11.1%, n=85) are able to achieve the minimum projected accrual within their planned accrual period. Almost two out of five trials in the sample did not achieve the minimum projected accrual by study closure. For phase I, I/II, and II studies did that achieve the minimum projected accrual goal, the project accrual time period is often under-estimated when compared to the actual time required. For the phase I, I/II, and II studies that did not achieve the minimum projected accruals with the expected time period, trials are opened to patient accrual 213.8%, 150%, and 130.8% longer than the expected to achieve the minimum projected accruals respectively. Phase III studies are unique because a higher percentage (61.4%, n=35) of trials closed without achieving the minimum projected accruals; however, trials that either close without achieving the minimum accrual goals or do achieve the minimum accrual goals do so before their expected time period.

We provide multiple observation points during the accrual period of a clinical trial that can be utilized to access the likelihood of a trial achieving minimum projected accrual. The findings demonstrate that the accrual performance of a clinical trial can be predicted as early as the time-to-first enrollment on a trial. Almost half of the studies (n= 379, 49.6%) enroll the first patient outside the first two months of the study enrollment, which translates into those studies having a statistically significantly lower odds of successfully achieving the minimum projected accruals at study closure (odds ratio: $\leq$0.637) when compared to the referent.

Furthermore, trial accrual performance can also be predicted at the expected period to achieve the minimum projected accrual goal. Even with the use of a more liberal definition for projected period to achieve the minimum projected accrual, a large percentage of studies (64.8%, n=391) fall into the category of not achieving at least 60% of the minimum projected accruals by the projected period and thus have a decreased likelihood of achieving the minimum projected accrual by study closure.

Adequate accrual to clinical trials is the most fundamental and easily quantifiable measure of performance for a clinical trial.[6] The ability to monitor clinical trial accrual performance allows for greater support for earlier decisions to be made regarding the management of clinical trials. Identifying studies with a decreased likelihood of achieving the minimum projected accrual may lead to trial decisions. Decisions can be made to add additional resources and/or funding to implement actions that may improve accruals, such as opening a study to multiple institutions, or closing studies early to release resources to support other trials with a greater likelihood of achieving their accrual goals. We do not advocate making decisions solely on accrual performance during these two observation points; rather, we advise utilizing accrual-monitoring metrics to complement the scientific judgment of completing accruals to each individual clinical trial when making decisions regarding the management of trials.

Closing studies due to poor accruals is not ideal in any circumstances. Large amounts of time and effort are consumed on the development of a clinical trial with poor accrual and the ultimately do not allow the intended scientific endeavor to come to fruition.[13-15] Patients maybe volunteering to participate on a study enroll on studies that do not help advance the state of medicine.[9] Sunk cost bias ingrained from the efforts

committed towards the development of the clinical trial can often jeopardize current resources to be allocated to poor accruing trials trial even beyond the likelihood of successfully completing the accrual requirements.

Assuming the cost to physicians for data management and other research expenses associated with enrolling a patient in a cancer clinical trial approximately $2000 per subject,[16] the 10746 participants enrolled on studies that closed without achieving the minimum projected accruals translate to almost $21.5M directed to studies that have limited contribution towards science and clinical practice. This amount does not include the unanticipated costs associated towards studies that open to accrual beyond the expected period of time and do not ultimately achieve the projected accrual goals in the form of nonclinical costs such as administrative support, IRB and FDA/regulatory review renewal fees, and recruitment fees.[7, 8, 17] How much of this allocated resources could have been directed towards other clinical trials earlier to support other endeavors? If the goal of conducting clinical trials collectively is to be able to provide the necessary scientific and statistical findings to support medical outcomes and to improve the standard of care to the general population given the limited amount of patient participation and resource, clinical trial managers must be able to make decisions earlier in both the development and the conduct of a clinical trial with regard to supporting or discontinuing studies.

The results presented in this paper are limited by the fact that findings are applicable for only NCI-CTEP studies. Perhaps similar accrual patterns may be observed across other medical domains and the question should be further investigated. Furthermore, there are numerous reasons why studies have low accrual or why studies close to accrual prior to achieving the minimum projected accrual. Continued research

should be conducted to identify characteristics that are attributed to studies with low accrual in order to reduce the occurrence of studies being closed without any sufficient accrual needed to gain the intended scientific objective.

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**TABLE 3-1: SUMMARY STATISTICS FOR NCI-CTEP SPONSORED ONCOLOGY CLINICAL TRIALS BY ACCRUAL PERFORMANCE**

| | Phase I | Phase I/II | Phase II | Phase III | Total |
|---|---|---|---|---|---|
| Accrual Performance of Trials Achieving Minimum Projected Accrual at Closure | | | | | |
| No. of Trials (% of Total) | 90 (64.3%) | 37 (58.7%) | 331 (65.7%) | 22 (38.6%) | 480 (62.8%) |
| Min Projected Accrual (median, IQR)[c] | 12 (6 - 20) | 18 (12 - 43) | 22 (18 - 50) | 535 (347 - 701) | 21 (15 - 49) |
| Projected Time to Achieve Minimum Projected Accrual, month (median, IQR)[a,d] | 4 (3 - 7) | 6 (3 - 12) | 7 (5 - 12) | 35 (24 - 45) | 7 (4 - 12) |
| Accrual Period (actual accrual period / planned accrual period, (%,median)[b] | 241.7% | 216.7% | 142.9% | 73.9% | 163.6% |
| No. of trials Achieving minimum project accrual within projected time (% of Total)[b] | 11 (7.9%) | 5 (7.9%) | 109 (21.6%) | 16 (28.1%) | 141 (18.5%) |
| Accrual Performance of Trials Not Achieving Minimum Projected Accrual | | | | | |
| No. of Trials (% of Total) | 50 (35.7%) | 26 (41.3%) | 173 (34.3%) | 35 (61.4%) | 284 (37.2%) |
| Min Projected Accrual (median, IQR)[c] | 18 (11 - 30) | 26 (20 - 51) | 36 (22 - 60) | 530 (370 - 1242) | 36 (20 - 80) |
| Projected Time to Achieve Minimum Projected Accrual, month (median, IQR)[ad] | 7 (5 - 11) | 10 (6 - 16) | 11 (7 - 18) | 48 (37 - 60) | 11 (7 - 20) |
| Accrual Period (period open to accrual / planned accrual period) (%,median)[b] | 213.3% | 150.0% | 130.8% | 47.2% | 127.9% |
| Total | | | | | |
| No. of Trials | 140 | 63 | 504 | 57 | 764 |
| Min Projected Accrual (median, IQR)[e] | 15 (6 - 25) | 22 (15 - 45) | 28 (19 - 53) | 530 (358 - 1054) | 25 (17 - 55) |
| Projected Time to Achieve Minimum Projected Accrual, month (median, IQR)[af] | 6 (3 - 9) | 7 (5 - 14) | 8 (5 - 14) | 40 (27 - 57) | 8 (5 - 15) |

[a] Rounded to the following month

[b] Based on time from first patient accrual to study closure

[c] minimum projected accrual: Phase I: p=0.009, Phase II: p<0.001

[d] projected time to achieve minimum projected accrual: Phase I: p<0.001, Phase I/II: p=0.017, Phase II: P<0.001, Phase II: P=0.003

[e] Minimum projected accrual: Phase I<Phase I/II (p<0.001), Phase I<Phase II (P<0.001), Phase I<Phase III (p<0.001), Phase I/II<Phase II (p=0.049), Phase I/II<Phase III (p<0.001), Phase II<Phase III (p<0.001)

[f] Projected Time to achieve minimum projected accrual: Phase I<Phase I/II (p=0.010), Phase I<Phase II(p<0.001), Phase I<Phase II (p<0.001), Phase I/II < Phase III (p<0.001), Phase II < Phase III (P<0.001)

**TABLE 3-2: UNADJUSTED ODDS RATIO FOR ACHIEVING THE MINIMUM PROJECTED ACCRUAL BY STUDY CLOSURE STRATIFIED BY THE TIME-TO-FIRST ENROLLMENT (WITH ADJUSTED VALUES)**

| | | | Unadjusted Analysis | | Adjusted Analysis* | |
|---|---|---|---|---|---|---|
| Time to 1st Patient Enrollment | n | Number of Studies Achieving Minimum Accrual Goals at Closure (%) | Odds Ratio (95% CI) | P Value | Odds Ratio (95% CI) | P Value |
| [1,2) (referent) | 385 | 272 (70.6) | | | | |
| [2,6) | 304 | 184 (60.5) | 0.637 (0.464 - 0.875) | 0.005 | 0.616 (0.447 - 0.851) | 0.003 |
| [6,12) | 57 | 19 (33.3) | 0.208 (0.115 - 0.376) | ≤0.001 | 0.209 (0.115 - 0.380) | ≤0.001 |
| [12, ) | 18 | 5 (27.8) | 0.160 (0.056 - 0.459) | 0.001 | 0.183 (0.063 - 0.531) | 0.002 |

* Adjusted for Study Size, Phase, Cancer Incidence, and Cancer Mortality

**TABLE 3-3: DISEASE TYPE BY SAMPLE SIZE, TIME-TO-FIRST PATIENT, INCIDENCE, AND MORTALITY**

| Disease Site | # of Trials in Sample | Time to First Patient, months | IQR | Min - Max | Incidences (per 100,000) | Mortality (per 100,000 cases) |
|---|---|---|---|---|---|---|
| Gastrointestinal (including colon and pancreas) | 119 | 2 | 1 - 4 | 1 - 12 | 84.4 | 43.5 |
| Lung, Mediastinal and Pleural | 86 | 3 | 2 - 4 | 1 - 8 | 63.9 | 54.1 |
| Miscellaneous Neoplasm | 75 | 2 | 1 - 4 | 1 - 19 | 19.7 | 13.4 |
| Leukemia | 64 | 2 | 2 - 2 | 1 - 13 | 12.3 | 7.4 |
| Breast | 58 | 2 | 1 - 3.25 | 1 - 22 | 126.1 | 25 |
| Female Reproductive | 57 | 3 | 1 - 4 | 1 - 16 | 47.3 | 15.9 |
| Skin | 46 | 2 | 1 -3 | 1 - 10 | 21.1 | 3.5 |
| Lymphoma | 44 | 4 | 2.25 - 5.75 | 1 - 18 | 22.2 | 7.8 |
| Central Nervous System | 41 | 3 | 1.5 - 4 | 1 - 14 | 6.5 | 4.4 |
| Male Reproductive (including prostate) | 36 | 3.5 | 1.25 - 6 | 1 - 16 | 168.4 | 27 |
| Kidney | 36 | 2 | 1 - 3 | 1 -22 | 13.2 | 4.2 |
| Head and Neck | 35 | 3 | 2 - 5 | 1 - 14 | 14 | 3.9 |
| Urothelial Tract | 18 | 4 | 2 - 5.25 | 1 - 11 | 21.2 | 4.3 |
| Soft Tissue | 17 | 3 | 2 - 5.5 | 1 - 12 | 3.1 | 1.3 |
| Myeloma | 13 | 3 | 1.5 - 3.5 | 1 - 7 | 5.6 | 3.7 |
| Endocrine | 7 | 2 | 1 - 2 | 1 - 2 | 9.8 | 0.8 |
| AIDS-related | 5 | 5 | 1 - 10.5 | 1 - 12 | 1.2 | n/a |
| Bone | 2 | 2.5 | 2 -3 | 2 - 3 | 0.9 | 0.9 |
| Immune Disorder | 2 | 4.5 | 4 - 5 | 4 - 5 | 0.7 | 0.8 |
| Germ Cell | 2 | 1.5 | 1 -2 | 1 - 2 | 0.4 | 0.2 |

**TABLE 3-4: UNADJUSTED ODDS RATIO FOR ACHIEVING THE MINIMUM PROJECTED ACCRUALS BY STUDY CLOSURE STRATIFIED ACCRUAL PERFORMANCE AT THE EXPECTED PERIOD (WITH ADJUSTED VALUES)**

| | | | Unadjusted Analysis | | *Adjusted Analysis** | |
|---|---|---|---|---|---|---|
| Percent of Minimum Projected Accrual Achieved at Expected Time of Acheivement | n | No. of Studies Achieving Minimum Projected Accrual at Study Closure (%) | Odds Ratio (95% CI) | P Value | Odds Ratio (95% CI) | P Value |
| [0% - 20%) | 97 | 42 (43.3%) | 0.065 (0.019 - 0.227) | p<0.001 | 0.060 (0.017 - 0.213) | p≤0.001 |
| [20% - 40%) | 159 | 93 (58.5%) | 0.121 (0.036 - 0.409) | p=0.001 | 0.103 (0.030 - 0.335) | p≤0.001 |
| [40% - 60%) | 135 | 93 (68.9%) | 0.190 (0.055 - 0.652) | p=0.008 | 0.169 (0.049 - 0.586) | p=0.005 |
| [60% - 80%) | 89 | 76 (85.4%) | 0.501 (0.134 - 1.871) | p=0.304 | 0.476 (0.127 - 1.792) | p=0.273 |
| [80% - 100%) | 38 | 35 (92.1%) | Referrant | | | |
| [100% - ) | 85 | 85 (100%) | N/A | | | |

* Adjusted of Study Size, Phase, Time-to-First Enrollment, Cancer Incidence, and Cancer Mortality

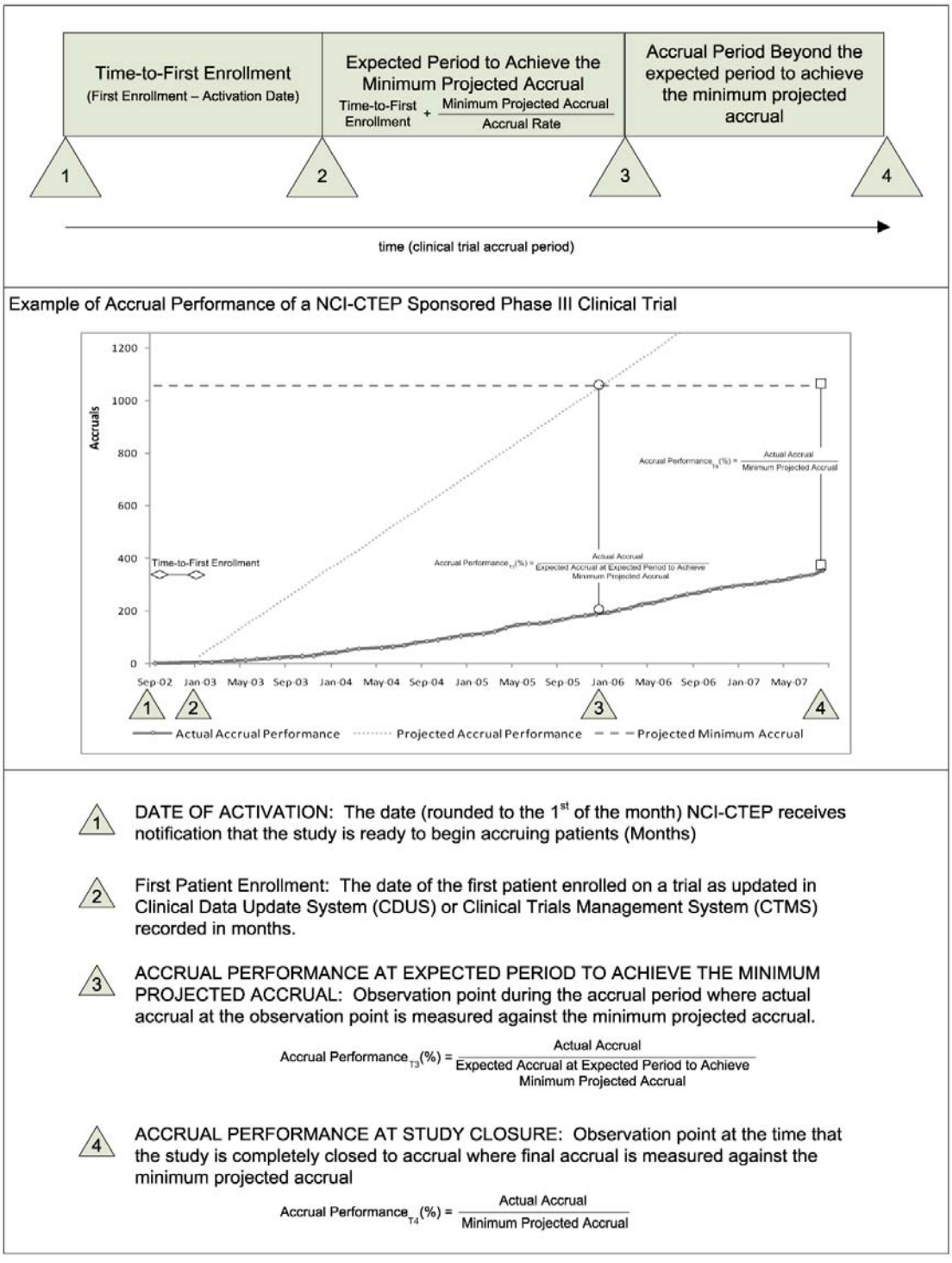


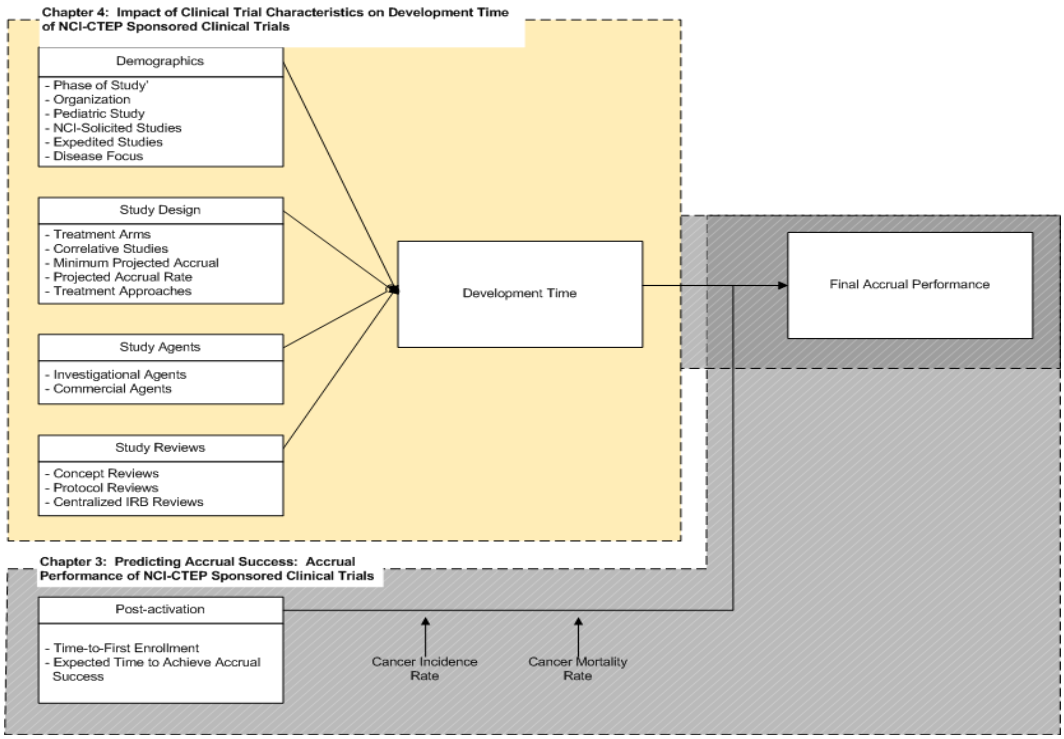

**FIGURE 3-1: DEFINITION FOR OBSERVATION POINTS AND TIMING ANALYSIS**

# CHAPTER IV

# IMPACT OF CLINICAL TRIAL CHARACTERISTICS ON DEVELOPMENT TIME OF NCI-CTEP SPONSORED CLINICAL TRIALS

## 4.1 PREFACE AND RESEARCH MODEL

The time to develop a NCI-CTEP sponsored clinical trial can take approximately 26 months to complete.[1] In the previous research, we have shown that increased development time has an inverse affect on the likelihood of achieving accrual success. Research in this chapter identifies clinical trial characteristics that impact this barrier to clinical research effectiveness. We extract characteristics from four different categories of characteristics: Demographics, Study Design, Study Agents, and Study Reviews. Understanding which characteristics attribute to development time is the first step to reducing the overall development time.



## 4.2 ABSTRACT

**Background** The median time required to develop an NCI-CTEP sponsored oncology clinical trial from initiation of concept to enrollment of first patient on trial has been found to consume a significant amount of calendar days. Furthermore clinical trials with greater development time have shown a decreased likelihood of achieving necessary accrual levels. This study examines the relationship between development time and the clinical trial characteristics. Understanding the underlying characteristics of clinical trials that impact development time will result in a better understanding the barriers to rapid clinical trial development.

**Methods** A total of 1030 National Cancer Institute (NCI) sponsored therapeutic oncology clinical trials through the Cancer Therapy Evaluation Program (CTEP) opened to patient accrual in an eight-year period (1/2000 – 12/2007) were investigated. Trial characteristics and development times were collected through the Protocol Information Office (PIO) of CTEP. Development time is defined as the difference between day that a protocol is submitted for concept review and the day that the clinical trial is activated, or opened for patient enrollment. Due to the extensive non-normality of the variable distributions, all data were ranked. Because Phase III trials have meaningfully different levels of trials characteristics, analyses were split between Phase III and non-Phase III trials. Multivariate analysis using linear regression of the ranked characteristics was used to calculate the variance in ranked development time for both data sets. .

**Results** Clinical trial characteristics accounted for 24.9% of the variation in development time for Phase I, I/II, II trials. A total of ten clinical trial characteristics were identified to contribute to the explaining the variance in development time. For phase III clinical

trials, clinical trial characteristics accounted for 30.2% of the variance in development time. Four clinical trial characteristics related towards explaining the development time. A multivariate linear regression analysis revealed that protocol and concept review was the most pronounced determinant of development time for all clinical trial phases.

**Conclusion** A number of clinical trial characteristics have been identified as predictive factors towards predicting the time to develop a clinical trial. Continued research to identifying additional clinical trial characteristics is needed to address the variance in development time.

## 4.3 INTRODUCTION

Challenges to improve the speed and efficacy of oncology clinical trials have been paramount within the National Cancer Institute (NCI).[1] Translating a research idea into a operational phase III clinical trial have been found to be an complex endeavor requiring nearly 26 months to prepare.[2, 3] Every clinical trial developed is meticulously planned, with no less than six reviews by multiple participants.[2-4] Additional reviews are required by trials sponsored by external organizations such as the NCI as well as at the multiple institutions that may be involved in accruing patients on the trial.[5] In a span of over two years for which a clinical trial is undergoing development, how much of the state of science has changed or what new trends in medicine may have occurred? Long trial development time can cause unnecessary delays before any potential results from the clinical trial may become available. The progress of clinical research evolves quickly and findings from the latest research results can often cause a trial under development becoming obsolete.[6] Competing trials also may occur because the development time cannot be predicted and may be completed a the same time as a separate trial utilizing the same patient population.[7] Excessive time to develop a clinical trial not delays the progress of cancer research, but it has also been found to be barrier in achieving success in terms of accrual goals.[8] Observations have estimated that approximately two in every five NCI clinical trials attempted fail to achieve the minimum accrual goal necessary to statistically support the intended scientific objective.

A first step towards reducing the development time of a clinical trial is to identify the underlying characteristics that may be correlated to development time. Identifying such critical trial characteristics can also begin to explain the variance in estimating time

necessary to effectively manage clinical trial development. From the perspective of the principal investigator or study chair who is designing the clinical trial, it is important to have an understanding of the cost, with respect to development time, that various trial characteristics may have, and the potential impact of such factors on the likelihood of completing accruals to the trial. Likewise, directors of medical institutions, such as NCI-CTEP, are interested in development time as it impacts the status of overall their portfolio of the clinical trials.[9]

This research identifies if general clinical trial characteristics can be utilized as indicators to estimate clinical trial development time. This research establishes a baseline framework to understanding and identifying barriers to long development time of oncology clinical trials sponsored by CTEP.

## 4.4 METHOD

### 4.4.1 Study Sample

The study sample was all therapeutic, phase I, I/II, II, and III oncology trials sponsored through NCI-CTEP and opened to accrual between January 1, 2000 and December 31, 2007. Trials submitted to NCI-CTEP from Cancer Centers, Comprehensive Cancer Centers, Cooperative Groups, Consortiums, and government agencies (i.e. National Institutes of Health and National Cancer Institute Branches) were eligible for this study (n=1046). Trials with incomplete timing data, specifically the date of receipt of the concept by NCI-CTEP, were excluded (n=409) due to the inability to calculate total development time.

To obtain the characteristics of the clinical trials in the sample, we collected information concerning both concepts and protocols per clinical trial from the CTEP-PIO database. Trials that seek NCI support are required to submit a concept or letter of intent (LOI) for evaluation by the CTEP scientific committee prior to pursuing the development of the clinical trial. Once the concept is approved and the clinical trial is developed, the clinical trial is required to be submitted to NCI-CTEP for scientific review of the completed protocol. A clinical trial can only be activated and ready for patient accrual provided that all the necessary reviews have been conducted. (For a detailed process to develop a clinical trial with CTEP support, we refer you to Dilts et al.[5]) A central repository of clinical trials maintained by the CTEP-Protocol Information Office (PIO) tracks a host of characteristics and clinical trial information. We compiled a comprehensive list of characteristics for each of the trials in the database on the available data.

### 4.4.2 Characteristics Organized in Factor Grouping

A total of 78 clinical trial characteristic variables were retrieved from the CTEP PIO-database (Table 4-1). Fifty-four (54) variables were not used for the analysis because of duplicate variables, variables unrelated to development time, or inconstant coding of the data. Three (3) variables were used to filter the final sampling set, and 18 variables were used to as the specific clinical trial characteristics for our research (Figure 4-1). The characteristics were categorized a priori into 4 different factor groups for ease of understanding: clinical trial demographics, scientific design, study agents and regulatory requirements, and scientific/ethical reviews (Table 4-3). Characteristics that

were identified but had ≤10% observations within the cohort were excluded from in the study.

Clinical Trial Demographics, the first factor grouping, included characteristics related to general characteristics of the trial such as phase and organization. Characteristics also included operational characteristics such as whether the trial was an NCI-solicited trial or an expedited trial. The NCI-CTEP can provide a solicitation for Phase I, I/II, and II trials in order to identify areas that are deemed to be scientifically or strategically important towards the direction of cancer research. Institutions can respond to NCI-CTEP solicitations by providing a letter of intent for review thus beginning the clinical trial development process. NCI-CTEP can expedite trials (particularly phase III trials) that are identified as having high importance or require timeliness to enrolling patients. Trials designated for the NCI expedited developmental process are assigned tighter deadlines for which reviews and revisions must be conducted. Also included in the clinical trial demographic characteristics was a variable that designates the trial focus on hematopoietic diseases such as leukemia, lymphoma, and myeloma or non-hematopoietic diseases, specifically solid tumors. The characteristic that identified pediatric trials among the cohort of trials was also included in clinical trial demographic category.

The Study Design factor group included trial characteristics related to the protocol scientific issues. Included in the scientific design group are variables related to trial size such as projected patients per month and projected minimum accrual. Both variables were specified in protocol during trial development. Correlative studies may also be conducted in combination with the clinical trial. These are secondary studies that may be

conducted prospectively, retrospectively, or conducted in conjunction with the treatment. Also with this group were trial characteristic of: additional treatment approaches beyond drug/therapeutic agents, specifically radiation therapy, surgery, stem cell transplant, gene therapy.

The third factor group, Study Agents Information, included variables that related to the therapeutic agents being used for the trial. Often times, trials examine whether a new treatment option compares with the existing treatment, or standard of care option. Factors included in this group include the number of therapeutic agents as well as the number of investigational agents that will be used. Investigational agents require additional Food and Drug Administration (FDA) involvement that may add additional reviews and processes before clinical approval.

The final factor group, Study Reviews factor group included characteristics of the number of reviews required to obtain approval by NCI-CTEP scientific review committee. Scientific reviews are conducted when a trial is submitted for review as a letter of intent (for phase I, I/II, and II trials) or as a concept (for phase III trials). Upon approval of a concept, the idea is developed into a protocol for review and then subsequently submitted for a complete scientific review. Often, the outcome of a review requires additional revisions to address stipulations from the review committee.[5] Additionally, the number of times a clinical trial have been reviewed and received an outcome of disapproval is also tracked. "Disapproval" outcomes are the harshest outcome whereby the trial is considered to have issues of major scientific deficiencies; yet the institution or the principal investigator has the option to resubmit the clinical trial for further review. NCI has also implemented the use of a centralized-institutional

review board (CIRB) that reviews clinical trials for ethical considerations. The CIRB was designated to reduce the amount of redundant processing steps created by multiple ethical reviews conducted for multi-institutional trials.[10]

### 4.4.3 Statistical Analysis

Based on a priori knowledge of the uniqueness of phase III trials compared to other clinical trials with respect to development time, trial size, and accrual performance, the analysis of phase III trials was completed separately from the other trials.[8, 11] Descriptive statistics of the characteristics by the two groups are summarized by median and interquartile ranges (IQR) for continuous variables and occurrences and percent of sample for discrete variables.

Because of the high non-normality of the data, all variables were transformed by rank with mean rank values assigned to cases with equal values. Hierarchical multivariate linear regression model was used to examine the association between the dependent variable of clinical trial development time against the characteristics within the four groups: clinical trial demographics, study design, study agents, and scientific/ethical reviews. Regression results were analyzed by each blocked category. A final regression model was created based on the significant findings from the regression analysis. The results are presented by ranked transformation for ease of interpretation. Statistical analyses were performed in SPSS (version 16.0, descriptive and hierarchical multiple linear regression).

## 4.5 RESULTS

A total of 1031 NCI-CTEP sponsored clinical trials that were opened to accrual between 1/2000 and 12/2007 met inclusion criteria. Phase II trials (n=526, 51.0%) constituted the majority of the trials followed by phase I (n=262, 25.4%), phase III (n=152, 14.7%), and phase I/II (n=91, 8.8%).

Clinical trials were subdivided by phase III and non-phase III trials. Figure 4-2 illustrates the finding that phase III trials are statistically significantly greater in development time compared to trials of other phases (Mann-Whitney: $p \leq 0.001$). For the cohort group focused on non-phase III clinical trials, it was observed a priori that there was no significant differences in development time between phase I, I/II, and II trials ($p=0.530$). Other trial characteristics related to phase I, I/II and II trials as well as to phase III trials are shown in table 5.

### 4.5.1 Phase I, I/II, II Clinical Trials

Table 6 reflects the findings from the hierarchical multiple regression results of phase I, I/II, and II trial characteristics as predictors of the variance of trial development time. Analysis between phase and treatment arms showed that there was a significant correlation between phase and treatment arms (Pearson Correlation=-0.660, $p \leq 0.001$), so treatment arm used in the regressions and phase I, I/II, II was excluded from further analysis. Other characteristics are not meaningfully correlated to phase (Pearson Correlation>0.40).

The first set of analyses was to explore the relationship between clinical trial demographics and development time. The presence of pediatric ($p=0.011$), solicited

($p \leq 0.001$), and hematopoietic ($p=0.010$) trials accounted for higher trial development time. However, there was no statistically significant relationship of organization on the development time ($p>0.05$) for these trial phases. Characteristics related to trial demographics accounted for 2.7% of the development time, which while statistically significant ($p=0.001$), was not meaningful.

The second analysis used hierarchical multiple regression modeling by regressing study design factors onto clinical trial demographic factors with respect to development time. This showed an increase in variance explained (adjusted $R^2=0.080$, $\Delta = 0.053$, $p \leq 0.001$). In addition to the previously mentioned characteristics, the study design characteristics that statistically contributed positively to the prediction of increased development time included trials that involved radiation therapy, surgery, stem cell transplant, image directed therapy, and/or genetic transplant ($p \leq 0.001$) and the number of correlative studies ($p \leq 0.001$). Interestingly, trials that had greater projected accrual rates (in terms of patient per month) negatively and statistically significantly impacted the variance in development time ($p=0.029$).

The third analysis explored whether the addition of study agents had an impact on development time in addition to clinical trial demographics and study design. The presence of investigational agents had a positive impact on the development time ($p=0.001$) but the number of commercial agents did not have any statistically significant effect ($p=0.227$). Adding the additional characteristics of study agents increased the amount of variance explained, or adjusted $R^2$ to 9.0% ($\Delta = 0.01$ from previous model).

The final analysis assessed the impact of scientific review factors, in addition to the previously mentioned factors. Both the number of concept reviews and the number of protocol reviews had a statistically significant positive impact on the development time of a clinical trial ($p \leq 0.001$). The inclusion of scientific review as a predictive factor did not drop any of the previously mentioned factors that contributed to assessing the variance of development time. Adding the characteristics of number of concept reviews and number of protocol reviews accounted for 24.9% of the variance in development time, ($\Delta = 0.159$ from previous model).

A total of ten characteristics were identified as having a statistically significant impact on total development time (Pediatric, NCI-Solicitation, Hematopoietic Diseases, Therapeutic Arms, Correlative Studies, Projected Accrual Rates, Additional Treatment Approaches, Investigational Agents, Concept Reviews, and Protocol Reviews) for non-phase III oncology trials. A final hierarchical multiple regression model including the characteristics that were identified to be statistically significant in explaining the development time variance as Block 1 and the remainder of the variables in Block 2 was conducted to verify the relationship of the characteristics on development time. The ten identified factors characterized in Block 1 represented 24.8% of the variance in predicting development time for non-phase III trials, while the remaining variables in Block 2 accounted for the remaining 0.1% of the variable thus confirming the findings of the analysis.

### 4.5.2 Phase III Clinical Trials

Table 6 summarizes analyses of phase III clinical trial characteristics on development time variance by means of hierarchical multiple regression. Because the overwhelming majority of NCI-CTEP supported Phase III clinical trials are conducted in the cooperative group setting (n=151, 99.3%), the variable of organization was excluded from the analysis.

The first set of analyses of phase III trials explored the impact clinical trial demographics factors on development time. A linear regression model resulted in predicting 5.8% of the development time variance (p=0.008). Pediatric trials were found to contribute to an explaining an increase in development time (p=0.036) while studies that were expedited through the development process was shown to have a decreasing impact on development time (p=0.007).

The second set of analysis explored whether the addition of the trial study design factor improved the underlying hierarchical multiple regression results. An increase of 2.9% in variance explained in the development time resulted in the second analysis accounting for 8.7% of the variance (p=0.008). An increase in development time was explained by trials that involve radiation therapy. Expedited trials were the only variable from the previous model that contributed to explaining variance in development time (p=0.008).

The third set of analyses added the factor related to study agents involved, particularly the number of investigational and commercial agents being used, to the previously established model. The addition of both characteristics did not statistically

significantly predict development time, but the overall regression model accounted for a total of 10.2% of the variance in development time ($\Delta = 0.015$ from previous model; $p=0.006$).

The final set of analysis for the hierarchical multiple regression model included the previous characteristics in addition to characteristics related to the scientific and ethical reviews factor. Both concept and protocol reviews resulted in being particularly strong indicators of development time ($p<0.001$ for protocol reviews, $p=0.009$ for concept reviews). The option to submit a clinical trial through CIRB did not influence the variance in the development time ($p=0.664$). In the final model, surgical trials positively impacted the development time ($p=0.026$) while expedited trials were found to explain a decrease in development time ($p=0.004$). All other factors were not statistically significant in the model. With the addition of scientific and ethical review characteristics, there was a marked increase from 10.2% of the variance accounted for in the previous model to predicting 30.2% of the variance ($\Delta = 0.20$ from previous model).

The characteristics of expedited trials, surgical trials, number of concept reviews, and number of protocol reviews were found to be statistically significant in predicting the variance of development time. Further verification of the final model was created by analyzing these four characteristics in Block 1 to assess total variance accounted for. The other characteristics were entered in Block 2 to ensure that the model was complete. The four identified characteristics accounted for 28.1% of the variance in predicting development time while the remaining 11 variables accounted for 2.1% of the variance.

Overall, characteristics related to scientific and ethical reviews contributed the greatest explanatory support for the variance found in development time for both phase III and non-phase III trials (Figure 4-3). The analysis of phase III clinical trials identified only 4 statistically significant factors, but accounted for a greater variance of development time compared to phase I, I/II, and II trials.

Beta weights for all factors are shown in Table 4-4.

## 4.6 DISCUSSION

This research provides a comprehensive investigation of the available characteristics that are recorded concerning oncology clinical trials in development under the CTEP mandate over an eight-year period. With over 70 variables available in the CTEP-PIO database, a total of eight variables were identified to contribute to the 24.9% of development time variance for phase I, I/II, and II trials. For phase III trials, four variables were identified to statistically account for 30.2% of the total development time variance. Further research is needed to what additional characteristics account for the development time.

The identified characteristics that relate to predicting development time variance can be grouped into two types: process-driven variables and trial-derived attributes. Process-driven characteristics are variables that can be changed based on decisions (either by the institution or NCI-CTEP) that are made at the onset of development such as the option to expedite a trial, solicit ideas for a trial, append a correlative study, reduce the number of reviews, and option to involve CIRB into the development. Trial-derived attributes are variables that are dependent on the trial itself as driven by scientific or

statistical requirements and hence cannot be changed without changing the underlying trial hypothesis and/or scientific objective. These characteristics include: number of treatment arms, disease focus of the trial, targeted patient population (i.e. pediatric trials), and projected minimum accruals.

Trial-derived attributes can only be used as passive predictor of development time to provide reasonable timelines and expectations as to when a trial will available to enroll participants. Such characteristics can be used to manage the portfolio of developing and ongoing clinical trials to help avoiding incidences such as trials being blocked because another, similar study is underway, and resource requirements to support future trials. Allowing for factors to support the prediction of development time extends portfolio management across a rolling-time horizon where forecasting the demands and requirements of future clinical trials can be accomplished.[12]

It is of interest to focus on characteristics that are process-driven variables where proactive decisions can be made which impact development time. From our research, it is found that both the decision to develop clinical trials through NCI-solicitations as well as to expedite trial a have a positive affect on decreasing clinical trials. With the knowledge that PIs may be able to complete the development of CTEP-sponsored trials provided that it is in response to a solicitation of idea may be help increase the number of trials that fit a strategic need or population demand set forth by the NCI. It is also shown that the expedited trials impact by decreasing development time. This finding is significant in the fact that it is observed that both the PI as well as CTEP should be able to fulfill specified timelines if they are defined early. Unfortunately, expedited trials still require a median of 464 calendar days to develop, which is approximately the same time

as a phase I, I/II, or II trial. Furthermore, it is unknown what the adverse impact on the development of other clinical trials in progress by such expediting as the resource requirements may be tied up on expedited trials required to satisfy the shorter timelines.

We have shown that the number of reviews at the concept and the protocol development stages are strong predictors of the overall development time. Findings from past research have shown that the process to complete a clinical trial can require numerous loops whereby processes must be repeated until approval is obtained.[13] Looping through the development process is a symptom of administrative barriers that are present within the institution and the interface between these institutions and external agencies such as CTEP.[4] The study findings presented here only account for the number of scientific reviews by the CTEP protocol review committee that is found to require a median 6-7 reviews (Table 4-3). Reviews of the clinical trial in development do not include the interchange within the institution and the PI, the industry sponsor, the Food and Drug Administration, or correspondence regarding financial or contract negotiations. Further research must be conducted to understand the underlying rational as to why clinical trials require the so many re-reviews.

Previous studies have shown that development time has a significant negative relationship on accrual performance. In addition to continuing to identify characteristics that impact development time, further research is suggested to identify better clinical trial predictor characteristics and to study their impact on the accrual performance of the trial.

It is important to note that these research findings are only applicable to NCI-CTEP sponsored oncology clinical trials. Furthermore, the variables that are used in the

analysis do not include any scientific evaluation into the quality of the trial nor the current state of science at the time the trial was developed. However, the findings of this research provide a strong foundation and framework to uncovering the barriers to the recently discovered barrier to development time.

## 4.7 REFERENCES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## TABLE 4-1A: AVAILABLE CONCEPT-RELATED CLINICAL TRIAL CHARACTERISTICS COLLECTED IN THE CTEP-PIO TRACKING AND MONITORING DATABASE

| Variable | Description | Action | Rational |
|---|---|---|---|
| Title | Title of the clinical trial at concept submission | Not used in analysis | No standardized terminology for titles |
| Phase | Phase of study at concept submission | Not used in analysis | Summarized by information at protocol submission |
| Organization | Organization submitting concept | Not used in analysis | Summarized by information at protocol submission |
| Status | Status of the review process | Used to filter studies | Only studies whose concepts were approved were included in analysis |
| Status Date | The date that the status was assigned to concept | Not used in analysis | Date only relevant to calculated concept time (see concept time) |
| Treatment | Identification of therapuetic studies | Used to filter studies | Only therapeutic studies were used for the analysis |
| Receipt Date | Date that the concept was received by CTEP | Recoded | Used to calculate the start date of clinical trial development |
| Solicitation | Identification of NCI-solicited Studies | Used in analysis | Determine if NCI-solicited studies make an impact on development time |
| PI | Priniciple investigator of submitted concept | Not used in analysis | Not enough sample size per PI for analysis |
| Drug/Immunotherapy | Identification of concepts that involved drug/immunotherapy | Not used in analysis | Summarized by information at protocol submission |
| Genetic Transfer | Identification of concepts that involve genetic transfer | Not used in analysis | Summarized by information at protocol submission |
| Stem Cell Transplant | Identification of concepts that involve stem cell transplant | Not used in analysis | Summarized by information at protocol submission |
| Image-Directed Therapy | Identification of concepts that involve image-directed therapy | Not used in analysis | Summarized by information at protocol submission |
| Radiation Therapy | Identification of concepts that involve radiation therapy | Not used in analysis | Summarized by information at protocol submission |
| Surgery | Identification of concepts that involve surgery | Not used in analysis | Summarized by information at protocol submission |
| Protocol Link - 1 | Resulting protocol(s) from concept submission | Not used in analysis | Used to link multiple databases |
| Protocol Link - 2 | Resulting protocol(s) from concept submission | Not used in analysis | Used to link multiple databases |
| Protocol Link - 3 | Resulting protocol(s) from concept submission | Not used in analysis | Used to link multiple databases |
| Total Protocols | Total number of resulting protocols | Not used in analysis | >90% of studies only have 1 resulting protocol to concept submission |
| PMB | Pharmaceutical Management Branch involvement | Not used in analysis | Incomplete data |
| AgentType | Identification of investigational agent of lead agents | Not used in analysis | Summarized by information at protocol submission |
| IND number | IND number assigned by FDA of investigational agent (if applicable) | Not used in analysis | Not enough sample size per agent for analysis |
| IND Holder | Identification of organization that holds the IND | Not used in analysis | Summarized by information at protocol submission |
| Lead IND | Name of lead investigational Agent | Not used in analysis | Not enough sample size per agent for analysis |
| Number of Agents | Number of agents involved in the clinical trial | Not used in analysis | Summarized by information at protocol submission |
| Number of Reviews | Number of concept reviews | Used in analysis | Identifies if concept reviews impact development time |
| Date of first review | Earliest date of review of the concept | Not used in analysis | Used only for concept time analysis - best summarized by number of reviews |
| Date of last review | Last date of review of the concept | Not used in analysis | Used only for concept time analysis - best summarized by number of reviews |
| Difference between first a | Calculated number of calendar days between reviews | Not used in analysis | Used only for concept time analysis - best summarized by number of reviews |
| Number of Disapprovals | Number of disapprovals received at concept review | Used in analysis | Impact of concept disapprovals on development time |
| Document Change | Number of document changes / revisions to concept | Not used in analysis | >90% of the studies have only 1 document change |
| Disease Category | Category of the disease which the clinical trial is focused on | Not used in analysis | Summarized by information at protocol submission |
| Disease | Specific disease which the clinical trial is focused on | Not used in analysis | No standardized diseases / not enough samples per disease entry |
| Number of Diseases | Number of diseases that the study is focues on | Not used in analysis | >90% of the studies focus on only 1 disease |
| Projected Start Date | Projected Start Date of the Trial | Not used in analysis | Summarized by information at protocol submission |
| Projected End Date | Projected End Date of the Trial | Not used in analysis | Summarized by information at protocol submission |
| Concept Development Tim | Calculated number of calendar days of concept development | Not used in analysis | Inconsitencies between concept receipt date |

## TABLE 4-1B: AVAILABLE PROTOCOL-RELATED CLINICAL TRIAL CHARACTERISTICS COLLECTED IN THE CTEP-PIO TRACKING AND MONITORING DATABASE

| Variable | Description | Action | Rational |
|---|---|---|---|
| Title | Title of the clinical trial at protocol submission | Not used in analysis | No standardized terminology for titles |
| Phase | Phase of the study at protocol submisison | Used in analysis | Identifies if phase has an impact to development time |
| Organization | Organization of the study at protocol submission | Used in analysis | Identifies if organization has an impact to development time |
| Status | Status of the protocol review | Used to filter studies | Only studies that have completed development used in analysis |
| Status Date | Date that status assigned to protocol | Not used in analysis | Activation Date used to determine complete development time |
| Treatment | Identification of therapuetic studies | Used to filter studies | Only therapeutic studies were used for the analysis |
| PI | Priniciple investigator of submitted protocol | Not used in analysis | Not enough sample size per PI for analysis |
| Drug/Immunotherapy | Identification of protocols that involved drug/immunotherapy | Not used in analysis | >90% of studies involve Drug/Immunotherapy |
| Genetic Transfer | Identification of protocols that involve genetic transfer | Used in analysis | Summarized in one variable for Phase I,I/II, II studies |
| Stem Cell Transplant | Identification of protocols that involve stem cell transplant | Used in analysis | Summarized in one variable for Phase I,I/II, II studies |
| Image-Directed Therapy | Identification of protocols that involve image-directed therapy | Used in analysis | Summarized in one variable for Phase I,I/II, II studies |
| Radiation Therapy | Identification of protocols that involve radiation therapy | Used in analysis | Summarized in one variable for Phase I,I/II, II studies; separate variable for phase III studies |
| Surgery | Identification of protocols that involve surgery | Used in analysis | Summarized in one variable for Phase I,I/II, II studies; separate variable for phase III studies |
| Receipt Date | Date that the protocol was received by CTEP | Not used in analysis | Best summarized by total development time |
| Activation Date | Date that the clinical trial was open to patient enrollment | Recoded | Used in calcualation of development time |
| Lead Agent | Name of lead agent | Not used in analysis | Not enough sample size per agent for analysis |
| Number of Agents | Number of agents involved in the clinical trial | Used in analysis | Number of agents used to understand relationship with development time |
| Therapeutic Arms | Number of therapeutic arms on the trial | Used in analysis | Number of arms on trial design used to understand impact on development time |
| Minimum Date | Earliest Date of protocol records | Not used in analysis | Not relevant to development time |
| Maximum Date | Latest Date of protocol records | Not used in analysis | Not relevant to development time |
| Document Change | Number of document changes / revisions to the protocol | Recoded | Best summarized by the number of protocol reviews (high correlation) |
| Number of Reviews | Number of protocol reviews | Not used in analysis | Reviews occur post-activation as well as pre-activation (see reviews prior to activation) |
| Original Reviews | Number of reviews to original submission | Not used in analysis | Summarized by number of reviews |
| Revision Reviews | Number of reviews to revision submission | Not used in analysis | Summarized by number of reviews |
| Amendment Reviews | Number of reviews to amendment submission | Not used in analysis | Summarized by number of reviews |
| Number of Reviews before | Number of pre-activation reviews | Used in analysis | Number of protocol reviews used to understand impact on development time |
| Number of Disapprovals | Number of disapprovals received at protocol review | Used in analysis | Impact of protocol disapprovals on development time |
| Active Status Date | Date that the clinical trial was assigned active date | Not used in analysis | Summarized by activation date |
| Number of Organizations i | Number of organizations for multi-institutional studies | Not used in analysis | Variable does not account of consortium or cooperative groups |
| Disease Category | Category of the disease which the clinical trial is focused on | Recoded | Recoded into solid tumor vs hematopoietic |
| Disease | Specific disease which the clinical trial is focused on | Not used in analysis | Not enough sample size per disease for analysis |
| Number of Diseases | Number of diseases that are involved in the clinical trial | Not used in analysis | >90% of the studies focus on only 1 disease |
| Correlative Studies | Number of correlative studies conducted with clinical trial | Used in analysis | Correlative study impact on development time |
| Projected Start Date | Projected Start Date of the Trial | Not used in analysis | Used for future analysis |
| Projected End Date | Projected End Date of the Trial | Not used in analysis | Used for future analysis |
| Projected Minimum Accrua | Projected minimum accrual goal of the study | Used in analysis | Projected minimum accrual goal impact on development time |
| Projected Maximum Accru | Projected maximum accrual goal of the study | Not used in analysis | Summarized by minimum accrual goal |
| Projected patients / montl | projected rate of accrual | Used in analysis | Rate of accrual impact on development time |
| Actual Accrual | Current accruals of studies opened to enrollment | Not used in analysis | Used only for analysis of post-activation |
| Hematopoietic | Solid Tumor vs. Hematopoietic Disease | Used in analysis | Distinguish if disease type has impact on development time |
| Pediatric Study | Clinical trials focused on pediatric studies | Used in analysis | Pediatric study impact on development time |

## TABLE 4-2: CLINICAL TRIAL VARIABLES BY FACTOR GROUPINGS

| | Definition |
|---|---|
| **Clinical Trial Demographics** | |
| Phase | The objectives of a clinical trial are generalized into the different phase of the study. A broad classification of studies conducted prior to outcomes being integrated into the standard-of-care practice can be grouped into four different phases: I, I/II, II, and III. The traditional outline of a drug or therapeutic development process will go through a series of clinical trials from phase I to phase III with ever increasing population sizes. |
| Organization | Clinical trials can be derived from a multitude of institutions including Cancer Centers, Comprehensive Cancer Centers, Consortiums, Cooperative Groups, and Government Agencies. For the purpose of this study, we exclude trials that originated from smaller institutions such as regional hospitals as well as international institutions. |
| Pediatric Study | Pediatric studies are unique primarily because of the focused enrollment group (Smith and Ho, 1996). The study design and the requirements necessary to develop the study design are more stringent because findings base on previously conducted adult studies do not always translate similarly to pediatric studies. |
| Hematopoietic disease | The primary disease focus of the study can be classified as residing in the blood cellular component or within the bone. Treatment options for these typese of studies are unique compared to solid-tumor cancers |
| Solicited Study * | An NCI-Solicited study are clinical trials that were created out of a response to a NCI published area of interest by which institutions can submit ideas for clinical trials. The NCI can select specific trials from the cohort of submitted studies based on the submitted concepts or ideas. |
| Expedited Study** | NCI CTEP can identify studies of importance which require faster development time. When a study is expedited CTEP sets a tighter deadline on various clinical trial setup activities. |
| **Study Agents** | |
| Number of Study Agents | Trials may contain number of both investigational and commercial agents involved with the study in order to compare new treatment approachs against/in addition to the standard-of-care. The number of therapeutic agents is calculated by the summation of the investigational agents with the commerical agents being used in the trial |
| Number of Investigational Agents | Agents that do not have FDA approval for approval for approved marketing and/or transportation are considered investigational agents. Federal law requires that a study agent obtains an exemption from the FDA to administer the treatment with the agent by means of an IND application. Clinical trials may utilize multiple investigational agents especially in the case in a multi-arm trial. |
| **Study Design** | |
| Study Arms | Oncology clinical trials often employ multiple arms, or treatment approaches, within a study to compare the outcomes of different treatment strategies.* |
| Correlative Studies | Additional correlative trials can be conducted in conjunction with the therapeutic trial in order to supplemental outcomes including laboratory studies, quality of life, and health economics. |
| Minimum Projected Accrual | The minimum projected accrual is the minimum number of human subjects that are required to achieve statistically supported scientific findings. This value is usually defined with discussions between the institution's biostatistician and the principle investigator. The minimum projected accrual is defined at the time that the protocol is submitted. While the minimum projected accrual in a studies with multiple arms is highly dependent upon the the outcomes of the previously completed arm, typically the value of the minimum projected accrual is constitutes the completion of a single arm. |
| Projected Patients per Month | The projected patients per month is the expected rate, as defined by the principle investigator, of accruals by month. The accrual rate is dependent upon the targeted study population. The expected accrual rate of a study can provide an estimation on how long a study will be open to accrual |
| Treament approaches | Clinical trials can can various treatment strategies for which the study design is focused on. Potential treatment approaches include drug and/or immunotherapy, genetic transfer, hematopoietic stem cell therapy, image directed local therapy, radiation therapy, and surgery. A study can have a combination of treatment approaches that are utilized in the clinical trial. For the purpose of this study, we stratify the treatment approaches as having only drug and/or immunotherapy approaches, studies with a combination of treatment approaches, and studies that do not involve drug and/or immunotherapy.* |
| **Scientific and Ethical Reviews** | |
| Concept Review | Trials are submitted to CTEP for review at the concept stage of development. The investigator or institution will compose a draft of the summarized idea in the form of a concept of Letter of Intent (LOI). This concept will the be reviewed with a decision submitted back to investigator and the institution. Development of the trial cannot continue without the approval of a concept which may take multiple |
| Disapproval Outcomes at Concept Review ** | Contingent upon the CTEP review of the concept or LOI, the clinical trial may receive an disapproval outcome. The investigator may have the option to resubmit the clinical trial regardless of the disapproved idea. |
| Protocol Reviews | Once a concept or LOI has been approved by CTEP, the investigator and Institution will formalize the idea into a protocol and submit it to CTEP for review. Dependent upon the type of study, the protocol may require a number of reviews. Outcomes of the protocol review are similar to the concept reviews with the outcomes being approved, approved with stipulations, revise and resubmit, tabled, and disapproved |
| Disapproval Outcomes at | Contingent upon the CTEP review of the protocol, the clinical trial may receive an disapproval outcome from the scientific review. The investigator may have the option to resubmit the clinical trial regardless of the disapproved idea. |
| Centralize IRB | The centralized instututional review board is an NCI initiative to reduce administrative burden on local IRBs and investigators. Studies that utilize the CIRB are required to go through additional ethics revview by the CIRB prior to opening the study to patient enrollment. |

* For Phase I, I/II, II trials only
** For Phase III trials only

**TABLE 4-3: CLINICAL TRIAL DEMOGRAPHICS FOR PHASE I, I/II, II TRIALS AND PHASE III TRIALS**

| | Phase I, I/II, II Trials | Phase III Trials |
|---|---|---|
| **Study Demographics** | | |
| Organization | | |
| Cancer Center, n (%) | 108 (12.3%) | 0 (0%) |
| Comprehensive Cancer Center, n (%) | 379 (43.1%) | 1 (0.7%) |
| Consortium, n (%) | 102 (11.6%) | 0 (0%) |
| Cooperative Group, n (%) | 235 (26.7%) | 151 (99.3%) |
| Government Agency, n (%) | 55 (6.3%) | 0 (0%) |
| Pediatric Study, n (%) | 73 (8.3%) | 35 (23.0% |
| NCI-Solicited Study, n (%) | 407 (46.3%) | n/a |
| NCI-Expedited Study, n (%) | n/a | 24 (15.8%) |
| Hematopoietic Disease, n (%) | 180 (20.5%) | 30 (19.7%) |
| **Study Design** | | |
| Therapeutic Arms, median (IQR) | 2 (1 - 6) | 2 (2 - 2) |
| Correlative Studies, median (IQR) | 2 (0 - 4) | 0 (0 - 30 |
| Minimum Projected Accrual, median (IQR) | 21 (15 - 36) | 564 (333 - 1232) |
| Projected Patient per Month, median (IQR) | 3 (2 - 4) | 14.5 (8 - 30) |
| **Other Treatment Approach** | | |
| Genetic transfer, Stem cell therapy, Image directed local therapy, Radiation therapy, Surgery, n (%) | 94 (10.4%) | n/a |
| Surgery, n (%) | n/a | 40 (26.3%) |
| Radiation, n (%) | n/a | 63 (41.4%) |
| **Study Agents** | | |
| Investigational Agents, median (IQR) | 1 (1 - 1) | 0 (0 - 1) |
| Commerical Agents, median (IQR) | 0 (0 - 1) | 4 (1 - 6) |
| **Scientific and Ethical Reviews** | | |
| Concept Reviews, median (IQR) | 2 (2 - 3) | 2 (1 - 3) |
| Protocol Reviews, median (IQR) | 4 (3 - 5) | 5 (4 - 6) |
| CIRB involvement, n (%) | n/a | 95 (62.5%) |

## TABLE 4-4: HIERARCHICAL MULTIPLE REGRESSION RESULTS FOR CLINICAL TRIAL DEVELOPMENT TIME REGRESSED ON CLINICAL TRIAL CHARACTERISTICS BY FACTOR GROUPINGS FOR NCI CTEP-SPONSORED CLINICAL TRIALS

| | Phase I, I/II, and II Trials | | | | Phase III Trials | | | |
|---|---|---|---|---|---|---|---|---|
| | B | SE B | β | Sig | B | SE B | β | Sig |
| Step 1: Clinical Trial Demographics | | | | | | | | |
| Organization* | | | | | | | | |
| Cancer Center | -0.99 | 0.095 | -0.057 | 0.294 | n/a | n/a | n/a | n/a |
| Comprehensive Cancer Center | 0.051 | 0.082 | 0.044 | 0.535 | n/a | n/a | n/a | n/a |
| Consortium | -0.052 | 0.1 | -0.029 | 0.604 | n/a | n/a | n/a | n/a |
| Cooperative Group | 0.027 | 0.086 | 0.021 | 0.754 | n/a | n/a | n/a | n/a |
| Pediatric Study | 0.204 | 0.08 | 0.097 | 0.011 | 0.237 | 0.112 | 0.172 | 0.036 |
| NCI-Solicited Study | 0.164 | 0.04 | 0.142 | ≤0.001 | n/a | n/a | n/a | n/a |
| NCI-Expedited Study | n/a | n/a | n/a | n/a | -0.342 | 0.125 | -0.216 | 0.007 |
| Hematopoietic Disease | 0.123 | 0.048 | 0.086 | 0.01 | -0.036 | 0.118 | -0.025 | 0.763 |
| Step 2: Clinical Trial Study Design | | | | | | | | |
| Organization* | | | | | | | | |
| Cancer Center | -0.014 | 0.094 | -0.008 | 0.886 | n/a | n/a | n/a | n/a |
| Comprehensive Cancer Center | 0.104 | 0.081 | 0.089 | 0.202 | n/a | n/a | n/a | n/a |
| Consortium | 0.087 | 0.101 | 0.048 | 0.387 | n/a | n/a | n/a | n/a |
| Cooperative Group | 0.157 | 0.091 | 0.12 | 0.084 | n/a | n/a | n/a | n/a |
| Pediatric Study | 0.139 | 0.079 | 0.066 | 0.079 | 0.219 | 0.126 | 0.160 | 0.084 |
| NCI-Solicited Study | 0.186 | 0.04 | 0.161 | ≤0.001 | n/a | n/a | n/a | n/a |
| NCI-Expedited Study | n/a | n/a | n/a | n/a | -0.347 | 0.128 | -0.219 | 0.008 |
| Hematopoietic Disease | 0.131 | 0.048 | 0.091 | 0.006 | -0.022 | 0.128 | -0.015 | 0.866 |
| Treatment Arms | -0.05 | 0.037 | -0.048 | 0.183 | 0.024 | 0.110 | 0.017 | 0.830 |
| Correlative Studies | 0.172 | 0.039 | 0.17 | ≤0.001 | 0.008 | 0.092 | 0.007 | 0.930 |
| Projected Minimum Accrual | 0.016 | 0.037 | 0.016 | 0.652 | -0.177 | 0.139 | -0.177 | 0.205 |
| Projected Accrual Rate | -0.081 | 0.037 | -0.079 | 0.029 | 0.091 | 0.142 | 0.091 | 0.522 |
| Other Treatment Approaches | 0.374 | 0.064 | 0.2 | ≤0.001 | n/a | n/a | n/a | n/a |
| Radiation Therapy | n/a | n/a | n/a | n/a | -0.236 | 0.100 | -0.202 | 0.019 |
| Surgery | n/a | n/a | n/a | n/a | 0.204 | 0.116 | 0.156 | 0.082 |
| Step 3: Study Agents | | | | | | | | |
| Organization* | | | | | | | | |
| Cancer Center | -0.015 | 0.094 | -0.008 | 0.876 | n/a | n/a | n/a | n/a |
| Comprehensive Cancer Center | 0.104 | 0.081 | 0.090 | 0.198 | n/a | n/a | n/a | n/a |
| Consortium | 0.110 | 0.100 | 0.061 | 0.265 | n/a | n/a | n/a | n/a |
| Cooperative Group | 0.173 | 0.091 | 0.132 | 0.058 | n/a | n/a | n/a | n/a |
| Pediatric Study | 0.183 | 0.080 | 0.088 | 0.022 | 0.172 | 0.141 | 0.126 | 0.223 |
| NCI-Solicited Study | 0.203 | 0.041 | 0.176 | ≤0.001 | n/a | n/a | n/a | n/a |
| NCI-Expedited Study | n/a | n/a | n/a | n/a | -0.353 | 0.127 | -0.223 | 0.006 |
| Hematopoietic Disease | 0.138 | 0.048 | 0.097 | 0.004 | -0.075 | 0.133 | -0.052 | 0.572 |
| Treatment Arms | -0.085 | 0.039 | -0.081 | 0.030 | -0.063 | 0.117 | -0.046 | 0.591 |
| Correlative Studies | 0.169 | 0.038 | 0.167 | ≤0.001 | -0.018 | 0.092 | -0.016 | 0.848 |
| Projected Minimum Accrual | 0.100 | 0.036 | 0.010 | 0.775 | -0.168 | 0.141 | -0.168 | 0.236 |
| Projected Accrual Rate | -0.080 | 0.037 | -0.078 | 0.031 | 0.019 | 0.148 | 0.019 | 0.896 |
| Other Treatment Approaches | 0.369 | 0.064 | 0.198 | ≤0.001 | n/a | n/a | n/a | n/a |
| Radiation Therapy | n/a | n/a | n/a | n/a | -0.211 | 0.100 | -0.180 | 0.038 |
| Surgery | n/a | n/a | n/a | | 0.224 | 0.117 | 0.171 | 0.057 |
| Investigational Agents | 0.181 | 0.054 | 0.120 | 0.001 | 0.257 | 0.131 | 0.225 | 0.052 |
| Commercial Agents | 0.048 | 0.040 | 0.043 | 0.227 | 0.194 | 0.119 | 0.193 | 0.106 |
| Step 4: Scientific and Ethical Review | | | | | | | | |
| Organization* | | | | | | | | |
| Cancer Center | 0.002 | 0.085 | 0.001 | 0.978 | n/a | n/a | n/a | n/a |
| Comprehensive Cancer Center | 0.054 | 0.074 | 0.046 | 0.466 | n/a | n/a | n/a | n/a |
| Consortium | 0.099 | 0.091 | 0.055 | 0.278 | n/a | n/a | n/a | n/a |
| Cooperative Group | 0.140 | 0.083 | 0.107 | 0.092 | n/a | n/a | n/a | n/a |
| Pediatric Study | 0.229 | 0.073 | 0.110 | 0.002 | 0.210 | 0.127 | 0.153 | 0.101 |
| NCI-Solicited Study | 0.173 | 0.037 | 0.150 | ≤0.001 | n/a | n/a | n/a | n/a |
| NCI-Expedited Study | n/a | n/a | n/a | n/a | -0.427 | 0.145 | -0.270 | 0.004 |
| Hematopoietic Disease | 0.136 | 0.043 | 0.095 | 0.002 | 0.059 | 0.120 | 0.041 | 0.622 |
| Treatment Arms | -0.119 | 0.035 | -0.114 | 0.001 | -0.004 | 0.104 | -0.003 | 0.969 |
| Correlative Studies | 0.110 | 0.035 | 0.109 | 0.002 | -0.028 | 0.082 | -0.026 | 0.730 |
| Projected Minimum Accrual | 0.003 | 0.033 | 0.003 | 0.923 | -0.121 | 0.126 | -0.121 | 0.338 |
| Projected Accrual Rate | -0.066 | 0.034 | -0.065 | 0.049 | 0.035 | 0.131 | 0.035 | 0.788 |
| Other Treatment Approaches | 0.302 | 0.058 | 0.162 | ≤0.001 | n/a | n/a | n/a | n/a |
| Radiation Therapy | n/a | n/a | n/a | n/a | -0.146 | 0.089 | -0.125 | 0.105 |
| Surgery | n/a | n/a | n/a | n/a | 0.232 | 0.103 | 0.177 | 0.026 |
| Investigational Agents | 0.120 | 0.049 | 0.079 | 0.015 | 0.142 | 0.117 | 0.125 | 0.228 |
| Commercial Agents | 0.034 | 0.036 | 0.030 | 0.356 | 0.114 | 0.108 | 0.113 | 0.293 |
| Concept Reviews | 0.149 | 0.034 | 0.130 | ≤0.001 | 0.205 | 0.078 | 0.194 | 0.009 |
| Protocol Reviews | 0.402 | 0.031 | 0.391 | ≤0.001 | 0.455 | 0.081 | 0.448 | ≤0.001 |
| CIRB Involvement | n/a | n/a | n/a | n/a | -0.049 | 0.114 | -0.041 | 0.664 |

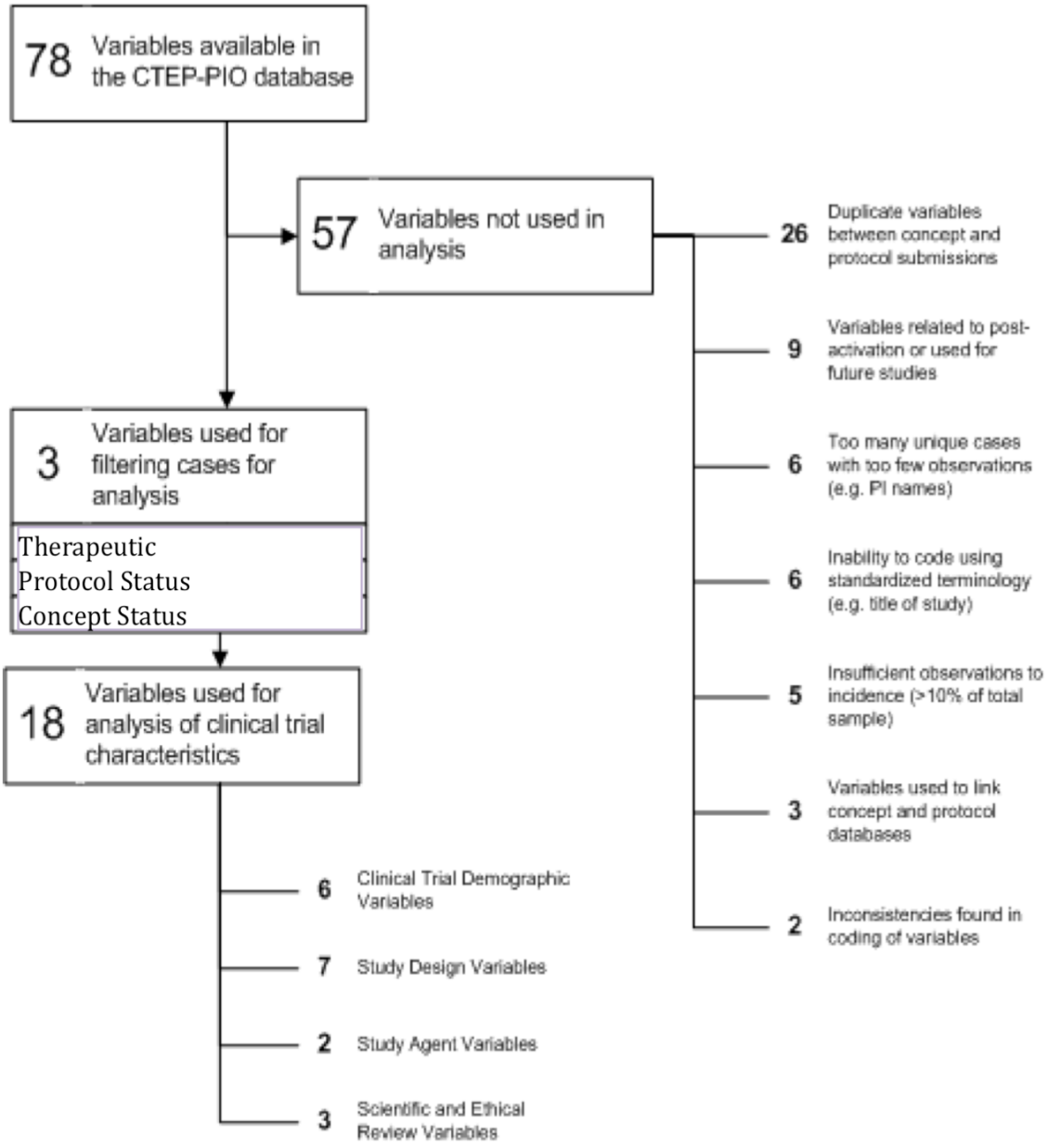
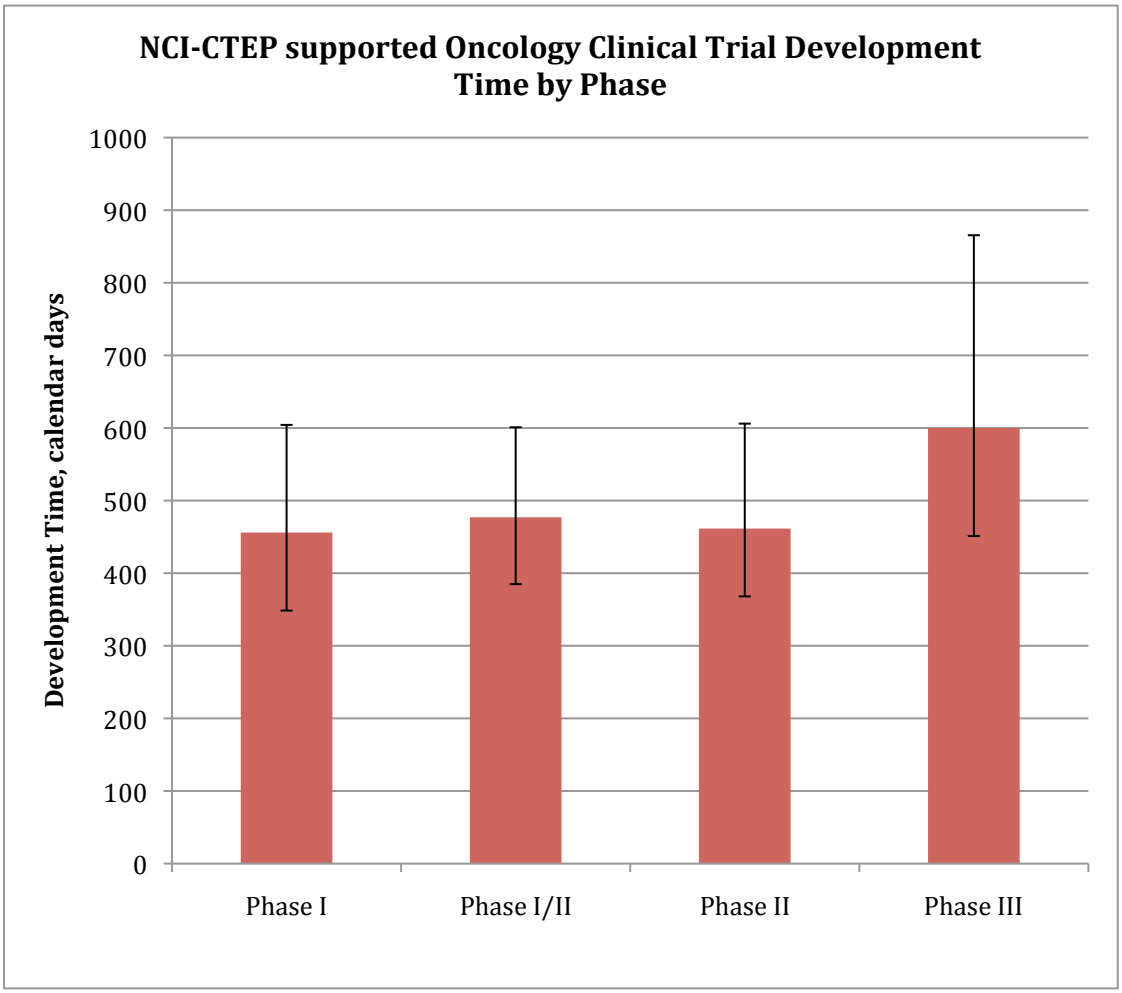



**FIGURE 4-1: SELECTION AND FILTERING CRITERIA UTILIZED IN IDENTIFYING VARIABLES IN ANALYSIS**




Phase III vs Phase I, I/II, II (Mann- Whitney two-sample P≤0.001)
Phase I, vs Phase I/II, vs II (Kruskal-Wallis n-sample P=0.530)

**FIGURE 4-2: DEVELOPMENT TIME OF CLINICAL TRIALS BY PHASE**

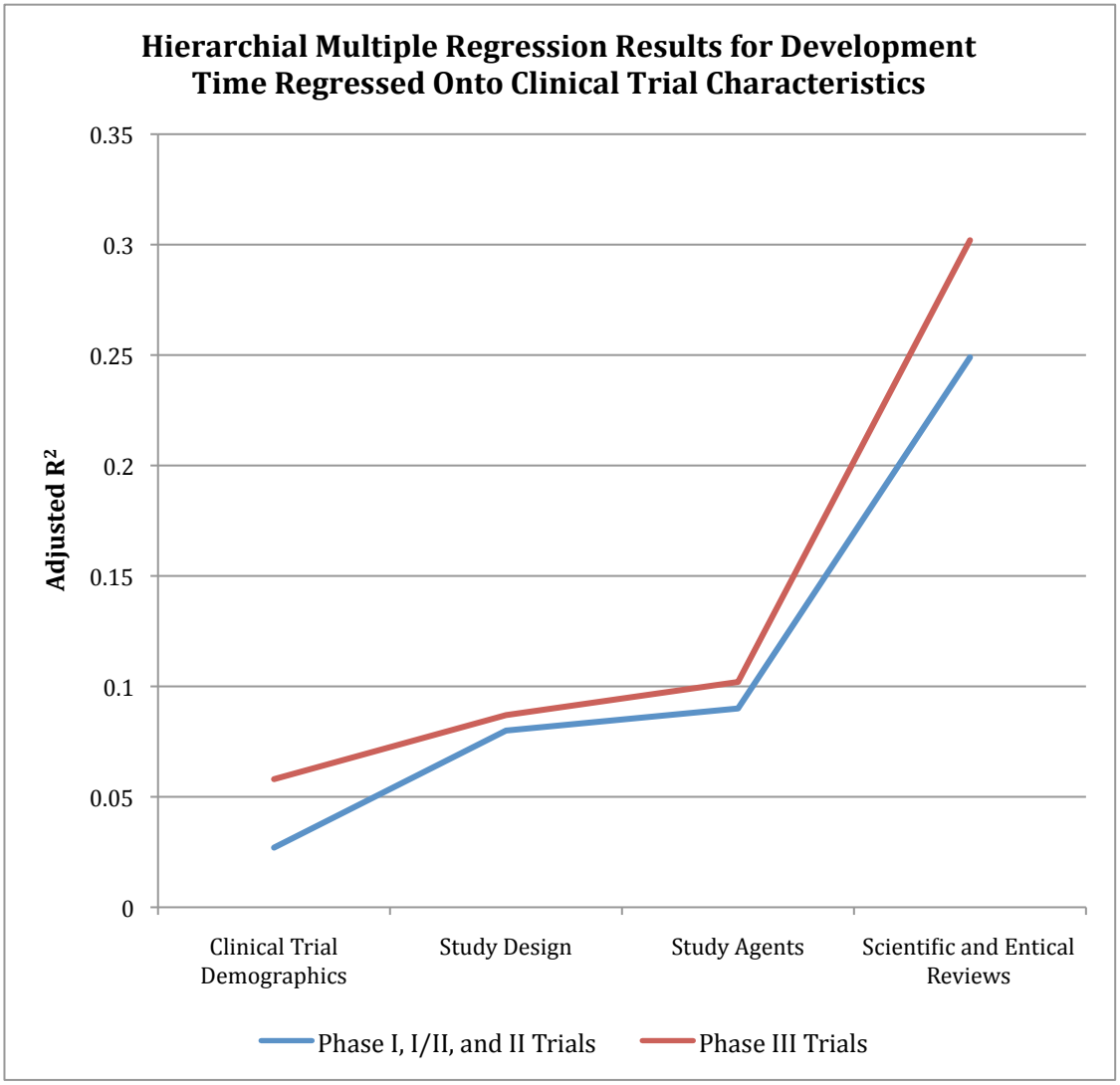



**FIGURE 4-3: COMPARISON OF FACTOR GROUPS BY PHASE**

# CHAPTER V

# CONCLUSION

This research investigated the impact of oncology clinical trial success indictors that occur during pre-activation (or the period required to develop a clinical trial) as well as early post-activation indicators as they relate to the likelihood of a clinical trial achieving accrual success. The research was divided into three main components: 1) the relationship between trial development time and accrual success, 2) the relationship between time-to-first patient enrollment to the clinical trial and the expected accrual performance with accrual success, and 3) the characteristics of clinical trials that relate to development time. The research findings provide insight into factors related to the success of achieving accrual goals as well as clinical trial characteristics related to development time and it broadens the horizon for future research in the areas of design and development stage of clinical trials.

## 5.1 IMPACT OF DEVELOPMENT TIME ON ACCRUAL SUCCESS

In Chapter II, development time was found to have a statistically significant and meaningful negative impact on the likelihood of a clinical trial achieving success in terms of its accrual goal. With regard to research investigating improvements to translational science, this finding uncovers barriers to clinical research effectiveness during pre-activation time and processes. Research focusing on causes of low clinical trial accrual must acknowledge that pre-activation clinical trial factors, such as development time, also impact enrollment, in addition to patient perception and physician's effort to recruit.[1]

My research shows that development time can be used as an indicator that provides quantitative support for decisions to continue or terminate a clinical trial during its development and immediately post-activation. Specifically, for NCI-CTEP sponsored oncology clinical trials, trials that extend development time beyond 12 months have decreasing likelihood of accrual success the more development times increase. Essentially, once an idea is conceived, there is a "countdown clock" during which the trial idea remains of interest and it avoids becoming obsolete, both in terms of scientific and popularity to the oncology community.

## 5.2 EARLY PREDICTORS OF ACCRUAL SUCCESS

In Chapter III, which studied early post-activation indicators of oncology clinical trial accrual success, it was found that both time-to-first enrollment as well as accrual performance at the expected deadline were predictors of achieving accrual success. These findings create opportunities conduct prospective observation points on clinical trials rather than retrospective analysis of completed trials. Public policy and health care management researchers can utilize these critical milestones to investigate what actions were conducted on clinical trials to improve accrual rates and whether these were effective in impacting achievement of accrual success. Preliminary findings of this research also hint at evidence that both the incidence of cancer and the mortality of cancer in the general population do not impact accrual rates. Therefore, the barriers to clinical trial accrual success of a study are found in other factors beyond patient population demand or urgency by cancer type.

Additionally, the second stream of research provides two well-defined milestones where the evaluation of clinical trial progress can be conducted. Time-to-first enrollment

is a milestone that all studies must fulfill (with the exception of studies that are so unsuccessful that they do not enroll a single participant) and is a standardize evaluation point that is easily measured. Studies that do not enroll the first patient as early as two months begin to show statistically significant signs of decreased likelihood in achieving accrual success. Early interventions of strategically or scientifically important studies therefore should be conducted as early as two months after opening. For example, critical studies that do not achieve this first accrual milestone may elect to begin efforts to extend a study to a multi-institution setting such as through Community Cancer Oncology Program (CCOP), a network that enables an increased number of patients and physicians to participate on a clinical trial, in order to increase the accruals.[2]

Expected time to fulfill the minimum projected accrual is a milestone that is defined by the principal investigator, trial statistician, and those involved with the protocol development. Findings from this dissertation show that few clinical trials are able to achieve the projected accrual performance goal within the pre-defined schedule. Decisions may be supported to either reward clinical trials for able to accruing the desired number of patients within the expected period of time, or punish those that do not. Identifying two accrual rate milestones sets the foundation for the application of portfolio analysis towards the health care setting of clinical trials management. Clinical trials accrual progress can be systematically evaluated and quantifiably measured with regard to likelihood of achieving the intended accrual goals.

### 5.3 CHARACTERISTICS IMPACTING DEVELOPMENT TIME

This research takes the initial steps in uncovering factors related to long development time based on the findings from Chapter IV. The research provides an

initial framework and methodological approach to understand the factors that are related to development time. Continued research can build off these findings by identifying additional factors that related to development time including subjective factors and currently unmeasured factors.

Practical applications of this research identify two types of factors or characteristics that impact development time: 1) Process-driven characteristics and 2) Clinical trial-derived attributes. Process-driven characteristics are factors that can be managed based upon the decisions and specific steps required to develop a trial. Clinical trial-derived attributes are those factors related to the science, statistical, and/or disease of the trial and cannot be changed without impacting the clinical trial design. Clinical researchers can have a better understanding regarding how long a study will require to develop. Findings from this research provide additional evidence that the characteristics that influence the development of Phase III trials are unique compared to non-phase III trials. In addition, the research finds that the greatest impact to development time is related to process-driven characteristics, particularly the number of scientific reviews, which can be addressed through quality and process improvements. Coordination between those conducting the scientific review and those responding to the review may be able to reduce the number of reviews and thus decrease the development time required.

## 5.4 LIMITATIONS AND FUTURE STUDIES TO ADDRESS LIMITATIONS

### 5.4.1 Research Setting

The results and findings from this research are only applicable within the context of oncology clinical trials, and specifically within the NCI-CTEP research setting. Oncology clinical trials can be conducted via multiple sponsors, including industry sponsored and at the local institutional level, i.e., a cancer center. Each of these sponsors require unique development processes, organizational structures, and clinical trial requirements. The uniqueness of each institution, including expertise brought forth by the clinical researchers and core competence of the institution, may result in different results if the research presented in this dissertation is replicated within the individual context. For example, an academic medical center may have a network of rural and affiliate institutions to participate on clinical trials in order to increase accrual rates and broaden participation on clinical trials.[3] Having this unique feature within the organization may allow for faster accrual rates and therefore early indicators during the accrual period of eventual accrual success, as presented in this research, may require modification.

Compared to other diseases, oncology clinical trials are the most prevalent type of trials.[4, 5] However, it is unknown whether clinical trials of other diseases also encounter similar barriers to development and accrual success compared to oncology clinical trials. Specific interest for further studies may be clinical trials that focus on cardiology diseases with it being the leading cause of deaths per year and highest incidence rate in the United States.[6] With fewer clinical trials compared to oncology and a high incidence rate, cardiology clinical trials may have different factors related to development time and

accrual. Interest in other diseases with less visibility and incidence rates compared to oncology such as sickle cell trials are also pertinent as the characteristics of the disease and organizational structure supporting clinical trials may result in different findings from this research.

### 5.4.2 Uncovering Additional Factors

Continued research to discover pre-activation factors is essential. The efforts summarized in the three primary chapters of this dissertation mainly focus on factors that influence timing data with respect to accrual.

The research presented in this dissertation has only begun the task of systematically uncovering the characteristic of clinical trial development time with the provided retrospective data. Identification of additional factors that may impact long development time would be beneficial in explaining a greater proportion of the variance in development time. It is expected, but not tested, that a large portion of the development time variance may be explained by subjective factors that can only be evaluated via prospective data collection through surveys and interviews. With the finding that an increased number of reviews result in increase development time, it would be interesting to track the miscommunication of comments of the reviewers (also known as stipulations) by the principal investigator and research associates developing the protocol. Perhaps the increased number of reviews is attributed to the inability to properly address the reviewers' comments either through vagueness of the comments or through misunderstandings of what is a required response to the reviews.

The research provides a foundation to begin addressing concerns for portfolio management of clinical trials. Decisions related to the management of a portfolio of clinical trials must be derived from a tradeoff between feasibility/operability as well as strategic importance.[7, 8] The research uncovers that development time is a vital measure to consider when supporting clinical trial portfolio decisions with regard to feasibility and operability. Furthermore, early indicators of accrual success can be measured of clinical trials as early as first patient enrollment. Typically, there is a pipeline of clinical trials within the various stages of development and execution. Clinical trials continually enter the system for development, opened to enrollment, and closed to accruals, continually monitoring clinical trials across a rolling-time-horizon is important. Several metrics have been identified; however the next step is to apply it to a decision model for the portfolio.

### 5.4.3 Clinical Trial Success

The measure of success utilized throughout this research was accrual performance of the clinical trial. It is important to acknowledge that a clinical trial achieving the minimum accrual goal is a very minimal measure of trial success. Additional measures of success of a clinical trial are also essential. One measure of success worth noting is that of the measure of publication and scientific importance of the outcomes of the clinical trial. With less than one in five clinical trials result in publication in a peer-reviewed journal, measuring clinical trials by the quality of the scientific findings are just as important as achieving accrual success.[9]

Future research to address these limitations should be continued by investigating what additional barriers to clinical trials are present with regard to factors beyond

development time. Barriers that obstruct the implementation of quality and scientific relevance into the study design may uncover additional factors that have been often overlooked.

## 5.5 FINAL CONCLUSIONS

### 5.5.1 For Researchers Investigating Clinical Trial Barriers to Success

This research delves into the critical intersection between management research and health care, specifically in the setting of oncology clinical trial operations. The research bridges the gap between clinical trial development efforts and clinical trial effectiveness. Efforts to reduce the development time therefore not only improve how quickly a trial can begin to enroll patients, but it also improves the likelihood of achieving accrual success. This research also provides indicators during the early accrual performance that can be used to predict accrual success, and it identifies clinical trial characteristics that are correlated to long development time.

Findings from this research impact future research related to the investigating clinical trial barriers by providing new opportunities to improve clinical and translational science effectiveness. With little research focused on pre-activation activities and early accrual performance of clinical trials; this research emphasis the importance of such research

Focusing on the issues regarding clinical trial operational effectiveness also creates opportunities to apply operations and management (OM) theories to investigate relevancy of past research towards a new research settings. Potential application of OM theory to the design and development of clinical trials is outlined with a focus of supply

chain management as well as a summary table for supply chain management, job shop scheduling, and new product development.[10] Continued efforts in this research may help established the applicability of current management theories to the health care setting or it may highlight the uniqueness of health care compared to other industries.

### 5.5.2 For Clinical Trials Offices and Others Developing and Managing Oncology Clinical Trials

From the perspective of those involved with the implementation of oncology trials, this research highlights the importance of both the development process as well as the early accrual period. Specifically, evidence has shown that greater development time has an adverse impact on accrual success. Unnecessary delays during the development of a clinical trial should be avoided and decisions to "tinker" or revise the clinical trial causing additional delays should be made with the consideration of the potential tradeoff in likelihood of achieving success.[11] For example, financial and contract negotiations have become integrally tied into the design and development of a clinical trial and can often cause delays due to the administrative barriers of synchronicity.[3] This research suggests that it is in the best interest of both the clinical researcher as well as the sponsor to have a clinical trial developed quickly and safely to improve the overall likelihood of achieving accrual success; without achieving the necessary accruals, all efforts related to failed clinical trials becomes non-value added. Yet, when negotiating contracts and financial agreements, both parties may only look out for the self-interest of the individual party thus building in potential delays into the entire process.[10] Careful consideration of the design and development decisions of a clinical trial must be made with regard to both the potential consequential delays and the impacts to the overall success of a trial.

From the managerial perspective for those who oversee oncology clinical trials, this research provides a foundation for identifying specific metrics by which to evaluate clinical trials in both the development stage as well as through the accrual stage. Identifying the metrics of development time, time-to-first enrollment, expected accrual performance, and process-related characteristics allows for the evaluation of all clinical trials across a standard set of criteria. This research address several metrics that can be used to determine the likelihood of achieving accrual success as well as predicting the expected period to which a clinical trial can complete the development time. These two pieces provide the initial components of both clinical trial performance and scheduling required to establish the ability to manage a portfolio of trials. Managers can utilize the findings from this research and couple it with the implementation of overall strategy which the organization (specifically NCI-CTEP) follows, in order to improve overall clinical trial effectiveness.

## 5.6 OVERARCHING CONCLUSIONS

The research of this dissertation is just the beginning of a growing area of interest to improve the operational and scientific effectiveness of clinical research. There are a host of other perspectives and academic disciplines that can be applied towards improving clinical trial effectiveness; this research embraces the management approach and applied it to issues of clinical trial development and operations. All interdisciplinary research efforts and application of research must continue with the utmost intention to achieve the ultimate goal of improving standard treatment options and standards of oncology practices benefiting the current and future populations afflicted with cancer.

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# CHAPTER VI

## EPILOGUE: APPLICATION OF MANAGEMENT THEORIES TO A HEALTHCARE SETTING

The past four years of investigating the clinical trial development process through multiple settings including four comprehensive cancer centers, three cooperative groups, and two government institutions has presented numerous examples and informal case studies on the application of healthcare towards management theories. The combination of countless interviews, collecting data from multiple perspectives, and documenting the processes required to develop a clinical trial have provided sufficient insight on how different participants and organization interact amongst each other. Three specific theoretical management lens of interest of how the development of a clinical trial is applicable include supply chain management, new product development and job shop scheduling.

To ignite the extension of management theory into the healthcare setting, research has begun to provide the foundation for future research on the theoretical level. The application of supply chain management to the development of clinical trials is presented in a formal article. Additional references that relate to new product development and job shop scheduling are presented in appendix A. Research findings are presented in the framework of administrative barriers denoted by structural, infrastructural, and procedural barriers.[1, 2]

## 6.1 ABSTRACT

The knowledge-based healthcare supply chain is plagued with the same dilemmas as those found in the manufacturing environment, hence theories and principles from operations management (OM), particularly those involved with supply chain management, may be able to be applied to improve overall healthcare system performance. The objective of this paper is to show how one aspect of the healthcare supply chain, that of pharmacological clinical trials, has a distinct need for the ideas and solutions that operations management can bring. Decision science techniques have been successfully applied in a variety of industries, yet little of this knowledge has been translated onto the decision processes required to design and activate drug clinical trials (Dilts & Sandler, 2006; Dilts, Sandler, Baker, Cheng, George, Karas, McGuire, Menon, Reusch, Sawyer, Scoggins, Wu, Zhou, & Schilsky, 2006). Using process and timing data collected from multiple sites concerning oncology clinical trials, we show that there is a wealth of opportunities to apply OM knowledge in healthcare.

## 6.2 INTRODUCTION

Total national healthcare expenditures within the U.S. rose 7.9% or 16% of the gross domestic product (GDP) in 2004, and are projected to reach 20% of the GDP in the next decade. This $1.9 trillion is 4.3 times the amount spent on national defense (Henry_J_Kaiser_Family_Foundation, 2007; National_Coalition_on_Healthcare, 2007). As research has noted, this explosive rise of healthcare spending and highest per capita spending of any country, does not necessarily translate to achieving better outcomes than

other countries who spend considerably fewer resources per capita on healthcare(Henry_J_Kaiser_Family_Foundation, 2007).

One particular healthcare sector, the pharmaceutical industry, continues to increase its expenditures in research and development at an even more alarming rate. This industry's top ten companies alone increased their research and development spending to $54 billion, with clinical trials accounting for more than 40% of the total research and development spending (Clinical_Trials_Today, 2007), this increase is more than an 147% increase from 1993 to 2003 (Medical_News_Today, 2006). Clinical trials are a critical step in the verification and validation of potential new therapeutics (drugs) prior to approval by the Food and Drug Administration (FDA).

Interestingly, while the development time for other new-to-the-world products have decreased from 41.7 months to 24 months from 1995 to 2004 (a decrease of 42%) (Adams & Boike, 2004; Slater, 2005), the time to develop a new drug has increased from 56.4 to 144 months (increase of 155%)(Slater, 2005) in the same time frame. And along with this increase in time is escalating costs. With cost reaching over $800 million per drug, pharmaceutical firms must rely on external partners, suppliers, and government agencies to aid in new product development (DiMasi, Hansen, & Grabowski, 2003; Adams & Brantner, 2006). With such a large investment reaping disappointing results as nine of ten drugs fail to successfully enter the market (Clinical_Trials_Today, 2007), the time has come to study whether decision–making techniques utilized in other industries can be applied to the healthcare industry to 1) improve outcomes and 2) reduce operational barriers.

Pharmaceutical firms do not work alone in the development and testing of novel drug therapies and indications. Compared to other industries, the pharmaceutical supply chain is highly disbursed across different levels of intermediaries, which includes healthcare professionals, government employees, research scientists, and hospital systems. However, considering the time and cost to develop a new treatment option, increasingly pharmaceutical firms are turning to their supply chain to aid them in developing new product. This is similar to what is occurring in manufacturing, where suppliers are becoming co-product developers (Handfield, Ragatz, Petersen, & Monczka, 1999). One key aspect of drug development is that of testing on human subjects, which is known as a clinical trial.

The clinical trials process is a long and arduous one that requires multiple individuals, in multiple institutions and with multiple job descriptions to interact to complete the initial tasks to test a drug or treatment. Development of a trial can require both internal coordination as well as external coordination with government agencies, such as the National Cancer Institute (NCI), a division of the National Institutes of Health (NIH). The NIH is the "primary federal agency for conducting and supporting medical research" (National_Institutes_of_Health, 2007), which includes clinical trials. As supply chain integration requires external and internal cooperation, the healthcare supply chain should be able to translate existing research into its unique needs. The need for such translation can easily be seen as research at one typical comprehensive cancer center showed that 55% of all studies that were opened for patient accrual resulted in such a low number of patients (<5) that the no statistically valid conclusions could be drawn from the trials. With months or years involved in the setup of a clinical trial, the clinical trials

process has significant room for improvement and it has been suggested that decreasing the times to conduct clinical trials will directly result in an overall decrease in the cost of treatments at the patient's bedside (DiMasi et al., 2003).

There are three types, or phases, of clinical trials (I, II, and III). From an initial limited number of patients, or accruals, required the number of accruals increase by phase. Each clinical trial phase can be divided into two aspects: 1) development of the clinical trial or testing protocol and 2) execution the trial and evaluation the results. Interestingly, while there is a great deal of literature in the medical domain about the second aspect, there is virtually none concerning the first. This is similar to the state of manufacturing knowledge pre-1970's: there were volumes of research on manufacturing execution but a dearth on setup reduction. Our paper demonstrates how OM manufacturing and service literature on setup can be used to address very similar issues in new drug development.

There have been numerous studies that have focused on reducing the time to execute a clinical trial, such as increasing accruals and improving communication of the announcement of studies (Comis, Miller, Aldige, Krebs, & Stoval, 2003; Corrie, Shaw, & Harris, 2003). While such investigations have lead to improvements of the operation of individual clinical trials, Dilts et al. (2006a,b) found that the potential of reducing time to completion and potential cost savings are found not only in the process of conducting a clinical trial, but also in the setup and development of the clinical trial. In one case, the mean time of clinical trial development at a oncology clinical trial cooperative group

(CTCG)[1] is 2.1 years; which is approximately half of the total time to complete the clinical trial (Dilts et al., 2006; Keyhani, Diener-West, & Powe, 2006). It is logical to assume that this set-up time is affected by some of the same causes as found in other service and manufacturing organizations.

Supply chain management knowledge has evolved greatly in the past four decades and has been the focus of numerous articles (Croom, Romano, & Giannakis, 2000; Gunasekaran, 2005) and books {Simchi-Levi, 2000 #6} in recent years. A supply chain is a collection of firms who, while maintaining local autonomy and decision-making capability, act jointly to fulfill customer requirements {Simchi-Levi, 2000 #6}.Yet the application of theory into practice of the healthcare supply chain is sparse.

Few have studied the components of operations management combined with decision science in this unique setting and there are great strides that could be made by sharing knowledge. For example, Tucker (2003) examined the impact of operational failures on hospital nurses and patients and found that failures occur with such regularity that they are "deemed inevitable". Her study notes that most operational failures are from breakdowns across organizational boundaries and that those most affected learn to compensate quickly for those failures, which may result in more organizational disconnects as the problem root cause is never discovered. Organizational behavior literature shows that organizational learning across systems is difficult, and it is nearly impossible when systemic problems are compensated for at difficult junctures by

[1] A group of researchers, cancer centers, and community doctors who are involved in studies of new cancer treatment, prevention, early detection, quality of life, and rehabilitation. Clinical trials carried out by cooperative groups are sponsored by NCI, and large numbers of patients take part in many locations. (www.cancer.gov)

different players, without the others knowledge of 1) a problem or 2) their decision's unintended consequences on other parts of the organization (Chinander & Schweitzer, 2003). As we will show, such problems are rampant in the clinical trial setting, much as it was in Tucker's hospital patient care setting.

## 6.3 STUDY SETTINGS

Healthcare is facing many of the challenges previously confronted by manufacturing. If one compares the development of semiconductor processes, chemical manufacturing processes, or any other generic manufacturing process, to that of the drug development process, one can easily see the similarities. While drugs are not being "assembled" per se, the processes required to "build" a successful drug, from laboratory to market, are analogous to those one would find in a classic job shop, new product development or supply chain management situation.

Rather than investigate all possible clinical trial types, we will focus on oncology clinical trials as a representative example. Cancer, one of the primary causes of death in America, has had a revolution in the number and types of drugs under development. From targeting cancerous cells directly, therapy has branched into targeting the "food supply", i.e., the blood supply to such cells. This has required the clinical evaluation of a host of additional therapeutics. Within the cancer clinical trials setting, the trials can be classified according to their purpose and development phase. For example, there are six primary types of clinical trials: 1) prevention trials, 2) screening trials, 3) diagnostic trials, 4) treatment trials, 5) quality of life trials, and 6) genetic studies; and four primary phases of human clinical trials: phases I, II, III and post market phase IV (NCI, 2003).

Our research setting focuses on the process of the largest and most complex types of clinical trials, that of phase III treatment clinical trials. “These (treatment) trials test many types of treatments, such as new drugs, vaccines, new approaches to surgery or radiation therapy, or new combinations of treatments (NCI, 2003)”. Phase III studies typically require more time and resources as well as patients.

Clinical Trials are conducted for many diseases and diagnoses in numerous organizational structures, including both private and government settings. We limit our research study population to cancer clinical trials in two specific government funded settings within the National Institutes of Health (NIH)’s National Cancer Institute (NCI): cooperative oncology groups and comprehensive cancer centers. There are two reasons for this choice. First, most Phase III clinical trials are government sponsored to a certain extent, so the two sites can be considered representative of oncology clinical trials sites. Second, phase III trials are the most complex, hence they will better show the potential areas of application of OM techniques in the healthcare supply chain. Because the infrastructure of the oncology clinical trial development is intricate and overlapping, we begin by discussing each of the major partners in the supply chain.

### 6.3.1 Supply Chain Partners: NIH, NCI, CTEP, CTCGs, CCCs, and Pharmaceutical/ Biotechnology Firms

The National Institutes of Health (NIH) is one of eight divisions in the Public Health Services, which is part of the Department of Health and Human Services of the Federal government (National_Institutes_of_Health, 2007). Their mission is to foster and provide medical and behavioral research to the nation. Currently, the NIH invests nearly $30 billion per year in medical research in the United States. While most of the institutes

and centers budget appropriations are scheduled to increase, one institution, the National Cancer Institute (NCI) projected 2008 budget is projected to decrease $9 million (National_Institutes_of_Health, 2007).

The NCI is the federal government's program responsible for conducting and supporting cancer research and training. Its vision is to have "a nation free from the suffering and death due to cancer by 2015 with dramatic reductions in cancer incidence"(NCI). Supporting more than 1300 clinical trials a year and aiding more than 200,000 patients, the NCI is organized is pervasive throughout the nation. With this amount research being conducted, it is important that coordination takes place and this is one of the primary mandates of the Cancer Therapy Evaluation Program (CTEP), which attempts to forge broad collaborations within the research community and works extensively with the pharmaceutical/biotechnology industry to effectively develop new cancer treatments (CTEP, 2006).

Although various groups and organizations, both for-profit as well as non-profit, may develop and sponsor clinical trials, two key groups who conduct clinical trials are: 1) Clinical Trials Cooperative Groups (CTCGs) and 2) Comprehensive Cancer Centers (CCCs), both sponsored by the NCI. Clinical Trials Cooperative Groups include researchers, cancer centers, and community physicians throughout the United States, Canada and Europe. CTCGs involve more than 1,700 institutions, enrolling more than 22,000 new patients each year (National_Cancer_Institute, 2007) This consortia of members allows CTCGs group studies to reach a larger patient population to enroll in cancer treatment clinical trials and they have been pivotal in completing Phase III trials (Comis, 1998).

The NCI also sponsors clinical research through approximately 60 cancer research institutions and 39 Comprehensive Cancer Centers (CCCs) located across the United States (NCI, 2006). Comprehensive Cancer Centers are those organizations that have proven to successfully initiate and conduct innovative trials and participate in CTCG trials. Selection as a NCI-designated comprehensive cancer center requires rigorous qualifications with the center integrating basic laboratory research, clinical research and public prevention and they are known as the elite of their specialties. In addition to the NCI-sponsored studies, CCCs also support and conduct clinical trials internally initiated by their own physician researchers and those sponsored by the pharmaceutical/biotechnology industries. All NCI funded studies at CCCs as well as at the CTCG group level must be approved through Cancer Therapy Evaluation Program (CTEP).

In addition to governmental support, pharmaceutical and biotechnology firms also conduct a significant number of oncology clinical trials, and the pace is increasing. For example, more than 100 claims approved for oncology treatment indications in 1990s far exceeded the total of those granted in the proceeding 40 years and the growth rate in FDA-approved investigational new drug studies for all phases has increased from 3,900 in 2001 to 4,500 in 2003 (Rothenberg, Carbone, & Johnson, 2003).

With such rapid growth and a wide variety of groups and organizations involved in oncology research, there is a wealth of potential applications for OM research application. We initially selected a comprehensive cancer center for the focus for data collection. However, additional funding allowed us to expand our data collection to include one major clinical trial cooperative group. While the results discussed in the

article are only for those two sites, we have also studied two additional CCCs and one additional CTCG. Those results are consistent with the data presented here.

### 6.3.2 The Clinical Trial Cooperative Group and the Comprehensive Cancer Center

The studied CTCG is a national clinical research group with its central office in the Midwest and its Statistical Center in the South. Since its founding, it has grown into a national network of nearly 30 university medical centers, over 200 community hospitals, and over 3,000 oncology specialists. It has been among the leaders in designing studies specifically for the elderly, studies that concern quality of life in cancer patients, and in introducing novel therapies and treatment approaches for patients with poor prognoses.

The investigated comprehensive cancer center is the only one in its state and is consistently recognized among the nation's leading centers for excellence in compassionate, individualized cancer treatment. It has nearly 300 investigators in seven research programs, with more than $150 million in annual research funding. There are on average 200 clinical trials ongoing or open to accrual at any given time. Finally, it is among the top ten in competitively awarded NCI grant support.

## 6.4 DATA COLLECTION

All clinical trials conducted between the years 2002 and 2005 inclusive were reviewed at both the clinical trial cooperative group and the comprehensive cancer center. Following Yin's (2003) case study methodology principles, an interdisciplinary team of experts from schools of medicine, engineering and management collected data from multiple sources through: 1) extensive staff personnel interviews, 2) analysis of existing

process documentation and records, 3) archival analysis of clinical trial initiation data, and 4) electronic mail and database records. Personal interviews permitted questions targeting the research objectives of identifying processes and barriers to the opening of clinical trials. Objective data collection for the identified sources were chosen because a) such documentation was broad and permitted multiple time frames, settings and events, and b) archival records are precise, quantitative and have less reporting and selectivity biases than documentation (Yin, 2003). One of the interesting findings we discovered in such a triangulation methodology was that there were inconsistencies between what was said was being done in the interviews, what the policies and procedures documentation said should be done, and what the clinical trial record review showed was actually done. Use of this three part methodology, implemented at both the CTCG and the CCC, resulted in capturing a complete understanding of the development of the process structure of the two organizations, and documenting an accurate reflective process map and data timing analysis. This research had two primary outcomes: a) process mapping and b) timing analysis.

### 6.4.1 Process Mapping

The first part of data collection was to identify and map existing process steps required to open an oncology clinical trial at both study settings. The conversion of the organizational tacit knowledge into a graphical representation resulted in the process map, that is, a graphical representation of the flow of inputs, resources, steps and processes required to create an output, and in this case to activate a study (Harrington, 1991). These data were collected by means of more than 30 initial onsite personnel interviews, additional follow-up e-mail correspondence, and a series of at least two

clarification teleconferences, with members of the cooperative group and the comprehensive cancer center. At least two additional onsite clarification interview sessions were conducted at each site prior to the final results presentation. It is important to note that the data from the two research sites were collected separately and remained confidential.

### 6.4.2 Timing Analysis

Once the process map was complete and verified as accurate, the calendar time needed for each of the major process steps required to activate a study was collected. These archival data were compiled by scanning more than four hundred historical e-mail correspondences per study, 15 file reviews, and a database of 268 clinical trial records. By conducting both the process and the timing of each process, the understanding of the yield variation will allow effective strategies for process and productivity improvements (Bohn, 1995; Sinha & Field, 2005).

Study selection criteria for detailed analysis included all Phase I, II, and III studies opened and completed within the last five years. Within the Comprehensive Cancer Center study section, clinical trial selection for this study included not only those studies, which originated in a cooperative group, but also, industry sponsored trials, as well as those trials initiated at the comprehensive cancer center by their clinical investigators.

There were multiple cross checks of steps and timing at different organization hierarchy levels. The interviews were conducted in both individual and group settings with the input remaining anonymous. The interview process included both open-ended

and close- ended questions. Upon completion, the interviewees were requested to clarify specific acronyms, decision point names, position titles and responsibilities. Objective data stored in databases or e-mails were crosschecked wherever possible with other, independent records.

## 6.5 RESULTS

### 6.5.1 Initial Observations

The clinical trials development process is different for the CTCG and the CCC, although they both have five main categories of processes. For the cooperative group, the five primary steps are: (1) initial concept development and approval, (2) protocol development, (3) CTEP approval, (4) Centralized Institutional Review board (CIRB) review, and (5) study activation (See Figure 6-1). For the Comprehensive Cancer Center, the processes are subdivided into five sections as well: (1) Initial Preparation (2) Approval Process (3) CTEP approval Process, (4) Budgeting and (5) Final Preparation (See Figure 6-1). For studies utilizing federal funds, they are evaluated by CTEP; hence, all CTCG studies must pass through CTEP process for concept (initial study idea), protocol review, and forms review; only those comprehensive cancer studies funded by NCI require CTEP approval.

Each of these phases for both organizations can be treated as individual tasks in the healthcare supply chain. In this supply chain, there are a greater than 27 different types of participants for the CCC and greater than 30 different types of participants for the CTCG (See Table 6-1). The number of processing steps are >110 and >370 for the

CCC and CTCG respectively. The number of decision points in the CTCG is >40, and the number of places in the process where a trial could loop for rework is nearly 30.

Because of the host of issues or barriers encountered, we have classified them into three categories: 1) procedural (policy differences), 2) structural (process differences), and 3) infrastructural (incompatibility of the support structures). Each is defined and discussed below.

Procedural barriers are policies, either formal or informal, that arise from the processes required to activate a study and that may inhibit problem-solving actions. For example, a procedural barrier occurs when, after a concept is approved by CTCG, the concept must then be reviewed by an outside agency (CTEP) before additional work can be done on the concept development. Such procedural issues are prevalent and occur throughout the development process occurring both internally and at the external interface with other supply chain members.

Structural barriers are created when different participants in the process follow a different ordering of steps, which can lead to miscommunication and confusion. An example of this barrier is a circular mismatch loop that arises because of multiple participants in the process. For example, a pharmaceutical sponsor may require information that can only be provided by the CTCG or CCC, who, however, will only supply the necessary information after the sponsor agrees to some condition. This can lead to a “Catch-22” situation: one group cannot collect the required information until they approve a condition, but they will not approve the condition without the information.

Infrastructural barriers concern how the underlying system is designed and how it supports the interconnection of various aspects of the systems. For example, we discovered that there were over seven different numbering systems used to track the progress of a clinical trial through a CCC by different functional areas, yet there was no master cross listing of identifying numbers. This is equivalent to a having seven different part numbers for the same part, with no mapping among the numbers.

Integration in the supply chain is important for reducing the amount of each of these barriers that are present in the clinical trial development process. Both sites studied exhibited characteristics of supply chain inefficiencies as identified in past supply chain literature. We will utilize supply chain theories as they apply to the healthcare supply chain and identify potential opportunities to improve the overall performance throughout the system.

### 6.5.2 Issues in Health Care Supply Chain Management

Before turning to supply chain issues in our research settings, we will briefly review applicable supply chain research. Supply chain management centers around the integrative coordination of material and information flow among various organizations involved with the process of producing a specific good or service {Chopra, 2003 #82; Simchi-Levi, 2000 #81}. Successful supply chain management requires the integration of processes from sourcing, to manufacturing, and to distribution across the entire chain (Maloni & Benton, 2000; Cooper, Edgett, & Kleinschmidt, 2001; Chopra & Meindl, 2003). Supply chains have become increasing complex as products and services expand in complexity to meet ever-higher customer expectations (Berry & Parasuram, 1991). Strategies for coordination across functions and across organizations have typically

assumed that some kind of centralization power is required in order to retain control of the chain (Maloni & Benton, 2000). Such supply chains tended to create oligopolistic environments, which relied on authoritative power in order to distribute of responsibilities across the suppliers (Maloni & Benton, 2000).

In the healthcare supply chain, because power is distributed across multiple participants, coordination and integration issues are significantly more problematic. While the overall process of developing a clinical trial utilize a similar set of processes, the participants in the supply chain are decentralized, locally autonomous, and they may be under different loci of control. Such fragmentation as well as the decentralization of decision-making makes it difficult for any single organization to dominate the actions of others(Burns, 2002). In clinical trials developed through the CTCG or the CCC, the supply chain is composed of various organizations including, but not limited to the industrial sponsor, the NCI, and the FDA. Each these organizations have similar but different objectives and requirements when developing a clinical trial. Additionally, each organization is composed of semi-autonomous internal groups. Specifically in the comprehensive cancer centers, the organization itself may fall under the umbrella of a cancer hospital, a general hospital or a major academic medial center, thus, the manager of the clinical trial supply chain must interface with various groups or departments, such as the Scientific Review Committee (SRC), Institutional Review Board (IRB), office of technology licensing, budgeting, and contracts & grants management. While none of these participants are solely dependent upon another for survival, the rapid development and successful completion of a clinical trial is crucial to the mission of each of committees or groups.

### 6.5.3 Change Management: Procedural Barriers In The CTCG Supply Chain

Changing customer demands and market conditions cause downstream disruptions in the supply chain, which results in an undesirable consequence to upstream suppliers (Magretta, 1998; Johansen, Comstock, & Winroth, 2005). This often-observed bullwhip effect occurs when the demand distortion causes large variations and propagates in an amplified form throughout the entire supply chain (Lee & Yano, 1988). Improving communication and coordination among all the participants of the supply chain has been suggested in order to avoid supply chain disruptions from this effect. Changes in customer demands and requirements can also result in design changes or rework (Love, Li, & Mandal, 1999). The additional rework has undesirable efforts in terms of total project costs, schedule delays, and quality of the product {Davis, 1989 #79}. In some instances, changes to the original design of a product results in the complexities outweighing the opportunities to maximize improvements (Mandal, Sinha, & Wright, 1997). Such changing demands and requirements can result in a *procedural* barrier in a supply chain where there is a conflict in decision- making between producing products on schedule to satisfy demand and the decision to change the product or service in the supply chain to meet new customer requirements (Naylor, Naim, & Berry, 1999).

In the clinical trial supply chain, there is a constant temptation to continually change the trial to meet the specific needs or condition for the various stakeholders. One primary stakeholder in the clinical trial supply chain is the principle investigator (PI), i.e., the researcher who initiates the study concept. However, while the PI may initiate the study concept, changes to the idea by any of the other stakeholders can occur at nearly any point of the clinical trial development supply chain.

One specific decision-based procedural barrier that plagues the clinical trial development process is the impact of the inclusion of modestly value-added modifications to the protocol. Such modifications, through the act of "tinkering", are defined as those changes that do not directly affect the safety of the patients on the study or significantly increase its scientific merit. For example, the addition of correlative studies, which focus on answering a secondary research questions but conducted in conjunction with the primary clinical trial, are often requested during the late stages of the development process. This creates additional barriers to the timely opening of the study, as the entire protocol may need to be re-reviewed by all stakeholders. While the inclusion of additional correlative studies may prove to be beneficial to the overall scientific body of knowledge, the delay in opening the primary clinical trial can diminish its overall performance as well as prohibit potential patients from benefiting from the most recent treatment options. It has also been estimated that are major financial implications where every day there is a delay to market the costs to the pharmaceutical manufacture averages $1.3M (Bodenheimer, 2000). Such tinkering is analogous to adding a minor feature to an automobile which is planned to be introduced within the next week, where it is estimated that for every day of delay of introducing a new product model results in a $1 million loss in profit {Clark, 1989 #81}. While the addition of these features can be of value, adding the new feature during the late stages of the development process will cause subsequent delay to market entrance and hence loss in potential profit. By allowing such decisions throughout the clinical trial development, the supply chain can be continuously disrupted, resulting in overall inefficiencies.

### 6.5.4 Transaction Costs: Procedural Barriers In The CCC Supply Chain

Policies outlining the standardization across the supply chain have been used to prevent procedural barriers from entering the system. Standardization allows a common shared mechanism to orchestrate transactions (Thompson, 1967). One acknowledged form of standardization is the process of conducting financial exchanges (Domowitz, 1995; Economides, 1999). Specifically, in manufacturing, contracts and negotiation rules are standardized in order to decrease the overall cost of trade among the different suppliers. Blanket contracts and purchase orders are one method of reducing the amount of transaction costs from financial negotiations. By creating blanket agreements, an initial purchase-order goes through an approval process by both parties. Any subsequent orders or agreements are then conducted under the pre-approved purchase-order thereby saving time and cost. Blanket agreements avoid the administrative expense of processing multiple agreements while also streamlining transactions between suppliers. The creation of blanket agreements, if initiated properly, allows procedural barriers to be reduced and non-essential steps to be removed from the supply chain process.

Organizations that are involved in the clinical trials development supply chain also conduct blanket agreements between the different suppliers, which are referred to as master agreements. While this step is conducted in order to decrease the time required for completing various components of the clinical trial, these benefits were not observed through the comprehensive cancer center studied. Procedural barriers were created when the different participants of the supply chain did not follow the processes and policies that were defined by the master agreement. For example, it was common for sponsors to resubmit different contracts when requesting a clinical trial, ignoring existing master

agreement. What this meant is that each contract had to be inspected to verify that it was consistent with the master agreement. Hence, any labor or time saving was negated by the need to inspect every agreement. This is similar to a manufacturing organization, which pre-qualifies vendors for quality but still does a 100% inspection of any part sent by that supplier.

### 6.5.5 Long-Term Supplier Relationships: Structural Barriers In The CTCG Supply Chain

Supply chain management has shown the effectiveness of a long-term perspective in order to increase the predictability of supply and demand. For example, it has been shown in the US auto industry that the selection of the supplier through cooperative long-term relationships is a strategic decision that provides a competitive advantage (Choi & Hartley, 1996). Choi and Hartley's research found the importance of consistency above all other factors in supplier selection. These long-term relationships with suppliers are vital throughout the supply chain, but as the dissolving of the Firestone and Ford relationship exhibits, the continued cooperation and collaboration is difficult to maintain. Often times, conflicts in the supply chain arise among participants that stems from the incompatibility and unclear roles between suppliers (Heide, 1994). Changing objectives can dramatically change the supply chain environments (Macneil, 1980; Heide & John, 1990). Because dissonance between suppliers is formed when cooperative behaviors are diminished, participants in the supply chain may cause structural barriers, such as following different ordering of steps or prompting inconsistencies throughout the processes. Structural barriers may also form unknowingly between participants in the supply chain because the two systems do not coincide with the needs of the other, for example, if the customer relationship management system of the supplier is not

compatible with the supply chain management system of the purchaser. Supply chain management literature has shown that reducing the number of suppliers and participants in the system, and working more intensively with those remaining suppliers to establish a long-term relationship may help avoid or minimize structural barriers in the supply chain (Cox, 1999).

The same principles and observations can also be applied to the healthcare supply chain. Specifically in the development of clinical trials, our results revealed that the time to complete the development of the clinical trial was impacted greatly by the specific participants involved. With more than 27 different types of groups or participants involved in developing a clinical trial, the number of different combinations of types of groups caused high variances in the processes and sequencing in the supply chain. Each type of participant involved in clinical trial development, such as the specific corporate sponsor's lawyer, followed different process steps. Hence, the supply chain must continuously adapt its steps according to which participant is involved, and at what decision point in the development of the clinical trial they become involved. Such is the case with coordination between a cooperative group and the CTEP. CTEP has the responsibility of reviewing the clinical trial for scientific merit, safety, and feasibility. Additionally, as each of the major trial components, such as the protocol is completed, CTEP must review the contents and may request modifications or rework, prior to its approval. Structural barriers arise because often a different CTEP reviewer is assigned, and not the original reviewer, to evaluate the resubmission of the clinical trial protocol addressing the issues identified by original CTEP reviewer. Consequently, reviewer preferences and experiences may lead to a conflict in the changes resulting in multiple

loops throughout the system. Furthermore, the original suggestions on how to resolve specific issues may be lost because of the changing participants.

### 6.5.6 Roles In The Clinical Trial Supply Chain: Structural Barriers In The CCC

The successful defining of roles and relationship among the supply chain participants are important to create an effective supply chain. By having defined relationships that integrate the supply chain, redundancy and the overlap of similar processes across the supply chain can be avoided (Lassar & Zinn, 1995). Overlapping processes often occur when supply chain participants are operating in multiple supply networks and such an overlap can lead to scope-creep, where the participant extends beyond the boundaries of their mandate. For example, many aeronautical firms are involved in producing products for both commercial and defense applications, hence product designers may make design decisions in order to capture synergies between the two supply chains, even though their mandate is to design parts for one system only. Such decisions may make the parts for the commercial aircraft significantly more expensive or the parts for the military less likely to achieve desired performance specifications.

Conflicts between the roles and scope-creep have been shown within the clinical trial supply chain for CCC studies. A clinical trial must receive approvals from the external agency (FDA) and the internal agency (IRB), prior to opening the study for patient accrual. The FDA has the primary role to ensure internal study validity and enable the generation of scientifically relevant results, while the IRB must determine if a particular study attains a minimal requirement for ethical conduct of research and patient safety. Conflict in decision approval of the IRB and FDA approval arises due to the

inconsistency created between scientific merit and patient safety (Mann, 2002). Often times, these two aspects of the clinical trial are interdependent and require mutual coordination between the two agents in the supply chain. The process of development a clinical trial is plagued with seemingly endless loops between multiple disagreeing parties, from the smaller departments of regulatory and the principle investigator, to the larger review boards such as the IRB and the FDA review. Towill (1996) suggests that supply chain processes can be greatly improved by simplifying the scope of decision-making of each supplier and eliminating excess procedures, which may create miscommunications. This conflict of the scope of the decision could benefit from the better communication between the two agents within the supply chain (Love et al., 1999).

### 6.5.7 Coordination Of Process Improvement: Infrastructural Barriers in the CTCG Supply Chain

Supply chain management requires continued process improvement in order to keep up with the changing dynamics of the market. Changes in the environment and the need to be more efficient due to limited resources, require an in-depth analysis of the underlying design of the supply chain (Beamon, 1998). Supply chain management has long stressed the need for collaboration among all participants in order to better satisfy customer demands and requirements (Ellram, 1990; Towill, 1996).One method of developing greater knowledge of issues with supply chain performance and interrelated interactions of suppliers is to use simulation techniques(Swaminathan, Smith, & Sadeh, 1998). Such techniques have been used to examine the impact of specific decisions on the entire system as well as to examine the performance and effectiveness supply chain reengineering (Frank, Drezner, Ryan, & Simchi-Levi, 2000).. In order to produce effective results across the entire supply chain, organizations must not only be efficient

internally, but must also maintain seamless processes across the entire supply chain (Towill, 1996). Because infrastructural barriers arise when the coordination is diminished, the performance of the highly integrated network of participants and stakeholders also is reduced. Improving processes within each individual supply chain participant is not sufficient; the interconnects throughout the entire system have been found to be critical in order to show overall improvements (Barbuceanu, Gray, & Mankovski, 1999).

For the clinical trial supply chain, we completed simulations on the healthcare supply chain. Through simulation depicting a dramatic reduction of processing time within the cooperative group, we observed only a decrease of 6.78% in time in the development of a clinical trial. In order to achieve the level of improvements sought, we discovered that joint improvements between both the internal processes and external organizations were required. Specifically, when the interfaces between CTEP, CIRB, and the Cooperative Group were accounted for there was a significant impact in reducing the time to develop a clinical trial: we observed an overall improvement of 39.27% with respect to the time required to opening a trial (Working Paper).

### 6.5.8 Standardization: Infrastructural Barriers In The CCC Supply Chain

Supply chain literature has shown that complications in planning and control of production are common across multiple suppliers (Chen, 2002). Each firm has individual information on the progress of the supply chain from a single unifocal perspective. This information can either be shared to gain cooperation of other suppliers or hidden in order to gain a strategic advantage (Gavirneni, Kapuscinski, & Tayur, 1999; Lee, So, & Tang, 2000). Not surprisingly, supply chains are shown to be most effective when its supply

chain participants cooperate (Ellram, 1990). For example, transaction costs are lower among all the participants in the supply chain when there is a policy in place to share full information (Cachon & Fisher, 2000). Included in cooperation is the transparency of product tracking so that participants in the supply chain have the ability to predict demand (Schary & Skjett-Larsen, 2001). One supply chain example of this is in the international flow of cargo, which requires both domestic and multi-national trucking, air transportation, and freight forwarding. It is only through the ability to share information using common standards of progress tracking can logistics optimization be conducted and transaction costs be reduced throughout the entire chain.

Interestingly, in oncology clinical trials, there is no such transparency in tracking individual trials. Our study of a comprehensive cancer center found that the tracking of a single clinical trial was being conducted based upon organizational divisions of each component rather than by the entire clinical trial itself. This resulted in seven different identifiers in seven different progress-monitoring databases. As one clinical trial had no less than seven different numbers assigned as a reference number for the various groups within the process, this lack of standardization could contribute to confusion when one department is contacting another department concerning study status as well dictate repetitive tasks (Burns, 2002). There is limited visibility into the entire process spanning across organizations; therefore the lack of communication when developing an individual clinical trial is apparent at many steps. Additionally, misinformed decisions made pertaining to the development of the clinical trial were being made because the lack of communication and information of other components.

## 6.6 CONCLUSIONS

Throughout this paper, we have illuminated numerous barriers in the clinical trials process and how they are similar or unique to those found in non-healthcare supply chains. In this conclusion section, we will concentrate on the implications of our research on the two primary study sites: the clinical trial cooperative group and the comprehensive cancer center. Additionally, we make recommendations toward how to overcome the identified barriers using supply chain theory (see Table 6-2).

### 6.6.1 To The Clinical Trial Cooperative Group

Unlike comprehensive cancer centers where the majority of barriers are internal, cooperative groups are challenged with more external barriers as they must satisfy and coordinate multiple primary external stakeholders, including governmental agencies (NCI, CTEP, CIRB, and FDA), multiple member academic medical centers (AMCs), and industry sponsors. External barriers present the additional challenges of lack of control and the inability to enforce certain decisions or protocol changes. Each of the above listed groups has the power to submit changes to a protocol at any point in time. For example, the Cancer Therapy Evaluation Program (CTEP) of the NCI must approve all cooperative groups studies. This government-sponsored program has series of checks and balances, which include approving an initial concept before the submission of a protocol, approval of specific forms to complete for the protocol, and review by the Centralized Institutional Review Board (CIRB). Even though a concept has been CTEP approved, the protocol often requires multiple iterations between CTEP and the CTCG and this does not guarantee that the ensuing protocol will receive approval. Such iterative processes occur with each of the supply chain members listed above.

Because of all these simultaneous iterations by the various supply chain members, it requires more than two years for a study concept to transition thought the development phase. During this time, the environment may change, with another drug with similar properties receiving a patent or receiving FDA approval. This is similar to the automotive industry where a new automotive design can take significantly more to develop a new car than the pace of market change. An example of this, is the multiple models of SUVs produced in the early years of the 21st century, while the subsequent demand dramatically decreased due to the consumer demand for more economy friendly vehicle; resulting in billions of dollars in revenue lost by all three of the major U.S. automobile manufacturers. Contrast this with Toyota's performance and its well-known reputation for rapid product development and supply chain excellence. What will happen to those clinical trials cooperative groups who are unable to timely adapt their supply chain to the rapidly changing nature of science and the market?

Another major barrier faced by CTCGs that they have a highly fragmented group of suppliers. For example, most study developers, known as principle investigators, are employed at academic medical centers and they volunteer their time to assist in creation of the clinical trial. As such, they are both fragmented physically (as they are in different geographic locations) and operationally (as they are controlled by different groups). Making the process even more difficult to coordinate is that the CTCG headquarters is sometimes located in a different location than the regulatory and statistics offices, and none of the cooperative groups are located in Bethesda, MD, where CTEP is located. The use of virtual co-location, as used by Boeing Rocketdyne, could assist in minimizing some of the communication disconnects and fragmentation of decentralization (Burns,

2002). In the study, the virtual organizations within Rocketdyne could observe the progress and stages of other departments located in another physical area. Similarly, as much of protocol writing relies on information from other departments, utilizing a computer infrastructure that permits collaborative access to track the protocol's development process could dramatically assist the individual teams in planning and completing their portions of the protocol as well as provide a means of accountability for timely section completion.

Another procedural barrier that the CTCG faces is that, due to the voluntary nature of their members coupled with their need for government approval, they often accept late stage changes after receiving initial CTEP or IRB approval. Examples of this include the adding of an additional "arm" or indication for a study or adding a correlative study to the original protocols. These late stage additions may require the protocol to cycle through the CTEP and IRB approval steps at least one additional time. As literature notes "everything that happens to a product (process) as it moves through the (supply) chain either adds cost or reduces costs. It either adds value or reduces value" (Burns, 2002). While these late stage changes may be beneficial, the CTCG should initiate a policy requiring that changes are requested in a timely manner, i.e., at the less costly early stages of development.

Unlike comprehensive cancer centers, who may receive financial support from multiple areas, CTCGs rely primarily on support from the National Cancer Institute and such funding is becoming more difficult to secure, as the National Cancer Institute is one of only two sectors of the National Institutes of Health expected to experience a decrease in its budget. Similar to the funding decreases experienced by Airbus, CTCGs must show

that they are utilizing the funds appropriately and efficiently; sometimes this should mean "cutting their losses" on a study and devoting their resources elsewhere, something that our data show cooperative groups rarely do. While these financial concerns are abound, until recently, the healthcare industry appears to have focused only on the downstream supply costs (i.e., direct patient cost), while ignoring the supply chain upstream costs(Burns, 2002). This leaves a great deal of room for application of OM techniques to overcome the barriers identified in this paper.

Expanding beyond the view of a clinical trial as part of a supply chain, it is also possible to view the clinical trial process as a serial new product development (NPD) process. NPD structural and infrastructural barriers are evident with the cooperative group's limited use of modularity design and portfolio management. Within the cooperative group setting are disease-based divisions, each of whom individually bases its request for protocol approval only on its existing pool of potential projects and it disregards the number of overall submissions or other division's submission requests. Each group submits as many proposals as it wishes without an imposed limit or prioritization list. By enlisting portfolio management techniques and requiring the disease team chairs to submit a prioritization list, the cooperative group can then form a better portfolio of the potential protocols within each disease group. This is currently being experimented with at the CTCG.

### 6.6.2 To The Comprehensive Cancer Centers

A comprehensive cancer center's most frequently encountered barrier is the multiple departments, itinerations and loops that a concept and protocol must go through prior to receiving final approval. As each department, such as regulatory affairs, has its

own set of requirements and identification codes, it is difficult in the extreme to track the progress of the trial from one department to another. Also, many of the process steps are completed in functional silos, and we discovered that many steps are repetitive and filled with time- consuming revisions. There is a pool of clinical trials underdevelopment at any one time and each major processing group is allowed to set its own priority for selecting a study to work on from this pool. This situation is analogous to the automotive manufacturer OEM supplying the parts for a truck while the assembly line is being set-up for a luxury car, while the marketing department has promised the release of a new hybrid. Similarly, in clinical trials development, the regulatory department may have its own imposed deadlines for particular studies or practicing firefighting with another clinical trial that has been opened but is encountering problems. Simultaneously, the contracts and budgets groups may be unaware of the progress (or lack thereof) of the regulatory group, and be vigorously pursuing a different path. Interestingly, both groups must come together for Institutional Review Board (IRB) submission, who, in turn, has its own unique, stringent requirements, timeline of submissions, and schedule of meetings.

Venturing beyond supply chains, the lessons learned from the job shop literature indicate that use of cellular teams may be an alternative to the comprehensive cancer centers functional silo set up (Hyer & Wemmerlov, 2002). The use of cellular teams may assist in reducing communication gaps between the involved departments as well as reduce the number of iterations required as each group is represented during meetings so that the changes to the protocol are made earlier in the process, leaving only minor

changes in the late stages of the clinical trial submission. As is well known, changes early in the development process tend to be less costly and less time consuming.

Comprehensive cancer centers are also faced with the daunting task of completing the requirements of opening numerous types of cancer studies by different financial sponsors, such as the government, internal institutional support, or pharmaceutical/ biotechnology industry. Surprisingly, the steps and order of the steps are different depending upon where the study originates (i.e., government, internal or industry) and, because of this, CCC often approach each study as if it were a radical innovation. However, our data show that most studies are actually incremental studies based on a previous Phase I or II investigation. For example, a prior clinical trial may focus on the drug efficacy and safety aspects, but not consider the patient's quality of life and the new proposed study's goal could be to assess the patient's quality of life. Another example is using an established a clinical treatment for different disease indication, e.g., using Bevacizumab for prostate cancer instead of lung cancer. Instead of using previous study design knowledge, the investigator and clinical trials department redo all the steps required for a new protocol, including such tasks as: determining drug dosage and side effects, and developing a completely new protocol template. These steps are redundant and consume valuable time in the process, as a "new" protocol requires more checks and balances than incremental protocol amendments.

One opportunity for improvement is the potential for use of modularity in protocol design and development. Because studies can originate from three different sources (government, internal or industry) with each having a different approval process, the standardization of any steps may shorten the process. For example, the use of the

USB interface standard allows for a wide variety of peripherals created by a wide variety of manufacturers. The standardization of protocol templates and department submission forms would dramatically reduce the amount of with repetitive information required by the various stakeholders.

### 6.6.3 The Potential for Operations Management Lessons from Clinical Trial Development

The synergies between clinical trials and manufacturing research are not one-sided. Lessons and observations from investigation the clinical trials development process and the healthcare supply chain can foster additional rigorous research in topics of direct interest to operations management researchers.

One particular instance that was found to be prevalent in our study was that both research sites had designed only one internal formal decision point to stop the clinical trials development process; although other members of the supply chain could halt its development. This process remained constant even for a study that was known to have major flaws and showed signs of failure, thus consuming resources that could have been utilized more effectively if devoted to studies that were more promising. Such application could have been applied to the FBI information management system, known as the Virtual Case File, a project that was intended to replace outdated technology in the wake of 9/11. It was canceled in 2005 at the cost of $104 million after achieving none of its original goals. Disturbingly, the project began showing signs of failure as early as 2003 (Paltrow, 2005). The decision to terminate the project in earlier stages of development could have benefited other projects, including the current project, the Sentinel project, which is now underway as a solution to the aforementioned failed

project. This failure to terminate in highly diverse settings of clinical trials and FBI IT points to a significant underlying operations system problem that deserves further investigation.

As with many development processes, the clinical trials development process has a degree of sunk cost bias, which assumes that once a trial idea enters the system it should continue development because of the work already spent on its development (Kahneman & Tversky, 1979). This bias, coupled with the internal organizational loyalties' was stated by interviewees as contributing factors to the low cancellation rate. However, while these biases may be present, our findings indicate that even without these additional influences, the current process does not have the means to stop studies that progress passes the one potential stoppage point to another.

Our research has illustrated that there are supply chain techniques that can be applied to improve the clinical trials development process. This theoretical lens provides options to overcome the barriers of this lengthy, complex and onerous process. Whether addressing the procedural barriers of numerous internal and external loops, or the infrastructural barrier of the hazards of inconsistent protocol numbering or performance measures, each lesson from the manufacturing literature and industry provides an invaluable untapped resource.

We trust that our research in only the initial foray into the complexity of new drug and treatment development. As we have shown in this final section, there are other lenses from which to view new drug development process, including perceiving it as a serial new product development issue or as a potential application of job shop sequencing and

scheduling research. We will be utilizing these additional lenses in order to reduce the time from drug development at the bench to the patient bedside. With over 1.4 million new cancer diagnoses every year, it is imperative that we apply known solutions to this problem in healthcare.

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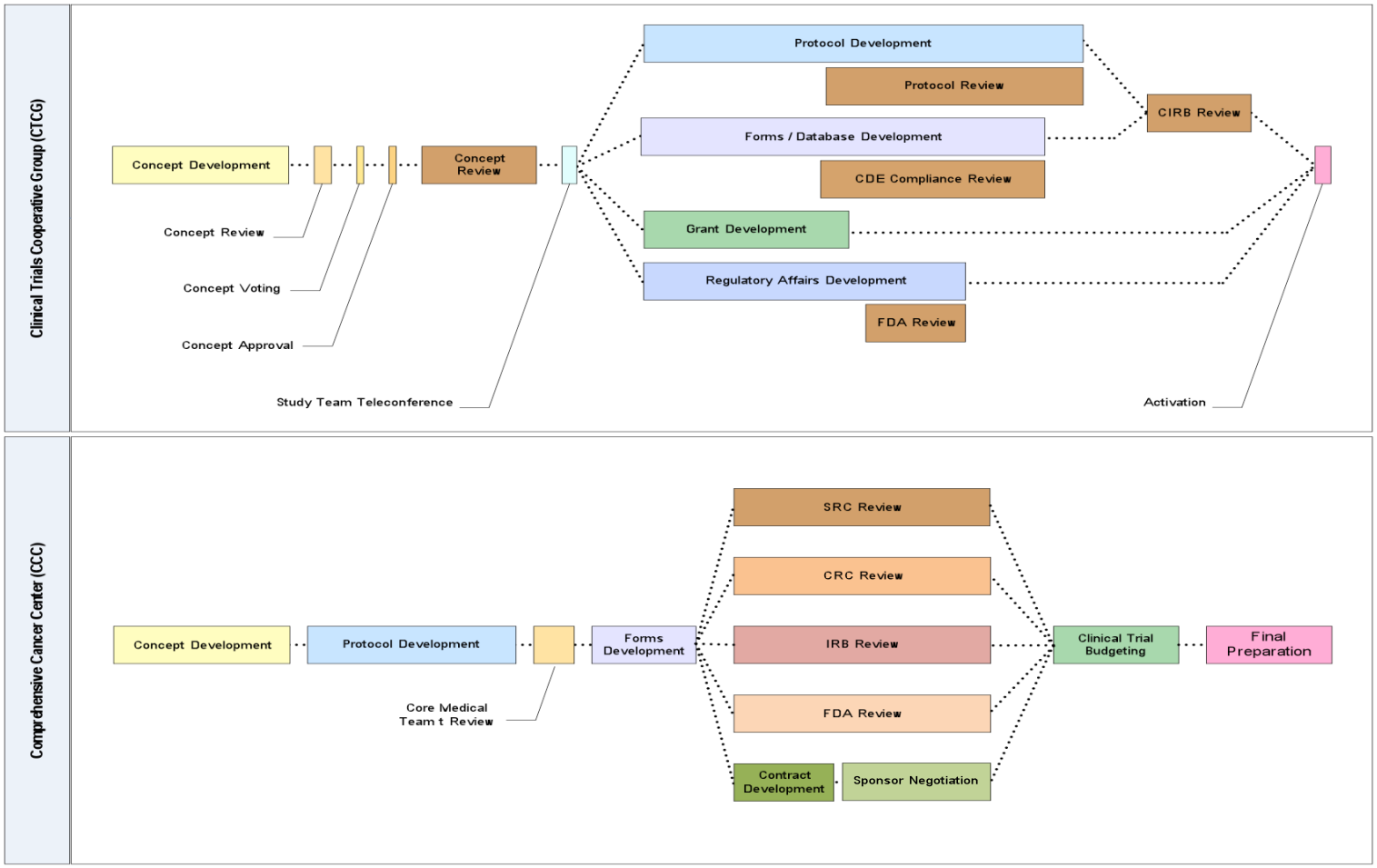


Figure 1. Level 0 process flow map for opening an oncology clinical trial at a Clinical Trials Cooperative Group and a Comprehensive Cancer Center. (As a result of printing restrictions, Figure 1 is a highly aggregated view of the process flow of opening a clinical trail. For a more comprehensive view, go to http://www.cmrhc.org/ClinicalTrialsProcess/ProcessMap.pdf to access the CCC Process Map and http://cmrhc.org/processmaps.htm to access the CTCG Process Map.) CDE, Common Data Elements; FDA, Food and Drug Administration; CIRB, Centeralized Institutional Review Board; SRC, Scientific Review Board; CRC, Clinical research center; IRB, Investigational Review Board;

**FIGURE 6-1: SUPPLY CHAIN NETWORK FOR THE CLINICAL TRIAL COOPERATIVE GROUP AND THE COMPREHENSIVE CANCER CENTER**

**TABLE 6-1: PROCESS AND TIMING DESCRIPTION FOR CLINICAL TRIAL DEVELOPMENT FOR CTCG AND CCC**

| | Number of Different Participants | Number of Function Steps | Decision Points | Median Time to Completion (Days*) | Range (Days*) |
|---|---|---|---|---|---|
| Clinical Trial Cooperative Groups | >30 | >370 | > 13 | 794 | 537 – 1130 |
| Comprehensive Cancer Centers | >27 | >110 | > 40 | 172 | 27 – 657 |

* Calendar Days

**TABLE 6-2: Application of Supply Chain Management Theories to the Health Care Supply Chain**

| | | Procedural Barriers<br>Policies either formal or informal, that arise from the processes required to activate a clinical trial and that may inhibit problem solving actions | Structural Barriers<br>Different participants in the process follow a different ordering of steps, which can lead to miscommunication and misunderstanding | Infrastructural Barriers<br>Underlying system design and interconnections of various system aspects which prevent coordination efforts |
|---|---|---|---|---|
| Supply Chain Management<br>a network of coordinated organizations and functions to transform ideas into clinical trials | Clinical Trial Cooperative Group | **CHANGE MANAGEMENT**:<br>Decisions should be made to prevent late-stage changes to the clinical trial which cause disruptions and delays throughout the supply chain | **LONG-TERM SUPPLIER RELATIONSHIPS:**<br>Consistent and long-term suppliers involved in the clinical trial development process will prevent miscommunication and misunderstanding between organizations | **PROCESS IMPROVEMENT COORDINATION:**<br>The impacts and effects downstream and upstream to the supply chain must be considered when conduction clinical trial supply chain optimization |
| | Comprehensive Cancer Center | **TRANSACTION COSTS:**<br>Decisions to prevent changes in blanket standard agreements should be enforced | **DEFINING ROLES:**<br>Consistent defining of stakeholder's roles allow the reduction of non-value added steps and process overlap throughout the supply chain | **STANDARDIZATION:**<br>Standardization of product tracking allow improved coordination efforts throughout all organizations |

**TABLE 6-3: APPLICATION OF MANAGEMENT THEORETICAL LENS TO THE HEALTH CARE SUPPLY CHAIN**

| | | Procedural Barriers<br>Policies either formal or informal, that arise from the processes required to activate a clinical trial and that may inhibit problem solving actions | Structural Barriers<br>Different participants in the process follow a different ordering of steps, which can lead to miscommunication and misunderstanding | Infrastructructural Barriers<br>Underlying system design and interconnections of various system aspects which prevent coordination efforts |
|---|---|---|---|---|
| Supply Chain Management a network of coordinated organizations and functions to transform ideas into clinical trials | Cooperative Group | Decisions should be made to prevent late-stage changes to the clinical trial which cause disruptions and delays throughout the supply chain | Consistent and long-term suppliers involved in the clinical trial development process will prevent misscomunication and misunderstanding between organizations | The impacts and effects downstream and upstream to the supply chain must be considered when conduction clinical trial supply chain optimization |
| | Comprehensive Cancer Center | Decisions to prevent changes in blanket standard agreements should be enforced | Consistent information flow between organizations allow the reduction of non-value added steps thoughout the supply chain | Standardization of product tracking allow improved coordination efforts throughout all organizations |
| New Product Development a complete processes of bringing a clinical trial concept to market | Cooperative Group | Designing various gates and stages through the clinical development process prevent potential clinical trial failures to continue | Standardization across modularity portions of the clinical trial development process provide consisent quality throughout the development | Portfolio management will ensure that feasible clinical trials will be developed that fit within the strategy of the organization |
| | Comprehensive Cancer Center | Evaluating all clinical trials to determine feasibility and organizational fit allows better resource allocation | Distinguishing between radical and incremental clinical trials will allow the proper developmental approach to be applied | Consistent performance measures across the clinical trials development process will allow uniform incentivization and goal alignment |
| Job Shop Scheduling an operational manufacturing of components of a clinical trial into a the final clinical trial | Cooperative Group | Policies enacting priorty dispatch scheduling rules must be uniform among all participants of the clinical trial job shop | Wasted resources to complete specific jobs for the clinical trial can be prevented by reducing the amount of work flow "spikes" caused by scheduling mismatch. | Understanding synchronicity of decisions and scheduling interactions allows better coordination throughout the dynamic clinical trials job shop |
| | Comprehensive Cancer Center | Reduction of unneccesary design of sequential job shop processes can improve the manufacturing time of a clinical trial | Batching decisions should only be conducted when system improvements through overall decrease in setup costs can be observed | Cellular organizational structures can add flixibility in the clinical trial job shop by improving coordination efforts across multiple systems |