EXPEDITED PROTOCOL DEVELOPMENT: BOON OR BANE?

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To my parents and brother, my inspiration to chase my dreams

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CHAPTER I

INTRODUCTION

Firefighting, defined as a situation where workers rush from task to task applying temporary solutions to problems without finding a final solution (Bohn, 2000) is the root cause of many problems across various industries; the problems range from unsatisfactory results in multi-agent projects (Hoopes, 2001), extreme resource crunches leading to commercial failure of most new product development activities (Cooper and Edgett, 2003), poor customer satisfaction in service industry (Young, Corsun, and Shinnar, 2004) and, at the extreme, to corporate downward spiral, failure and bankruptcy (Sudarsanam, and Lai, 2001).

Lack of a well planned strategy for resource allocation is a major trigger for firefighting (Atkinson, 2004), (Sudarsanam, and Lai, 2001), (Houlden, 1986), (Spoede, and Jacob, 2002), (Cooper, and Edgett, 2003), (Perlow, 1999). However, when plagued by lengthy development times, firms expedite jobs, resorting to ad hoc resource allocation (Terwiesch, Bohn, and Chea, 2001). Instead of decreasing the time to market, these well meaning efforts result in firefighting, causing major problems leading to the frequent failure of the development activity (Terwiesch, Bohn, and Chea, 2001), (Cooper and Edgett, 2003). Lengthy development times and the resulting high drug prices have troubled the pharmaceutical industry for a long time (Angell, 2000), (Keyhani, Diener-West, and Powe, 2005), (DiMasi, 2002), (Dickson and Gagnon, 2004). National Institutes of Health (NIH) efforts thus concentrate on shortening the drug development times in an

effort to develop cheaper drugs (DiMasi, 2002), (Dickson and Gagnon, 2004), (Angell, 2000). High priced drugs, like cancer drugs have been at the center of NIH efforts (Keyhani, Diener-West, and Powe, 2005), and expediting certain cancer drug development activities is a solution that is being tried to alleviate the problem of lengthy drug development activity (Keyhani, Diener-West, and Powe, 2005). However in other industries, expediting has a negative effect on the development system (Terwiesch, Bohn, and Chea, 2001), (Cooper and Edgett, 2003), (Hayes, 1981) resulting in a perpetual state of firefighting (Bohn, 2000).It would be interesting to see if it affects the productivity of the drug development process in a similar fashion.

Let us look at the drug development process in detail. The drug development process for any disease including cancer is divided into three major phases (See Figure 1).

First is the Preclinical Phase, where the compound is tested in vitro and then in vivo in laboratory animals to evaluate the toxic and pharmacological effects (US FDA, 1999). If the compound is found promising the investigator files an Investigational New Drug Application with the Food and Drug Administration (FDA) and, if FDA approves the application the investigator moves on to the Clinical Trials Phase (Dickson, and Gagnon, 2004). Clinical trials are conducted by cooperative groups, cancer centers, hospitals and local physician offices, and can be sponsored by National Cancer Institute (NCI), pharmaceutical companies or medical institutions (NCI Website, 2006). NCI is a leading sponsor of clinical trials for cancer drugs with over 1,500 NCI supported trials conducted annually in the United States (NCI Website, 2006). NCI can conduct these trials through

cooperative groups, cancer centers, clinical grants or clinical oncology programs; NCI conducts most of its clinical trials through cooperative clinical trials groups (NCI Website, 2006). Co-operative Groups are an affiliation of research institutes, and the researchers affiliated with a particular co-operative group jointly conduct the clinical trials in a multi-institutional setting (Ansher, and Scharf, 2001). The results of these studies are then collected and published by the co-operative Group (CALGB Website, 2006). The clinical trials phase can be divided into Phase I which involves testing of the new compound in healthy human subjects, Phase II to test the efficacy of the drug in a small number of patients and Phase III which is the safety and efficacy testing in a large patient population (Rogers, Gupta and Maranas, 2002). Before a NCI sponsored study idea can go into any one of these phases through a co-operative group, it has to be approved by various committees at the co-operative groups (CALGB Website, 2006). Every trial has a person in charge called the principal investigator (NCI Website, 2006). Once the study is approved, the principal investigator drafts the protocol with the help of statisticians, data coordinators and protocol editors (CALGB Website, 2006). Supply of drugs for the study, legal and regulatory issues are also taken care of by the employees of the co-operative group (See Appendix B).

The efforts to design a protocol are coordinated by protocol coordinators (See Appendix B). Most of the tasks involved in protocol development are highly specialized, and in depth knowledge of that particular disease and modality is required for it (See Appendix B). Hence employees in co-operative groups are assigned to a particular disease and modality and are involved in the development of only those protocols (See Appendix B).

Once the protocol draft is ready and has been reviewed internally by the co-operative group, it is sent to external NCI bodies for approval viz. Cancer Therapy Evaluation Program (CTEP) and Central Institutional Review Board (CIRB). CIRB reviews the completed protocol, the informed consent form and related material in order to ensure the protection of human research participants (CIRB Website, 2006) while CTEP is a clinical research program under the National Cancer Institute (Ansher, and Schraf, 2001) that acts as a gatekeeper to the clinical trials phase (Ansher, and Schraf, 2001). Once the protocol is approved by CTEP, the cooperative group is free to start the clinical trial phase. After the Clinical Trials Phase the investigator files the New Drug Application with the FDA and the FDA review process starts (Keyhani, Diener-West, and Powe, 2005),(Dickson, and Gagnon, 2004). FDA reviews the results from the clinical trials and determines whether the benefits of the treatment outweigh the potential risks of the treatment or drug (NCI Website, 2006). FDA evaluates two main conditions: a substantial evidence of the treatments effectiveness and the safety of the product under the conditions of use in the proposed labeling (NCI Website, 2006). Once the final approval from FDA is obtained, the drug manufacturer is free to market the drug under the label approved by FDA (NCI Website, 2006).

This entire process takes about 12 to 14 years, of which clinical trials phase takes a major portion, an average of 8.6 years (DiMasi, 2001), (Reichert, 2003),(Dickson, and Gagnon, 2004). A 25 % reduction in the clinical trials phase would decrease the capitalized total cost per approved drug by 16% or $129 million (DiMasi, 2002); NIH thus places much

importance on reduction of this phase length (Kaitin, and Cairns, 2003), (DiMasi, 2002), (Reichert, 2003). In an effort to decrease its length, CTEP expedites studies for certain cancer drugs. When a study is expedited CTEP sets a tighter deadline on various clinical trials setup activities. At the co-operative group, expedited studies are assigned a higher priority over the non-expedited studies; the co-operative group employees are encouraged to finish the protocol development activities for the expedited studies by the deadline assigned by CTEP (See Appendix B).

Literature shows, when employees perform under tight deadlines there is a tendency to work around problems and to compensate for operational failures in order to meet task deadlines (Tucker, 2004); Tucker (2004) studied nurses in hospitals and concludes that the they concentrate at completing the task at hand on time and the hence deal with the issues that prevent its timely completion on a case by case basis. The underlying problem causing these issues ignored and hence never resolved. This leads to considerable time being devoted to dealing with symptoms (Tucker, 2004). Similar observations of firefighting under time pressure has been made in the service industry (Young, Corsun, and Shinnar, 2004) which in the end leads to a considerable increase in resource requirements (Young, Corsun, and Shinnar, 2004), (Tucker, 2004).

Expediting jobs has shown to create similar effects in the manufacturing industry (Repenning, 2001) and new product development activities (Hayes, 1981) leading to a decrease in the quality of output (Terwiesch, Bohn, and Chea, 2001). When Perlow (1999) studied a software development firm she found that tight deadlines cause a

permanent state of crisis and a marked drop in the quality of software produced. Another study on a scientific modeling firm by Hoopes (2001), shows that tight deadlines lead to a perpetual state of firefighting resulting in a significant drop in the productivity of the system. Similar results were found by Cooper and Edgett (2003) in new product development activities.

This negative impact of expediting and tight deadlines on the productivity of the system lead us to the following propositions in order to find the impact of expediting on the protocol development process.

CHAPTER II

PROPOSITIONS

Research in varied fields has shown that expediting jobs negatively impacts the productivity of the product development system (Terwiesch, Bohn, and Chea, 2001). My study proposes that expediting the development of study protocols will have a similar negative impact on the productivity of protocol development. In the past, changes in system behavior, as a consequence of policy changes have been studied with the help of system dynamics (Santos, Belton, and Howick, 2002), (Lyneis, Cooper, and Els, 2001), (van Ackere., and Smith, 1999). System dynamics presents the concepts useful to represent, analyze, and explain the dynamics of systems (Sterman, 2000); systems with various stages and delays in flows and feed back loops. Hence, I use the concepts provided by system dynamics to capture the structure of the protocol development system and the interactions of its parts.

The number of products that a system outputs within the time period is used as a measure of the productivity of the system in that time period (Black, and Repenning , 2001). Protocols that are approved by CTEP for activation is the output of the protocol development system, and hence the impact expediting on the productivity of the protocol development system can be measured by measuring the number of approved protocols that exit the system.

This concept can be crystallized in following proposition:

P1a: Percentage of expedited studies significantly affects the outflow of CTEP approved protocols from development system.

System output also depends on the number of products it can simultaneously work on. In our study the rate of system output depends on the number of ideas accepted into the system. When a system goes into firefighting more resources are allocated to rework than on new development activities, thus reducing the number of studies that can be simultaneously worked upon (Black and Repenning, 2001). It is proposed that the number of new ideas that can be accepted into the system is impacted by the percentage of expedited study protocols being processed in the system.

P1b: The number of ideas that can be accepted into the protocol development system is impacted by the percentage of expedited studies.

A study in the manufacturing industry shows that, amount of rework required to be done on the product significantly affects the productivity of the product development system (Repenning, 2000). Hence my study looks at the proportion of rework done on a protocol before it is finally approved by CTEP, as a measure of the productivity of the protocol development system:

P1c: The ratio of rework to total CTEP submission is impacted by the percentage of expedited study protocols.

All of the above propositions study the impact of expediting on the performance of the system. They are based on past studies in other industries where time pressure has been shown to have a negative impact on performance and quality (Perlow, 1999), (Terwiesch, Bohn, and Chea, 2001).

Waller, et al., (2001) studied the working habits of individuals under time pressure. They found that deadlines motivate groups to pace themselves and complete the allotted work on time; and up to a point, deadlines increased productivity. If the time pressure reaches a limit where the employees cannot handle it, time pressure has a negative impact (Perlow, 1999), (Terwiesch, Bohn, and Chea, 2001). Our study looks for similar effects in the protocol development system. Expediting is said to have a positive effect on the system if the productivity of the system goes up due to expediting. As seen above the productivity of a system can be measured by measuring the output of CTEP approved protocols from the system, the number of studies the system simultaneously works on and the rework needed. This gives us the following propositions:

P2a: When a specific percentage of studies are expedited, the outflow from the system peaks and then the outflow drops.

P2b: When a specific percentage of studies are expedited, the number of ideas accepted into the system peaks and then the number of ideas accepted start drops.

P2c: When a specific percentage of studies are expedited, the ratio of rework to the number of studies submitted to CTEP hits a minimum and then it begins to rise.

CHAPTER III

MODEL DESCRIPTION

In order to study the system behavior using system dynamics, the structure of the protocol development system and the interaction of its various parts need to be captured. Conceptualizing the system in a quantitative system dynamics model is an important step in capturing structure and the interactions of it various parts (Santos, Belton, and Howick, 2002). The underlying physical structure of the system is represented by stock and flow diagrams (Sterman, 2000) while the actual interaction of variables is better represented by visualizing the feedback structure through causal loop diagrams (Sterman, 2000), (Santos, Belton, and Howick, 2002), a method of representing the system as a set of variables linked through feedback loops, with time delays between action and consequence (Sterman, 2000).

System dynamics modeling advocates the creation of a model using a rich source of information; information is obtained from formal and informal sources (Forrester, 1980). This method is suggested to help in the development of a model reflecting the real life system as closely as possible (Forrester, 1980). Forrester (1980) suggests the usage of mental, written and numerical data to build a model. Mental data is the data stored in the collective memory of domain experts, obtained by observation and experience, this information when written down as a concepts form written data. These forms of data is used to build the physical model and the also to specify the behavioral linkages between the variables in the model. The parameter values are then obtained from numerical data.

Our study obtains mental data from interviews with the staff of a leading co-operative group responsible for protocol development. Personnel involved in the design, development and internal review of a study protocol are interviewed over a period of two months. The steps followed by the staff to develop study protocols are noted down in detail. Communication between the personnel via email and mail is also used.

The model investigates the behavior of the system over a five year period and hence data on all the studies passed through the system over a five year period is collected. Information is gathered from written data viz. documents of thirteen different Phase III studies that passed through the system and the policies and procedures manual. Values for different parameters are obtained from the interviews and documents of the studies that passed through the system. The data so obtained is used to develop a causal loop diagram shown in Figure 2.

The diagram is composed of two loops, a reinforcing loop representing the relationship between the *Availability of resources*, the *Quality of output*, *Rework* that is needed before the final product i.e., a CTEP approved protocol is ready, *Actual protocol development rate* and the *Gap* which is the difference between the *Required protocol development rate* and *Actual protocol Development rate*; and a balancing loop representing the relationship between the *Approved ideas* i.e. the number of study ideas accepted into the system, the stock of protocols already under development and the *Availability of Resources* which is the resource requirement of the system expressed as a fraction of available resources.

When the *Availability of resources* is low the *Quality of output* goes down, lower the quality of output higher will be the rework needed before the final product (in this case protocol) is approved. An increase in the amount of rework needed before the protocol is finally approved decreases the rate at which the protocols are developed viz. the *Actual protocol development rate* goes down, increasing the *Gap* between the *Required protocol development rate* and the *Actual protocol development rate* increasing the resource requirement, further deteriorating the *Availability of resources*. Higher the *Gap* between the *Required protocol development rate* and the *Actual protocol development rate* lower will be the number of *Approved protocols* churned out by the system.

The balancing loop is explained as follows: when more ideas are accepted into the system the number of study protocols under development increases, as the stock of protocols under development increases the resources requirement increases which in turn decreases the *Availability of resources*. The decision to approve ideas into the system is taken on the basis of the resource situation in the system. If the *Availability of resources* is low, the number of ideas that are accepted into the system is lowered, this is turn has a positive impact on the *Availability of resources*. Interaction between the *Availability of resources*, *Approved ideas* and *Protocols under development* leads to a balancing loop that settles down into a steady state.

The diagram also the shows two delays in the feedback loops. One is between the *Quality of output* and *Rework*, it signifies the time delay between a change in the quality of output and its effect on the rework needed before the final protocol version is approved. The

other delay is between the *Availability of resources* and *Approved ideas*; higher number of ideas approved by the system for further development when the *Availability of resources* is high.

In order to study the effect of expediting certain studies on the efficiency of the system we now introduce the *Percentage of expedited studies* variable which gives us the causal loop diagram shown in Figure 3. As the *Percentage of expedited studies* in the system increases, tighter deadlines are set and the rate at which the protocols are required to be churned out increases, this phenomenon is captured by the variable *Required protocol development* rate. *Gap* is the difference in the *Required protocol development rate* and the *Actual protocol development rate*.

When a study is expedited the required development rate increases, however the actual development rate is constrained by the *Availability of resources* and the *Rework* required, this introduces a gap between what is required and what is possible, this increases the resource requirements in the system thus lowering the *Availability of resources*.

At the same time when the *Percentage of expedited studies* in the system is increased, tighter deadlines result in a decrease in the length of time the protocol remains in the system thus reducing the value of *Average length of development.* Protocols are created faster and the resource situation is eased; this is captured by a balancing loop as shown in Figure 2.

Key Assumption

In order to keep the model simple it implements all delays as 'fixed delays'. This implies that 'first come first serve' in protocol development is a key assumption in the model. However, as the model studies if expediting affects the efficiency of the system; this entails the total throughput of the system and does not differentiate one study from another, thus the order of delay in processing is not important; only the average duration of delay is of concern.

Detailed Structure (Work accumulations and flows)

The basic stock and flow structure of the model is shown in Figure 4. Arrows with valve symbols represents the flow of tasks in the system. There are five stocks in the system. *Approved ideas* flow represents the flow of ideas into the system which gets pooled in a stock of *Approved ideas*. Some of the ideas in this pool will be given an 'expedited study' status by CTEP, protocols for these studies will flow through the expedited protocol development flow rate into the stock that contains all the expedited study protocols under development. The studies that are not given 'expedited status' will flow through the regular study development flow rate into the stock that contains all the regular study protocols that are under development. In either case once a complete protocol is developed it is submitted to NCI bodies, CTEP and Central Institutional Review Board (CIRB) for approval (See Appendix B). While CIRB approval for a protocol is mandatory, it is important to note that CTEP acts as the final gatekeeper for protocol approval and CTEP approval time is inclusive of CIRB approval time[2]. To keep the model simple it implements CTEP and CIRB as one stock, and referred to as CTEP submission.

The protocol submitted to CTEP is represented by the stock *CTEP CIRB (Regular)* for regular studies and *CTEP CIRB (Expedited)* for expedited studies. Protocols submitted to CTEP can be sent back to the co-operative group for revisions, this is captured by the *Rework (Regular)* and *Rework (Expedited)* flow rates, protocols sent for rework adds to the stock of study protocols under development.

The model implements protocols under development and protocols undergoing revisions as the same stock, as they draw resources from the same pool and so for the purpose of this study affects the system productivity in the same way. Study protocols that obtain final approval flow out of the system as studies ready for activation and is represented by *Ready for activation (Regular)* and *Ready for activation (Expedited)* flow rates. The sum of these rates represents the output from the system. A full model with all the feedback loops is shown in Figure 5.

While an equation by equation description of the model is given in Appendix A, the key structures and formulations are discussed below.[1]

Percentage of studies that are expedited by CTEP is the critical parameter in this model. Depending on this percentage, the flow rate through *Protocol development (Expedited)* and *Protocol development (Regular)* is determined. A fixed delay of 1 month is assumed for both the flow rates (See Appendix B). Thus when the percentage of expedited studies

in the system is determined by the variable *Expedited factor* the equation for the flow rate through Protocol Development (Expedited) is given by:

Protocol Development (Expedited) = DELAY FIXED(Approved Ideas*(Expedited Factor), 1, 0) (1)

Expedited Factor is the percentage of studies that are expedited; the above equation shows that the protocols under expedited development are calculated by finding the fraction of study ideas that are approved for expedited protocol development. *Approved ideas* enter the stock of studies after a fixed delay of one time step. When the model is simulated there are no protocols under development at time step 0.

Similarly we get the equation for Protocol Development (Regular) is given by:

Protocol Development (Regular) = DELAY FIXED(Approved Ideas* (1-Expedited Factor), 1, 0 (2)

Another important equation in this model is the rate at which the study protocols are submitted to CTEP.

The CTEP submission rate of protocols for regular studies is given by:

Submission (Regular) = min(Maximum Study Submission Rate, Potential Study Submission Rate) (3)

The rate at which protocols under regular development are submitted to CTEP is equal to the minimum between the *Maximum study submission rate*; the maximum rate at which the studies can be submitted to CTEP, and the *Potential study submission sate*; the maximum rate at which the studies can be submitted to CTEP considering the resource constraints.

Maximum Study Submission Rate is calculated as follows:

Maximum Study Submission Rate = Protocol draft and Rework/Minimum Revision Time (4)

Maximum study submission rate is the ratio of the *Protocol draft and rework,* the studies under development and the *Minimum revision time* which is the minimum time that is required for revising the protocol once.

The *Potential study submission rate* is calculated using the equation:

Potential Study Submission Rate = Available Resources/Resource Per Unit (5)

The *Potential study submission rate* is the ratio of *Available resources*; the resources available in the system and the *Resource per unit* which is the resource needed to process one unit of work i.e. the resource needed to process one study protocol.

The CTEP submission rate of expedited studies is given by the following formula:

Submission (Expedited) = Expedited Protocol draft and Rework/Minimum Exp. Revision Time (6)

The submission rate of the expedited study protocols is not limited by resource. The submission rate of expedited studies is the ratio of the *Exp. protocol draft and rework;* the number of study protocols under expedited development and the *Minimum exp. revision time* which is the minimum time required to revise an expedited protocol.

Now, let us look at the calculation of the main restraining factor in the model viz. Resource requirements. The desired throughput for expedited study protocols is given by:

Desired Throughput (Expedited) = Expedited Protocol draft and Rework/Target Expedited Process (7)

The protocol development system has a target time duration to output a study protocol, which it aims for; the *Desired throughput (Expedited)* is the ratio of the studies under expedited protocol development, *Target expedited process* which is the target time duration.

The desired throughput for of regular studies is given by:

Desired Throughput (Regular) = Protocol draft and Rework/Target Regular Process (8)

Desired throughput (Regular) is the ratio of the studies in regular development, *Protocol draft and rework* to the target time duration for the regular processing of studies, *Target regular process.*

The total resource requirement of the system is then calculated as:

Resource Required = (Desired Regular Throughput + "Desired Exp. throughput")*Resource Per Unit (9)

The total resource required by the system, *Resource required*, is found by summing up the desired regular throughput of the system, *Desired regular throughput,* and the desired expedited throughput of the system, *Desired expedited throughput,* and then multiplying that with the *Resource per unit.*

The next important concept in the model is the concept of quality and impact of resource availability on the quality of protocols developed. *Quality* is an attribute of the protocols that flow through the system. The model implements this attribute in a coflow structure as recommended by Sterman (2000). The flow rate into the coflow structure for expedited study protocols is given by the equation:

Quality = Expedited Submission *Quality Factor*Availability of Resources (10)

Exp submission is the rate at which expedited protocols are submitted to CTEP, *Quality factor* is the factor that determines the quality of the protocol, and *Availability of resources* is the total resources available in the system.

The flow rate into the coflow structure for regular protocols is given by the equation :

Inflow =Quality Factor * Submission*Availability of Resources (11)

The quality of the protocols in development at any instant is determined from the average quality of the stock of the respective coflow structures. The probability that the protocol will be sent for revision by CTEP depends on this quality.

Now that we have looked at the important equations in the model lets look at the behavior generated by these equations.

CHAPTER IV

MODEL BEHAVIOR

First the model is simulated with the percentage of expedited studies set at 0. This is the base case against which all sample results will be compared. The system efficiency for the base case is measured by the values of *Approved ideas*, *Percentage revisions* and *Total outflow*. N=200 and for each simulation the value for *Ideas generated* which serves as the input variable. It is obtained from a random normal distribution with a minimum value of 4, maximum of 7, mean of 5.5 and standard deviation of 2 (See Appendix B). Model output for 120 time steps signifying 120 months is obtained.

Figure 6 represents data on *Approved ideas* from a base simulation. When the model is simulated the system starts from time step zero, hence the system requires time to reach a steady state. *Availability of resources* at time step zero is at maximum as there are no studies in development, hence all the ideas that are generated get approved and *Approved Ideas* is at its maximum value. After a 10 time steps, study ideas under development leads to a resource crunch. After about 40 time steps, the system settles down into a steady state of one idea per month. *Total outflow* on the other hand steadily rises from zero, peaks after about 10 time steps to a value of 1.75 studies per month, and then gradually declines to reach a steady state of 1.5 studies per month (See Figure 7).

%Revisions rises sharply to peak at a value of 90% at around five time steps, drops sharply and then it gradually rises to attain a steady state of 66% (See Figure 8).

The above graphs show that it takes about 40 time steps to attain a steady state. The protocol development system that is being studied has been in operation for a period of more than 5 years (60 time steps), in order to get representative data from the first 60 time steps is discarded. The remaining 60 periods represent a five year period, after the system has attained a steady state of operation. The output of the simulations is analyzed to obtain the median values for the variables of concern viz. *Approved ideas*, *Percentage revisions* and *Total outflow* as these variables serve as a measurement of the productivity of the system (Black, and Repenning, 2001), (Repenning, 2000), (Perlow, 1999), (Terwiesch, Bohn, and Chea, 2001). Table 1 summarizes the results for the base case.

With the base case values obtained, the impact expediting has on the system productivity is studied. This is done by simulating the model with different percentage of expedited study protocols, the percentages vary from 0 to100 in steps of 5%. For each case; the median value of that variable for that case is then found (Figures 9 through 14 and Table 2).

Figure 9 shows how the percentage of expedited study protocols in the system affect the number of new ideas that can be accepted by the system. *Approved ideas* represent the new ideas that are accepted by the system and Figure 9 shows the change in the median

value of *Approved ideas* with a change in the percentage of expedited studies. Figure 10 shows the percent change in *Approved ideas* with respect to its base case value.

Approved Ideas increase initially, peaks when percentage expedited is about 15% and then declines. In order to narrow down on the percentage expedited where *Approved Ideas* simulations on a higher resolution are run on the model. The model is simulated with percentage of expedited studies in the system ranging from 10% to 20% is steps of 1 (See Table 3).

It is clear that when the percentage of expedited studies is in the range 0%-16% the number of new ideas that can be accepted into the system viz. *Approved ideas* gradually increases; it peaks at 16% and then gradually declines (See Table 3). Value of *Approved ideas* is higher than its value at base case (0% expedited) till the percentage of expedited studies is lower than 35%. Once the percentage expedited crosses 35% value of *Approved ideas* drops below its base case value of 91.2 *Approved Ideas* in 5 years. When the percentage expedited is 100% the value of *Approved ideas* is 30.8% below its base case value (See Table 2).

Total outflow represents the outflow of CTEP approved protocols from the system and Figure 11 shows the change in the median value of *Total outflow* with a change in the percentage of expedited studies. Figure 12 shows the percent change in *Total outflow* with respect to the base case value (See Table 2).

Total outflow increase initially, peaks when percentage expedited is around 15% and the starts dropping. In order to narrow down on the percentage expedited where *Total outflow* simulations on a higher resolution are run on the model. The model is simulated with percentage of expedited studies in the system ranging from 10% to 20% is steps of 1 (See Table 3).

It is clear that when the percentage of expedited studies is in the range 0% -16% the number of CTEP approved protocols gradually increases; it peaks at 16% and then gradually declines (See Table 3). Value of *Total outflow* is higher than its value at base case (0% expedited) till the percentage of expedited studies is lower than 35%. Once the percentage expedited crosses 35% value of *Total outflow* drops below its base case value of 91.2 CTEP approved protocols in 5 years. When the percentage expedited is 100% the value of *Total outflow* is 30.8% below its base case value. This is same as the effect expediting has on *Approved ideas* (See Table 2).

Figure 13 shows how the percentage of expedited study protocols in the system affect the percentage of rework that needs to be done on a protocol, *Revisions* represent this value. Figure 13 shows the change in the median value of *Revisions* with a change in the percentage of expedited studies. Figure 14 shows the percent change in *Revisions* with respect to its base case value as the percentage of expedited studies in the system is changed from 0% to 100%. Table 4 shows the data in a tabular format.

The revision required increases constantly as the percentage of expedited studies in the system increase. At 100% expedited the revisions required increases by 25% compared to base case value of 66%(See Table 2).

CHAPTER V

DISCUSSION AND PRACTICAL IMPLICATIONS

These results support existing literature on the effects of expediting and time pressure in other industries. (Waller et. al., 2001) discusses the positive effects of time pressure on increasing the productivity of a development system. This effect is clearly seen in our results; the throughput of the system and the number of new ideas that are accepted into the system increase as the percentage of expedited studies in the system increases from 0 to 16 percent (See Figures 9 and 11 and Table 3). The percentage of expedited studies affect the average time spent on drafting a protocol (See Appendix B). Expedited studies have tighter deadines and resources are devoted to meet these deadlines. The higher the percentage of expedited studies, the higher are the resource requirements. Due to a tighter deadline, resource requirements for the initial drafting increases. If the resource requirement is very high a resource crunch situation might arise and the quality of the draft deteriorates, resulting in more rework ultimately increasing resource requirements. On the brighter side, protocol drafts are finished faster, submitted to CTEP earlier and therefore should gain approval faster. When the percentage of expedited studies is between 0% and 16%, the positive effects of expediting override the negative effects. In spite of an increase in percentage rework, faster approval of protocols at CTEP frees up sufficient resources to enable the system to accept more studies than was possible with no expediting. The system has sufficient resources to process these studies by the deadline and the productivity of the system increases.

However, as soon as the percentage of expedited studies in the system crosses 16% the positive effects of expediting starts decreasing (See Table 3). Perlow (1999), Terwiesch, Bohn, and Chea (2001), conclude that when the employees cannot handle the workload due to extreme time pressure the quality of the output drastically drops. This result in an increase in rework required (See Figure 13) with further increases the workload, worsening the situation and decreasing its productivity (See Figures 9 and 11). This explains the loss of productivity of the protocol development system at higher percentages of expediting.

These simulation experiments make an important point. Expediting studies in an effort to increase the productivity of the system might not always give the expected results. This dynamic played a significant role in the situation found at the studied co-operative group. One of the interviews brought up an important point, all studies belonging to a particular disease and modality are expedited by CTEP, this is akin to 100% expediting. As a result, all the studies that are handled by the employees assigned to that disease and modality are given a high priority. The employees put in extra hours to meet the strict deadlines set by CTEP for protocol submission. However, when data on studies opened by the co-operative group in the past 5 years is inspected, it was found that the time taken to open an expedited study is not shorter than that taken to open a non - expedited i.e. regular study.

This phenomenon is easily explained by the simulation results. When the percentage of expedited studies in the system crosses 40%, the simulation shows that the productivity

of the system drops below its base case value (See Figures 9 and 11). At 100% expedited the productivity of system is 30.8% below its base case value (See Figures 10 and 12). At the same time the percentage of effort spent on rework increases by 25% (See Figure 14). Employees handling only expedited studies not only spend longer hours at work to get the protocol done on time, they also spend longer hours on rework(See Appendix B) All this extra work though does not result in increased productivity; the productivity might even be lower than base case i.e. when no studies are expedited. This might lead to an overall reduction in the productivity of the entire system.

However, it is important to note that the simulation results show that though rework required on studies increase as the percentage of expedited studies in the system increase; with in a certain range of expediting all this extra work actually pays off. The system throughput increases as the percentage of expedited studies in the system increases from 0 to 16% (See Figures 9 and 11 and Table 3). This shows a possibility of expediting benefiting the productivity of the system is factors like resource availability are considered.

CHAPTER VI

CONCLUSION AND FUTURE WORK

Firefighting and the corresponding decrease in the productivity of a development system in the context of expediting has been studied in various industries ranging from software development and modeling (Perlow, 1999), (Hoopes, 2001), new product development (Terwiesch, Bohn, and Chea, 2001) to hospitality (Young, Corsun, and Shinnar, 2004).

This study focused on the cancer drug protocol development system, a part of drug development activities of the pharmaceutical industry. The results agree with the findings in other industries, expediting does affect the protocol development system in a similar fashion. As the percentage of expedited studies in the system is increased the productivity of the system first increases, peaks and then decreases. After a particular percentage the productivity goes below the base case value of zero expedited studies (See Figures 9, 11 and 13).

Conclusion

This study shows that expediting with in limits can be beneficial to the productivity of the protocol development system, but care should be taken to keep the percentage of expedited studies below the threshold value.

Future research

Figure 13 clearly shows that as the percentage expedited in the system increases, the proportion of rework done on the study increases. Terwiesch, Bohn, and Chea (2001) and

Perlow (1999) talk about drastic drop in the quality of the output as the time pressure in the product development system increases entailing additional rework while (Young, Corsun, and Shinnar, 2004) and (Tucker, 2004) mention the rework that is a result of a firefighting mode of operation in a system where the deadlines are short and resources are tight. This additional rework is because the underlying issue causing quality glitch goes unresolved, the urgency to solve the problem takes importance and hence the symptom is treated instead of the root problem (Young, Corsun, and Shinnar, 2004), (Tucker, 2004). The model developed in this study does not allow differentiation between rework due to direct drop in quality and rework due to firefighting. An advanced study with a fine grained model differentiating rework due to a direct drop in quality and rework due to firefighting, would aid in the better understanding of effects of expediting and the resultant system behavior.

Figures 9 and 11 show when the percentage of expedited studies in the system is below a certain value, expediting improves the productivity of the system. This phenomenon provides an opportunity for further research. The effect of resource availability on this threshold value below which expediting would be beneficial would be of interest to policy makers of various development systems. Policy decisions regarding staffing of co-operative groups will benefit, from an answer to this question.

Notes:

1. The model is written using VENSIM software produced by Ventanna Systems Inc

Table 1: Base case values

Base Case		
Variable	Value	Unit
Percentage Expedited	0	%
Approved Ideas	91.24	Ideas/5 years
Total Outflow	91.23	Studies/5 years
Percentage Revisions	66	%

Table 2: Median values as percentage expedited is changed from 0 to 100.

Percent Expedited	Total Outflow	Revisions	Approved Ideas	ΔTotal Outflow	ΔRevisions	ΔApproved Ideas
0	91.2	0.7	91.2	0.0	0.0	0.0
5	96.2	0.7	96.3	5.5	2.4	5.5
10	101.7	0.7	101.8	11.5	4.6	11.6
15	107.4	0.7	107.6	17.8	6.6	17.9
20	105.4	0.7	105.4	15.5	8.3	15.5
25	101.1	0.7	101.1	10.9	10.1	10.8
30	97.2	0.7	97.1	6.5	11.8	6.5
35	93.5	0.8	93.5	2.5	13.3	2.4
40	90.1	0.8	90.1	-1.2	13.3	-1.3
45	87.0	0.8	86.9	-4.7	13.3	-4.7
50	84.0	0.8	84.0	-7.9	13.3	-8.0
55	81.3	0.8	81.3	-10.9	13.3	-11.0
60	78.7	0.8	78.7	-13.7	13.3	-13.8
65	76.3	0.8	76.3	-16.4	13.3	-16.4
70	74.0	0.8	74.0	-18.8	25.1	-18.9
75	72.0	0.8	71.9	-21.1	25.1	-21.2
80	70.0	0.8	70.0	-23.3	25.1	-23.3
85	68.1	0.8	68.1	-25.3	25.1	-25.4
90	66.4	0.8	66.3	-27.3	25.1	-27.3
95	64.7	0.8	64.7	-29.1	25.1	-29.1
100	63.1	0.8	63.1	-30.8	25.1	-30.9

Table 3 Median values as percentage expedited changes from 10 to 20 in steps of 1.

Percent Expedited	Approved Ideas	Total Outflow	% Revisions
10	101.8	101.72	69.82
11	102.92	102.85	70.10
12	104.06	103.99	70.38
13	105.22	105.14	70.66
14	106.31	106.32	70.93
15	107.56	107.44	71.21
16	108.6	108.63	71.39
17	108.12	108.15	71.60
18	107.19	107.22	71.85
19	106.28	106.31	72.09
20	105.38	105.41	72.34

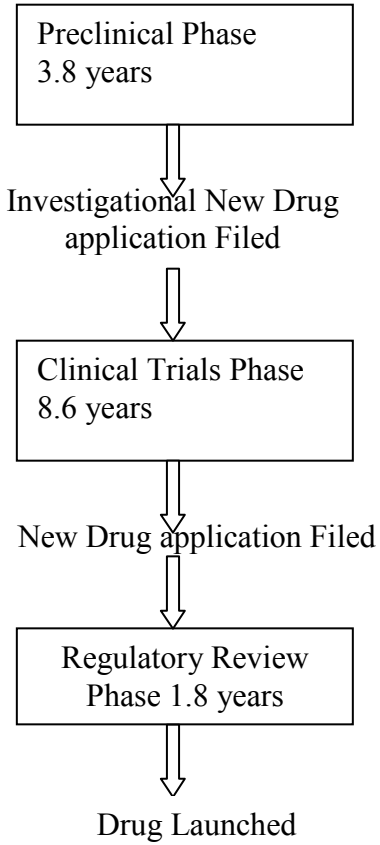

Figure 1: The Drug development process

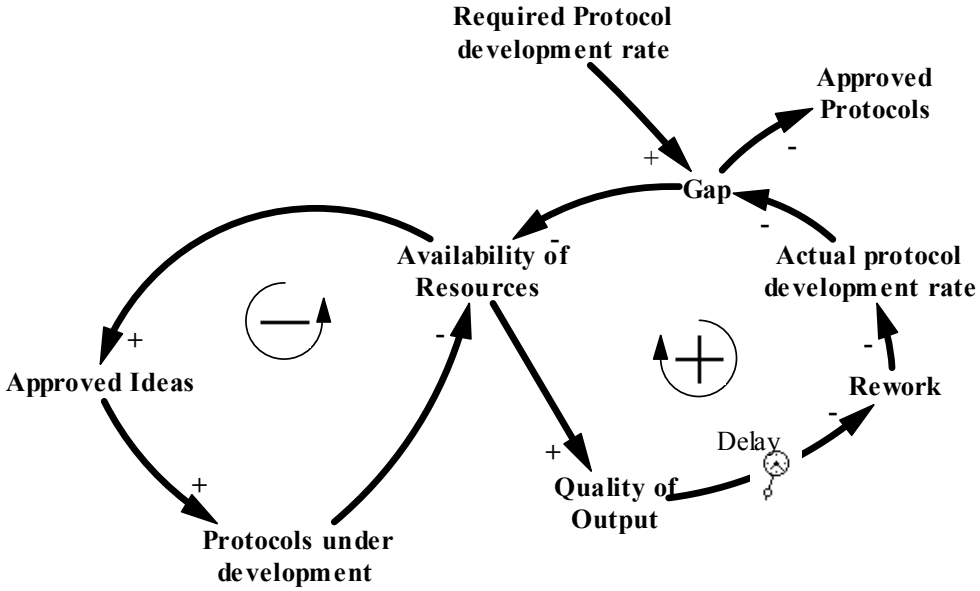

Figure 2: Causal loop representing the protocol development system

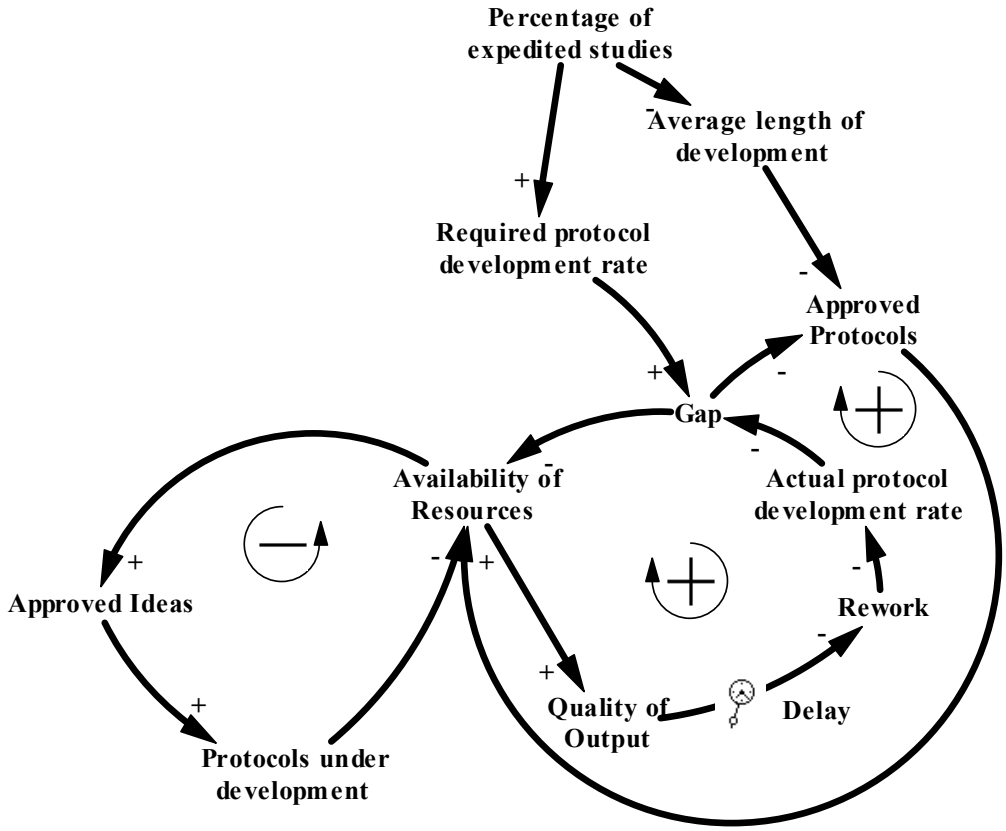

Figure 3: Causal loop diagram representing the protocol development system with a certain percentage of expedited protocols

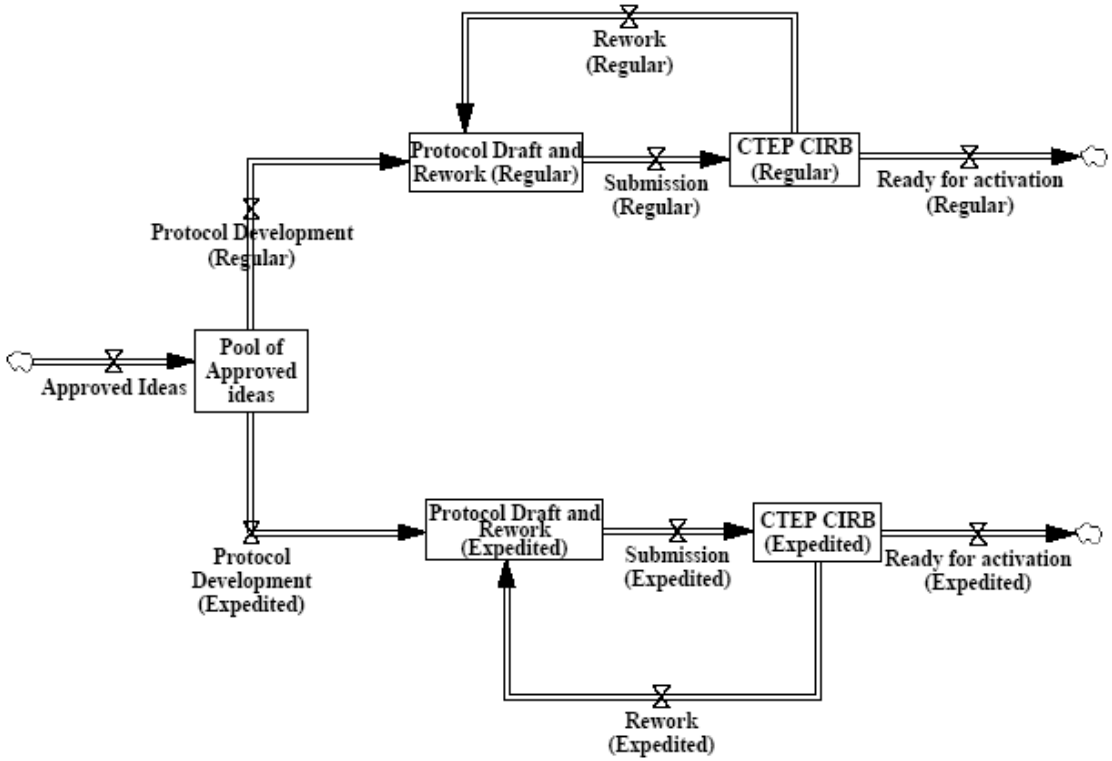

Figure 4: The basic stock and flow model

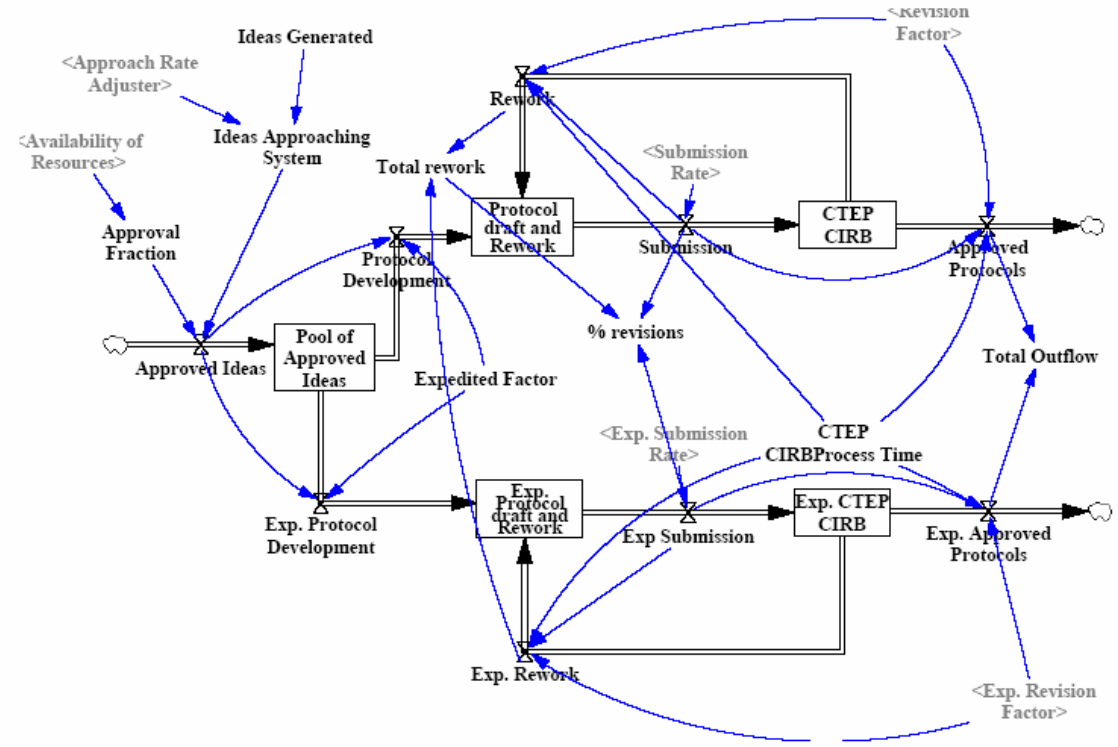

Figure 5: The protocol development process

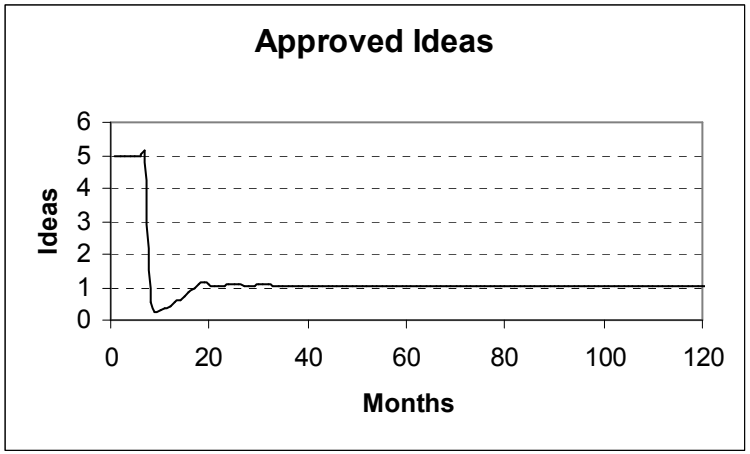

Figure 6: Approved Ideas over 120 time steps

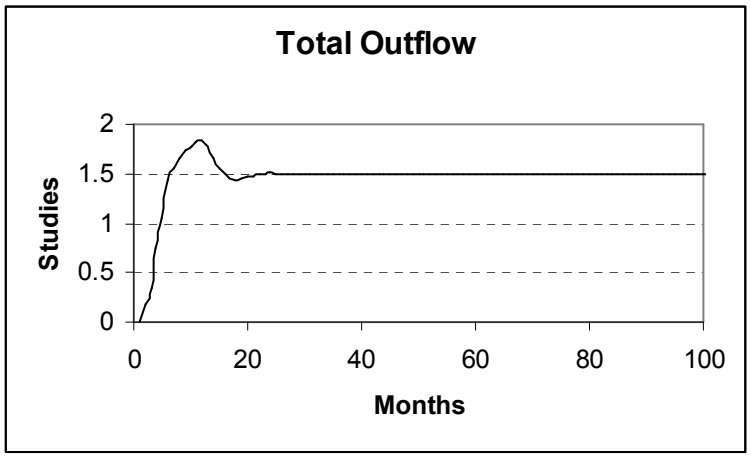

Figure 7: Total Outflow over 120 time steps

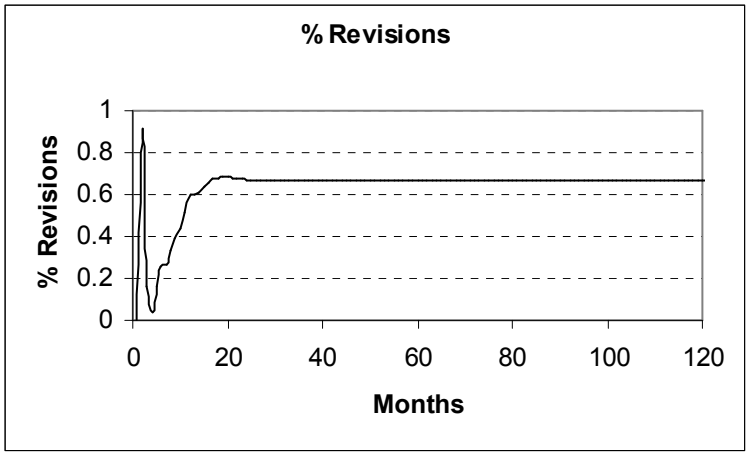

Figure 8: %Revisions over 120 time steps

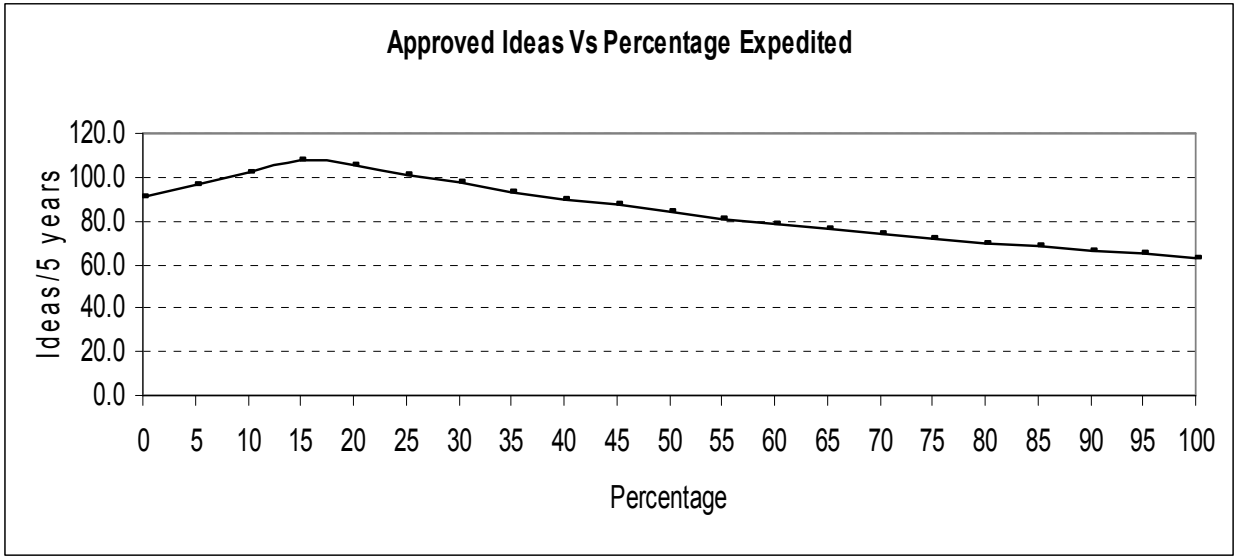

Figure 9: Median ideas approved per month as the percentage of expedited studies is changed from 0 to 100

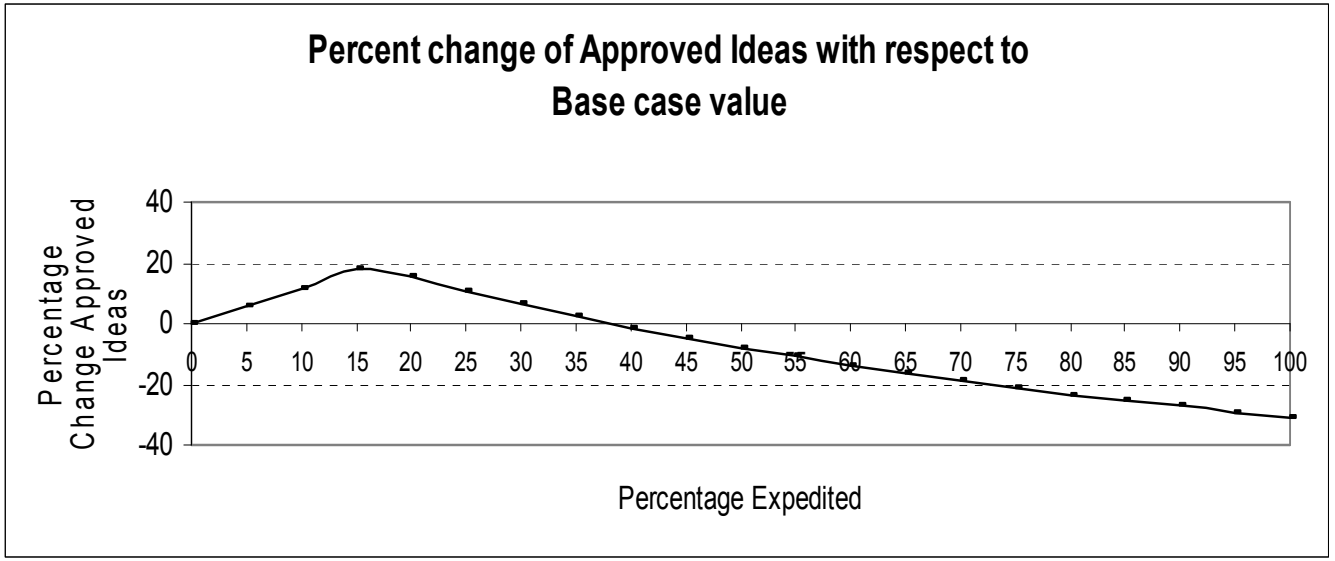

Figure 10: Percent change in Approved Ideas with respect to the base case value

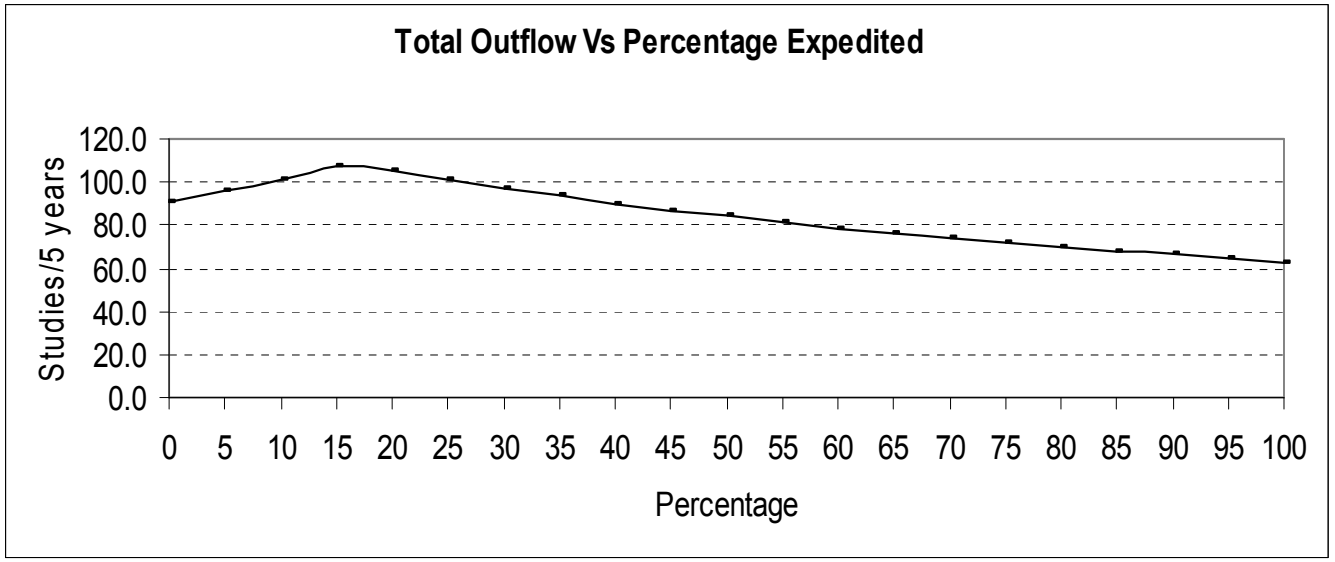

Figure 11: The Total Outflow of CTEP approved protocols per month as percentage of expedited studies changes from 0 to 100

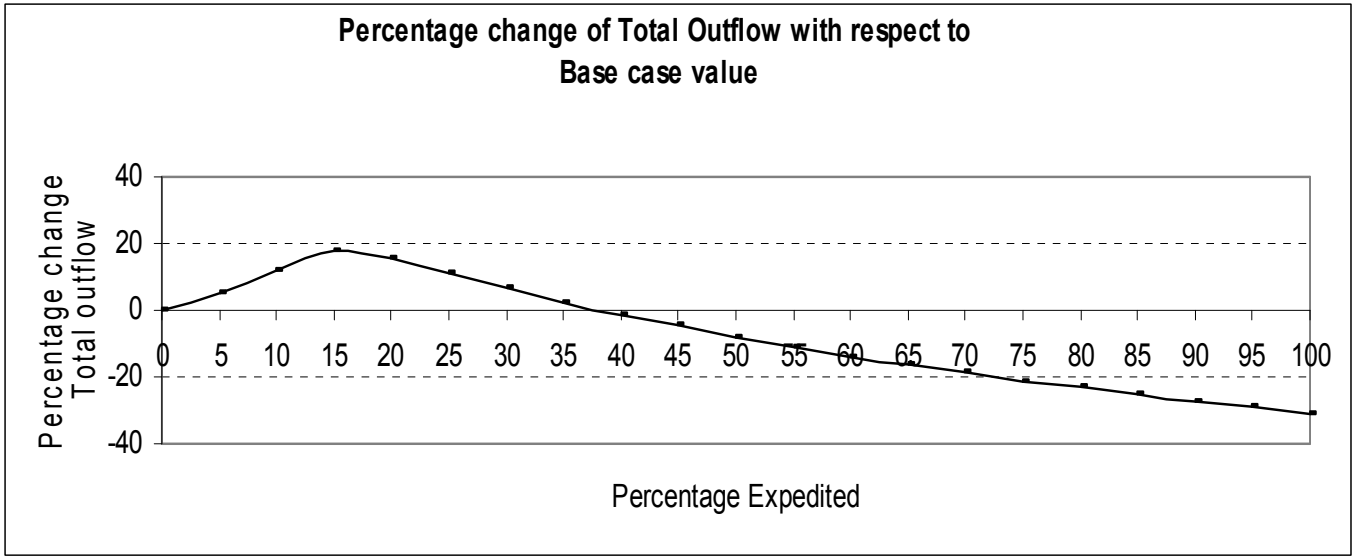

Figure 12: Percent change in Total Outflow with respect to the base case value

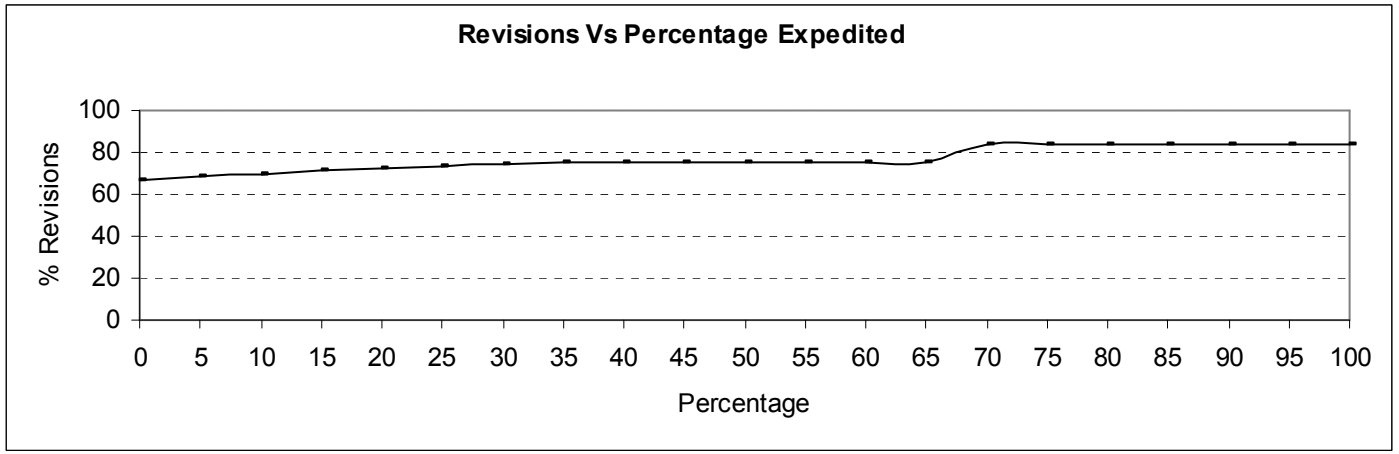

Figure 13: The number of studies ready for activation per month as percentage of expedited studies changes from 0 to 100

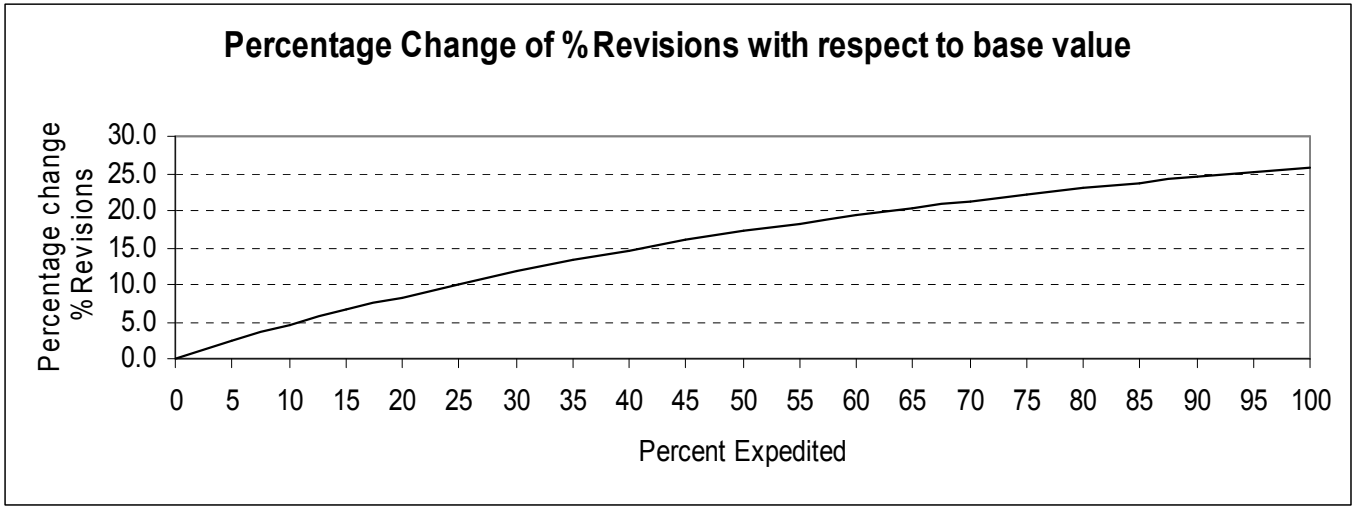

Figure 14: Percentage change in %Revisions with respect to base class value

APPENDIX

A. MODEL EQUATIONS

(01) "% revisions"=ZIDZ(Total rework,(Exp Submission+Submission))
Units: Dmnl

(02) Approach Rate Adjuster = WITH LOOKUP (Availability of Resources,
([(0,0)1,1)],(0.0030581,0.00877193),(0.152905,0.0570175),(0.363914,0.0964912
),(0.620795,0.20614),(0.785933,0.25),(0.862385,0.328947),(0.948012,0.52193
),(0.98471,0.701754),(0.993884,0.986842),(1.00306,0.907895)))
Units: Dmnl

(03) Approval Fraction = WITH LOOKUP (Availability of Resources,
([(0,0)(1,1)],(0.0030581,0.00877193),(0.100917,0.0175439),(0.247706,0.0263158
),(0.400612,0.0394737),(0.538226,0.0877193

),(0.730887,0.162281),(0.816514,0.236842),(0.920489,0.350877),(0.978593,
0.618421),(0.993884,0.780702),(0.996942,0.991228
)))
Units: Dmnl
This is the value that represents the fraction of studies that
are approved depending upon the resource availability in the
system

(04) Approved Ideas=Approval Fraction*Ideas Approaching System
Units: Study/Month

(05) Approved Protocols=DELAY FIXED(Max(Submission*(1-Revision
Factor),0),2*CTEP CIRBProcess Time, 0)
Units: Study/Month

(06) Availability of Resources=(Available Resources/Required Resources)
Units: Dmnl

(07) Available Resources= 45
Units: persondays/Month

(08) "Average Exp. Quality Points"=XIDZ("Cumulative Exp. Quality",Exp Submission,0)*"Exp. Unit Factor"
Units: Dmnl

(09) Average Quality Points=ZIDZ(Cumulative Quality,Submission)*Unit factor
Units: Dmnl

(10) CTEP CIRB= INTEG (+Submission-Approved Protocols-Rework,1)
Units: Study

(11) CTEP CIRBProcess Time=1
Units: Month

(12) "Cumulative Exp. Quality"= INTEG (Exp Inflow-"Exp. Outflow",0)
Units: Quality Points

(13) Cumulative Quality= INTEG (Inflow-Outflow,0)
Units: Quality Points

(14) Delay Factor=XIDZ(1,Availability of Resources,5)*5*Delay Time
Units: Month
This factor determines the delay i processing a study protocol,
it depends on the resource availability in the system

(15) Delay Time=2
Units: Month

(16) "Desired Exp. throughput"="Exp. Protocol draft and Rework"/"Target Exp. Proces"
Units: Study/Month

(17) Desired Regular Throughput=Protocol draft and Rework/"Target Regular. Process"
Units: Study/Month

(18) Exp Inflow=Exp Submission*Quality Factor*Availability of Resources
Units: Quality Points/Month

(19) Exp Submission="Exp. Submission Rate"
Units: Study/Month

(20) "Exp. Approved Protocols"=DELAY FIXED(Max(Exp Submission*(1-"Exp. Revision Factor"),0), CTEP CIRBProcess Time, 0)
Units: Study/Month

(21) "Exp. CTEP CIRB"= INTEG (Exp Submission-"Exp. Approved Protocols"-"Exp. Rework",1)
Units: Study

(22) "Exp. Outflow"=DELAY FIXED(Exp Inflow, Delay Factor , 0)
Units: Quality Points/Month

(23) "Exp. Protocol Development"=DELAY FIXED(Approved Ideas*(Expedited Factor), 1, 0)
Units: Study/Month

(24) "Exp. Protocol draft and Rework"= INTEG (+"Exp. Protocol Development"+"Exp. Rework"-Exp Submission,1)
Units: Study
This represents the pool of expedited protocols being developed and revised

(25) "Exp. Revision Factor" = WITH LOOKUP ("Average Exp. Quality Points", ([(0,0)5,1)],(0.0152905,0.995614),(0.29052,0.925439),(0.703364,0.837719),(1.23853,0.697368),(2.14067,0.539474),(2.84404

,0.434211),(3.77676,0.267544),(4.60245,0.179825),(4.93884,0.157895)))
Units: Dmnl

(26) "Exp. Rework"=DELAY FIXED(Exp Submission*("Exp. Revision Factor"), CTEP CIRBProcess Time, 0)
Units: Study/Month

(27) "Exp. Submission Rate"=
"Maximum Exp. Submission Rate"
Units: Study/Month

(28) "Exp. Unit Factor"=
1
Units: Study/(Quality Points*Month)

(29) Expedited Factor=
0.95
Units: Dmnl [0,1,0.1]

(30) FINAL TIME = 120
Units: Month
The final time for the simulation.

(31) Ideas Approaching System=
Approach Rate Adjuster*Ideas Generated
Units: Study/Month

(32) Ideas Generated=
6
Units: Study/Month

(33) Inflow=
Quality Factor*Submission*Availability of Resources
Units: Quality Points/Month

(34) INITIAL TIME = 0
Units: Month
The initial time for the simulation.

(35) "Maximum Exp. Submission Rate"=
"Exp. Protocol draft and Rework"/"Minimum Exp. Revision Time"
Units: Study/Month

(36) Maximum Study Submission Rate=
Protocol draft and Rework/Minimum Revision Time
Units: Study/Month

(37) "Minimum Exp. Revision Time"=
3
Units: Month

(38) Minimum Revision Time=6
Units: Month

(39) Normalized Submission Rate=Expedited Factor*"Exp. Submission Rate"+(1-Expedited Factor)*Submission Rate
Units: Study/Month

(40) Outflow=DELAY FIXED(Inflow, 2*Delay Factor , 0)
Units: Quality Points/Month

(41) Pool of Approved Ideas= INTEG (Approved Ideas-"Exp. Protocol Development"-Protocol Development,3)
Units: Study

(42) Potential Study Submission Rate=Available Resources/Resource Per Unit
Units: Study/Month

(43) Protocol Development=DELAY FIXED(Approved Ideas*(1-Expedited Factor), 1, 0)
Units: Study/Month

(44) Protocol draft and Rework= INTEG (Protocol Development+Rework-Submission,1)
Units: Study
This represents the pool of protocols being developed and revised

(45) Quality Factor = WITH LOOKUP (Availability of Resources,([(0,0)-(1,1)],(0.0030581,0.991228),(0.0672783,0.982456),(0.217125,0.947368),(0.385321,0.907895),(0.501529,0.868421),(0.568807,0.846491),(0.608563,0.833333),(0.770642,0.798246),(0.874618,0.7631),(0.920489,0.75),(0.938838,0.741228),(0.969419,0.736842),(0.987768,0.714912),(0.993884,0.692982)))
Units: Quality Points/Study

(46) Required Resources=(Desired Regular Throughput+"Desired Exp. throughput")*Resource Per Unit
Units: persondays/Month

(47) Resource Per Unit=10
Units: persondays/Study
This is the resource that is needed to process one study.

(48) Revision Factor = WITH LOOKUP (Average Quality Points,([(0,0)-(5,1)],(0.0152905,0.995614),(0.29052,0.925439),(0.703364,0.837719),(1.23853,0.697368),(2.14067,0.539474),(2.84404,0.434211),(3.77676,0.267544),(4.60245,0.179825),(4.93884,0.157895)))
Units: Dmnl

(49) Rework=DELAY FIXED(Submission*(Revision Factor),2*CTEP CIRBProcess Time , 0)
Units: Study/Month

(50) SAVEPER = 1
Units: Month [0,?]
The frequency with which output is stored.

(51) Submission=Submission Rate
Units: Study/Month

(52) Submission Rate=min(Maximum Study Submission Rate,Potential Study Submission Rate)
Units: Study/Month

(53) "Target Exp. Proces"=4
Units: Month

(54) "Target Regular. Process"=8
Units: Month

(55) TIME STEP = 1
Units: Month [0,?]
The time step for the simulation.

(56) Total Outflow=Approved Protocols+"Exp. Approved Protocols"
Units: Study/Month

(57) Total Quality Points="Average Exp. Quality Points"*(Expedited Factor)+Average Quality Points*(1-Expedited Factor)
Units: Dmnl

(58) Total rework= "Exp. Rework"+Rework
Units: Study/Month

(59) Unit factor=1
Units: Study/(Quality Points*Month)

B. LIST OF INTERVIEWS

Our study relied heavily on information provided by domain experts, viz. the employees at a leading co-operative group. Documentation of the protocol development process as described in the policies and procedures manual is complemented by extensive interviews conducted over a period of two months. Table 3 lists interviews conducted.

Designation	**Job Description**
Protocol Coordinator	Coordinates the development of the protocol draft.
Data Coordinator	Reviews the protocol drafts ensuring that there are clear and consistent definitions of study objectives, eligibility criteria, primary analysis endpoints, evaluation criteria The registration instructions are checked for clarity, especially for studies with multiple treatment phases.
Statistician	Responsible for the design and production of randomization materials for new protocols, producing treatment assignment lists for each stratum defined by prognostic factors.
Forms Designer	Designs the data collection forms
Financial Affairs Director	Tracks potential sources of grant support and conveys information to investigators regarding the availability of funding opportunities that are relevant to CALGB research. Organizes and coordinates the development of CALGB budgetary proposals from the University of Chicago and provides consultation services to member institutions submitting CALGB-related funding proposals and progress reports.
Regulatory Affairs	Ensures that the Group and its investigators are in compliance with the Office of Human Research Protection (OHRP) regulations.

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