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Rameez KHALID

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Progress in Transferable Work-load Projects: Development of a Robust Method for the Evaluation and Forecasting of Distributed Progress

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Laboratoire de Génie Chimique

Directeur(s) de Thèse :
Jean-Marc LE LANN, INPT-ENSIACET, Toulouse
Philippe DUQUENNE, INPT-ENSIACET, Toulouse

Rapporteurs :
Emmanuel CAILLAUD, Université de Strasbourg
Jean-Michel RUIZ, Ecole Centrale de Marseille
Bogdan NICOARA, Universitatea Politehnica din Bucuresti, Roumanie

Membre(s) du jury :
Bogdan NICOARA, Universitatea Politehnica din Bucuresti, Roumanie, Président
Jean-Marc LE LANN, INPT-ENSIACET, Toulouse, Directeur de thèse
Philippe DUQUENNE, INPT-ENSIACET, Toulouse, Directeur de thèse
Emmanuel CAILLAUD, Université de Strasbourg, Rapporteur
Jean-Michel RUIZ, Ecole Centrale de Marseille, Rapporteur
Alain HAÏT, ISAE-SUPAERO, Toulouse, Membre

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CHAPTER I

INTRODUCTION

I. INTRODUCTION

With the passage of time, markets for industries are becoming more and more competitive, that means the end product is required to be: of improved quality, developed at the lowest possible cost and be quickly developed. Industries, today, for becoming competitive, frequently use techniques described in project management, industrial engineering, and operations research literature. These tools are a pre-requisite for success in today's tough economic and industrial environment. New skills are in demand for making the product of highest quality by overcoming technological barriers, at the lowest cost and then landing the product quickly into the market before the competition can develop and thus increase the profit. For this, scientists, engineers and researchers are working day in and day out to improve understanding and expand the knowledge base in every field of our life, from nanophysics to immunology, from medicine to aeronautics, and from dairy products to robotics.

The phenomenon of globalization is now everywhere around us and is getting important, since its inception in the 1980s'. In this era of economic globalization, industries are looking out for converting their products into blockbusters, and for this they use methods of globalized trade and outsourcing to name a few. Today the most important factor for product development is "time to develop", which is the time from the conception of the product to its arrival to the market. For the improvement of this and other factors, affecting the product's development life-cycle, the use of project management is indispensable. And with the wide-spread use of outsourcing and globalized trading, the significance of project management tools and techniques has been revolutionized. Globalization, if used with right governance and management, can do great things like lifting people out of abject poverty as in the case of the third world or under developed countries [1].

Along with general methods, tools and techniques, industries feel a serious requirement for industry specific project management skills and methods. Therefore new methods, concepts and ideas are coming on the table for aiding a project manager in decision making. This is mostly done by using benchmarking strategies, global information exchanges, learning by others' experiences and by creating "creative swarms" [2] – a self-encouraged group of people from different backgrounds integrating their efforts for a common goal and for the benefit of every stakeholder. These new ideas if coupled with traditional project management can give us an innovative approach to management.

I.1. PROJECT MANAGEMENT

Project management continues to grow as a very important research field in Industrial Engineering. Fortunately it helps us finding solutions to various problems as it deals with the complete organization of activities throughout the life cycle of project. But the project is prone to changes on the course of its completion as it is not an isolated process rather it very much depends on the evolution of its environment. That is why unusual and inexperienced environments and situations are always the biggest threats which bother Project Management.

For avoiding these uncertain dangers or Murphy's Law[1], proper planning, measuring progress and re-planning or forecasting are the tools at our disposal, with objectives expressed in terms of cost, time or quality. Thus, the project starts with the establishment of performance indicators, and then the gathered information on its advancement is monitored.

Every project is unique at some level, which in turn requires specific methods for the resolution of problems that it encounters. The references of Project management such as IPMA[2], PMI[3] and APM[4] are general in nature i.e. they do not consider solving the problems that are specific to a certain type of projects, they rather define general processes of project management.

I.1.1. Project Management Processes

When an objective is to be achieved, there are a number of steps to reach that objective. These steps in the project life-cycle are known as "Stages", "Phases" or "Processes", which are widely used terms in the project management literature. These steps are equivalent to the problem solving steps in the renowned Deming's plan-do-check-act cycle. Some references define a "Stage" as comprising of a number of "Phases" [3]. While other references in project management like PMI defines these steps as "Phases" or "Stages" comprising of "Processes" in their guide to Project Management Body of Knowledge (PMBoK®[5]) [4]. According to PMBoK, there are five major process groups, namely: Initiating, Planning, Execution, Monitoring and Control, and Closing process group. These process groups are repeated in every phase till the completion of the project. There are about forty-six processes and sub-processes defined in nine major project management knowledge areas, which are executed as required by a process group defined above.

APM developed a process-driven project management method called PRINCE2® (PRojects IN Controlled Environments), which is very popular for project management in the UK. It consists of eight processes from "Starting up a project" to "Closing a project" [5]. These processes also comprise, their respective, in total 45 sub-processes. There are technical stages and management stages in PRINCE2. It defines the product life cycle as: Conception, Feasibility, Implementation, Operation and Termination, but it treats only the Implementation phase [6].

I.1.2. Monitoring and Control

Project monitoring can simply be defined as "Knowing where we are" as defined by Lewis [7], as well as "Knowing where we will be" in terms of progress and performance. Once we know our status we can compare it with our plans to see where we should have been, and thus implying to use corrective or controlling actions or re-plan for the achievement of objectives. In this work we will stay, most of the time, in this process of "Monitoring and Control" of the project life-cycle and apply controlling actions after accomplishing the progress measurement.

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[1] Muphy's Law : "If something can go wrong, it will go wrong."
[2] International Project Management Association
[3] Project Management Institute
[4] Association for Project Management
[5] Commercial names for products and organizations are used throughout this thesis. The author absolutely acknowledges the property rights of the respective organizations.

I.2. TRANSFERABLE WORK-LOAD PROJECT

This thesis treats a special type of project which we call: the *transferable work-load project* (TWLP) which is a project where the work load is *transferable*[6] among a number of resources. These resources share the same capabilities and skills that is why the work-load can be transferred among these resources without any requirement of special set-ups. Resources can vary in their capacities but not in capabilities, for example if in a situation it is required that the work-load be transferred to another resource. For this, it is only possible if that resource is free or not fully loaded. If it is not free then the resource does not have the capacity to realize that transferred work-load. "Whether to transfer or not?" and "When to transfer the work-load?" are questions the manager has to answer on the course of the project. These projects can lead to a number of situations due to the presence of numerous variables and thus presents an interesting problem to study and research for the augmentation of our theoretical and practical comprehension of these projects.

I.3. THESIS STRUCTURE

This thesis has been organized in the following way. The introduction of the study is completed with the end of this chapter. The background of the problem is presented in chapter 2, i.e. a problem involving a TWLP project related to pharmaceutical industry in which patients are recruited in different countries for the evaluation of the effectiveness of a given treatment, as shown in fig. 1.

In chapter 3 we discuss the literature pertinent to our subject matter. Academic literature on project management treating this type of transferable work-load environs with forecasting is very much limited especially in empirical studies. Various topics relevant to our study are discussed in this section such as project organization, planning, monitoring and control, progress measurement and forecasting as shown by the dotted lines in fig. 1.

Then a mathematical model of our problem will be formulated in chapter 4. First a simple version of the problem is presented which then by moving in an evolutionary fashion will generate a more detailed model so that the complexity of the real problem can be revealed. The planning involved and the estimation of initial budget will also be presented here. In this section we will explain the application of reallocation of the patients to be recruited for the forecasting of project duration, on the basis of the project progress.

The computer-based procedure will then be presented in chapter 4, which is developed using Visual Basic Applications in Microsoft Excel, for deriving solutions to the problem from the model. The results will be thoroughly analyzed with the emphasis on fundamentals that can improve the solution.

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[6] In this thesis, *transferable*, *interchangeable* and *shareable* are used interchangeably. Here *shareable* may not be confused with work which is shared by a number of entities, because this definition is true for most of the projects as the realization of every project is more or less shared among different departments or companies.

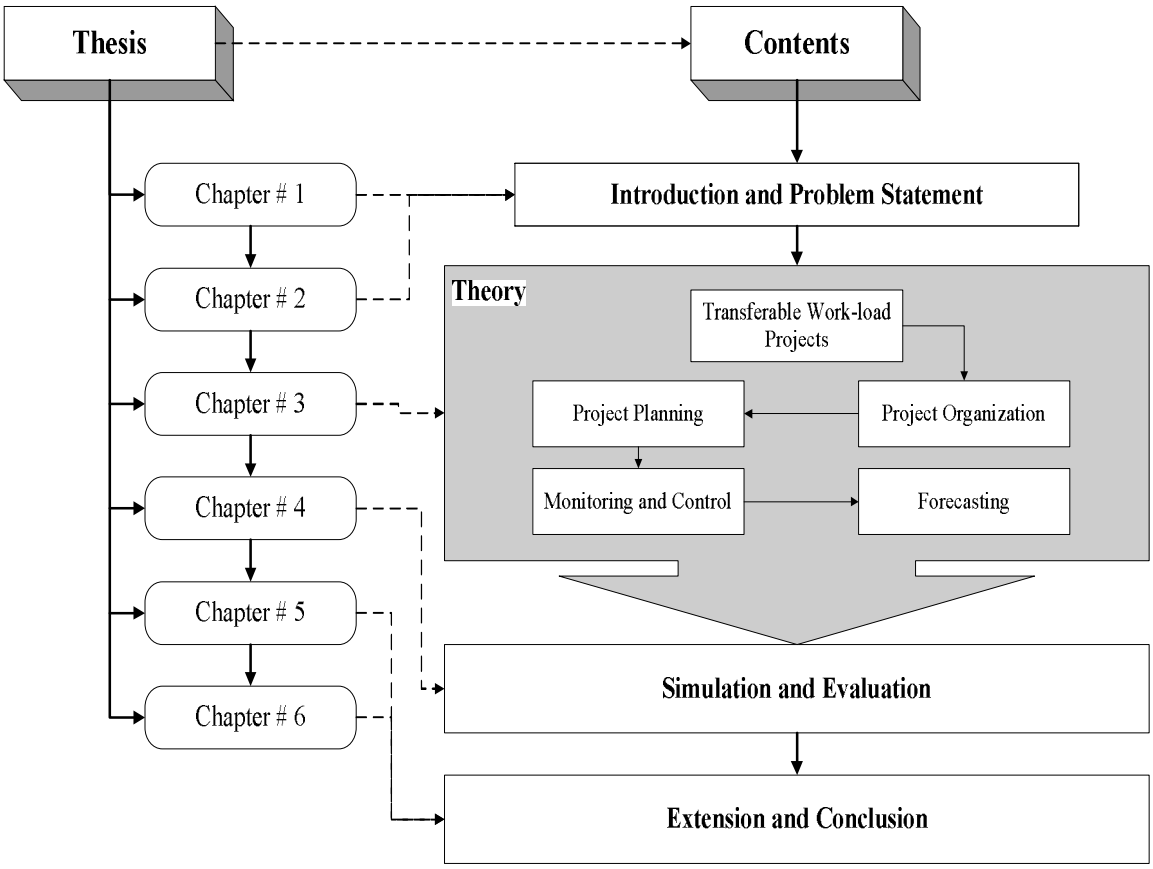

Figure 1. Thesis Structure

The questions like "What are the lessons learned?" and "How this problem can be extended for future research?" are addressed in chapter 5. This study augments the theoretical and practical comprehension of distributed progress in TWLP projects and also our findings propose extensions for further study.

Chapter 6 will conclude the thesis with the identification of contributions of this study.

CHAPTER II

PROBLEM STATEMENT

II. PROBLEM STATEMENT

This chapter presents the background of the study, along with the presentation of challenges described in literature. It basically emphasizes on the research questions. It also defines the contribution our study makes in the better comprehension of the challenges.

II.1. CONTEXT

The problem addressed in this study is related to the pharmaceutical industry, where new medical treatments, remedies, medicines or therapies for a particular disease or ailment are researched and developed every now and then. Basically, the pharmaceutical industry came out of chemical industry, as both of them have a number of similar methods and production processes. Though these industries are now segregated, many industrial experts still classify both industries into one "Pharmaceutical-Chemical Industry". Products produced in pharmaceutical industry are broadly named as "Life Sciences Products" that include: vitamins, plant and animal medicines, and fine chemicals (materials used for producing final pharmaceutical product) [8].

The drugs or medicines can be classified as prescription and non-prescription drugs. Also these drugs or treatments can be generic medicines (i.e. drugs without patents) or brand medications (i.e. drugs with registered patents). These treatments are developed after a long and complex development process. The development process involves the application of these medicines to patients i.e. by a process of *clinical trial*, so that their effectiveness in every possible aspect i.e. time, cost and quality can be examined, e.g. whether a particular treatment of a disease is making any improvement in the condition of the patient, if yes then at what rate. The benefit of this R&D is obviously enormous as it is also a moral and ethical duty of every human being to value life and to try whatever resources he or she has to save or improve life.

The importance of project management skills, to astutely choose and effectively develop new therapies in today's global climate, is undeniable. Without effective management there is no possibility of success no matter how large a pharmaceutical firm invests in their product's R&D. Because the drug development is a very complex process comprising multiple and dependent steps, with a long duration of sometimes 15 to 20 years and involves millions of dollars. This is why project managers are so important in the pharmaceutical industry now, as they can use the past for solving problems in present and effectively forecast actions to avoid future risks.

In spite of the development of new R&D techniques and so much spending, the ability to produce new medicines is going down, and the pharmaceutical industry is under huge pressure to improve the situation [9]. For resolving this problem of slow development, proper use of project planning, monitoring and control are required, as we know that the quicker the process of clinical trials is completed and results gathered, the quicker the drug can land in market. Also the high prices of new treatments is the real enemy in this declining situation of the pharmaceutical industry, for which there is no proven benefit to cost analysis [10]. Costs, with the help of proper management, if reduced will impact on the high prices of the new medicines and thus, will be a certain support to the industry.

This study concentrates on the process of *monitoring and control* of a project life cycle, i.e. here a method for the monitoring and control of a clinical trial is presented, with the objective of optimization of process duration. Thus, tools of operational research and project management are applied and a robust method for progress measurement or status tracking along with forecasting is developed, for aiding us in optimizing the duration of clinical trials and hence minimizing the duration and the cost of pharmaceutical product development.

It is also interesting to note here that pharmaceutical industries for resolving the problem of slow development are integrating their efforts by sharing their technical expertise in new drug development and thus also sharing the risk. For this, huge pharmaceutical companies are merging together for using the advantage of synergy and to provide an added value to the investor [8]. This can also be achieved using outsourcing, which is getting work done through contracting (mostly offshore), for example in a project that covers a large geographical area or requires work to be done in a distant country where the test conducting company has no expertise or knowledge. This trend has started a couple of years back and right now is booming as the best budget cutting tool available [11]. So, there is a constant flow of knowledge between these sponsors and contractors alliances. This is done by contract research organizations (CROs) which are expert in clinical trials [12], and can be of a huge help due to their knowledge of each and every variable affecting progress of the project. Once again it is vital to note here that poor project management could undo all of what has been achieved through the above collaborations.

II.1.1. Major Phases in Drug Development

Drug development is a complex process comprising of a number of properly sequenced steps, with each step having different duration, cost, risks involved and resources requirements. It has a technical as well as a managerial aspect, involving several scientific domains integrating for the sole purpose of producing a new drug. It has a highly regulated environment, with most of the regions in the world defining their standards and regulations for the regional pharmaceutical firms to follow for developing and then marketing their products. In the US it is the FDA[7] which regulates the drug development process, while it is the MHRA[8] in UK and the EMEA[9] in Europe. This regulatory environment has a significant affect over the total drug development duration, risks and marketing opportunities [8].

Pharmaceutical firms start the process of drug development by an effort to understand a disease. The advancement in science and technology is playing a vital role in this endeavor, as scientists are gradually gaining knowledge of genomics, pharmacogenetics and proteomics, for it is now found out that many diseases are linkable to genetics after the sequencing of human genome in 2001 [13]. For successful drug development there is a requirement of the best minds of the industry, huge amount of resources, state of the art technology and effective project management. Drug development takes about 10-15 years, and costs on the average from $800 million to $1 billion [14].

The drug discovery process is shown in fig. 2, and it shows that the process starts with a step called *Pre-Discovery*: where an understanding of the diseases is established from the level of genes, proteins, cells, tissues and to the global effect of the disease on the patient. Government

[7] Food and Drug Administration, USA
[8] Medicines and Healthcare products Regulation Agency, UK
[9] European Medicines Evaluation Agency

and public, academia and industry, i.e. everyone is involved as an interdependent partner in bringing hope to millions of patients [14]. The *discovery* process continues with the identification of a 'target' molecule which is involved in a disease and which is also 'drugable' (that can interact with or get affected by a drug). The next step is the testing of the 'target' molecule for the confirmation of its role in the disease by complicated tests. Once this is established, scientists are ready to find a suitable compound called 'lead compound' that, if successful, can become a new drug. Lead compounds are then tested for their safety i.e. the ADME/Tox[10] properties or 'pharmacokinetics'. A process known as Lead Compound Optimization is then performed to optimize the surviving lead compounds so that they can become more effective and safe [14].

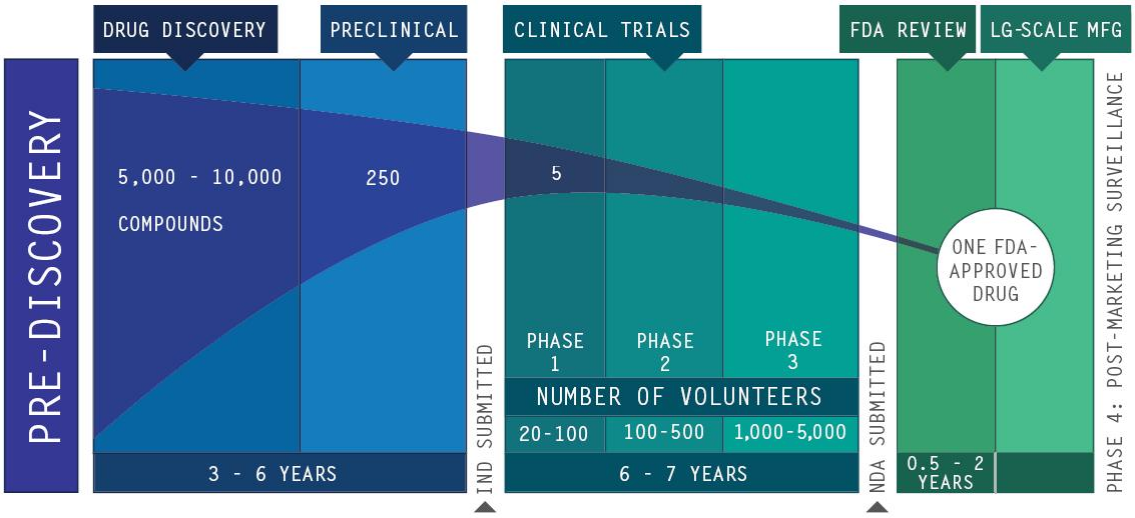

Figure 2. The Drug Discovery Process. **Source: [14]**

Next step in the process is *Preclinical testing*, where two types of tests are performed using the lead compounds 'in vitro' i.e. in test tubes and 'in vivo' i.e. in living cell cultures and animal models. These tests finalize the discovery phase, where scientists have narrowed down the number of lead compounds between one and five, after several years of research and testing. An IND[11] application is required to be submitted to the regulatory authority before continuing into the next phase. This application contains all the results of the preclinical testing, its chemical structure, side effects if any and the details of the plans for clinical trials [14].

The next major phase of development now commence as shown in fig. 2, where *Clinical trials* are carried out in 3 steps. Phase 1 clinical trial is performed by the application of treatment on healthy volunteers, where the pharmacokinetics (ADME/Tox) and pharmacodynamics (side effects and efficacy) of the candidate drug are found out [14]. Here drug interaction studies are also carried out for commonly used co-medications [9]. Phase 2 clinical trials involve the application of treatment to a small number of patients with the targeted disease. Here again the efficacy and safety of the medication, along with the proper dose range is evaluated. If the drug is

[10] Absorption, Distribution, Metabolism, Excretion and Toxicological properties, that means a lead compound should be absorbed in the blood stream, distributed to the required site, metabolized effectively, successfully excreted and proved to be non-toxic.
[11] Investigational New Drug application

still assuring success we continue to the most significant Phase 3 clinical trial, where a larger group of patients are exposed to the treatment. It is the costliest and longest of all other phases, and it requires proper coordination and management of data as these trials are mostly carried out at different sites due to the involvement of a large number of patients [14].

A NDA[12] is submitted to the regulating authority for the approval to market the drug. It contains all information from previous years, clinical trial results, and proposals for drug manufacturing, packaging and labeling. If the drug is approved, it can be produced on a large scale by following Good Manufacturing Practices (GMP) [14]. Pharmaceutical companies monitor the performance of the drug even after marketing authorization using techniques such as 'Yellow Card' reporting, where prescribers may fill out a form describing any side effects or adverse cases which can be submitted to the regulating authority. A direct reporting of adverse events by patients is in effect from 2004 in UK, a move well appreciated by the pharmaceutical industry [13]. These steps in drug development are not fixed rather they may vary but are widely executed by industries in this order.

II.1.2. Clinical Trials

For the purpose of developing a widely recognized product, pharmaceutical industries apply clinical trials around the world. These clinical trials comprise a greater part of the R&D budget of a pharmaceutical firm. There are a number of factors affecting the progress of this research [12]: patient availability, patient recruitment, moral considerations, geographical locations, laws and regulations, market potential, timelines and costs. It should be realized that drug development is a difficult process with inherent intricacies and unpredictable outcomes, so realistic expectations should be established. Also the larger the project the more numerous potential problems arise. Every factor as described above that can affect the progress of development should be given attention in such a way that a balance could be reached to ensure none can act as a hurdle in project progress [12].

Pharmaceutical companies usually market their products in US, Europe and Japan, for which products are clinically tested in these regions, following strict standards. While there is a trend of carrying out clinical trials in Asia, Latin America and Africa too, but physicians may prefer products tested in one of the main pharmaceutical regions [12]. India, China and Mexico are becoming important day by day due to the availability of patients and their low cost services as compared to the major medical markets. Especially China with a huge population and her booming economy has caught everyone's attention for outsourcing [15].

Our problem is concerned to the third phase of clinical trials in drug development, as defined in the previous section. A clinical trial consists of two stages namely: recruitment and treatment. Once the patient is admitted or recruited, then he or she can be treated. After treatment stage, results or data of this clinical study are gathered. Patients are recruited at different sites or clinics or hospitals, but this recruitment can vary from site[13] to site or country to country i.e. some sites can recruit more patients in less time than others. The treatment stage can consist of one or more than one phase, where each phase has a part of treatment, a cost and a different duration. The summation of all the costs and durations of all the phases will give us the total cost and duration of the whole treatment stage for one patient.

[12] New Drug Application

[13] Terms such as sites, countries and partners are used interchangeably.

Time required and costs of clinical trials are central to the decision making process. The major factor affecting the duration of the clinical trials is the availability of patients and then their recruitment. That's why those regions where patients are available and which are known for the quality of their clinical data are always preferred. Also if the region of trials is far from the base site, then there will be a requirement of monitoring visits, which can be expensive so should be anticipated and included in decision making process. This is where outsourcing comes into play, and most of the time is cost effective, but sometimes cutting costs can also deteriorate the quality of the project [12]. It is expected from outsourcing that it will not only ameliorate the development speed but also the capacity and capability of drug development. A word of advice here would be to sign an agreement so that all royalties and intellectual properties rest with the pharmaceutical company and not with the contract organization [8].

As defined earlier that clinical trials take the largest part of the R&D budget and time, so their proper management is significant to faster drug development. Clinical trials require the best available project management techniques, as they have more problems related to management than to science. Experts are indicating that these clinical trials need serious improvements, finest monitoring and controlling techniques because an increase in patient enrolment or recruitment time has been observed along with other problems, thus testing the managerial skills of a project manager [9].

II.1.3. Challenges and Risks

Pharmaceutical industry faces a number of challenges to be successful. The foremost is the entrance of fewer new drugs in the market, which is still gradually declining. This is the only significant parameter of success for this industry i.e. the number of new drugs produced per year and it is something not positive since a couple of years. Besides, the expenditure for R&D is increasing, that shows the amount of effort inserted by the pharmaceutical firms. Big names in the business have hit a wall of resistance to new drug development and these drugs also have higher prices [10]. Unlike other industries, in pharmaceutical industry projects are terminated due to scientific reasons and not economic reasons. Along with scientific, there are technological, biotechnological, and pipeline management[14] challenges to drug development.

Statistics about the pharmaceutical projects are not telling us a good story as only one of the nine projects starting a preclinical testing process is submitted for NDA, and here it should also be kept in mind that not all projects put forward for approval are approved [9]. One of the major reasons behind this small number of new drugs is the project failure. Most of the projects fail in the ending stages, thus proper decision making is the key to terminate the project as soon as it shows a hint of failure, to avoid a huge investment loss and time wasted. The drugs that we see on the market end there after surviving from many disqualification tests and experiments. A number of reasons why a project cannot become a product are shown in fig. 3. These are the threats a lead compound has to overcome before becoming a blockbuster drug.

[14] Pipeline Management : In Pharmaceutical project management, this term refers to the management of new drugs in various development processes in the pipeline of a pharmaceutical company. A strong pipeline with blockbuster products is the ideal objective of any pharmaceutical firm [8].

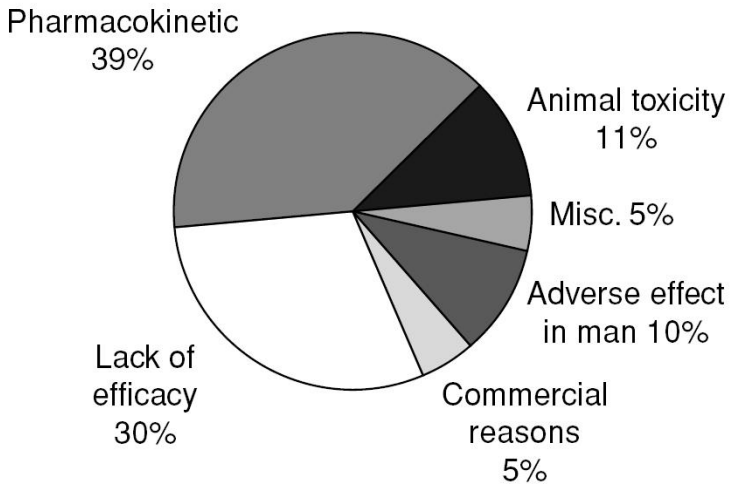

Figure 3. Reasons for project failure. **Source: [9]**

Apart from the above challenges and risks, there exists a tough competition and rivalry among pharmaceutical firms with time-to-market, product prices, intense advertisements, and global distribution strategies, as the parameters of success in the game. Sometimes, regulations and laws are introduced by a country for regulating the production and use of a particular drug, which is another challenge for pharmaceutical firms. Most of the challenges can be overcome by the use of proper and specific project management, and decision making strategies along with the use of advanced technology. Certain firms have shown success by concentrating only on the commercial success for each of their products rather than to compete for the number of new products developed [8]. Pharmaceutical firms now use a phenomenon of R&D internationalization for overcoming the challenges of product growth, decreasing huge costs by doing R&D in countries where costs are lower and making use of knowledge available globally.

II.1.4. Costs and Durations

Bringing drugs to market is very expensive nowadays as compared to 15 years before when the developing costs were less than $300 million but now drugmakers are used to these high investments or gambles [16]. As it is discussed earlier that the drug development process costs from $800 million to $1 billion and can take 10 to 15 years, it is beneficial here to point in the direction of minimizing this duration and cost. R&D internationalization, outsourcing and globalization are in wide use, in almost every industry and pharmaceutical industry is no exception to that, because they can bring strategic and tactical advantages with knowledge integration. If a project is outsourced for R&D, clinical trials or manufacturing as almost every process in drug development can be contracted out, there are a number of key issues for the sponsor or parent company (sole responsible) to take care of, such as: the scope of work, responsibilities, commitments, required resources and skills, data processing, performance monitoring, regulatory issues, delivery dates, coordination, and communication between the sponsor and the contractor, supplier or clinical research organization. Research has shown [9] that outsourcing has a positive impact over project durations i.e. outsourced projects tend to end faster, and it can spare some time for the parent company to concentrate on important decision making issues. Thus project management (see next section), well thought-out outsourcing and

effective decision making in all areas of drug development with especial attention to high cost, critical and bottleneck areas can minimize the duration of drug development, high project failures and expenditures [9].

II.1.5. Project Management in Pharmaceutical Industry

The importance of project management as a core to success in pharmaceutical projects is needless to describe. The high level of biological uncertainty, huge investments, and risks involved require the most sophisticated project management tools, skills and techniques, as most of the steps in drug development face managerial rather than scientific problems [9]. Goal of this project management is to fully exploit the strengths and competencies of the pharmaceutical company by applying good strategies to transform a molecule into a medicine by availing every opportunity found on the way and avoiding most of the threats by previewing the future, and thus landing the product on a profitable market in the shortest possible time and with lowest possible cost. The first step is to choose the right project that has a bright chance of becoming a product, most companies use NPV[15] method for this [8]. NPV or Present Worth Analysis is a widely used method in economics used for finding the best among various alternative projects [17], and thus aid us in the project selection decision. As money has a time value then costs and revenues along with the varying interest rates are used for determining the Present Worth of an investment or project [18], and the project will be chosen which has the highest Present Worth.

Risk management is vital and a major part in pharmaceutical project management, for planning a risk taking and risk avoiding strategy for the challenges and risks faced by the pharmaceutical industry, defined earlier. A project manager in this industry is required to thoroughly know how to handle these risks, issues out of his or her control, specialized techniques for this complex environment and regulations applicable to his or her product's approval [8]. With the extensive use of cross-functional or interdisciplinary teams present in different parts of the world and outsourcing in every pharmaceutical project, the value of specific project management techniques for developing an effective communication between them has increased. Clinical Trials, as the basic part of drug development, are now extensively project-managed.

II.1.6. Future Trends

In spite of the challenges, risks and threats to the pharmaceutical industry, its future looks bright. For an exciting future every entity linked to the industry has to discover its maximum potential and thus bring a revolution to this industry. The flow of knowledge (by open innovation) should be improved, along with the destruction of barriers to R&D, which can lead this industry to the bright future it deserves. R&D internationalization is going to become a universal truth, which will improve the performance of R&D functions of a company by sharing knowledge with external partners from a broad set of fields [8]. As more and more companies are merging, so it is predictable that in future there will be lesser companies with more final products. Due to these mergers and inherent complexities, new business and organizational models will be required. There is a need for transferring business and market information to the scientists so that a shift from product-based to patient-based strategy is possible. Data is generated in huge quantities which highlight the need for effective and quick information analysis

[15] Net-Present-Value method

techniques, algorithms, and efficient databases. Another avenue requiring our attention is a properly skilled and trained human resource, which is a very basic requirement for a successful future of the industry [8]. The above discussion describes the major elements that will prove a strong basis, if incorporated in a strategy, for the creation of miracles the pharmaceutical industry is capable of performing.

II.2. TRANSFERABLE WORK-LOAD PROJECTS

Transferable work-load project (TWLP), as defined earlier, is a project in which the work-load is transferable between a number of resources. These resources share the same capabilities and skills i.e. the work-load can be transferred among these resources without any requirement of special set-ups.

TWLP is not a new type of project; rather numerous examples exist in Task Scheduling, Work-flow Management, Supply Chain Management and Vendor Management. TWLP in the context of pharmaceutical industry can be defined as global contract-based clinical trials, where contract research organizations (CROs) based in different parts of the world are contracted for clinical trials required to be carried out in that particular region or more precisely in that country where a CRO is situated. As these CROs have more or less the same set of skills, so work is transferable between these CROs and if a situation arises that requires redistribution of work then some work will be withdrawn from one CRO which is not recruiting or treating as planned and be given to other that is working as planned or better than what was previewed for it. This redistribution of transferable work-load is applied for completing the project within planned duration. A typical TWLP is shown in fig. 4 where a work package is required to be transferred from site 1 to any other available site. First, site 2 is checked for this transfer but it is found out that this site is fully loaded. Then site 3 is checked, after knowing about its availability for transfer and also about its satisfactory performance, the work is transferred to site 3. If site 3 was also not available or was not working with required performance then this checking process would have been continued.

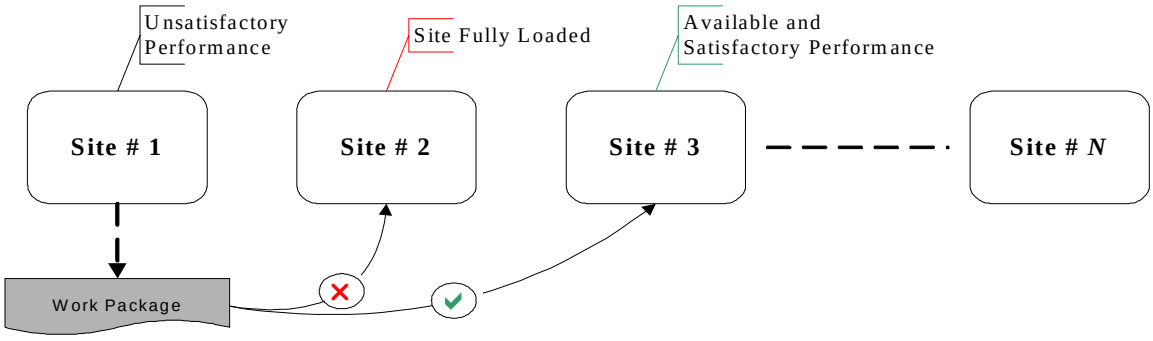

Figure 4. Transferable Work-load Project

We in this thesis are interested in TWLPs and their characteristics. One aspect of TWLPs that fascinates us is if the project is large or global i.e. for example a multinational or globally distributed project, and for this a wide range of literature is reviewed which will be presented in the next chapter under the section of *globally distributed projects*[16]. Another aspect of concern is the concept of distributed progress among various partners i.e. overall or global progress of the project is derived from the individual progress of every partner or resource, as described above using the example of pharmaceutical industry. Determining this global progress is the most difficult task for a project manager in this distributed or global environ, because of the complexity and the size of information to handle.

There are other projects which have some part and not whole of their work, in their Work Breakdown Structure, defined as transferable. This is why the scope of work in a project should be clearly and thoroughly defined; especially when the work-load is transferable, so that in a situation of work transfer to another entity or site no chance of any conflict can arise. This *scope definition* is an important part of project management, and in fact one of the very first activities a project manager performs, for describing in detail the complete work to do, with well defined responsibilities, division of work or future possible duties.

II.3. RESEARCH FOCUS

In the previous sections a background of the study was discussed, here the description of the problem will be presented. As defined earlier, a project has five processes namely: Starting a project, Planning, Executing, Monitoring and Control, and Closing a project. The project under study is a clinical trial project, which has already been started and planned. As this project is in operation, the monitoring and control has also begun, and we are interested in this process of Monitoring and Control for managing the project. The project is closely monitored and evaluated at every step by comparing the actual progress with the plan, and if required with the help of a controlling action the project can be maneuvered back on track.

The recruitment of patients is the most critical factor in clinical trials, which can increase the duration of the project single handedly but it depends upon the disease for which the clinical trial is being conducted and the population of the region where these tests are being carried out. This is why the region, where the probability of recruiting patients of the treated disease is high and the quality of clinical data can be assured, is always high on the list for clinical trials. After the planning for the previewed recruiting stage is completed and as the project enters into the actual recruitment stage, progress is measured for status tracking by comparing the actual progress with what was planned. If the manager finds any deviation, he or she can take any controlling action suitable for the situation.

Outsourcing as defined in previous sections is of prime interest to us and a clinical trial project where the trials are carried out in different parts of the world by a number of clinical research organizations, present an attractive problem. The project, we are concerned with, are the *transferable work-load projects* (TWLPs). TWLP is a project where the work load is *transferable*

[16] We are concerned to projects which are globally distributed or dispersed and where the work is transferable i.e. why for us these two terms *globally distributed projects* and *transferable work-load projects* are interchangeable, but for the sake of clarity the latter term was preferred and used for this thesis.

among the resources. In this study a clinical trial is conducted in parallel at different sites or more precisely in different countries. This work can be contracted out to contract research organizations (CROs) in each country of interest. The target is to recruit a required number of patients and then treat them. This required number of patients is divided among countries depending upon the country's population and competence in conducting a clinical trial with quality. For making a product a blockbuster, every company has to convince each and every collaborator, regulator and physician present between them and their customers, only by using excellent clinical data which are likely to come from large-scale global clinical trials [12].

The basic objective of this study is to optimize project duration. In pharmaceutical industry's context, this optimization of duration for clinical trials will minimize the drug development duration. As the patients are recruited and the manager finds it difficult to complete the project with in planned duration, he or she has a number of options to solve this problem. Before defining the options, it is better to find out the reason behind this increase in actual duration as compared to the planned project duration. As the work is done in parallel in different countries, one or more countries may not be recruiting patients as it was previewed at the time of planning, and this can produce lateness in project duration. Once those countries which are not working according to plan are identified, the manager has the option of letting the project run as it is and then there will be no change in the duration of the project. Besides, the manager can transfer the work-load from the countries which are the bottlenecks to countries that are working according to or better than what was planned. Here transferring work-load is equivalent to transferring patients from one country to another, not physically but simply by subtraction and addition.

This *redistribution*[17] of work is used for the optimization of duration of the project in an environment of offshore outsourcing or in a globally distributed environment. This means an environment where people are situated at different sites which are in different locations on the globe. From the above presentation of our research focus, a number of interesting questions emerge in mind: What are the tools to aid us in the management of TWLPs? How to measure progress of a project in this global environment? How to re-plan and forecast on the basis of the past progress? How to optimize the project duration with the help of *reallocation*[18]? These questions will be answered in chapters to come.

II.3.1. Planning

Planning is the core reason behind a project's success or failure [7]. It is a process of making a plan that can optimize performance, time and cost. Planning in pharmaceutical projects varies with the phase of drug development. In the first phase of research not much can be planned as each step depends upon the lead compound to successfully pass a test or experiment, so in this phase planning is restricted to the outcome of each step. Besides, the second phase of development is properly planned till the completion of the project [9].

Pharmaceutical companies should always plan for procuring sites that will be good at recruiting patients. A plan is required for the investigators to find out where to conduct clinical trials and what the duration of the project will be, which are known as patient recruitment plans.

[17] In this thesis, *redistribution* is the distribution of work among resources after re-planning when actual performance is not according to plan.
[18] *Reallocation* and *redistribution* are used interchangeably.

A patient recruitment plan defines the number of patients required to be recruited by the site, skills required by the staff conducting tests and a realistic recruitment schedule, and if the site signs this plan then the site will become more accountable [12]. Plan for managing risks i.e. a contingency plan is also valuable, so should also be made. A contingency plan in clinical trial's context will define more sites to select than needed, consider the addition of a new site or country and do benchmarking [12].

For this study a realistic recruitment schedule is planned for the clinical trial by experience and the study of related research. On the basis of this plan, the planned duration and budget of the clinical trial project is calculated. Depending upon the availability of committed patients in each country, the total number of patients required to be recruited for the study are divided among the countries in such a way that every country completes the recruitment stage within the same duration and more precisely on the same date. The planned budget is simply estimated by assuming as if everything will go according to plan.

After a patient is recruited or admitted, he or she is treated. It is known by experience that some patients quit before the completion of their treatment, so this should be taken into consideration in the contingency plan. Therefore more patients are recruited than required for the study, so that if some of them leave before the treatment ends, it may not affect the progress of the project. This aspect of a pharmaceutical project presents a real challenge while planning for contingencies as one never knows whether a particular patient will quit or not, if yes then "When?" is another question adding a variable for this uncertainty.

II.3.1.1. Recruitment Periods

In the planning process of clinical trial TWLP project, the recruitment of patients has been seen to take the pattern of S-Curve. S-Curve is widely used in a variety of fields for different purposes like showing growth or development, performance evaluation and resource usage. In project management, S-Curve evaluates performance of the effort by plotting the cumulate effort against time. The execution process in a project's life-cycle takes three periods as defined by the S-Curve, namely: learning, working and ending periods as shown in fig. 5.

Learning period is defined by its slow rate of working, as in the start of any project there is little experience, knowledge and high resistance to change. But as the experience is gained the project picks momentum and enters the working period shown by the increase of the working rate. This working period is the longest period in execution and major work is done in it. Ending period in most projects is marked by phases requiring less resources and efforts than the working period, resulting in a flattening of the cumulate effort curve. That means the ending period manifests retardation, which can have a number of reasons. One of the reasons is Parkinson's Law: "*Work expands to fill the time available"* [19], so work is slowed down to be completed during the allotted time. On the other hand if we work continuously with the rate as in working period we can end the project in advance to what was planned or previewed. In this context, the reason for retardation in pharmaceutical projects can be defined by the influence of external partners on the progress. These external partners are the contract clinical investigators, who may not take the pain to complete the project before the allotted time i.e. why a reward fee can be paid to recognize the efforts of the investigators for the early completion of the project. Another reason, the one that is true in our case, for this retardation is the intentional lowering of effort. In our case of a patients recruitment campaign, this retardation may result from a decrease of recruitment communication efforts when the number of recruited patients nears the total number

required to be recruited, in order to avoid accepting (and paying) more patients than contractually covered by the test-conducting company.

It is also possible to represent days in which work is halted due to holidays or attention is diverted to some other important project, using a horizontal line on the S-Curve. Fig. 5 shows the point where learning period ends and working period starts as POI "*Point of inflection*". This POI depends upon the experience gained, so it can be reached by getting required experience. That means in this study, POI can take two values; either POI is reached after a pre-specified number of patients have been recruited or after a pre-specified duration has been elapsed. Also a second POI can also be inserted at the end of the working period and the start of the ending period.

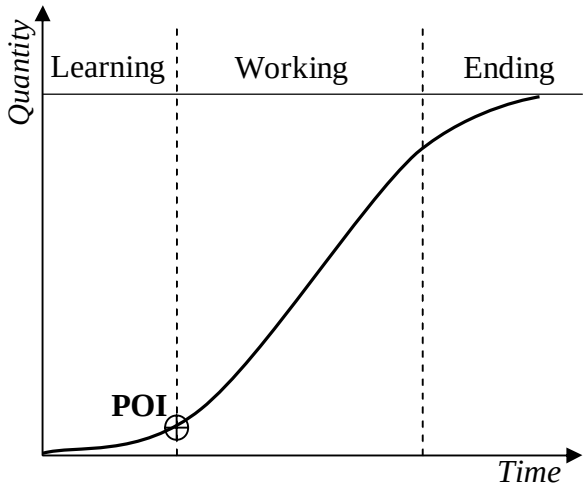

Figure 5. S-Curve showing three periods in Project life-cycle with POI

II.3.2. Monitoring and Control

You cannot manage what you cannot measure; the old saying defines the importance of measuring anything we want to manage. Progress of a project is required to be measured for the proper management of the project. Once the progress is correctly measured, it is evaluated by comparing it with what was earlier planned. This process of measurement and evaluation is known as *monitoring*, while *control* is correcting errors and minimizing the deviation of actual status from the plan. This process of monitoring and control is a long process that starts when the planning process has started and ends with the end of the project [4].

In this thesis, actual recruitment data are created as a percentage of planned data i.e. the actual performance is a percentage of what was planned. The manager monitors and controls the project at every update. It is possible for the manager to insert a previewed state of the problem for the next update. And on the next update he or she can insert the actual data for the situation and can compare the actual data with what he or she has planned. He or she can apply redistribution at a stage where it is felt necessary, when the duration of the project gets out of bound. This transferring of patient or redistribution of work-load also costs to the pharmaceutical company, as the country to which extra number of patients are being transferred or in simple words the country which is now getting more and urgent work to do will do it on higher price. So, the manager has to decide whether to apply the redistribution or not, taking into account the

trade-off between duration and cost, as being cost-effectiveness is more important than cost alone. If redistribution is chosen then, "when to apply redistribution?" is a question worth finding answer for.

From the beginning to the end of the project, the budget can be calculated which gives an update-to-update expenditure schedule of the project. As it is defined earlier that the treatment can take one or more phases, with each phase having a different cost and duration also shown in fig. 6. Actual budget at every update is calculated taking into account the phases completed by all the patients since the last update. In this budget, the transfer fee payable to the sites or countries getting the extra jobs is incorporated, which can certainly raise the cost of the project.

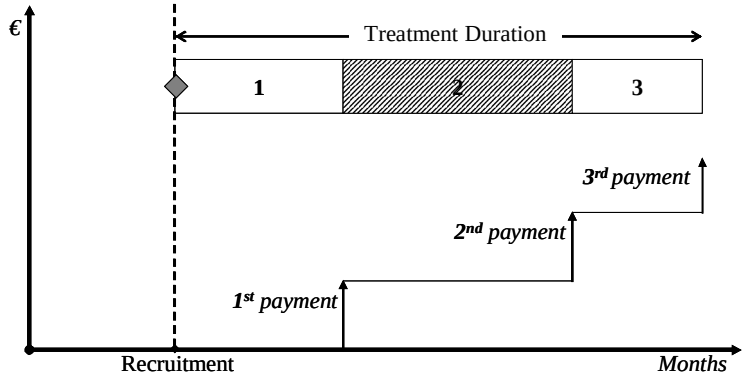

Figure 6. Phases of treatment with different durations and costs

In this thesis, we concentrate over the duration of the project, but we will present trade-offs between project duration and cost as we advance. There are multiple cases possible while monitoring the project of this problem, so there cannot be a single controlling action. These uncertain situations due to the presence of a number of variables make this problem interesting to study. For instance, in a situation where there is no site or country that can take extra work i.e. any transfer of work is not possible as some sites can be fully loaded and others may not be working as planned, then in this crisis the manager has as an exit strategy to open a new site or in other words to make a new contract in another country. But this decision or controlling action depends upon the economic feasibility and how much the completion of the project within planned duration or with the least possible lateness is important to the management or in our problem's case to the pharmaceutical industry.

II.3.3. Forecasting

Forecasting is a very difficult process of projecting or previewing what will happen by a certain time because predicting the reaction of an environment is not easy. For predicting the future precisely, accurate knowledge of the system and its environment is indispensable i.e. the strengths and weaknesses of marketing, R&D, production, financing, man-power and management [20]. And in TWLPs it is evidently difficult to predict precisely due to the size and number of variables involved, thus forcing us to watch the system closely for improved fore sighting. In this thesis a *linear hypothesis* will be presented, with the help of which the actual recruitment rates can be estimated. The date when the real point of inflection will occur can also

be found out with its help. This evaluation can aid us in doing redistribution once we know where we will end.

II.4. CONCLUSION

This chapter has discussed the problem under study, i.e. related to pharmaceutical industry, by first presenting the background. The condition of the pharmaceutical industry was described in detail along with the challenges faced in today's complex and competitive environment. Importance of project management skills and techniques was emphasized for success in pharmaceutical projects. Description of clinical trials and their significance to drug development was then presented, as found in literature.

A continuation of what was presented in Chapter 1, about transferable work-load projects (TWLPs) is presented. This led us to present monitoring and control, and duration optimization that were defined as the focus of our research, and then the problem under study was introduced. Requirements of clinical trials were outlined, with a discussion of their stages. First recruitment and then treatment are the two stages in a clinical trial. In this thesis, the duration of a clinical trial is optimized, using redistribution which is the distribution of the remaining work among the sites working on the project.

The planning of the recruitment stage of the clinical trial project was next elaborated. A patient recruitment plan and a contingency plan were suggested to establish for achieving the objectives successfully. The working or execution of any project comprises of three periods: learning, working and ending, which were discussed in the description of S-Curve. Monitoring and control of the project was then covered, which is the most important process in the life-cycle of the project. The chapter ends with the discussion of forecasting as used in this study.

In the next chapter i.e. chapter 3, we will discuss the topics reviewed for building the theory relevant to our problem. TWLPs will be discussed in detail, with focus on the globally distributed aspect of these projects. Project Management, as the fundamental part of this study will be explored for theory development. Chapter 3 will also try to answer the basic questions raised in the section, Research Focus. In chapter 4, the model along with its simulation will be presented. The results gathered by simulating a number of instances will then be thoroughly analyzed. Chapter 5 will discuss the extendible avenues of this problem, both specific and general areas for future research. The thesis will end with chapter 6 presenting a summary and conclusions from lessons-learned.

CHAPTER III

THEORY

III. THEORY

This chapter presents the project management and operational research literature explored for discovering the approaches that are related to the problem under study for increasing comprehension. This chapter will search for answers to questions put forward in the section 'Research Focus' of the last chapter. First, the motivation behind building sound knowledge of the subject is discussed, and then literature reviewed related to Transferable Work-Load Projects of distributed nature will be presented. For managing these projects, literature is reviewed for a number of processes in the project life-cycle such as Project Organization, Project Planning, Monitoring and Control, Forecasting and Risk Management. Special attention is given to the process of Monitoring and Control, for reviewing various techniques of progress measurement and control that are beneficial to our research. Then at the end, project management related software packages will be briefly discussed.

III.1. MOTIVATION FOR LITERATURE REVIEW

In majority of the literature on Project management, the projects are considered as fundamentally similar therefore this literature is general and not specific. But there is an utmost need for the development of industrial specific project management techniques. As the need for project specific literature is rising, it is equally important to know the types of projects, for which Shenhar [21] suggested a two-dimensional model for project classification as shown in fig 7.

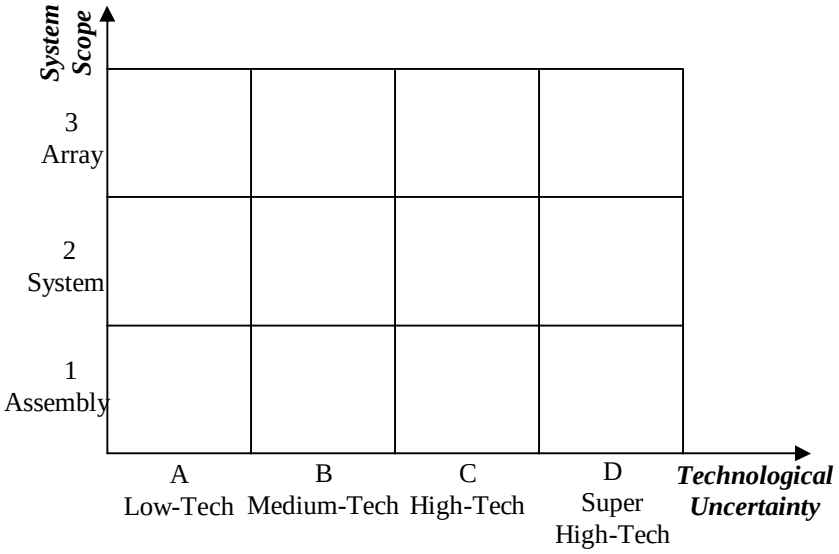

Figure 7. A two-dimensional typology of engineering project. **Source: [21]**

It is hypothesized that the result orienting activities and decisions are affected by the technological uncertainty (which is the horizontal axis). The terminology of Scope, used by PMI, is adapted for system complexity (which is the vertical axis). As we move horizontally from A to D, use of technology, communication and profit margins increase, while increased planning and

documentation will be required as we move vertically from 1 to 3. This model serves very well for getting a global idea of what to do right now and what to expect in future if we know the type of a project [21].

In this study we are interested in Transferable Work-Load Projects (TWLPs) as defined earlier. Literature on TWLPs is scarce, and thus defines our motivation to pursue in this direction. This lack of research on these types of projects depicts the need of more work and thus emphasizes the importance of this study of TWLPs. This study attempts to improve the understanding of TWLPs and then applies the knowledge gained for improving various processes. Managing large transferable work-load projects becomes an uneasy task if proper attention is not given to various variables in different processes of the project life-cycle. As described in PMBoK [4], project management is carried out by following five processes namely: project Initiating, planning, execution, monitoring and control, and closing. The interaction between these processes is shown in fig. 8, which also depicts that the process of Monitoring and control starts with the initiating process and finishes with the end of the closing process.

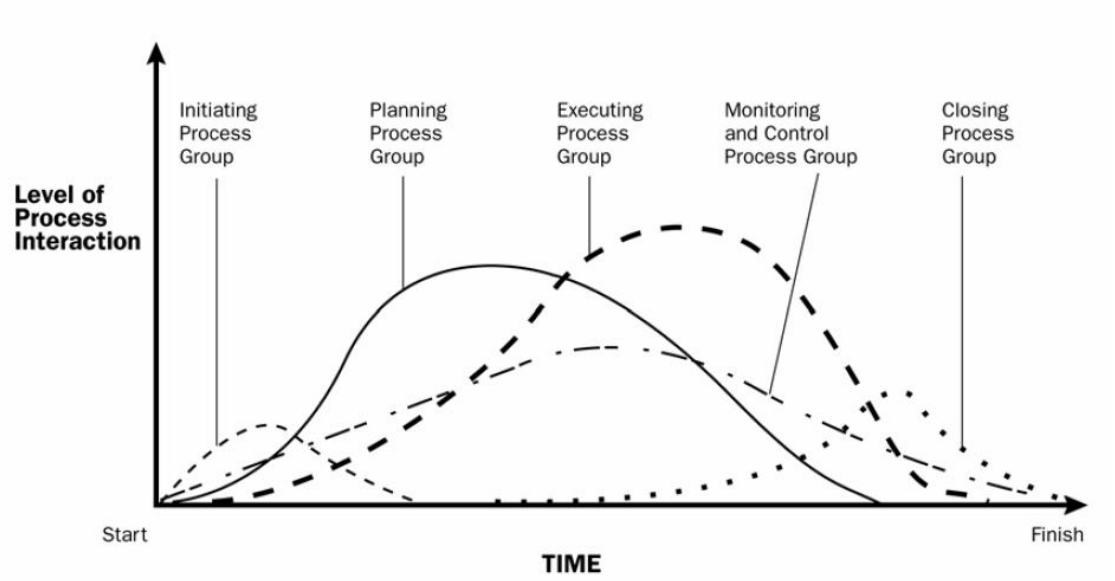

Figure 8. Interaction between project management processes. **Source [4]**

Large projects due to their span can be very complex and thus every process in their progression should be vigilantly achieved. That is why in this chapter, literature related to these processes is explored and will be presented in the context of TWLPs. We present in this chapter an evaluation of the application of project management to TWLPs or pharmaceutical projects; these projects fall in the category of *C3* type projects using the classification proposed by Shenhar [21]. The classification '*C*' is because these projects are high-tech and innovative projects using new technologies for drug development which also describes the level of uncertainty involved due to more dependence on new technology. Though these projects change their scope as they progress but their scope can be defined as '*3*', due to the dispersed nature of these projects with various partners at different locations putting their efforts for achieving a common objective. This C3 classification asserts the importance of the application of highly formal methods to manage these projects.

This thesis is based on finding answers to the questions raised in the previous chapter, as shown by the theory building process of fig. 9. Dashed lines connect questions to the relevant sections or sections in which the answer can be found. This chapter addresses the first three questions, while chapter 4 will answer the fourth:

1. What are TWLPs? And what are the tools for their management?
2. How to measure progress in a distributed environment?
3. How to re-plan and forecast?
4. How to optimize project duration by using *reallocation*?

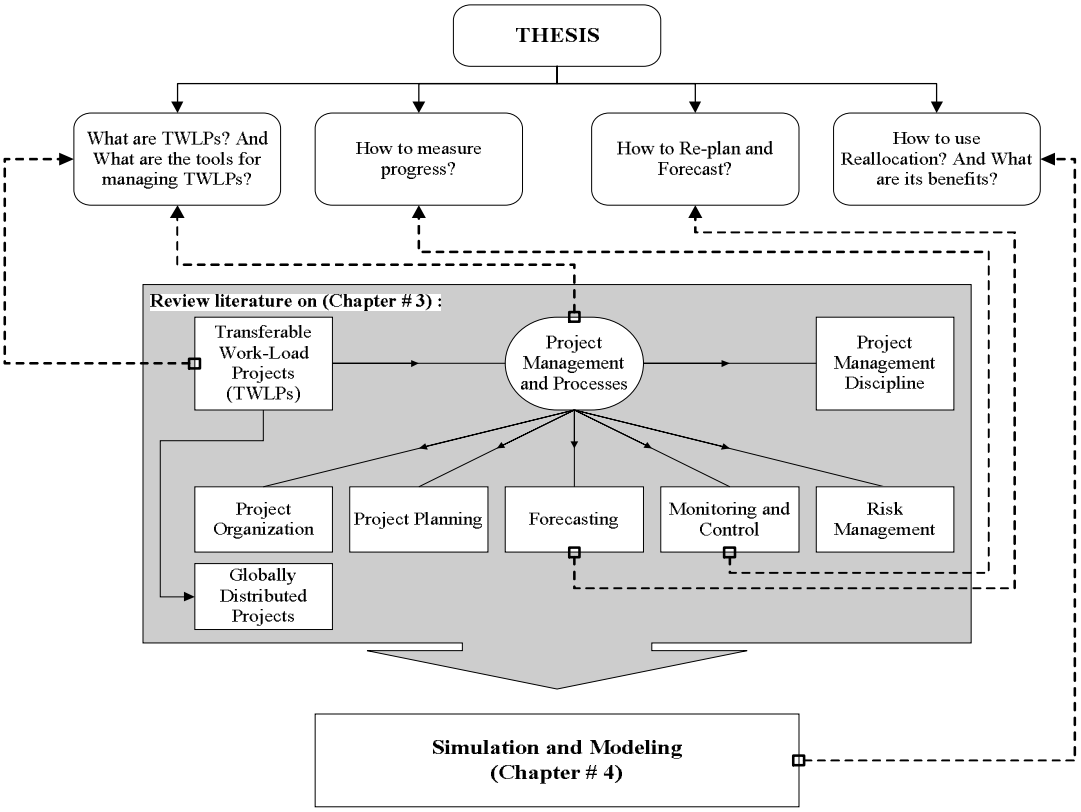

Figure 9. Theory building process of this thesis.

III.2. PROJECT MANAGEMENT DISCIPLINE

Project management as a discipline came under spotlight in 1970s, since then it has emerged as one of the most indispensable part of any process, business or industry. Though it is widely implemented, Maylor [22] points out using the data from interviews that most managers do not have any project management training. This article also indicates that project management body of knowledge, prepared by professional associations, is founded on empirical data and thus lacks strong theoretical base. The openness of project management to absorb any new idea or technique can make it theoretically strong, as techniques used by the Japanese industries like Toyota are worth studying to add non-traditional tools and techniques in parallel to the traditional project management methods [22].

On its course of extension, project management is sub-divided into new research fields and others come under its umbrella. Due to its wide application, there are a number of perspectives kept by various practitioners depending upon the project, industry and environment they are working in. According to Kolltveit et al. [23] there are six perspectives on project management as revealed by literature: *task, leadership, system, stakeholder, transaction cost* and *business by project* perspectives. It is concluded in this article that task and leadership perspectives are the most highlighted perspectives by the authors of project management books and articles, and it is suggested that stakeholder perspective should be given adequate attention in future.

In the last couple of decades new ideas are continuously being generated; the researchers and practitioners have guided the project management philosophy to change its direction of thought to shape its present ideology. Pollack [24] has discussed the paradigms that have shaped project management, namely hard and soft paradigms. Hard paradigm is a quantitative paradigm with problem solving as objective, while soft paradigm is a qualitative paradigm with problem structuring as objective. This article, on the basis of the past literature review, identifies hard paradigm as the most influencing paradigm on establishing the project management theory, but suggests a paradigm shift from hard to soft paradigm as a requirement of this new era.

Different industries customize project management techniques to suit their processes, environment and organizational culture. In an interesting article Wirth [25] tries to find the extent to which the project management profession is transferable between different industries. A sample of 41 projects from five different industries: construction, utilities, pharmaceuticals, information systems and manufacturing, is analyzed using scoring method for a number of project characteristics and it is concluded that the transferability across utilities, manufacturing and pharmaceuticals is feasible. A comparison of pharmaceutical industry with mature and less mature industries is shown in fig. 10.

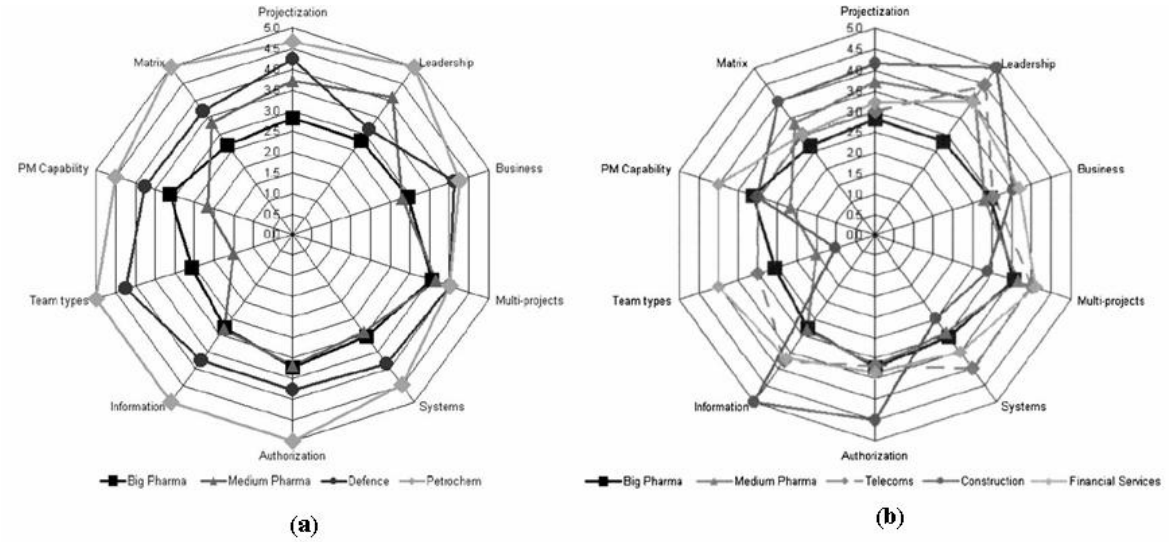

Figure 10. A comparison of pharmaceutical industry with: (a) more mature and (b) less mature industries. **Source [26]**

Cooke-Davies and Arzymanow [26] present an investigation of various project management models used in different industries, and they found that petrochemical and defense

industries are the leader as they use highly developed models by using scores of data from questionnaires and interviews. It is interesting to note that project managers from top pharmaceutical R&D companies have established a research society known as PMKN[19] for sharing their experiences, best practices and methods.

III.3. TRANSFERABLE WORK-LOAD PROJECTS (TWLPs)

This study relates to the monitoring and controlling of a transferable work-load project, i.e. a project in which work is transferable or interchangeable from one resource to another and even if the job processing has already started. We are especially interested in projects related to pharmaceutical industry, for some of them typically correspond to this description of transferable work-load projects. The resources in TWLPs have similar capabilities and because of this the work is interchangeable between them. Not much articles are found in literature about the problems of this type of projects.

An aspect of our interest in TWLPs is when these projects are large, distributed or global. This characteristic adds complexity to the problem and makes it interesting, worth studying and closer to real situations. Literature explored is presented here on the globally distributed character of a project.

III.3.1. Globally Distributed Projects

Globally distributed projects are large projects and they can be defined as large in respect of: *number of decisions to make, significant cost, size of information to handle, substantial risks involved and may be at different geographical positions;* and these projects are distributed such that: *they depend on more than one entity for their completion which may be two departments in one company or numerous collaborators distributed in different parts of the world ; moreover, we assume that the project (or at least significant part of it) can be indifferently distributed to one or another resource*.

Here it should be noted that firstly we are interested in the *distributed* nature of the project that means a number of resources present at different geographical locations are required to integrate their efforts to accomplish the project objectives. And secondly the *transferability* of the work between these resources interests us, as it presents an appealing problem to study.

The reason for discussing globally distributed projects here is because we are interested in the measurement of globally distributed progress. These projects where work-load is transferable within different and globally dispersed resources, present an interesting issue for which expansion of knowledge is desired. In globally distributed projects, the state of the project is most of the time ambiguous as every partner respond to the question of 'How everything is going?' by simply mentioning 'Everything is going fine', which is not the case in reality, and due to this the project monitoring and control can never be optimal. This is why there is so much emphasis on communication, monitoring and control in our problem.

For the development of theoretical foundation, an interesting assessment is presented by Fenema and Kumar [27], on the influence of the shared environment on the work interdependencies and, coordinating and controlling activities, by analyzing a matrix having four

[19] Project Management Knowledge Network

different configurations of globally distributed projects as shown in table 1. Projects may follow multiple configurations simultaneously or sequentially. For the better organization and control of global projects first their configuration should be found out so that we can preview the stimulus of the system. Authors imply the need for extending the body of knowledge of project management for the better organization of globally dispersed projects.

TABLE 1
FOUR CONFIGURATIONS OF GLOBALLY DISTRIBUTED PROJECTS *Source*: [27]

		Uncertainty of Interfaces between Modules	
		Low	*High*
Synchronicity of WBS & Geographical Work Allocation	*High*	**Configuration 1** Synchronous Allocation of Structured Work	**Configuration 3** Synchronous Allocation of Uncertain Work
	Low	**Configuration 2** Asynchronous Allocation of Structured Work	**Configuration 4** Asynchronous Allocation of Uncertain Work

The performance in this environment depends upon the working, adaptability and flexibility of partners because objectives are well defined but there are many factors (e.g. Division of Work DOW) not fully defined in the beginning, including cultural and strategic differences between partner companies [28]. Industries linked with large-scale projects face various troubles on the course of the projects due to the complexities. To measure the progress and then to decide on the basis of the results, 'What to do?' is one of these problems, a project manager has to face in this globally distributed environment. Egginton [28] addressed some major problems faced by projects of multi-national or multi-company nature and proposed effective measures to treat them. These multi-nationals are formed for fulfilling the needs of customers, supply and finance or for mutual cooperation [28]. MNCs[20] are required to acquire new techniques through global innovation for being competitive as discussed by Fallah and Lechler [29]. Effective global innovation is achievable by the efficient sharing of valuable information between globally dispersed projects, that's why the more disperse the company is, the more it collaborates with universities and institutes involving R&D [30].

These large distributed projects have a great impact on the organization, planning and execution processes of the project, so these processes must be ameliorated every now and then. An effective planning phase is vital for a large shared project to complete within resources and temporal constraints. Bachy and Hameri [31] discussed the importance of creating an effective project management plan, implemented in the early stages of a large project, which sets the basis for cost and schedule control through Work Breakdown Structure (WBS) for a R&D project of Large Hadron Collider (LHC). For better performance of these projects, communication between

[20] Multinational Corporations

partners is the most important of all the factors influencing the progress of the project. That is why Laufer et al. [32] rightly described the flow of communication in a project as the traffic in a metropolitan city.

Traditional project management sometimes appears to be obsolete while facing various inevitable situations in distributed environment. Jolivet and Navarre [33] describes a new form of management replacing the classical project management (traditional methods of managing projects in classical firms - 'matrix organization' and 'coordination by project') and they discovered by experience that it was more beneficial to manage big projects with a large unknown factor, using limited number of project specific criteria and management rules. This directive is based on 17 meta-rules (5 organizational principles and 12 management principles) applicable to all projects regardless of their nature and environment and they operate like the constitution works for a country.

III.3.2. Transferable Work

Work that is interchangeable or sharable between different resources without the need for different setups is known as *transferable work.* Examples of transferable work or problems having closely similar characteristic can be found in Production Management, Work-flow Management, Supply Chain Management and Vendor Management. In production management, more precisely Task Scheduling in parallel machines environment present a comparable problem. The problem under study in this thesis is a simple problem having transferable work, which can be placed under *Configuration 2* as defined in table 1 because the work is well defined but is asynchronously distributed in an uncertain environment; while more complex problems can be studied in future for getting more insight on the nature and effects of transferable work on a project's performance, cost, time and scope.

In the next section we will resolve the problem of management of transferable work-load projects.

III.4. PROJECT ORGANIZATION

For a globally distributed TWLP, the first and crucial step is project organization i.e. organizing all the required information and knowledge necessary for the accomplishment of project objectives. This step includes all the tasks required for project formation, integration and initiation, but we can observe that this step has its impression all over the project life-cycle. It involves the establishment of project objectives, problem statement, project scope statement or Statement of Work (SoW) and Work Breakdown Structure (WBS). SoW is an explanation of work to achieve the project goals, which should be vigilantly established along with the project specification, because any misinterpretation at this stage can lead to heavy monetary losses. Poor definition of the requirements and extreme optimism are the usual causes of the failure of a plan from the part of project manager [20]. A discussion on WBS will be presented in this section shortly.

As this step of project organization has a great impact on the project processes to come, a technique known as Concurrent Engineering (CE) can by used for organizing the most if not all of the processes of the project. If we say that today the competition felt by various industries is highest as compared to the industries in the past then it will not be correct as case studies show

that sometimes the situation was worse than today [34]. Industries for becoming competitive to their rivals employ the techniques of CE or Simultaneous Engineering or Design for Manufacture and Assembly (DFMA); various names for the similar thinking for better organization. CE will be presented later in this chapter.

III.4.1. Work Breakdown Structure (WBS)

Once the project objectives and SoW are defined, WBS can be established. A WBS is a simple presentation of the subdivision of complex activities in a project as defined by René Descartes (1596 - 1650) *"divide each difficulty into as many parts as is feasible and necessary to resolve it"*. Bachy and Hameri [31] clearly state that a WBS is the strength behind project planning, execution and control which is built as soon as the project starts and it is almost impossible to generate a proper activity network without establishing the WBS of the project. They explain how Product Breakdown Structure (PBS), Assembly Breakdown Structure (ABS), WBS and Organization Breakdown Structure (OBS) contribute to the project management plan of the Large Hadron Collider (LHC) which will provide a way to look further into the structure of matter.

Wysocky and McGary [35] define WBS as the hierarchical or tree type decomposition of work, requirements and services required for the realization of project objectives. A WBS hierarchy has a number of levels, starting with the objectives then activities, tasks and work packages. It has usually six levels as described by Kerzner [20] and where the work is decomposed at each level to arrive at a level where work is reduced to the smallest possible task known as *work package* which is the smallest chunk of work that can be easily and most clearly executed, monitored and measured. For the identification of activities in the WBS, two approaches can be used namely: top-down and bottom-up approaches, depending upon the choice of building the WBS that is either starting with the objectives and ending with the work packages or vice versa.

It is a very important point to keep in mind that an over-detailed breakdown results in extra administrative work and one too loose leads to poor control [31]. For simple and small projects a technique called *mindmapping* can be employed for generating a WBS, which is always built as a group work. Deriving from brainstorming, mindmapping is a graphical representation of an idea, method or problem that can help us in building WBS by viewing major activities globally; mindmapping can be done using a number of software packages like Microsoft Visio and Mindjet MindManager. However for large projects it is impractical to assemble the whole planning team for making a WBS, rather the lower levels of the WBS are completed by responsible departments. There is no one correct method to construct the WBS but generally these three are used: Noun-type, Verb-type and Organizational approaches [35].

III.4.2. Concurrent Engineering (CE)

We can find the concept of CE in the days of the single-craftsman, who is an individual responsible for all the activities in the product's life [36]. It is one of the best tools for the organization of projects. Smith [34] in his inspiring article presents the history of CE and constitutes that good engineering practice was in the past and will always be in the future, the integration of customer, manufacturing, and all other relevant functions into product design and development. For a distributed TWLP project this can be interpreted as the integration of various

partners in the project taking into account their individual competence, handling capacity and organizational culture. Even the suppliers may also join as a partner for the realization of a CE project, thus customer, supplier and manufacturer working for the same goal as one unit [37]. This is precisely the basic definition of a project, when steered by a real project-team.

In order to have a product reach the market earlier, CE is considered as inevitable and thus making a company more competitive with reductions in cost and time of processes with increased quality of the product due to the involvement of the customer as a partner in product development. There are numerous definitions of CE, but the one found very simple is, *CE is an integration effort of all aspects of product development, by performing sequential activities in parallel* [38]. On the other hand it is important to note here that if the cross-relations between these concurrent activities are increased, it will in turn increase the duration of activities and thus the duration of the project which will then be difficult to manage [39]. It is defined by Williams et al. [39] that as the relationship between concurrent activities increases the activities become more parallel and thus increases activity duration by raising what they call *feed-back loops* or a *vicious circle*. So, a balance is required to achieve for executing CE activities so that any feed-back loop can be avoided.

Four fundamentals of CE can be [34]:

1. Design for Manufacturing (DFM): product is designed by keeping manufacturing concerns in mind.
2. Establish Cross-functional Teams: to keep an eye on every major aspect of the project.
3. Customer oriented design: product is designed by integrating the customer in the design process and thus giving extra care to the requirements of the end user.
4. Time to market: is the determining factor of how well the above three ideas are executed for placing the product on the market in the shortest possible time.

For promoting CE practices in US industry, DICE[21] program is introduced by DARPA[22] initiative [36]. But Constable [40] in 1993 through a survey in a magazine *Engineering*, concludes that many industries were aware of CE but only 20% of them have decided to use it. Also he agrees on the basis of industrial case studies that manufacturing costs can be reduced as high as up to 70% by establishing a multi-disciplinary team. But in 2000 Ainscough and Yazdani [41] concludes on the basis of data gathered through an industrial survey for British industries that 100% of large companies (employees > 500) employs CE, while companies with 101-500 people only 63% and with 1-100 people only 50% practice CE.

The steps of implementation of CE or its basic elements differ among researchers and practitioners, but the creation of cross-functional or multi-disciplinary teams is considered to be the core by majority of researchers and industry practitioners. Also Probert [42] rightly defines Project Management as Guerilla warfare, so a well equipped, multi-skilled team is essential for better organization. Lawson and Karandikar [43] in their sparking article present various statistical conclusions about the steps of adoption of CE, barriers to CE and results of using CE. Hong Zhang and Daguang Zhang [37] have also given a review of CE.

[21] DARPA Initiative in Concurrent Engineering
[22] Defense Advanced Research Projects Agency

CE is an effective approach to manage a globally distributed project from its initiation till it is closed and thus partially answers the first question in our objectives as a tool to aid in managing TWLP. So, proper CE training should be provided to personnel involved in industries carrying out these projects. CE is more suited for the distributed side of a project but does not present a satisfactory solution for transferable work. From this study it can be inferred that if CE is implemented in companies jointly responsible for the realization of a project, then monitoring and control will easily be executed and the project will end well within monetary resources and time limits.

III.5. PROJECT PLANNING

As the proverb goes that "*a goal without a plan is just a wish*", the real start of a project is with the commencement of the single most important and continuous process in the life-cycle of a project i.e. planning. Kerzner [20] defines planning as *the development of a preordained plan in a forecasted environment*. It is an iterative process done for reducing risks, better comprehension of the project's objectives, better monitoring and control, completion within time, and cost savings. As the most important job of a project manager is to control the project until it has achieved its objectives, and to imagine having project control without a plan is like having a project deadline of 30th February i.e. close to impossible; it is rightly defined by Lewis [7] as, *no plan no control.*

Planning can be done on strategic, tactical and operational levels depending upon the type of decisions linked and the duration for which it is being done as shown in fig. 11. Long term decisions comes under strategic planning, while medium and short term decisions come under tactical and operational planning.

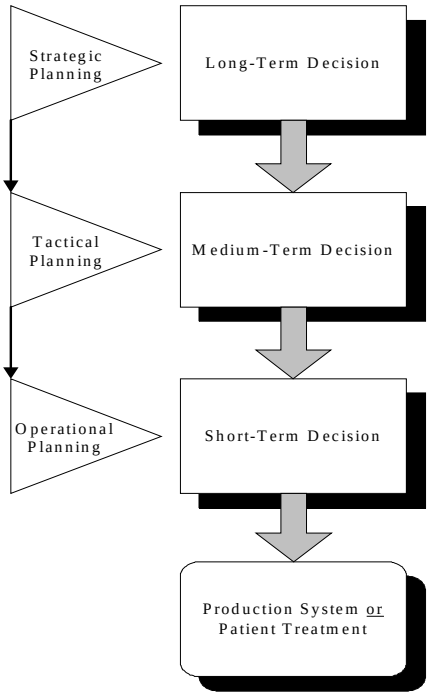

Figure 11. Multi-level approach to planning.

Here it should be kept in mind that the durations vary from project to project. Strategic planning requires more attention, skill, and vision; it provides the basis for the activities in the next two levels. As strategic planning requires more and more statistical forecasting for the determination of optimal strategy, it is frequently undependable. Tactical planning transforms the strategy devised in the last level into reality, so it is the implementation of the strategy. On the other hand operational planning is the planning of the day to day work or operations required to be carried out to achieve the long term objectives. Operational level requires efficient communication between every actor involved and for this frequent memos and weekly meeting are used to improve coordination.

Before entering into the phase of planning, the project has already passed through feasibility and benefit to cost analysis. It is interesting to know that about 50 percent of resources can be irreversibly engaged before execution begins, the reason being the required quality because quality should be planned-for and designed-in than to be inspected. It is also important that executives, project managers and line management should know their roles in the planning process and should be in agreement on the final plan for making it successful [20].

Planning starts with a good understanding of the project goals. Careful planning must be done if a project is complex, as it is the case for a large transferable work-load project. Kerzner [20] has pointed out the information required for project planning, which includes: the Statement of Work (SoW), project specifications, milestone schedule and Work Breakdown Structure (WBS). A project planning and controlling system is shown in fig. 12.

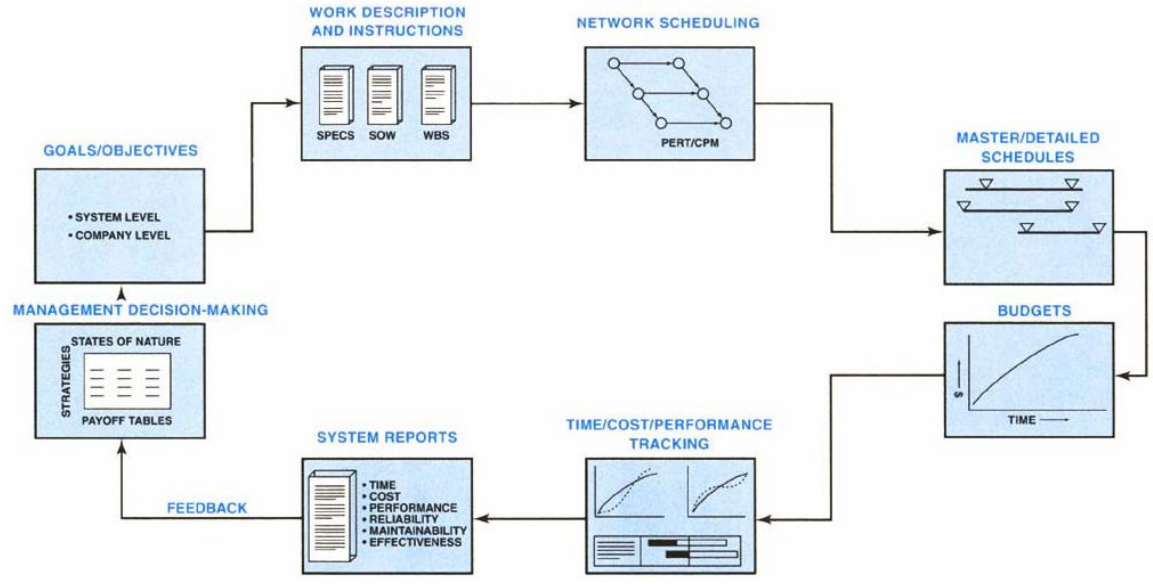

Figure 12. The project planning and controlling system. **Source: [20]**

These steps correspond to operational planning and may not be strictly applicable in all kinds of projects. After the establishment of the WBS, Network scheduling is done through PERT/CPM. Detailed or master schedules are also required for the doers as well as summary schedules are required for the planners. For this schedule creation, resources are first allocated and then leveled according to their availability. Creating a budget (i.e. planned costs) for the project becomes the last step in project planning, with execution as the next process in the life-

cycle of the project. Using Pareto principle, project managers spend 80% of their time doing planning and execution while only 20% of their time analyzing and evaluating [44].

Taking into account the risks at this stage of the project is very important as will be discussed in risk integration. In the execution of many projects sometimes re-planning is required, this situation frequently occurs in large transferable work-load projects, during monitoring and control, due to changes in the objectives or other variables of the project. With the help of the above tools, the planning and in turn the management of projects can become easier; a short discussion on these tools is presented here.

III.5.1. Network Diagrams

There are two ways of visualizing project scheduling [35]: Gantt charts and network diagrams. Network diagrams, due to their detailed representation of the relationships and dependencies between activities, are beneficial for large project i.e. having a high-level or global view of the details of a large and complex project. On the other hand Gantt chart is used for simple and short projects; it is the best tool available for a lower-level schedule representation i.e. for a specific collection of tasks, which removes confusions by using less detail. A *project network diagram* or *logic diagram* is a simple graphical representation of the order of activities to achieve the project objectives [35]. Once the WBS of the project has been built, network diagrams; Precedence Diagram Method (PDM), Program Evaluation and Review Technique (PERT), Critical Path Method (CPM) or Graphical Evaluation and Review Technique (GERT) can be established. During the establishment of WBS we weren't concerned about the sequence of activities but at this point the sequence has to be established by the means of determining the predecessors and successors of each activity, which will ultimately provide us with the project schedule.

There are two basic types of networks we find in literature: Activity-on-Node and Activity-on-Arrow diagrams, in which Activity-on-Node is mostly used. It is better to schedule at a level of detail that the team can easily manage. The rule of scheduling is to simply diagram logically i.e. what is possible and then deal with the issue of resources afterwards [7]. The fundamental objective of building these networks is the determination of the minimum project duration, which is the duration of the critical path on the network. Critical Path is the sequence of those activities which if encounters delay will consequently increase the project duration. There are two computational passes to calculate the duration of the project; first one is the forward computational pass for calculating the earliest start and completion times of activities, and the second is the backward computational pass for calculating the latest times. Floats or slacks are determined on the network i.e. the difference between the latest start and the earliest start of an activity. The activity which is critical has zero float.

PERT and CPM are widely used, but there are some basic differences between them [20]:

1. PERT is event oriented that is milestones are important in it, while CPM is activity oriented.
2. Percent Complete: It is close to impossible to determine percent complete in PERT due to its being event oriented, while in CPM it can be determined.
3. PERT is better for R&D while CPM is suitable for construction and process industry.

PERT/CPM are the main planning systems for large projects but as they consider all activities to be independent so if any problem arises they assume the cause to be the current activity which is not true in reality as most activities are dependent in large projects [45]. Once the network is completed, it is analyzed for its agreement with planned completion dates. If it is not the case then the schedule is required to be compressed by looking for activities that can be divided into smaller and parallel tasks, or by changing dependencies between activities which may generate a new critical path [35]. Once this is done, resources are assigned to the schedule and resource leveling is carried out if the schedule is still impossible to achieve depending on the available resources. This step completes the project schedule.

GERT is another network diagramming technique presented by Pritsker and Happ in 1966, devised for the analysis of stochastic networks. It is a tool which is based on the PERT and flowgraph theory integrating it with stochastic. This technique presents better results for decision making due to the derivation of probabilities for each path (or branch) taken and a probability function for the time required for this path. This advantage of looping or what-if scenarios comes at the price of the complications involved in using this technique which makes the analysis of a difficult problem more complex [46].

PERT/CPM does not work frequently and almost daily projects encounter cost overruns, late completions and other problems, and thus a new approach or an improvement is indispensable as justified by Rand [47]. This article is almost a review of the concepts defined in the novels of Eli Goldratt “The Goal”, “Critical Chain” etc., discussing “Theory of constraints” (TOC) and “critical chain”. These theories then became the basis of a number of software programs and new methodologies.

TOC is defined as [47]:

1. Identify the constraints (or bottleneck or critical chain is that part of the system which is standing between the project and its objectives)
2. Exploit the constraints; actions to minimize the bottleneck
3. Subordinate everything else; concentrate on the highlighted constraint only
4. Elevate the constraints; this step is similar to step 2 and thus searches for more ideas to minimize the bottleneck
5. If the constraint is broken, go to step 1

The core reason for project overrun is the misuse of the safety time (added within estimated times for each activity) which is defined by Goldratt as *student syndrome* i.e. no need to worry about time as safety time is already in the estimates and thus leaving everything to the last minute [47]. For correcting this psychological dilemma Goldratt proposes to add the safety time at the end of the project as safety or project buffer as shown in the comparison of this approach of TOC to PERT/CPM in fig 13.

Critical activities should not wait in any case for sub-critical activities; feeding buffers should be provided for this purpose at the end of non-critical activities. Likewise resource buffers may also be needed to secure the critical chain from resource shortage at the end of the critical activities [47].

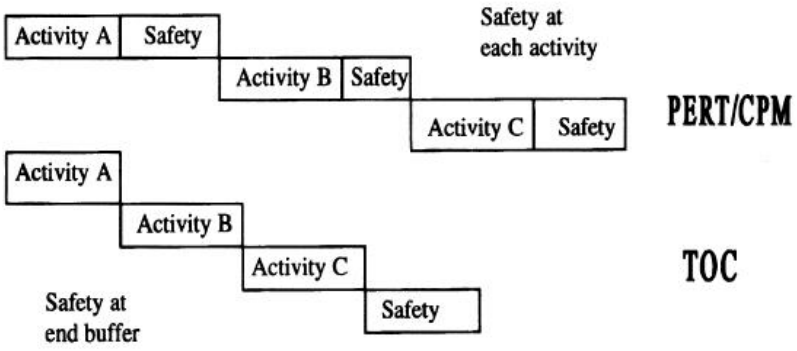

Figure 13. Comparison between TOC and PERT/CPM. **Source: [47]**

III.5.2. Risk Integration

There is practically no project that does not face risks, uncertainties or unanticipated changes. We have to be vigilant from the project initiation process till the planning process ends, as in these processes major risks are identifiable. Therefore it is not only possible but always preferable to integrate risks in project scope, definition, mission and ultimately in project plans. The first step in avoiding failure is to select a project after thoroughly investigating its pros and cons i.e. integrating risk analysis and risk management with project management. The project will then be selected or will be accepted with some changes after adapting for risks involved or will be rejected. Bougaret [48] presents an interesting valorization process of a project in a portfolio, taking into account the uncertainties and risks involved; this work proposes a model that is applied on a pharmaceutical R&D project for reducing uncertainties in drug development process and indicates the value of the project using new information at each step, thus adding flexibility to the valorization process.

The process of planning is important for risk management as there will be major undetected risks if there is no plan. SWOT analysis[23] is found to be helpful while doing risk planning. Also projects that require quick decision to make and execute require more risk integrated planning [49]. The importance of risk integration in planning cannot be overstated for large and complex projects like a globally distributed TWLP, as it will certainly shield against chaos and catastrophe ambushing in the project execution process.

Chapman and Ward [50] propose three types of plans for risk planning, which are developed in steps. First is the *reference plan* that is used as a reference to the project scope and schedule. Reference plan is a simple description of the project. Second is the *base plan* that is the basic plan, the foundation of project execution; it is established by integrating risk analysis into the reference plan. It contains project execution and implementation strategies, risk management measures, and various action plans. And third type of plans is the *contingency plan* that is used in the case of a specific risk arises i.e. they are supplementary plans to base plans. Base plans are operational when some risks don't realize but if they do, separate contingency plans will be operational. Base plans are built to respond proactively while contingency plans are built to respond reactively [50].

[23] SWOT analysis: An analysis of the Strengths, Weaknesses, Opportunities and Threats involved in taking a decision.

Projects that involve an inexperienced environment are more prone to failure than projects that have some history and well known steps for their management. These projects are known as projects having *agile environment*. Classical planning process as defined in the previous sections does not present a complete solution for these projects. Mostly we don't know "what unseen risks and uncertainties these new projects are hiding?" In this situation Chin [51] has described to perform detailed planning for shorter periods i.e. important milestones should be setup and planning is done up till these important positions. For these projects, the determination of activities is a difficult step as there is no past experience. Less detailed and frequent planning is better for projects that are described more risky, while more detailed and less frequent planning for less uncertain projects [51]. Network diagrams are preferable to Gantt chart for agile projects. Chin [51] defines project planning as a continuous process in agile projects as compared to classic project environment as shown in fig. 14.

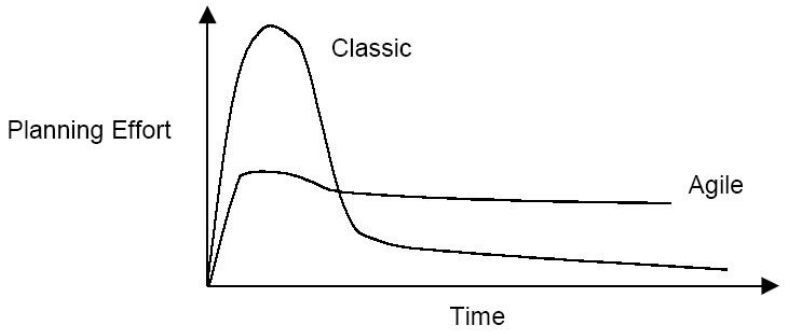

Figure 14. Planning in classic and agile project environments. **Source: [51]**

For small and simple projects traditional deterministic methods are appropriate but for large and complex projects it is better to apply probabilistic and, fuzzy or possibilistic approaches. Fuzzy approach is more theoretical than practical, but Bonnal et al. [52] propose an approach that uses temporal linguistic descriptors and which is easy to understand and to implement for project scheduling practitioners to take into account the possible outcomes.

III.5.3. Re-Planning

Re-planning is simply planning so it requires the same actions described in the planning process to be repeated, as defined by Lewis [7] that planning is to get ready to re-plan. The need for re-planning arises mostly in projects that have an uncertain environment or prone to frequent changes and globally distributed TWLP project is an example of such a project. Requirement for re-planning is reducible, if not completely avoidable. Effective risk management and other proactive project management techniques provide the solution for avoiding the need of re-planning, because if planning is done properly taking into account the significant risks and uncertainties then the plan will have everything that it requires and thus will be well equipped. As the plan is adjusted to the new realities, this new plan takes into consideration the changes anticipated in the future, i.e. forecasting which will be presented in a later section of this chapter shortly.

III.6. MONITORING AND CONTROL

Once the planning is finished and the project starts its execution process, it is utmost important to monitor the progress of the project. Knowing 'Where we stand?' is significant for better performance of a project, as it ensures timely completion of the project and within available resources and budget, through the necessary modifications as the need of re-planning arises. In this section, in addition to *Earned Value Analysis* we will discuss some other methods of progress measurement found in project management literature, which will also evaluate the accuracy of our planning, such as *Status Reports*, *Progress Plotting*, *Milestone* and *Resource Slip charts*, and metrics using *Performance Indicators*. As Egginton [28] marked "In projects, there is only one constant: change", so changes need to be properly monitored as well as controlled because proper monitoring and control guarantees the successful completion of the project avoiding unnecessary delays, and this is exactly what is expected of a project manager.

The renown Deming cycle which is used for problem solving is shown in fig. 15 [53], its two steps namely: check and act come under this process of monitoring and control, that is the hardest of all the processes in the project life-cycle; it can well place our finger on the pulse of the project and with the help of which we may eventually diagnose the right treatment if a problem arises [54]. Monitoring is a continuous process of finding the status of project progress for achieving better control [55]. Control has two connotations as defined by Lewis [7]; one meaning is power and supremacy, and the other is to check 'where we are?' against 'where we should be?'. And it is the later meaning, we are interested in. Timing is a key to proper control as right actions at the right time are indispensable for successfully achieving the objective as planned. The more control we have the lower will be the risk of project failure, maybe with a higher cost. Control can be carried out in three steps [35]:

1. Find out the progress or status of the project.
2. Determine the variance from plan.
3. Identify suitable corrective actions to bring the project back on track.

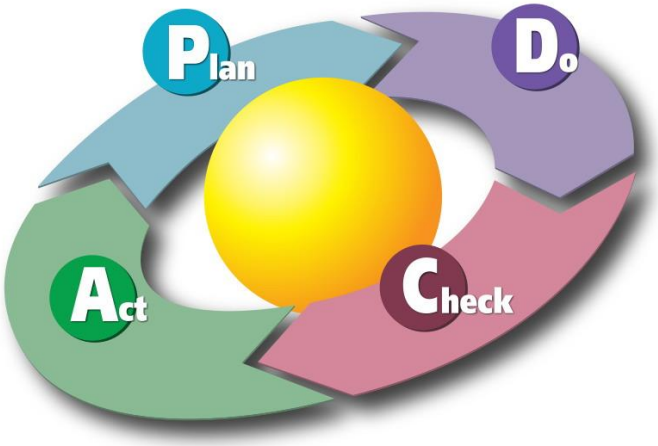

Figure 15. Deming Cycle. **Source: [53]**

This process of monitoring and control is core to our problem in this thesis. We mostly find ourselves carrying out controlling actions while executing a TWLP project albeit we are fortunate that the work is interchangeable or partitionable among various partners, so *redistribution* is the corrective action in this situation. If every actor in the project execution applies the proper project control then various status measuring techniques will only become a system of checks and balances, which is the ideal condition [7]. Coordination and collaboration between partners is essential for globally distributed projects; the nature of collaboration for different projects is shown in fig. 16, where a geographically dispersed project with intense collaboration is our target [56].

As the literature is reviewed for monitoring and control we find various interesting project control systems. A Multidimensional Project Control System (MPCS) is proposed by Rozenes et al. [57] where in a vectorial representation of the entire project, the gap between the planning and the result vectors is minimized with respect to the Global Project Control Specification (GPCS). Crawford and Bryce [55] proposes an improved 3D Logical Framework Approach (LFA) matrix also known as *logframe*, which is used for the purpose of building Monitoring and Evaluation Information System (MEIS) that provides information to the progress reporting process of aid projects. LFA is also a basic requirement for the approval of funding from majority of the leading donor agencies for global aid projects.

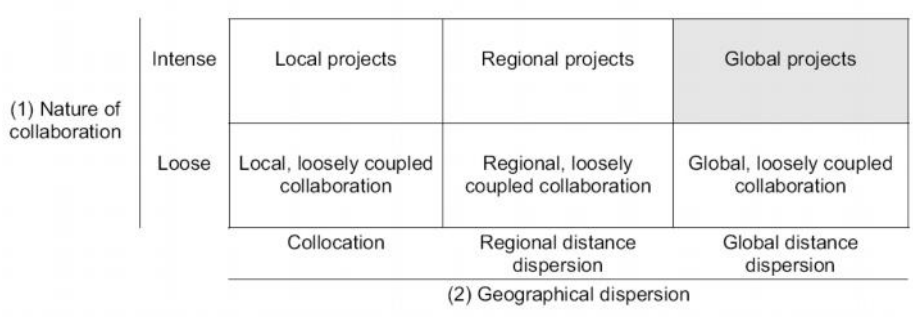

***Figure 16. Nature of collaboration for differently dispersed projects. Source* [56]**

III.6.1. Status Reports

Status reports are widely used as a controlling device. These are periodically prepared throughout the life of the project for sharing information, reporting project status, pointing to existing and anticipated problems and last but not the least, suggesting solutions. There are various types of project reports and an organization or a project manager can customize a status report as it suits them. There are five basic types of project status reports that can be generated using project management software [35]:

1. Current period reports: as the name implies it presents the information of the most recent or current times.
2. Cumulative reports: it presents the history of the whole project i.e. from the start to the current update.
3. Exception reports: this is for the senior management with a summarized project status.

4. Stoplight reports: it is a symbolic representation of the project situation i.e. if a project is going fine it is shown by green color on the top of the report or by red if there is a serious problem. It can be used for above reports.
5. Variance reports: it presents the deviation from plan.

III.6.2. Earned Value Management (EVM)

Earned value analysis, curves or matrices has served the purpose of project control for years, as EVM and its improvements are still considered to be an effective weapon in a project manager's arsenal as described by Pillai et al. [58]. In EVM theory, three basic elements (or indicators) universally used are:

1. Budgeted Cost of Work Scheduled (BCWS),
2. Budgeted Cost of Work Performed (BCWP) and
3. Actual Cost of Work Performed (ACWP).

Project Management Institute (PMI) has replaced these with Planned Value (PV), Earned Value (EV) and Actual Cost (AC) respectively in the PMBoK. Using the above measurements two variances can be generated:

1. Schedule Variance: SV=EV-PV and
2. Cost Variance: CV= EV-AV

Negative variances indicate behind schedule or cost overrun. Fig. 17 shows a mindmap of Earned Value Management System as discussed in various articles. This mindmap presents the EVM system's short introduction, history, basic concepts and advanced concepts as described in various sources.

Estimate at Completion (EAC) is also an estimate of cost or duration at the completion of the project as discussed in detail by Kerzner [20]. For global and complex projects it can be a very hectic task to do Earned Value analysis but it gives proper control on the project's output as the tradeoff [59].

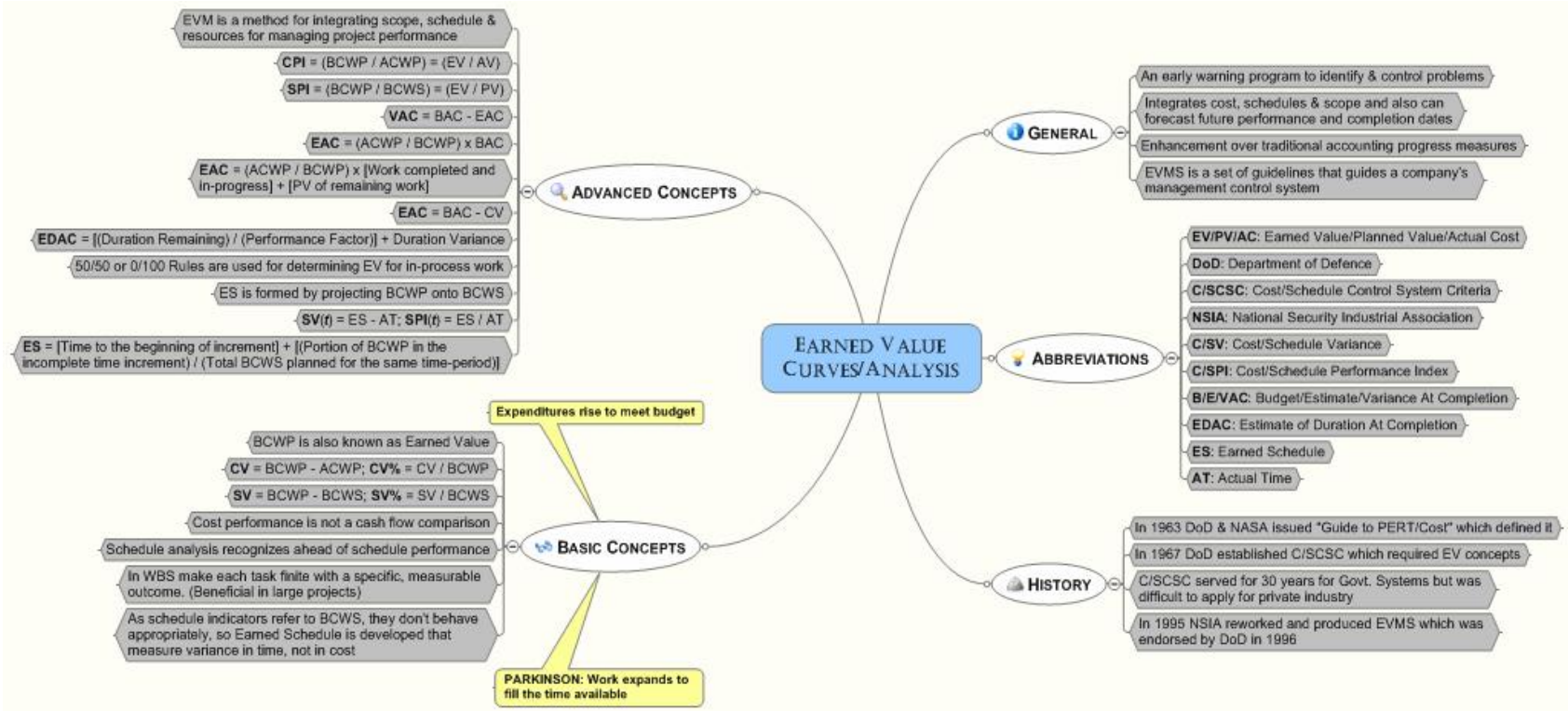

Figure 17. MindMap of Earned Value Management System. **Source: [20, 33, 69, 70, 71]**

III.6.3. Progress Plot

As the probability of project's finishing in time is illegible from traditional PERT or GANTT charts therefore Schmidt [60] proposes Progress Plot, a tool for monitoring and controlling a project, differentiating between small and large problems on the course of the project. For this, first the PERT chart is created and then only the critical path (CP) is taken out of it. This plot is drawn with horizontal axis representing time while vertical axis representing progress as a percentage of CP as shown in fig. 18. Control lines are used which are drawn to show a certain probability of completion of the project on or before schedule. The extent to which the actual progress line either deviates or hugs the original plan line represents planning accuracy [60].

It is important to note that if the manager during the course of the project deviates from the original plan, i.e. applying more or less resources than originally planned for a specific task, then the original control line probabilities are not valid during that task. The major advantage of the progress plot is that it reveals planning mistakes, as fig. 18 illustrates consistently underestimated task times [60].

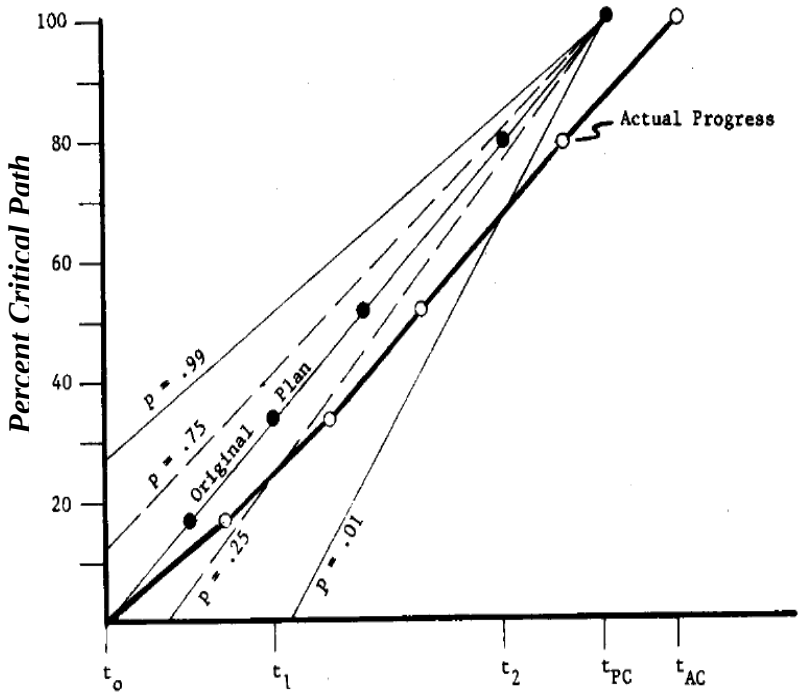

Figure 18. An example progress plot. **Source: [60]**

In fig. 18 the circled points are CP events while lines with a p-value are the control lines. Progress plot is like PERT in the sense that once the critical path is changed, the plot will no longer be valid and thus a new plot with the updated critical path is required to be developed.

III.6.4. Milestone and Resources Slip Charts

The accuracy of a PERT chart can be evaluated by a project manager by using Milestone slip charts as presented by Elphick [61] which is a progress evaluation tool incorporating a number of review stages on the course of the project, at which re-estimations can be done taking into account the delays and problems in the history of the project. Elphick [61] declared that past is a very strong pointer to the project manager as to how likely they are to move in the future. Fig. 19 shows the milestone slip chart as an example, in which the 1st row of dots show the expected milestone achievement dates which are also valid for the 2nd row, but at the end of the first quarter of 1991 as represented by the milestone C1 that it was not achieved on the date it was expected or planned.

This chart is a valuable indicator as if the project is on track or not but it tells us little about why the performance is poor. The paper further defines an expected profile of resource use for a project by constituting: the use of resources increases steadily during the opening phase and decreases steadily in the closing phase of the project. As now it is easy to determine the dates corresponding to the expected number of resources used, a resource slip chart can be made which depicts lack, excess or underestimation of resources [61]. These progress measurement tools can be used for transferable work-load projects integrating with forecasting to preview the future with the help of the past. And thus re-planning is done if redistribution of work is indispensable for the timely completion of the project.

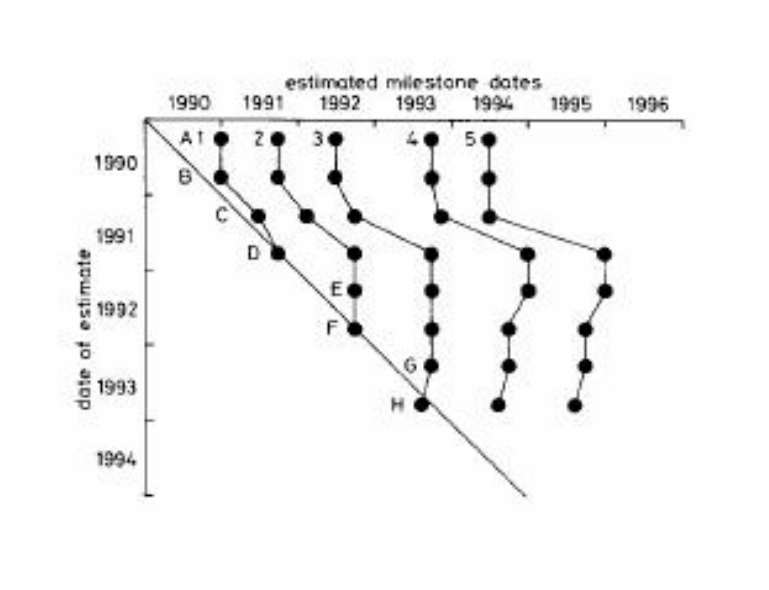

Figure 19. Hypothetical Milestone Slip Chart. **Source: [61]**

III.6.5. Performance Indicators

Various Performance indicators specific to a project also help a manager to evaluate his or her project's performance at any point in the life time of the project. Pillai et al. [58] proposes a model for performance evaluation of R&D projects by identifying important project phases, key factors in these phases and then integrating these factors into an Integrated Performance Index.

This approach is useful in transferable work-load project context as it deals with all the phases in a project collectively in comparison to traditional performance measurement approach [58].

Meyer et al. [62] also propose a model for the performance measurement of R&D projects focused on product platform and they called these measures as Meta-Metrics. Clemens et al. [63] presents an interesting case study done at the Nike's European Operations department, in which a performance measurement system (PMS) is designed, by developing and monitoring various distributed performance indicators (PIs), for the improvement of the supply chain process of the sportswear producing giant. They propose a "balanced scorecard" approach to performance measurement which will include various financial and non-financial measures along with the concentration over the possible relationships between measures. The scorecard consists of 3 layers and its prototype is developed in MS Excel. Performance measures should be adjusted as the information about a certain process is received so attention should also be given to the update of the performance measures [63].

For distributed projects a performance metrics is also discussed by Bourgault et al. [64] which is based on three dimensions: Value Chains which defines process of creating value for the customer, Balanced Scorecard for a more integrated and global view of the project and the partners involved, and building reliable Indicators. This paper urges the need for continued research in distributed projects for the development of a Distributed Project Measurement System [64]. Benchmarking can also be employed, as a method of comparing one entity with one which is considered to be the best, and is not copying or imitating but it is a structured approach to searching for the best way and thus to pick out the key performance indicators (KPIs) for improvement [65].

III.6.6. Other Considerations

Delay in progress arises due to various reasons such as, redesign, rework, lack of resources, lack of updated information and conflicts. Assaf and Al-Hejji [66] discussed reasons of delay and concluded from a construction point of view that owners blame contractors and contractors in return blame owners for delay, but according to them *change orders* from the owners is the most common cause of delay in construction projects. Thus delays in responses from the clients are the major source of delay, so should be given importance in large transferable work-load projects as this can cause a serious duration and cost overrun issues if treated with carelessness. This problem can be avoided if CE, already discussed, is used in which customers are included while designing and planning.

Though Configuration management (CM) has not met the wide industrial attention but CM techniques can also be employed for having up-to-date data throughout the project life cycle as inaccurate information leads to waste of time and efforts [67], while CE addresses the delays arising from redesign and rework. CM is indispensable for large transferable work-load projects as any small error can lead to grave failure of the project because the project is distributed among different partners at different geographical locations and the information at every location should be updated accurately.

III.7. FORECASTING

Forecasting is a very difficult process of projecting or previewing what will happen by a certain time because predicting the reaction of an environment is not easy. For predicting the future precisely, accurate knowledge of the system and its environment is indispensable i.e. the strengths and weaknesses of marketing, R&D, production, financing, man-power and management [20]. And in large transferable work-load projects it is evidently difficult to predict precisely due to the size and number of variables involved, thus forcing us to watch the system closely for improved fore-sighting. In literature we find forecasting methods for predicting demand or requirement for a certain product, commodity, human resources or entity in the future and methods for duration forecasting, which will be presented in this section.

III.7.1. Demand Forecasting

Forecasting is applied to a wide range of projects related to economics, product development, government policies, sales, weather forecasting, stock market, manufacturing, insurance, inventory management etc. to name a few. One thing should be kept in mind that it is impossible to predict the future correctly every time, no matter what specialized methods are applied. Forecasts are required for predicting the future demand or need: of a product in production, sales and yield, or of staff for a particular service. The methods of forecasting are divided into two major groups [68]:

1. Judgmental forecasting methods: produces qualitative results.
2. Statistical forecasting methods: produces quantitative results.

Judgmental forecasting methods depend upon expert's advice to forecast a certain variable. These methods are especially useful in situations where little or no historical data are present to help us predict the future. So we depend upon experience, common sense and collaboration to establish a forecast. *Bottom-up approach* is a useful method in which forecasts or estimates are provided by the salesperson that are then sent up and are accepted after a detailed managerial review; another widely used method in judgmental forecasting is using the advice of a panel of experts known as the *jury of executive opinion* [68].

Statistical forecasting methods use historical data for the forecasts, so it requires the drill of collecting huge amount of data for establishing a forecast of acceptable probability. For statistical forecasting, the notion of *time series* is used for historical data i.e. a series of random variables over time. This past data or time series can have a pattern which can be formulated into a mathematical model and that is used to generate forecasts. Three frequently found time series patterns are shown in fig. 20, and can be used for generating forecasts for a problem showing a pattern close to any of these models [68]. The methods widely used for statistical forecasting are: ARIMA or Box-Jenkins method, exponential smoothing, moving-average method and linear regression. Judgmental forecasting methods are used most often than statistical forecasting methods because data collection is quite difficult to carry out and also top management is unfamiliar to statistical methods but surveys show a change in this trend [68].

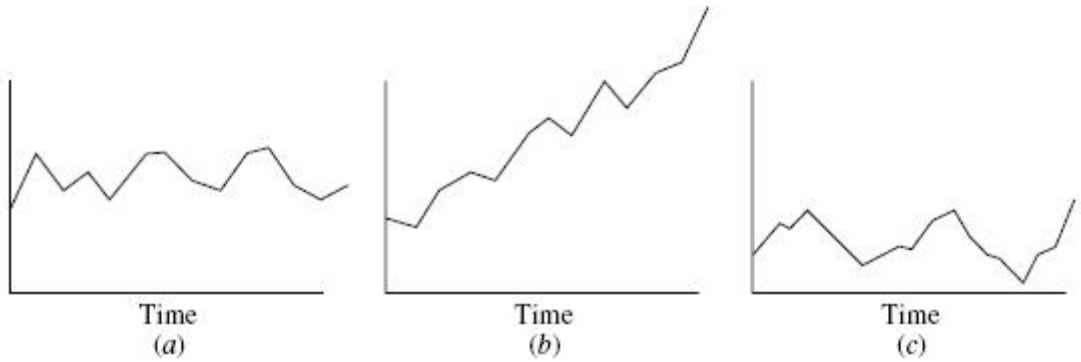

Figure 20. Time series patterns: (a) Constant Level, (b) Linear Trend, and (c) Seasonal Effects. **Source: [68]**

III.7.2. Duration Forecasting

In the objectives of any project, *planned duration* is the single most important goal to achieve, but managers find most of their projects getting late due to uncertainties or poor planning. Whatever the reason, at this point re-planning comes into play with the use of duration forecasting methods. There are three project duration forecasting methods [69], all generated from EVM theory:

1. Planned Value method,
2. Earned Duration method and
3. Earned Schedule method.

Numerous articles have explained and extended EVM theory for forecasting the project duration [69-71]. Using Estimate at Completion (EAC) or the proposed Estimate of Duration at Completion (EDAC) a project schedule can also be forecasted [70]. It is significant to note that Schedule Variance (SV) is not a reliable factor as it reverts to zero at the end of the project. It serves us the task of comparison only i.e. whether the project is behind or ahead of schedule and once the schedule is achieved albeit late SV will become zero. Therefore Jacob [70] proposes a formula for duration forecasting at a specific point in time which is a method of "Earned Duration":

$$\mathbf{EDAC = [DR + PF] + DV}$$

where,

DR = Duration Remaining = Planned Duration – Actual Duration, if PD<AD then DR=0

PF = Performance Factor = 1, if rest of the project will progress as planned *or*

PF = Schedule Performance Index (SPI), if rest of project will progress with current SPI

DV = Duration Variance = AD / SPI

EVM as an early warning system can communicate problems in project progress and thus enables the manager to take corrective actions before the project gets out of control. EVM is widely used for cost management but Vandevoorde and Vanhoucke [69] claim on the basis of recent research that now EVM is also used as a tool for project duration forecasting. In this article the authors have compared the three methods presented above and concluded that though all

methods have equal validity but Earned Schedule (ES) is the most reliable throughout the project. ES is a concept similar to Earned Value where *time* is used for measuring schedule performance in place of *cost*; the schedule indicators are also modified in ES to behave properly, for example the problem associated with SV (defined earlier) is rectified in ES [71]. Thus ES is a straight forward method, where the confusions arising due to the use of cost for measuring schedule in lieu of time, are eliminated.

As specified earlier, planning can be strategic, tactical or operational, so for strategic and tactical level planning it is difficult to forecast the status of the project. At these levels the uncertainty involved is high, as future changes year to year. But for operational level planned projects, forecasting can be done with high level of certainty as the variables are clearly definable. It is wise to consider more than one set of data for forecasting and also to critically examine the assumptions behind a forecast, as the professionals are generally too optimistic [20]. Academic literature is considerably less on the topic of project duration forecasting.

III.8. RISK MANAGEMENT

In the section of project planning we have already discussed the integration of risk in planning, but risk management is something that commences with the start of the project till its closing i.e. it is integrated in every process of project life-cycle. This is not only true for large and complex projects but also true for small projects. For pin pointing every risk the project is prone to face, the knowledge of project scope, objectives and mission is indispensable.

III.8.1. Risk

Risk is defined as *the consequence of an uncertainty*; it has an effect over the project objectives which can be positive or negative i.e. it can result in a loss or gain [72]. It is unfortunate that most people see risk as a threat to success or a bad thing, while if this perspective is changed this same risk can be used as a positive energy for finding improvements, strengths and opportunities in the same system which an instance earlier was shaky and unstable [50]. There are two types of uncertainties as indicated by Chin [51], internal and external uncertainties. Internal uncertainties are controllable while external uncertainties are mostly out of a project manager's control. If risk is identified for a collection of events then it is known as *Macro-Risk*, while if it is characterized for a specific event then it is known as *Micro-Risk* [49]. Risk can be illustrated by a simple formula [49]:

Risk = Loss × Likelihood

III.8.2. Risk Management Process

On the basis of the above description of risk, we can define risk management as an enjoyable process of finding threats and opportunities for the success of our project objectives. Risk management ensures that the project achieves its goals satisfactorily and safeguard against catastrophic situations i.e. ensuring there is no need for carrying out crisis management. Risk management process involves four fundamental steps [51]:

1. Risk Identification.
2. Risk Assessment.

3. Risk Treatment.
4. Risk Monitoring.

The steps in risk management process as defined by Cooper et al. [72] are shown in fig. 21. In risk identification, some basic questions about the uncertainties are answered. As Mulla Nasreddin[24] said *"good judgment comes from experience but experience comes from bad judgment"*, we can use past experience or bad judgments collected through brainstorming, risk checklists, surveys and questionnaires to help us in risk identification [72].

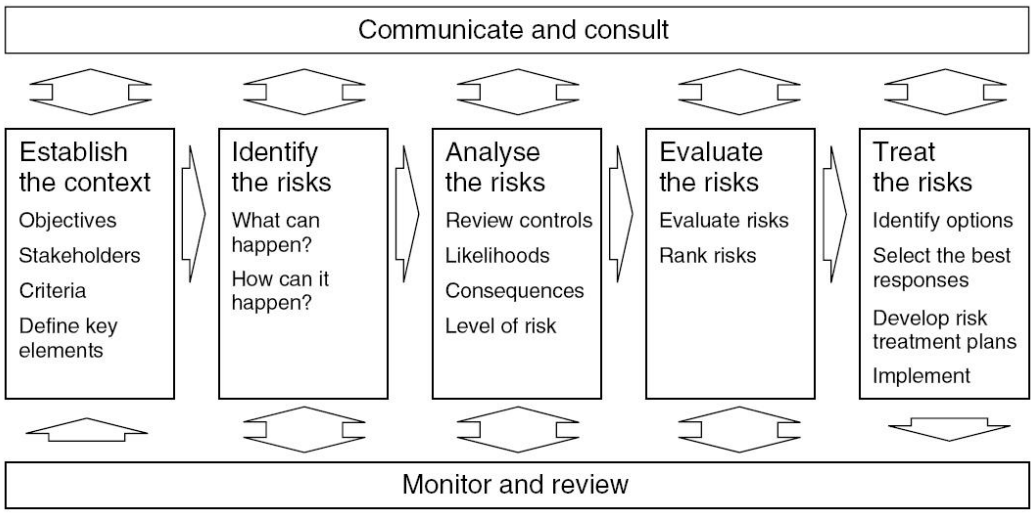

Figure 21. Risk management process. **Source [72]**

In the next steps of risk analysis and evaluation or assessment, a deeper knowledge of the risks is achieved along with the categorization or classification of these risks. This classification involves the concept of likelihood or probability of risk occurrence and the level of consequence or impact of the risk as shown by the risk assessment matrix in fig. 22, which is a qualitative risk assessment method. At this stage two methods are applicable for risk evaluation, namely: qualitative and quantitative methods. Quantitative methods require more effort than qualitative methods but in return they give precise results as a reward [49].

Quantitative techniques include statistical methods, decision trees, NPV, ROV[25], and risk modeling and simulation. But these methods have a problem of rigidity that means it is difficult to adapt them for changing circumstances of a project. In case of high uncertainty ROV is better than NPV which is used in situations of low uncertainties. For pharmaceutical problems, ROV techniques are especially useful and also ROV has the flexibility of changing decisions as appropriate for the changing environment [73]. ROV determines the updated real option (option having the best time to take a decision generating maximum benefits) in an uncertain and changing environment.

[24] Mulla Nasreddin was a 13th century satirical sufi figure who is claimed by numerous nations to be their own. His anecdotes and stories are famous for their message and humour.
[25] Real Option Value techniques

Risk modeling and simulation, as an extension of forecasting, is another quantitative method which is used mostly for large, complex or sensitive projects for revealing the impacts of risks simulating the original scenario using software packages like Microsoft Excel Spreadsheets, @Risk or Crystal Ball [72].

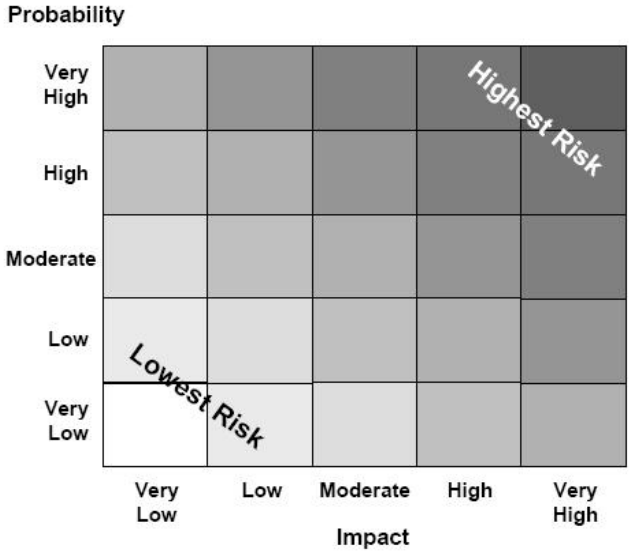

Figure 22. Risk assessment matrix. **Source [49]**

Once a prioritized list of risks is established, risk action plans or contingency plans can be made for the step of risk treatment, where a risk is treated on its occurrence. In this step risk prevention and avoidance strategies are implemented that use alternative paths in plan for avoiding a certain risks [51]. The tighter the plans are prepared for risk management the more will be the cost of the project so a compromise between the treatment of potential risks and overall project cost should be achieved, and a plan incorporating this is known as *risk efficient plan* [50].

The professional associations provide general risk management standards and guidelines, so project specific methods and guides are always a necessity. Cooper et al. [72] provide an interesting comparison of the standards devised by the professional sources such as: AS/NZS4360, PMBoK, PRAM Guide, M_o_R[26] guidelines. This comparison is helpful in determining the best standard to follow in a particular environment, albeit all these standards and guidelines cover the earlier defined risk management process.

III.9. SOFTWARE PACKAGES

Also many software packages now provide managers to monitor progress of their projects using controlling methods along with GANTT Charts. Gokhale and Bhatia [74] used Project Monitoring Data Acquisition System with Decision Support (PMDAS-DS), plus PERT for research projects, which is capable of storing plans, indicating bottlenecks, editing activities and reporting financial and milestone status. The software packages in market usually have various

[26] Management Of Risk guidelines

limitations and this is the frequently reported drawback, as very few project management software packages provide the capability of tracking shared resources as concluded through a survey by White and Fortune [75]. Software packages on the market can be divided into four categories [76]:

1. Project Planners
2. Simulators
3. Scheduling Tools
4. Personal Information Systems

The problem under study is similar to what Drabble [76] defines as *wide area project management* problem, where the business is dependent on geographically separated entities; the author argues that existing project management software packages does not provide even close to adequate management of projects, in this wide area environment. This paper proposes the establishment of agents responsible for the whole planning process which can be applied to other processes; the information from other project management tools is then integrated using a common project management communication language, that will eventually provide a great deal of help to project manager in making important decisions. Whatever software package is chosen for implementation, it is necessary to develop human resources accordingly with the proper project management and the particular software's training [20].

III.10. CONCLUSION

This chapter presented a review of the literature related to our study, starting with project organization and planning. Different methods of monitoring and control were also discussed. Towards the end, the literature on forecasting and risk management was evaluated. This chapter provides the important theoretical basis for the problem under study and becomes a prequel to the next chapter.

In the light of the information gathered in this chapter, the next chapter will model the problem under study and then simulate it. An analysis of the results from the simulation will also be discussed.

CHAPTER IV

SIMULATION AND EVALUATION

IV. SIMULATION AND EVALUATION

Simulation is done to gain better understanding of the behavior of a problem in relationship with the whole system and its environment. It is carried out in a number of steps, in which the most important is the formulation of a simulation model. *Simulation models* are formulated to simplify and represent complex problems involving a large number of variables and parameters [77]. Some general steps of simulation are as follows as listed by Hillier and Lieberman [68] :

1. Formulate the problem and plan the study.
2. Collect data and formulate the Simulation Model.
3. Check the accuracy of the Simulation Model.
4. Select Software and construct program.
5. Test the validity of the Simulation Model.
6. Plan the simulation to be performed.
7. Run the simulation and analyze the results.
8. Present recommendations to Management.

The problem under study was presented in chapter 2, which is related to the monitoring and control of the phase of clinical trials in drug development and thus is related to the pharmaceutical industry. In this chapter a mathematical model of the problem will first be formulated. Then the simulation of the phase of clinical trials will be carried out using a computer. After completing the simulation process, the results will be evaluated and thoroughly analyzed. For this purpose an in-depth theoretical background was presented in Chapters 2 and 3, which becomes a fundamental for building the simulation model.

IV.1. MODELING

In order to formulate an acceptable model representative of a problem, data relevant to the problem are required which include different variables and parameters. Winsberg [78] defines a process of model building which in five steps transforms an initial mechanical model into a true representation of the phenomena of interest. In this section a mathematical model of the problem under study will be presented.

The problem in this thesis is defined in detail in Chapter 2; here a summarized reminder with an extension will be presented. The problem involves the determination of the effectiveness of a medical treatment by carrying out clinical trials. Patients are first recruited or admitted and then treated, so *recruitment* and *treatment* are the two stages of the project. These patients are recruited at sites distributed globally in a number of countries or sites. The number of patients required to be recruited in each country are divided depending upon the population, competence and handling capacity of the respective country. Recruitment and treatment, as planned, take 18 months (globally) and 12 months respectively for each patient. The stage of treatment has three phases, each phase with a certain part of treatment, duration and a different cost.

IV.1.1. Planning

Planning for the recruitment stage is produced by experience and benefiting from previous studies. Planning defines the number of patients to be recruited on a monthly basis, thus a schedule is established for this problem. It is also important to note here that in pharmaceutical projects it is known by experience that a number of patients will quit the system before their treatment ends. This aspect is taken into account while creating recruitment schedule and budget.

IV.1.1.1. Schedule

Every country has the full set of resources and competencies required for accomplishing a treatment, and thus each country is completely responsible. Schedule for an instance of the problem is shown in table 2 which depicts the cumulative number of patients planned to be recruited on a monthly basis. This schedule recruits more patients than required, safeguarding against the number of quitting patients which in this case is taken as 20% of the total recruitment.

The data for planning are developed from experience and using previous studies, and which are quasi-linear. Due to this characteristic of the data, this problem is described in this thesis in the form of a linear model. Linear regression is used on the data for transformation. As we get the schedule ready, we calculate the scheduled monthly budget depending upon the number of patients treated and the phases they are in, as described earlier that treatment is divided into three phases each with a different part of treatment, duration and cost. Each country is paid for the phase completed by a patient since the last update. Patients quitting the system before the completion of their treatment are also incorporated in the budget.

TABLE 2
SCHEDULE OF PATIENTS RECRUITMENT FOR FIVE COUNTRIES

MONTH	COUNTRY 1	COUNTRY 2	COUNTRY 3	COUNTRY 4	COUNTRY 5	CUMULATE
Dec-04	0	0	0	0	0	0
Jan-05	0	0	7	7	9	23
Feb-05	0	9	22	29	39	99
Mar-05	9	39	57	69	84	258
Apr-05	27	99	122	144	169	561
May-05	57	199	242	274	324	1096
Jun-05	102	349	402	434	514	1801
Jul-05	132	476	522	554	654	2338
Aug-05	152	566	622	654	762	2756
Sep-05	212	716	782	814	949	3473
Oct-05	312	886	962	994	1140	4294
Nov-05	432	1046	1132	1164	1314	5088
Dec-05	562	1186	1282	1314	1468	5812
Jan-06	692	1316	1427	1459	1627	6521
Feb-06	821	1445	1587	1619	1807	7279
Mar-06	951	1575	1747	1779	1989	8041
Apr-06	1071	1695	1892	1924	2155	8737
May-06	1185	1809	2033	2065	2311	9403
Jun-06	1285	1909	2163	2195	2452	10004

As the planning is completed and the project enters the execution process, monitoring and control of the project becomes more important. At this moment real recruitment data are generated depending upon the performance of each country. Actual performance of countries can vary i.e. some countries can recruit faster or can work as planned, while others can be slower or behind schedule and thus introduce a lateness in the schedule. There are two approaches to achieve results for this problem namely without-reallocation and with-reallocation[27], will be discussed in detail later. If reallocation is applied then a number of patients are required to be

[27] The terms redistribution, reallocation and with-reallocation are interchangeably used in this thesis.

transferred from a slow to a fast working country. But this is done at a cost which will be added as transfer costs to the actual cost of the project. It is important to mention here that the POI is taken as fixed and equal for all countries that means all countries will complete their learning periods on the same date. The problem where each country has a different POI can be treated as an extension of this study.

IV.1.1.2. Linear Hypothesis

The linear model assumed for our problem led to the definition of a *Linear Hypothesis*. The explanation of the point of inflection POI is already presented in Chapter 2 under the discussion of S-Curves; POI is the point of change where the learning period enters into the working period. A POI is planned in the schedule but due to certain reasons in the execution of the project this POI may not occur as scheduled so for the determination of "When the real POI will occur in time?" and the real rate of recruitment in the working period, this Linear Hypothesis is used which is a relationship between the real and planned states of the project. It is also equivalent to SPI (Schedule Performance index). It is based on the linearity of the learning and working periods of the planned and real curves, as in fig. 23. Linear hypothesis:

$$SPI = \frac{I}{I^0} = \frac{s_l}{s_l^0} = \frac{s_w}{s_w^0}$$

where,

SPI = Schedule Performance Index

I^0 = Date where the planned learning period ends

I = Date where the real learning period ends

s^0_l = Recruitment Rate for the previewed learning period

s^0_w = Recruitment Rate for the previewed working period

s_l = Recruitment Rate for the real learning period

s_w = Recruitment Rate for the real working period

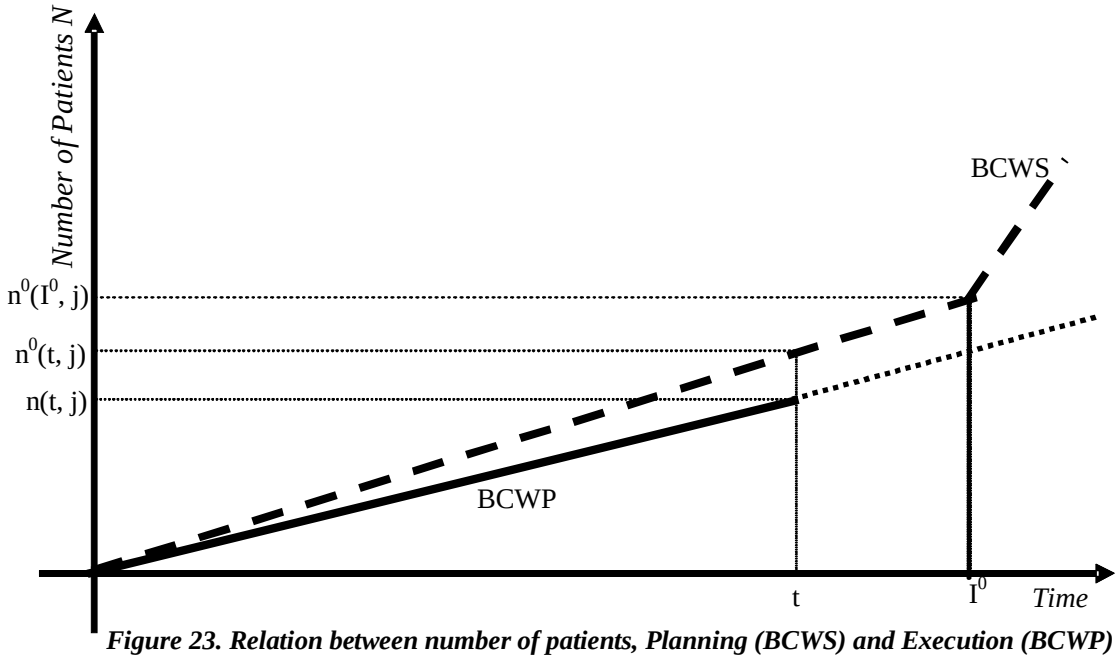

Figure 23. Relation between number of patients, Planning (BCWS) and Execution (BCWP)

In Planning:

Earned Value theory can be used for the explanation of Linear Hypothesis. For this the curves of Budgeted Cost of Work Scheduled (BCWS) or Planned Value (PV) is used to represent the planning in terms of time and not in cost, as in fig. 23. Also Budgeted Cost of Work Performed (BCWP) is used to represent the work completed as compared to what was planned during the elapsed duration.

Let us consider one unique country "*j*", the objective for which is the recruitment of $N^0(j)$ patients. The scheduled number of patients to be recruited at a date t [counted from the beginning date t=0] is $n^0(t, j)$ and follows a two-slopes curve as shown in fig. 23.

- During the learning stage:

  For $t \leq I^0$, $\quad d[n^0_l(j)] / dt = s^0_l(j)$,

  and $\quad n^0_l(t, j) = s^0_l(j).t$

  until a date I^0 corresponding to $n^0_l(j)$ patients recruited.

- During the working stage:

  For $t \geq I^0$, $\quad d[n^0(j)] / dt = s^0_w(j)$

  and $\quad n^0(t, j) = n^0_l(j) + s^0_w(j).(t - I^0)$

- The finishing date $T^0_f(j)$ for this country is thus:

$$\boldsymbol{T^0_f(j) = I^0 + (N^0(j) - s^0_l(j).\, I^0) / s^0_w(j)}$$

Here, the superscript "0" denotes planning.

***In Real*:**

At the beginning of learning phase, the real number of patients recruited is $n_l(t, j)$. As this number is an indicator of work progress, we can plot the BCWS curve on a number-of-patients-versus-time diagram. On this diagram, the actual number of patients recruited $n_l(t, j)$ is representative of the Budgeted Cost of Work Performed (BCWP) or the Earned Value (EV).

- We thus can define a schedule-performance index $SPI(t)$:

$$SPI(t) = \text{BCWP}(t) / \text{BCWS}(t) = \text{EV} / \text{PV} = n_l(t, j) / n^0_l(t, j)$$

If it appears that this index exists (which means that it is constant: $SPI(t) = SPI\ \forall t$), as it is the case in fig. 23 where, at any date between 0 and t, BCWS and BCWP (or $n_l(j)$ and $n^0_l(j)$) are in the same ratio, we can assume that this schedule-performance index reveals a steady difference between expected and measured recruitment rates, and that this index will not be affected whether we are in the learning or the working stage. Thus proving the Linear Hypothesis for the country "*j*":

$$SPI = n_l(t, j) / n^0_l(t, j) = [d(n_l(j)) / dt] / [d(n^0_l(j)) / dt]\ \forall t$$

$$\Rightarrow \boxed{\boldsymbol{SPI = s_l(j) / s^0_l(j) = s_w(j) / s^0_w(j)}}$$

IV.1.1.3. Budget

As the working capabilities and environments of countries are considerably dissimilar therefore their S-Curves will be dissimilar too. The reason for this is different recruitment rate (d)

of countries. As described earlier there are two stages in this problem namely: recruitment and treatment of the patients. Planning is done for the recruitment of patients and completed with a schedule illustrating the number of patients scheduled to be recruited at every update until the total number of patients are admitted or recruited by each country.

Scheduled budget is created with the help of this planned recruitment schedule. For making a scheduled budget, the following information is produced: Recruitment dates (*Rd*), Durations (*D*) and Quitting dates (*Qd*). *Rd* for a patient is generated as a uniform random number between two dates within which the patient was planned to be recruited according to the schedule. Then *D* for quitting patient is determined as a uniform random number, as for the others *D* is simply the standard duration of the treatment. Quitting dates are then calculated as a sum of the Recruitment date and Duration.

$$\mathbf{Qd = Rd + D}$$

As *Qd* is calculated we can determine when each patient will complete the three phases of treatment as shown in fig. 24. This phase calculation is very important because depending on it the scheduled budget is made. And as described earlier that each phase of treatment has a different cost, so from update to update scheduled budget is established by determining how many patients have completed a particular phase since the last update. The determination of the duration D of the project indicates the duration the patients stayed in the system. And if D is lower than the standard duration for a patient then it means that the patient has quitted before the treatment ends and thus will be incorporated in the phase calculations, which will be used for budget estimation.

Patient	Random No.	Rec Date	Duration	Quit Date	Phase 1	Phase 2	Phase 3
1	0.734940827	6	365	371	128	250	371
2	0.661685407	24	365	389	146	268	389
3	0.900091708	21	365	386	143	265	386
4	0.625094116	2	365	367	124	246	367
5	0.864227116	22	365	387	144	266	387
6	0.943426073	31	365	396	153	275	396
7	0.499234259	16	365	381	138	260	381
8	0.588666141	2	365	367	124	246	367
9	0.677976906	9	365	374	131	253	374
10	0.541588247	48	365	413	170	292	413
11	0.35242039	62	365	427	184	306	427
12	0.494880378	54	365	419	176	298	419
13	0.881756604	42	365	407	164	286	407

Figure 24. Phase calculations of a country for making scheduled budget

Scheduled monthly cumulative budget of an instance is shown in fig. 25. Here it can be seen that in the beginning of project there are zero payments to countries because not a single patient has completed the first phase of treatment. But as project progresses patients start to complete the first and then second phases and so countries are paid depending upon how many patients have completed which phase.

Considering the number of variables involved this problem is interesting to study and also presents a challenge to manage for a project manager. POI, performance, number of quitting patients, phase durations and costs, and recruitment rates are among variables of this problem which make this problem complex. We are interested in the minimization of the project duration

at a lower cost of the project with the knowledge of how the problem reacts in a particular situation, as multiple situations are reachable in this problem. We also want to analyze the effect of the frequency of using work redistribution or reallocation on the duration and cost of project.

MONTH	COUNTRY 1	COUNTRY 2	COUNTRY 3	COUNTRY 4	COUNTRY 5	CUMULATE
Dec-04	0	0	0	0	0	0
Jan-05	0	0	0	0	0	0
Feb-05	0	0	0	0	0	0
Mar-05	0	0	0	0	0	0
Apr-05	0	0	0	0	0	0
May-05	0	0	9000	9000	12000	30000
Jun-05	0	10500	16500	27000	39000	123000
Jul-05	13500	40500	48000	58500	66000	349500
Aug-05	24000	82500	88500	105000	120000	769500
Sep-05	43500	150000	196500	201500	257500	1618500
Oct-05	63000	219500	251500	276000	339500	2768000
Nov-05	70000	275500	292500	304000	345500	4055500

Figure 25. Scheduled monthly budget in €

IV.1.2. Monitoring and Control

As the planning process ends, actual recruitment data are produced from one update to another depending upon the performance of countries. Performance (*P*) can be defined as a percentage of the planned recruitments i.e. for example a country can work with a performance of 80% of what was planned. So, multiple cases are achievable by varying both the performance in the initial stages of actual data generation and the recruitment rate in later stages of the project for each country. The manager has to decide at every update, what controlling actions are vital to keep the project within planned project duration.

For producing the data for actual scenario, POI is also required, so should be provided. Once the POI and the performance of a country is provided, the real recruitment data, i.e. the real number of patients recruited, can be generated till the next update. Data are generated from update to update with the provided performance for a country until the POI is achieved. Once POI for a country is reached, the manager can now define a previewed recruitment rate for that country to work with it until the next update. Obviously if the country has started with 100% performance i.e. as planned, manager can let it work with the planned recruitment rate. On the next update, as the manager can view how the country has performed so he or she can compare planned performance with real or actual performance. Accordingly manager can change the previous previewed recruitment rate with the real recruitment rate. With this he or she will also provide the previewed recruitment rate for the duration until next update and this process of monitoring and control goes on to produce real recruitment data until all the patients required to be recruited by a country are admitted.

There are two approaches to this problem, namely: “Without-Reallocation” and “With-Reallocation”. In without-reallocation as the name implies, we simply do nothing and let the project go on as was described previously, raising a situation where some countries are not actually recruiting as planned i.e. are working poorly while others are working as planned or going in advance of planning. In this situation, completion date of the last country completing recruitment becomes the finishing date of the project. Here it should be noted that: *if we don’t*

start well then we will not end well either. Two behaviors of a country's performance are shown in fig. 26, with (a) as working better and (b) as working slower than what was planned (shown by the solid line).

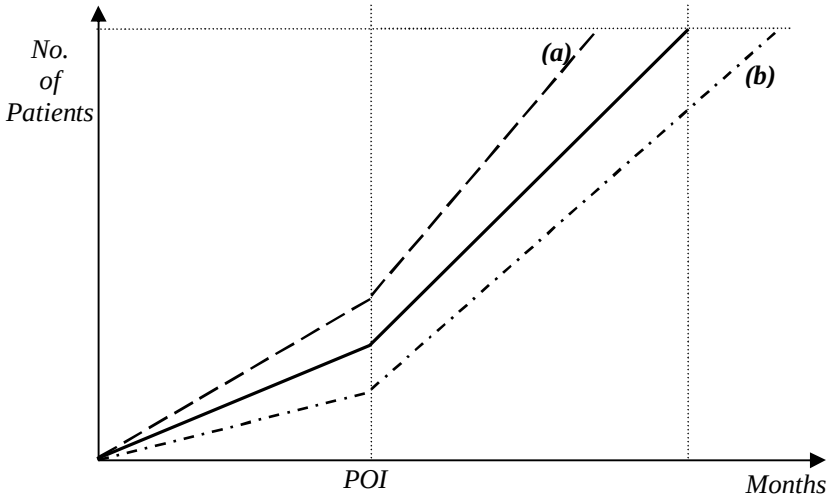

Figure 26. Behaviors of a country's performance along with the planned performance (solid line)

On the other hand if with-reallocation is used, the total remaining number of patients will be shared among countries depending upon their rate of recruitment i.e. countries having (a) behavior as in fig. 26 will get more patients to recruit while countries with (b) behavior will get to recruit less patients. In this way the project can be ended as soon as possible with little or no lateness. Also every country will end work on the same date if with-reallocation is used. In this study the frequency of using with-reallocation is also investigated, when using redistribution of work produces better results for project duration and cost.

This reallocation comes at a price which we call as transfer costs as it is the cost of transferring or assigning more patients to a country that has initially less patients to recruit. Also there could be a situation in which the work can be performed at a new site in a different country different than those initially in the project. This allocation of work to this new country will also come at a cost, increasing the scheduled budget; therefore the results of this problem will guide a manager to take the best decision in a particular situation.

IV.1.2.1. Re-estimated Completion Dates of Partners

As the project goes off-track, completion or finishing date has to be re-estimated or forecasted by taking the necessary controlling actions. This re-estimation depends upon the definition of POI i.e. either as pre-specified duration or pre-specified number of patients for each country (partner).

POI as Pre-specified Duration:

In this case, the position of I^0 will be the same in the planning and in the real stages of the project i.e. $I^0 = I$, as shown in fig. 27. The number of patients recruited in country "*j*" is:

- During the learning stage:

$$n_l(t, j) = s_l(j).t = SPI.\ s^0{}_l(j).t, \qquad [\text{since } SPI = s_l / s^0{}_l]$$

so the total number of patients recruited during this phase is:

$$n_l(j) = SPI.\ s^0{}_l(j).\ I^0 = SPI.n^0{}_l(j) \qquad [\text{since } n^0{}_l(j) = s^0{}_l(j).\ I^0]$$

- For the working stage, the number of patients recruited is:

$$n(t, j) = n_l(j) + s_w(j).(t - I) = SPI.\ n^0{}_l(j) + SPI.\ s^0{}_w(j).(t - I) = SPI.[\ s^0{}_l(j).\ I + s^0{}_w(j).(t - I)]$$

- If the finishing date is $T^0{}_f(j)$and the total number of patients required to be recruited is $N^0(j)$ for country "j" then:

$$N^0(j) = n_l(j) + s_w(j)_j.(\ T^0{}_f(j) - I)$$

- The re-estimated finishing date will then be $T_f(j)$, so that :

$$n\ (T_f(j)) = N^0(j) \Rightarrow N^0(j) = SPI.\ n^0{}_l(j) + s_w(j).(T_f(j) - I)$$

$$\Rightarrow \boldsymbol{T_f(j) = I + [(N^0(j) / SPI) - s^0{}_l(j).\ I] / s^0{}_w(j)}$$

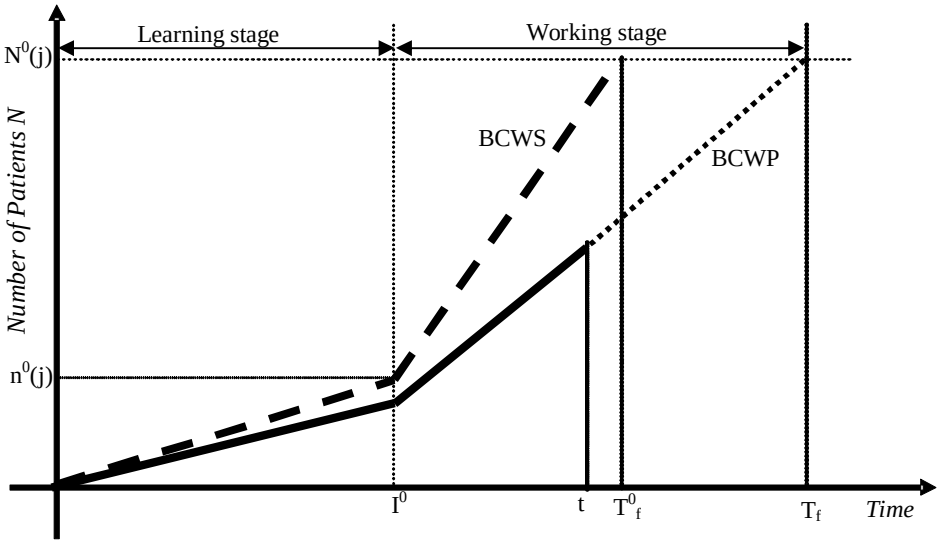

Figure 27. POI defined by Pr-specified Duration

- Since $T^0{}_f(j) = I + (N^0(j) - s^0{}_l(j).I) / s^0{}_w(j)$, then schedule variation $\Delta T_f\ (j)$ can be determined as:

$$\boldsymbol{\Delta T_f\ (j) = T_f\ (j) - T^0{}_f(j) = (N^0(j) / s^0{}_w(j))\ x\ (1/SPI - 1)}$$

We can note from the above equation that $\Delta T_f\ (j)$ positive indicates a delay and in this case *SPI* will be important because the smaller the value of *SPI*, the longer will be the delay. And $\Delta T_f(j)$ negative indicates an advance in schedule.

POI as Pre-specified Number of Patients:

In this case, the date of the transition will be defined by the number of patients recruited. The process will operate on learning recruitment rate until a given number of patients ($n^0{}_l(j) = s^0{}_l(j).\ I^0(j)$) have been recruited. So there will be two POIs, one *planned* I^0 and the other *real I* as shown in fig. 28.

- The POI date will then be modified from $I^0(j)$ to $I(j)$ where,

$$n^0{}_l(j) = s^0{}_l(j).\ I^0(j) = s_l(j).\ I(j)$$

$$\Rightarrow I(j) = s^0{}_l(j).\ I^0(j) / s_l(j) = I^0(j) / SPI \qquad [\text{since } SPI = s_l(j) / s^0{}_l(j)]$$

- The total number of patients, actually recruited after completion of the learning stage is then:

$$n(t, j) = n^0{}_l(j) + s_w(j).(t - I(j)) = s^0{}_l(j).\ I^0(j) + SPI.\ s^0{}_w(j).(t - I(j))$$

- The re-estimated finishing date for country "j", $T_f(j)$ is given by:

$$\text{since } N^0(j) = n(T_f(j)) = s^0{}_l(j).\ I^0(j) + SPI.\ s^0{}_w(j).(\ T_f(j) - I(j))$$

$$\therefore\ \boldsymbol{T_f(j) = I^0(j) / SPI + (N^0(j) - s^0{}_l(j).\ I^0(j)) / (SPI.\ s^0{}_w(j)) = T^0{}_f(j) / SPI}$$

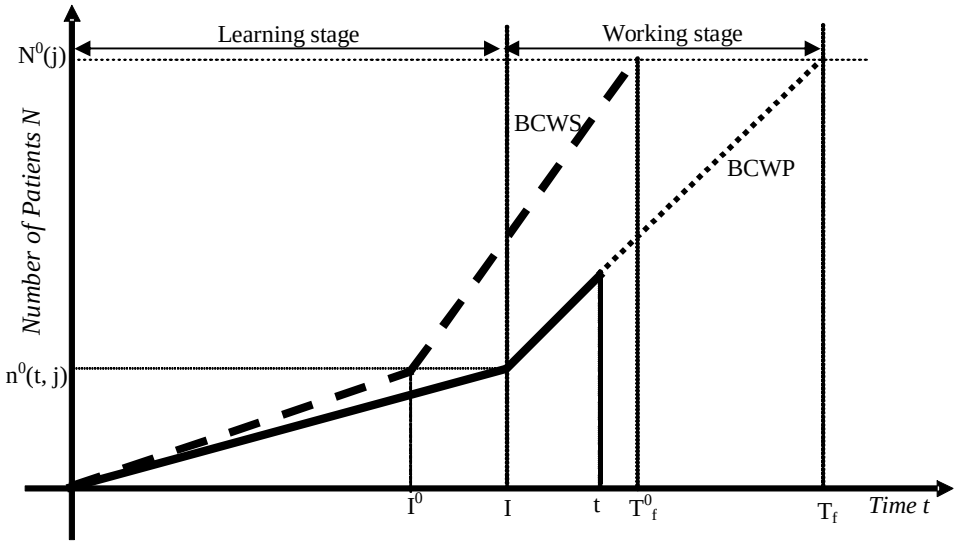

Figure 28. POI defined by Pre-specified Number of Patients

- As previously, we can express the schedule variation $\Delta T_f\,(j)$:

$$\boldsymbol{\Delta T_f\,(j) = T_f(j)\ - T^0{}_f(j) = (1/SPI - 1).\ T^0{}_f(j)}$$

And as previously defined, the lower the value of *SPI*, the longer will be the delay.

IV.1.2.2. Re-estimated Finish Date of Project

For the determination of new finish date of the whole project it is assumed for all the countries (partners) that the mechanism for defining transition between the learning and working stage will be the same i.e. driven either by a pre-specified duration (may vary from one country to another) or by a pre-specified number of recruitments accumulated (may vary too), as discussed in previous sub-section. This assumption is raised in order to simplify equations for a numerical model, as the learning mechanism for the occurrence of POI may be different for each country.

Without work reallocation:

Here, we assume that the project was planned such that every work-package would be completed at the same date T^0_f.

$$\forall j,\ T^0_f(j) = T^0_f$$

The new finish date of the project T_f, taking into account that for each country things don't go exactly as planned, will now be the latest of all the dates of completion for all the work-packages i.e. the recruitments of the required number of patients from each country:

$$\boldsymbol{T_f = \max_j \{T_f(j)\}}$$

- If the learning phase is defined by a fixed duration, the schedule variation for each country is given by:

$$\boldsymbol{\Delta\, T_f(j) = T_f(j) - T^0_f = (N^0(j) / s^0_w(j)) \times (1/SPI - 1)}$$

  Calculations of the delay for the whole project will need the examination, for each country, of the respective values for $N^0(j)$, $s^0_w(j)$ and SPI.

- Things are easier in the case of a fixed experience i.e. the given number of patients, driving the transition time as:

$$\boldsymbol{\Delta\, T_f(j) = T_f(j) - T^0_f = (1/SPI - 1).\ T^0_f}$$

  In this case the delay for the whole project will be given by the country having the lowest value of schedule-performance index SPI.

With work reallocation:

Objective of the project is the recruitment of N^0 number of patients, so:

$$N^0 = \Sigma_j\, N^0(j)$$

If we assume that all the countries are in their working stages, then their actual recruitment rates in working stage can be measured, so we know at a given date t, the total number of patients recruited by each country:

$$n(t) = \Sigma_j\, n(t, j)$$

And the *total recruitment rhythm*, i.e. the sum of all the recruitment rates of countries with the deduction of $s_w(j)$ from $s_l(j)$ using Linear Hypothesis for countries still in learning stage, is given by:

$$s = \mathrm{d}(n) / \mathrm{d}t = \Sigma_j\, \mathrm{d}[n(j)] / \mathrm{d}t = \Sigma_j\, s_w(j)$$

The remaining estimated work to complete the project is then:

$$W_{tc} = N^0 - n(t)$$

And the average remaining duration to complete the project should be:

$$D_{tc} = W_{tc} / s$$

From above, the finish date of the project can be determined easily:

$$\boldsymbol{T_f = t + D_{tc}}$$

Suppose the remaining work has been re distributed between the different resources or partners or countries in such a way that each country can complete its job at the same date. So, for each country, the total number of patients to be recruited will change from $N^0(j)$ to $N(j)$, where:

$$N(j) = n(t, j) + D_{tc}. s_w(j)$$

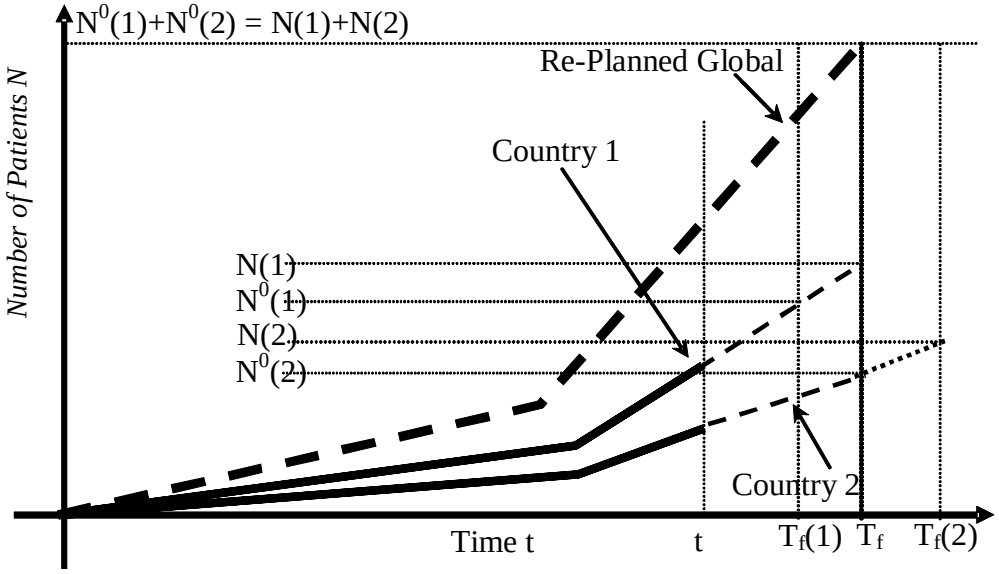

Figure 29. Work Reallocation with two countries with Country1 in advance and Country2 late

As an example, performance of two countries is shown in fig. 29, which depicts country 1 working faster and country 2 slower. At an update "*t*" a re-planning is performed using reallocation, so that the remaining work is shared and the final duration of project transforms from T^0_f to T_f. Country 1 and 2 will then end recruitment at T_f instead of $T_f(1)$ and $T_f(2)$ respectively, with $N(1)$ and $N(2)$ patients to recruit in place of $N^0(1)$ and $N^0(2)$ patients respectively, as shown in fig. 29. The dashed line shows the global re-planning for both countries.

VI.1.2.3. Adding the notion of Cost to the Model

The notion of cost will be added in this section to the model. Here, the model represents a situation where a number of sites are not working according to plan and their lateness is alarming. The decision for redistribution can reduce the amount of lateness if not all. The project manager decides to transfer patients between sites such that a compromise between project cost and duration can be achieved. The notion of a fixed *Negotiation Cost* will also be added into the model, which is fixed for each transfer that means the more transfers are made to different sites, the more negotiations will be done. Also the more patients are transferred to sites; the more will be the *Transfer Costs*.

If $C_f(j)$ is the final cost for treating a patients at site "*j*", and C_k is the cost of a patient completing phase "*k*" then:

- Cost of site "*j*" for treating $N^0(j)$ patients, and total cost of the project if all patients complete their treatment:

$$C_f(j) = N^0(j) \,.\, \Sigma_k\, C_k$$

$$C_f = N^0 \,.\, \Sigma_k\, C_k = \Sigma_j\, C_f(j)$$

- As it is anticipated that a number of patients will quit before completing their treatment, so the costs defined above will change:

$$C_f(j) = \Sigma_k\, (n_k(j) \,.\, C_k)$$

where,

$n_k(j)$ = No. of patients completing phase "*k*" of treatment on site "*j*"

$$C_f = \Sigma_j\, C_f(j)$$

- ***Real State*:**
    - If at $t > I$ the previewed duration of the project is greater than the planned duration that means there is a lateness in the project:

$$T_f > T^0_f$$

    - As there is no penalty for lateness then the cost C_f of the project remains same.
    - So, the project manager has to distribute patients taking into account the negotiation costs C_N and the final duration of the project.
    - We are also interested in finding an optimized value for both cost and duration i.e. by minimizing both cost and duration up to a point that provides the best settlement between these two variables.
    - For developing the model for this situation, two sets are assumed for "*j*", which are:

$j = 1, 2, \ldots, 5$

$S = \{2, 3, 5\}$ = Sites or countries working as planned or better

$S' = \{1, 4\}$ = Late sites

    - At $t > I$, real recruitment rates for all the sites will be:

$$s_w(j) < s^0_w(j) \qquad \forall j \in S'$$

$$s_w(j) = s^0_w(j) \qquad \forall j \in S$$

    - For sites in S', the total duration changes from $T^0_f(j)$ to $T_f(j)$:

$$T_f(j) = t + (N^0(j) - n(t, j)) \,/\, s_w(j)$$

And if no distribution takes place the total duration of the project will be, as in section "*without work reallocation*" of IV.1.2.2.:

$$T_f = \max_j \{T_f(j)\}$$

    - Lateness introduced in the project by individual sites in S' will be:

$$\Delta t(j) = T_f(j) - T^0_f(j) = T_f(j) - T_f$$

- At this point the project manger selects site 2 for transferring patients from only one of the site in S'. The site from S' will be selected on the basis of a better compromise between project duration and cost. The whole situation can be seen from fig. 30, where black lines show the planning for each site, while blue lines show deviation. Also at this point negotiation costs C_N will be considered constant: that means the work will be distributed to only 1 site so there will be only one negotiation. Assumptions for the model are:

$$\Delta N(4) > \Delta N(1)$$

$$\Delta t(1) > \Delta t(4)$$

$$C_N = \text{Cost of one negotiation}$$

- In this situation only that site will be selected from S' that has the maximum value for the relationship between lateness (i.e. large project duration) and number of remaining patients (that indirectly represent cost as the more patients transferred the more will be the transfer costs):

$$\text{Site for Distribution} = \max_j \{\Delta t(j) / \Delta N(j)\}$$

This relationship will be called "*lateness-to-patients relationship*".

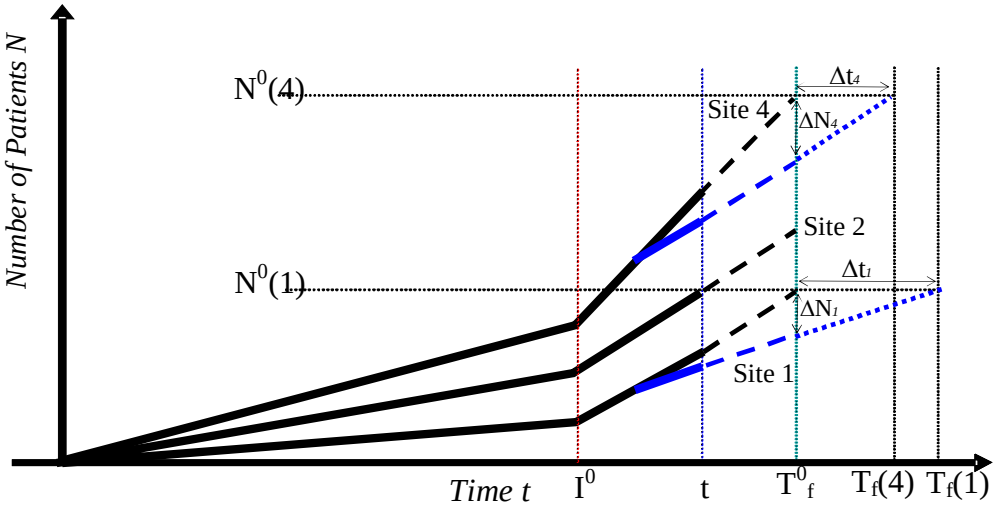

Figure 30. Determining which country will bring more improvement in duration and cost.

This can also mean that if a site in S' has fewer patients to share and the lateness introduced by this site is also greater than others in S' then this site becomes the best candidate for distribution, as it gives a better compromise between site cost and duration. By selecting this site greater lateness will reduced at a lower cost as fewer patients will be required to transfer.

- In this situation site 1 is selected as it has the maximum value of the lateness-to-patients relationship. After this selection patients will be distributed between site 1 and 2 which was earlier selected by the project manager. Distribution will be carried out following the model described in section "*with work reallocation*" of IV.1.2.2.

- Cost of the site to which patients are transferred (in this case site 2) then will be estimated as:

$$C_f(j) = \Sigma_k \, n_k(j).C_k + N_T \, . \, C_T$$

where,

N_T = No. of patients transferred

Also,

$$N(j) = n_l(j) + n(T_f - I^0, j) + N_T - \textbf{Quitting Patients}$$

- Cost of the site from which patients are transferred (in this case site 1) then will be estimated as:

$$C_f(j) = \Sigma_k \, n_k(j).C_k$$

while,

$$N(j) = n_l(j) + n(T_f - I^0, j) - N_T - \textbf{Quitting Patients}$$

- Cost of the all other sites that have not taken part in redistribution will be estimated as:

$$C_f(j) = N^0(j) \, . \, \Sigma_k \, C_k$$

- If Z is a set of sites that have not take part in redistribution, Z' represents a set of sites from which patients are transferred and Z'' is a set of sites to which patients are transferred, then the overall project cost will be estimated as:

Z = {3, 4, 5} = Sites taken no part in distribution

Z' = {1} = Selected sites from which patients are transferred

Z'' = {2} = Selected site to which patients are transferred

$$C_f = \Sigma_{j \in Z} \, C_f(j) + \Sigma_{j \in Z'} \, C_f(j) + \Sigma_{j \in Z''} \, C_f(j) + C_N$$

IV.2. SIMULATION

A numerical model of the problem is presented in the previous section. In this section a computer simulation model will be created and presented, continuing the ideas proposed in the last section. First a logic flow chart of the simulation model is established, which will be followed as a road map for writing of the computer program. As the computer program is presented, various ways will be sought out to optimize it to get better results.

IV.2.1. Logic Flow

Logic flow is the basis of any program, which shows how the decision making process progresses. It shows the behavior of the program i.e. 'what will happen in a particular situation?', as it is the algorithm with which a particular decision can be reached. There are two techniques widely used for depicting the logic flow namely, *Flowchart* and *Pseudocode*; flowchart is utilized for the presentation of the logic flow of the problem in this thesis. First the logic flow of the

planning process will be presented which will follow the logic flow of the execution and control of the problem.

IV.2.1.1. Planning

The logic flow for this process of the problem is depicted in fig. 31. In this figure, the process of planning starts by displaying Form#1 of the program (which will be presented and described in detail in later sections), which needs planned recruitment data for continuing the process. The only action taken in this process is the generation of the scheduled budget which is the output of planning process; budget is estimated using the given planned data. This process terminates as the output is generated.

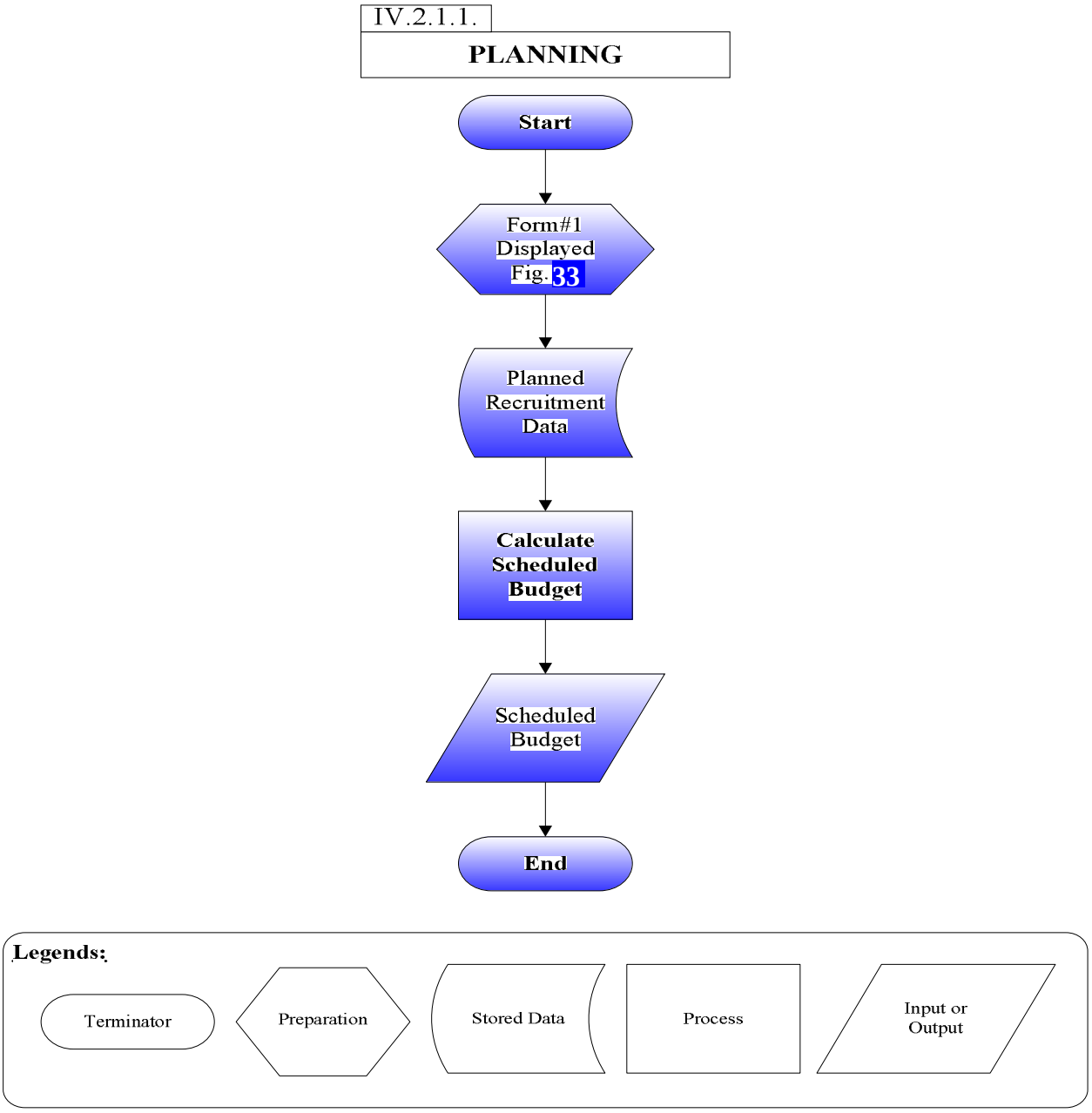

Figure 31. Logic flow of the planning process of the problem.

IV.2.1.2. Monitoring and Control

As the planning is completed with the generation of scheduled budget, the project enters the execution process where the process of monitoring and control is more significant than in other processes of the project life-cycle. Fig. 32 shows the logic flow of the processes of execution and control.

This process starts with the insertion of the data in Form#2 (which will be presented and described in detail in sections to come) as it comes up after the completion of Form#1 in planning. First the performance (P) of each country is inserted as recorded after a number of updates which will generate the actual data until the POI can be achieved. This is a manual input of performance as shown by the shape of the block in fig. 32. This generation of actual data is the first action taken on this flow chart which has the actual data as its output and that functions as an input to the next decision process.

After this the logic enters into the major part of the problem, where a decision is required to be taken from a number of possible and logical options. First major option is to enter previewed recruitment rates with which each country is expected to work until the next update is achieved. If this option is chosen then on the next update the manager will have actual data and he or she can compare the previous recruitment rate entered with the actual values. If the value was wrong then the manager is now required to enter the correct value. Whether the recruitment rate entered was already correct or it was corrected afterwards, the manager has now a decision to make, i.e. either to continue this way and follow the same process for the next update or to apply redistribution which is the second option.

The second major option is to apply redistribution right away as the problem achieves POI. Actual recruitment data is then generated as an output which becomes an input to the process of calculating the actual cost or EAC[28] of the project. Actual cost is calculated by applying transfer costs as the redistribution is used and patients are transferred from slow working to better working countries. Actual cost and the final duration of the project are the final output of this logic flow chart as every option applies redistribution at a certain time.

Third major option is to add a new site; the new site or country is added as the need arises. As this new site is added, redistribution will then be applied and the remaining work can then be shared among countries. This new site is established at a cost which is also taken into account while calculating the cost of the whole project. It is worth repeating here that if a new country or site is added, it should be kept in mind the delay it can cause by taking time to learn and then it will enter the working stage to recruit at a faster rate. Thus, this decision should be taken only if it is beneficial in terms of duration as this decision will increase costs and brings an unavoidable initially slow working rate.

[28] Estimate At Completion

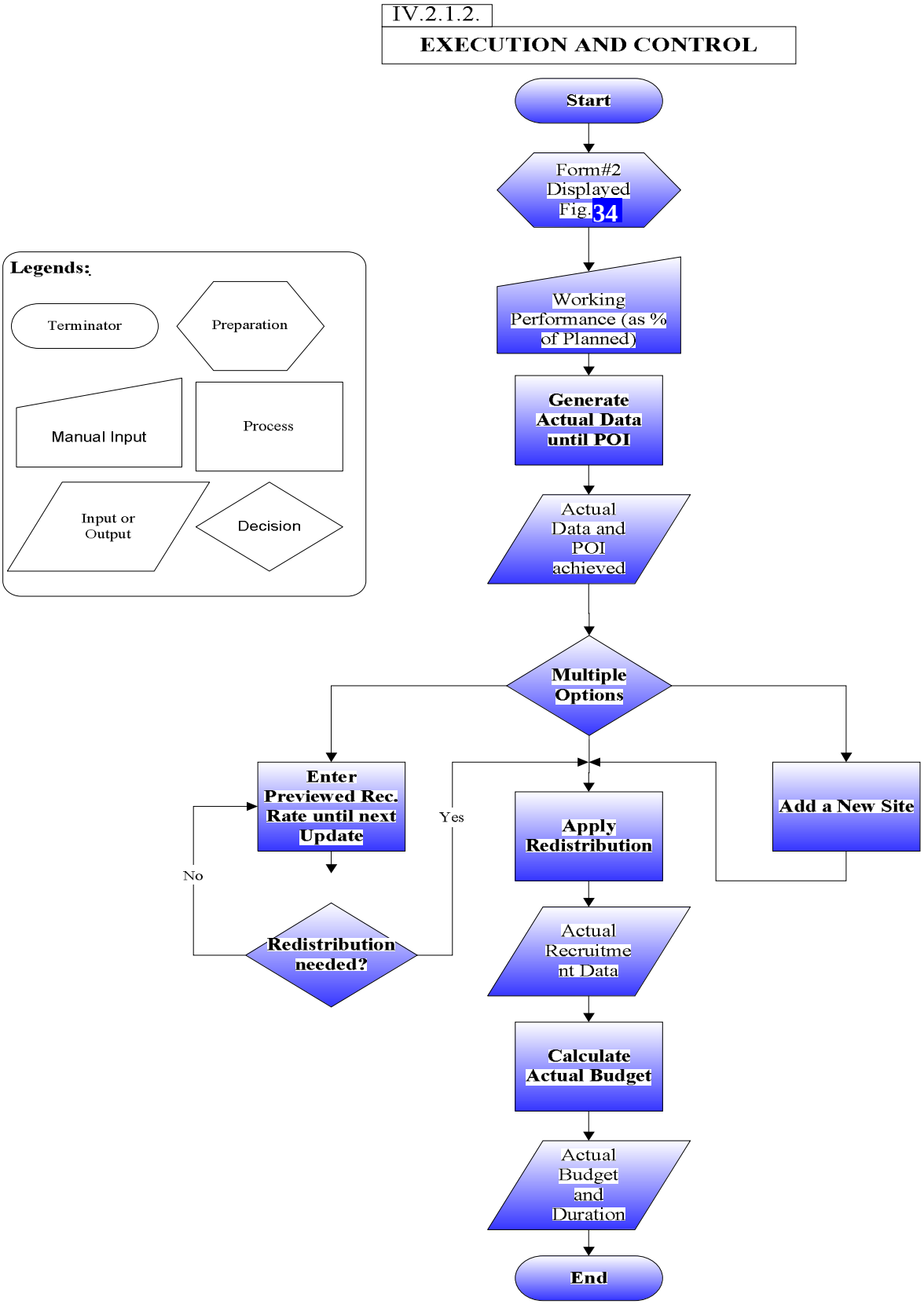

Figure 32. Logic flow of the execution and control processes of the problem.

IV.2.2. Program

The program is built in Microsoft Excel with programming in Visual Basic Applications. If a user opens the file of pharmaceutical problem, the screen will show the Form#1 as it is shown in fig. 33. The process on this Form#1 follows the logic flow described in fig. 31. The user will input information on this form for the generation of real recruitment data. As it can be seen from fig. 33 the user will have to input number of countries where the treatment will be provided and next the update of information after required number of months. Then the user is provided with two options to choose from, for inserting the planned recruitment data i.e. either the planned recruitment data is copied in this file of pharmaceutical problem with the relevant fields inserted in text boxes, or if the data is in another excel file then its link along with relevant fields filled in by the user.

This is followed by the fields where the cost of treatment are provided by the manager; the cost for each phase of treatment i.e. for this problem there are three phases of treatment which can have different costs and thus are required. As it is anticipated that a percentage of the patients will leave the system before completing their treatment, this percentage will then also be required and thus provided by the user depending upon experience. The check box at the bottom, if not checked indicates that the user only wants to generate scheduled budget. Besides if it is checked and the button at the bottom of the screen displaying "Solve" is pressed will generate scheduled budget and then continue on the way for creating real recruitment data.

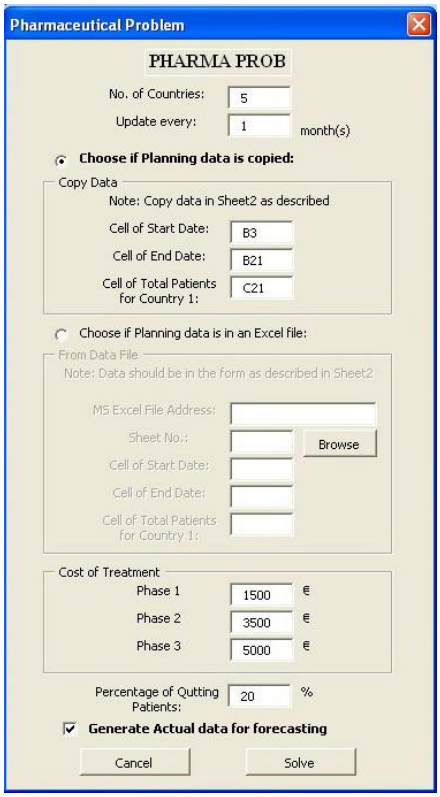

Figure 33. Form#1: Planning in problem

Once the scheduled budget is generated, Form#2 comes up while Form#1 vanished away as its job is done. For the generation of real or actual recruitment schedule with budget, requires input on Form2 from the user, which is shown in fig. 34. First the POI is inserted for each country selected from a drop down list. This POI is known by experience, to occur at a certain point in time. The button "Save" is then pressed to save the inserted POI for a particular country. Next the real performance for each country is filled for generating initial, real recruitment data as a percentage of the planned recruitment data for each country. It is inserted after the project has started, and enough information is received by the manager to know how a particular country is performing. For example if 90% is inserted for country#1, it means that country#1 starts with the recruitment of 90% of patients that were planned to be recruited by this country until the first update.

The number of months after which the progress should be updated is to be inserted next. The button in this frame displaying "Generate Real Data" will then be pressed for generating real recruitment data for starting the project with the performance provided for each country. The real recruitment chart for a country selected from the drop down list (given under the chart) will be displayed in the chart box. It can be seen from fig. 34 that the frame with the title of "Point of inflexion: Achieved" is disabled. It is disabled until the POI is achieved, once the POI for a particular country is reached this frame will be automatically enabled and provide a number of options to the user for choosing the appropriate one to continue this real recruitment data generation until the next update as shown by another instance of Form#2 in fig. 35.

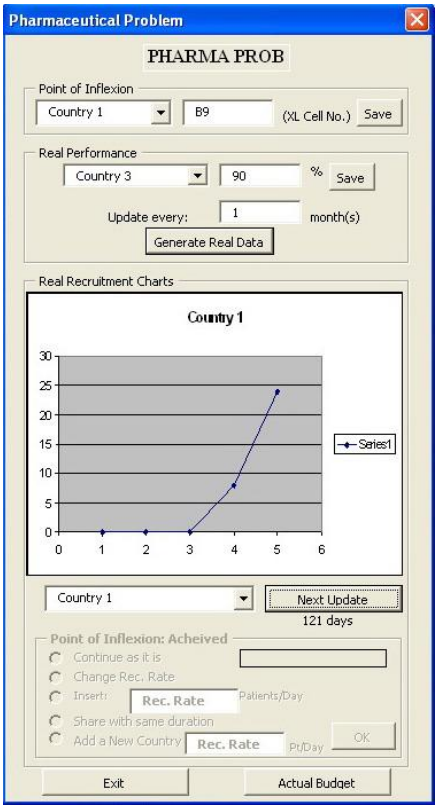

Figure 34. Form#2: Execution in problem

The POI is reached by pressing the "Next Update" button, which basically generates data update by update and by pressing it a couple of times the POI can be achieved for a particular country, enabling the frame with options. These options were divided into three major decisions as explained in the description of the logic flow in fig. 32. Here Form#2, shown in fig. 35 presents more options, where the first option if chosen will not change anything as it is clear by the name "Continue as it is" i.e. the real recruitment will be done according to the performance initially provided. The second option if selected will change the recruitment rate (as patients per day) to what is required for the country to recruit the total number of patients within project duration. This required recruitment rate is also shown on the title of this option. Third option will provide a space for the user to provide the required recruitment rate. Here the manager can provide a previewed recruitment rate as he/she predicts the situation to change.

The next option is the major decision in this work, where the remaining number of patients to be recruited are shared among countries i.e. with-reallocation or redistribution. Patients are transferred, to be recruited and then treated, from a country with poor recruitment rate which is making the project late in achieving its targets to another country which is working as-planned or better than what was planned. This redistribution is done in a way that all countries complete their work in the same duration or on the same date. This is done using linear programming in MS Excel behind this option which will do the trick. After this redistribution of work, a button on the Excel sheet naming "Generate Actual Budget" is pressed for calculating the actual cost of the project, this cost is equivalent to the EAC.

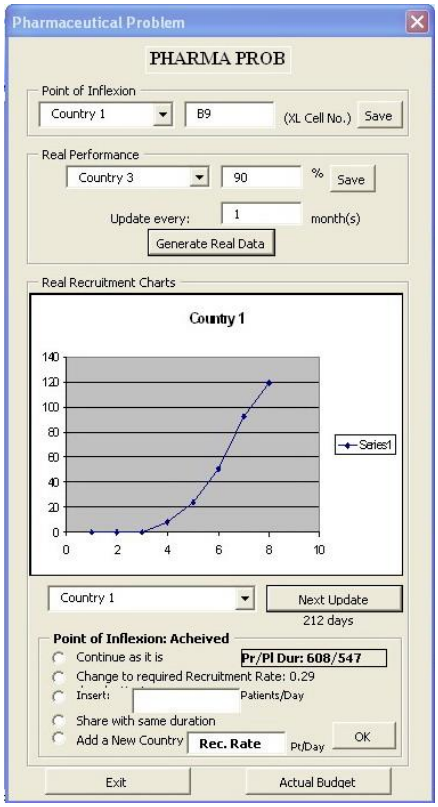

Figure 35. Form#2 with the enabled frame of options.

The last option on this frame is “Add a New Country” which, as its name implies adds a new country or site to this problem. A cost is added to the actual budget for inserting this new country into action. The text box adjacent to the option requires a recruitment rate previewed by the manager for the new country to work with. Once this is inserted the same steps are followed as for redistribution i.e. linear programming is applied for the distribution of the remaining patients among the countries including this new country. Then again the actual cost can be generated.

If one of the top three options is selected by the manager as he/she previews a particular country to work and the button that says “Next Update” is pressed as shown in fig. 35, the data will be generated until the next update and this process can be continued so on until the end of the project. But as the “Next Update” button is pressed, a new form comes up which is Form#3 as shown in fig. 36. This form basically provides the manager an opportunity to correct the behavior of a particular country as they have forecasted. As by this time they may have the actual data of the country’s behavior which can be compared to what was predicted, and if the prediction was wrong then it can be corrected using Form#3. The chart on this form depicts two different lines, the blue line represents planning while the pink line shows the actual path. The last dot on the pink line is the predicted value. Charts for each country can be viewed by selecting the required country from the drop down list. There are two options on this form to choose from. The first one, if chosen describes that the predicted behavior for this country was correct and in reality the prediction holds true. Besides if the prediction was wrong the manager has to choose the second option where he/she can insert the real recruitment rate and then press the “Save” button. This process is continued until the end of the project i.e. all the patients are recruited and then the button “Actual budget” is pressed which will estimate the actual budget or actual cost of the project update by update.

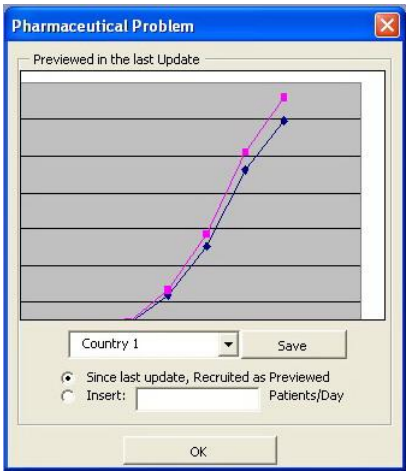

Figure 36. Form#3: Monitoring and Control in problem

In the situation where the fourth option is selected by the manager, that is if the reallocation is applied, then the manager can generate the actual cost of the project by clicking the “Generate Actual Budget” button on the MS Excel Sheet. After estimating the cost of the project, the manager can continue monitoring the progress of the project. The real recruitment data along with the cost now become the plan and scheduled budget respectively for the project. With the passage of time there is a possibility that certain countries may not work as previewed after the reallocation, and the manager decides to apply the reallocation for the second time. For

this, a button “Re-planning” on the Worksheet can be pressed by the manager which will allow him or her to apply this second reallocation.

IV.2.3. Optimization

In this section a discussion over the optimization of the computer program i.e. ‘how the program was optimized?’ and ‘how it can be improved?’ will be presented.

After overcoming various programming and logical errors in the program, it is improved by placing the data as a model only after the application of regression. Transfer costs are added as a fixed cost by the program automatically which is 10% of the total treatment cost for a patient. Also the cost of adding a new country is taken by the program automatically. The program can be optimized and made more realistic by asking an amount for these costs using a text box over the forms. There is enough room for improvements in the programming techniques applied so that functions are optimized in such a way that simulation time may be reduced. At the moment it takes about 368 seconds to complete the simulation with little requirement of manual data insertion and one reallocation; this value can be decreased to some lower value.

IV.3. RESULTS

This problem, due to the presence of numerous variables, offers interesting insight for managing transferable work-load projects with the emphasis on following a standard procedure for the definition of variables or performance indicators. These variables if properly defined and vigilantly watched can improve the results of the problem.

One instance of the problem is shown in Form#1 in fig. 33 in which five countries are going to be involved in this endeavor. Costs of the first, second and third phases are 1,500€, 3,500€ and 5,000€ respectively. It is expected that 20% of patients will quit the system before their treatment completes. Table 3 shows the planned number of patients to be recruited at each country and in total 10,000 patients are required for recruitment. This division of patients is done taking into account the capabilities, capacities and population of each country. As Form#2 comes up on the screen as shown in fig. 34, POI is inserted as the address to the corresponding cell (in MS Excel) of the date for each country. The initial real performances of the countries are inserted but if not mentioned for a country then the program will take it as 100% for that country.

TABLE 3
PLANNED DISTRIBUTION OF PATIENTS TO BE RECRUITED

Country 1	Country 2	Country 3	Country 4	Country 5	Total
1285	1909	2162	2194	2450	10000

Numerous instances of the problem are created by changing the values of different variables so that the results could be gathered for a number of situations. These instances are created for studying various objectives, which will be presented shortly.

For every situation first results are gathered for without-reallocation and then with-reallocation is applied to the same situation, so that a comparison is achievable for the better

comprehension of the problem. Table 4 shows the results for two instances which are created by varying the performances of countries. Planned duration for this project is 547 days.

IV.3.1. 1st Instance: Reallocation versus No-Reallocation

In the first instance two countries that are 1 and 3 are working with a lower performance of 90% and 75% respectively (i.e. SPI = 0.9 and 0.75 respectively), while the other countries work with the planned performance (SPI = 1) throughout the life time of the project. If no reallocation is applied then the project will take 730 days to finish, besides if the reallocation is applied the project duration will be 669 days i.e. certainly an improvement over the previous project duration. Here it should be kept in mind that this project duration is the duration of patient recruitment, i.e. the duration of treatment is not included as it takes close to a fixed amount of time for treatment while recruitment varies.

TABLE 4
RESULTS OF TWO INSTANCES OF THE PROBLEM

Performance of	Without-Reallocation	With Reallocation	Planned Duration
Country 1 and 3: 90% and 75%	Duration: 730 days	Duration: 669 days	547 days
Country 2, 4 and 5: 110, 120 and 70%	Duration: 1551 days	Duration: 539 days	

IV.3.2. 2nd Instance: Reallocation versus No-Reallocation

In the second instance of the problem, three countries that are 2, 4 and 5 are working with performances mentioned in table 4. Countries 2 and 4 are working better than what was planned for them (SPI = 1.1 and 1.2 respectively), while country 5 is working poorly (SPI = 0.7). If no redistribution is applied then the project will take 1,551 days to complete, and if reallocation is applied it will take 539 days. Here it should be kept in mind that this reallocation is applied at a certain update, and the estimated project duration may change if reallocation is applied on some other update. It can be inferred from table 3 that country 5 is very important because it has the largest chunk of work to perform, and in this second instance this same country is supposed to work poorly which really degrades the situation by taking 1551 days for the project. It means that apart from other reasons, lateness also depends upon the particular country that is the reason behind this lateness.

It is not surprising to note from the results of table 4 that with-reallocation up till these tests comes out to be the champion approach for the optimization of project duration in a transferable work-load environment, as it considerably improves the project duration as compared to when reallocation is not applied.

IV.3.3. 3rd Instance: When to use Reallocation?

It is also interesting to know when to use reallocation to produce better results. For this, a 3rd instance is created where reallocation was applied on the 1st update after the POI and the results were noted, then starting all over again and using reallocation on the 2nd update instead of

the 1st update after POI for the same scenario and so on. This process of application of reallocation is continued until the last update. Patients transferred for recruitment from one country to another are then recruited by the other country at an additional cost called *transfer cost*. Transfer costs are then added for the number of patients transferred which can be added in a number of ways. In this problem it is taken as a fixed cost which is 10% of the original cost of treatment that means the treatment of a transferred patient will cost 10% more.

Fig. 37 (ordinate: cost at completion, expressed as % of budgeted cost; x-axis: actual duration) shows the results of the instance for the determination of when to use the reallocation. From this figure we can see that the cost of the project is getting closer to 100% i.e. planned cost, as the reallocation is applied in later updates (arrow showing the direction of study), with project duration also getting close to planning or towards a duration with minimum lateness. This decrease in the cost is mainly due to the number of patients transferred decreases as the time passes by. That means the later the reallocation will be applied, the less patients will be required for transfer and the less transfer costs will be incurred. So, we can infer that reallocation if used in later stages of the project, with around 2/3rd of the project duration passed will produce better compromise between duration and cost.

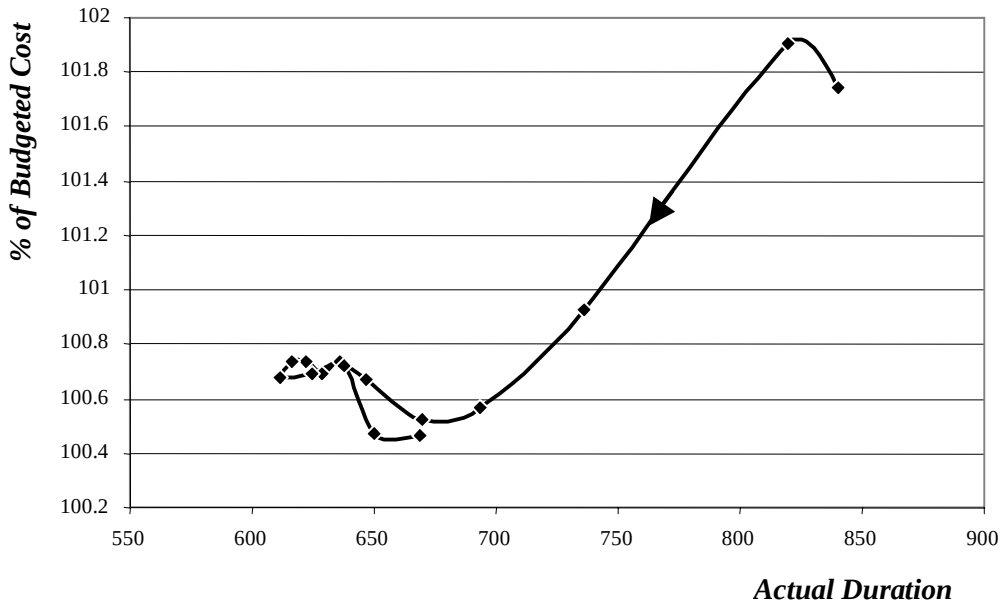

Figure 37. Use of reallocation in different stages of project

It can also be seen from fig. 37 that towards the end the project duration increases as the reallocation is applied in last couple of updates. It means that towards the end it is not a great benefit to apply redistribution as it does not bring a huge change to the project duration.

IV.3.4. 4th Instance: When to use Reallocation?

The same trend discussed above can also be seen from fig. 38, which shows another instance of the problem where again redistribution is applied from 1st to the last update as in the previous instance (each update after the POI, on which the redistribution is applied, is denoted by Test on the vertical axis in fig. 38). In this figure the duration is getting closer to the planned

duration (in this case 547 days) as redistribution is applied after 2/3rd of the planned duration has passed. In this instance Country 1 and 4 are working with 70% performance and at each update after the achievement of POI, reallocation is applied one by one. Again we can observe here that towards the end, the project duration increases rather than decreasing, suggesting against the use of redistribution towards the end of the project.

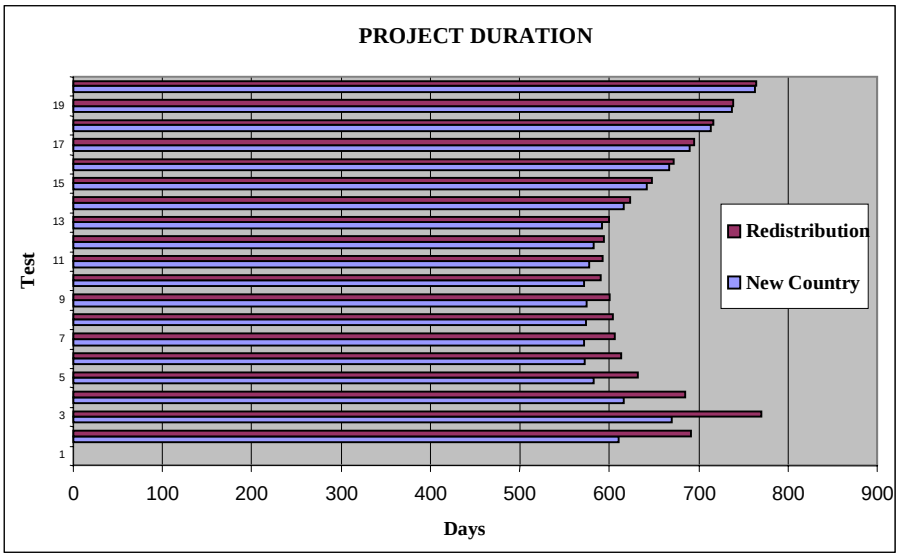

Figure 38. Effect of Redistribution on Project Duration

(before and after adding a new country)

Also fig. 39 shows us for an instance the effect of redistribution on the project cost. The cost of the project gets closer to what was planned as the redistribution is applied from update to update. In the case where no penalty for being late is incorporated, the redistribution applied as late as possible will be best for reducing costs but again it will produce no good results for project duration, and a compromise between the two is suggested to be search for.

IV.3.5. 5th Instance: When to add a New Site/Country?

Another situation of interest is when a requirement for a new country to share the load of treating patients comes up. There could be numerous reasons for this requirement, one being the completion of the project within planned duration or with as minimum lateness as possible. This situation is examined with the focus of our interest on knowing *when* in the execution of the project, it is better to take this decision of adding the new country. This new country or site costs greater than other sites that are in the project from the beginning. As there is a cost of adding a new country, so the manager has to decide if the trade-off of adding this new country is satisfactory enough in comparison to the cost and duration of the project with simple reallocation.

For finding this out, simple reallocation is applied for a fixed situation with five countries, where country 1 and 4 both work with a performance of 70%, as in the previous instance. For the comparison the whole test as in the previous instance is repeated and this time a new country is added on the 1st update after the POI has achieved and then the redistribution is applied and so on.

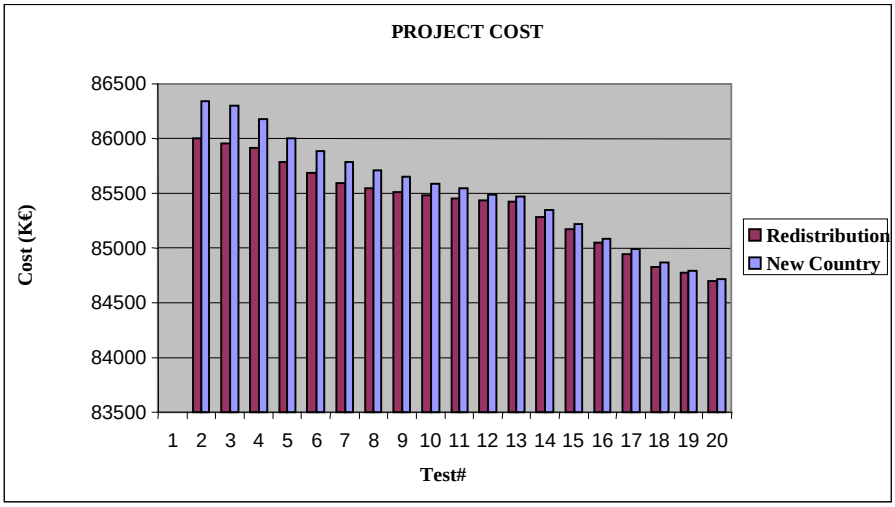

Figure 39. Effect of Redistribution on Project Cost

(before and after adding a new country)

Results of the comparison for duration and costs are shown in fig. 38 and 39, which show that if a new country is added as soon as it is realized that the project will end late can optimize the project duration but at a higher cost as shown in fig. 39. This can also be seen using fig. 39 that adding a country in the later stages of the project is not beneficial as it can only raise the cost of the project as compared to no country addition rather than giving a substantial decrease in project duration. Fig. 40 again emphasizes the same point that in the later stages of the project the duration of the project increases, so there is no more good the added new country can do in terms of project duration. The rise in the duration of the project in the initial application of redistribution is due to the wrong estimation of the occurrence of POI i.e. the end of the learning period, which is why this increase occurred taking into account the slower recruitment rate of the learning period.

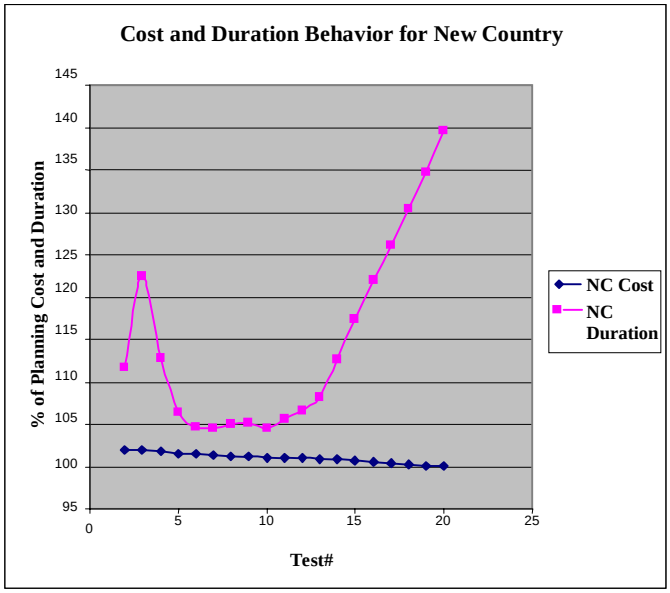

Figure 40. Cost and Duration for adding a New Country/Site.

Thus, it can be concluded from fig. 38, 39 and 40 that it is beneficial to take this decision of adding a new country as 1/3rd of the project duration has passed, because if it is added earlier than this, the cost of the project will be considerably higher along with the short comings of the addition in the later stages already discussed.

IV.3.6. 6th Instance: When to use second Reallocations?

A new instance is created to find out whether it is better to use another reallocation, after using it before. In reality a manager comes across this problem where after sharing the work between resources one time, he or she feels the need for another reallocation after some time as the project is again previewed to be late. So, this is interesting to find out what will happen in terms of project cost and duration, when multiple reallocations are used.

For this objective an instance is created, which is similar to the previous used instances i.e. with country 1 and 4 working with 70% performance (SPI), but on the fourth update after the achievement of the POI the first reallocation is applied. This first reallocation produces another schedule with previewed project duration and cost estimates. When the project was started the original project duration was 547 days with costs of 84.7 M€, and after the first reallocation this plan is changed with a number of patients transferred from one country that is not working well to another country of better working rate. This new data created after the application of the first reallocation now becomes the plan replacing the old plan. This new plan forecasts a project duration of 685 days with project costs of 85.9 M€ that incorporates the transfer costs of transferred patients whose treatment will cost 10% more than the non-transferred patients.

Once this is done, the project is again started from the update where the first reallocation was applied. This time if nothing is changed and if it is supposed that each country works with the previewed working rate then the project will end as planned taking the re-planned duration. That means if there is no change in the SPI then there is no need for the second reallocation as it will give the exact result as the first one. But for the sake of studying the affect of another reallocation, the working rates of country 1 and 4 are changed to 0.5 patients per day (i.e. SPI = 0.90 and 0.25 respectively) which is an inferior working rate than what was re-planned for these countries.

This action again produces lateness in the project, stressing a manager to apply after certain time another reallocation. This second reallocation is then applied on the first update after the project is re-planned then the results for project cost and duration are gathered then again the process is repeated and the second reallocation is applied on the second update after re-planning and so on. Fig. 41 shows the effect of the application of second reallocation, on the project duration, as it is applied from the first update after re-planning to next 20 updates before the project's new finish date.

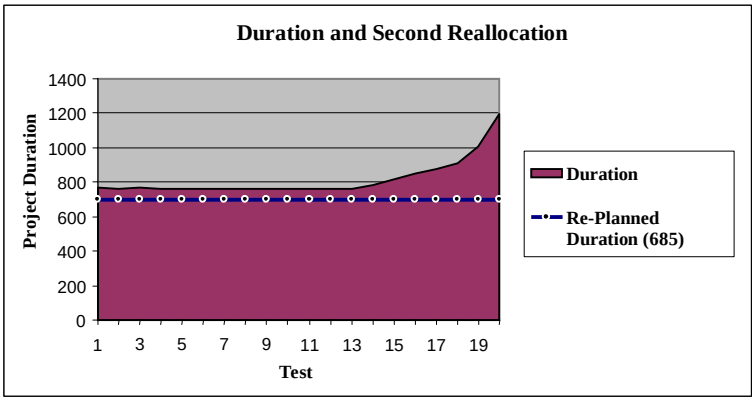

Figure 41. Duration and second Reallocation

The new project duration with no-reallocation has become 2,587 days as compared to 685 days which was previewed as shown by the horizontal line in fig. 41. It can be seen from fig. 41 that the second reallocation minimizes the project duration to 765 days as it is applied on the first update after re-planning. Also this project duration remains the same, as the second reallocation is applied on the next thirteen updates which mean it does not minimize the project duration any more. And the last part of the graph shows an increase in the project duration i.e. there is no benefit in applying the second reallocation as the half of the new project duration has passed.

Now the effects of this second reallocation on project cost will be discussed. Fig. 42 shows a gradual increase in the cost of the project as the second reallocation is applied. Here the cost is estimated incorporating transfer costs, but it is interesting to note that the treatment of patients transferred due to this second reallocation will cost 20% more than non-transferred patients as compared to 10% more treatment cost for patients transferred in the previous reallocation. The horizontal line defines the re-planned cost of the project previewed after the first reallocation in fig. 42. If this increasing trend of project cost is compared to the almost fixed project duration in fig. 41 during this time, it can be inferred that this stable project duration is maintained at a gradually ascending cost. While on the downstream a comparison of fig. 41 and 42 shows that cost decreases and the duration increases, suggesting against the use of second reallocation in the later stages or when half of the new project duration has already passed.

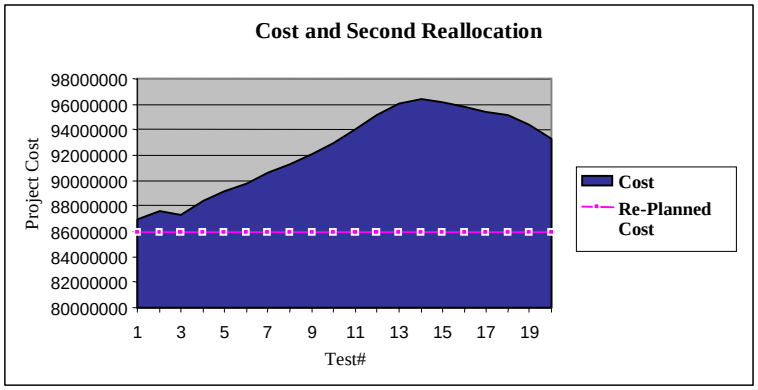

Figure 42. Cost and second Reallocation

IV.3.7. 7th Instance: When to use second Reallocations?

For studying this, another instance is created where all the parameters remain same as in the previous instance with only one change and that is the first reallocation is now applied on the ninth update after the achievement of POI. The new plan which is created after the first reallocation forecasts a project duration of 566 days with project costs of 85.1 M€. This now becomes the new planning. Then the working rates of country 1 and 4 are changed to 0.5 patients per day (i.e. SPI = 0.90 and 0.25 respectively). After this the second reallocation is applied from one update to other as described in the previous instance and results are gathered.

The new project duration with no-reallocation has become 1,735 days as compared to 566 days which was previewed as shown by the horizontal line in fig. 43. It can be seen from this figure that the second reallocation minimizes the project duration as it is applied on the first update after re-planning. Also this project duration rests close to planned duration and then increases. The last portion of the graph shows an increase in the project duration as found from the previous instance emphasizing that there is no benefit in applying the second reallocation as the half of the new project duration has passed.

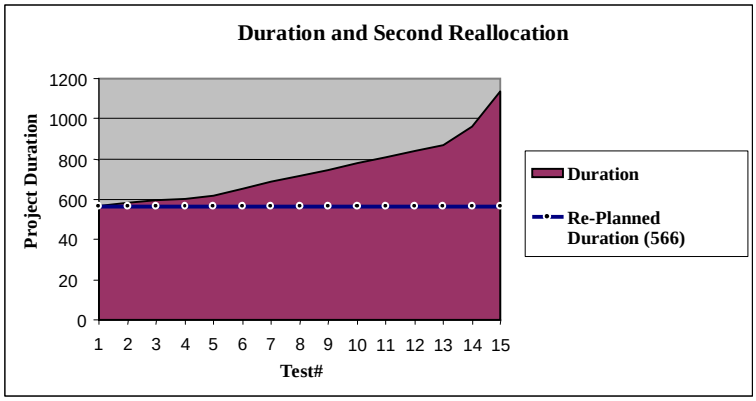

Figure 43. Duration and second Reallocation

Now the effects of this second reallocation on project cost will be discussed. Fig. 44 shows an increase in the cost of the project as the second reallocation is applied as seen in the previous instance. Here again the cost is estimated incorporating transfer costs as described in the previous instance. The horizontal line defines the re-planned cost of the project previewed after the first reallocation in fig. 44. If this increasing trend of project cost is compared to the project duration i.e. close to planned in fig. 43 during this time, it again proves that this stable project duration is maintained at a gradually ascending cost. While on the downstream a comparison of fig. 43 and 44 shows a decrease in cost while an increase in duration, again suggesting against the use of second reallocation in the later stages or when half of the new project duration has already passed. This diminishing of cost in the later stage of the fig. 44 is due to the lesser number of patients required to be transferred, which means lower transfer costs as this cost is a factor of number of patients being transferred.

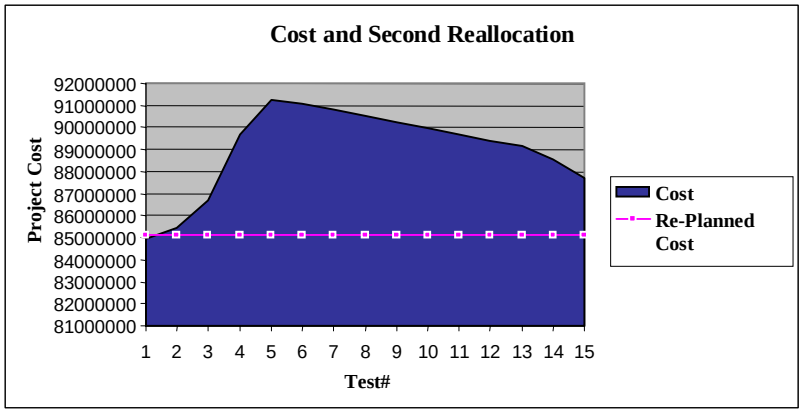

Figure 44. Cost and second Reallocation

Fig. 45 (abscissa: Project Duration; ordinate: Percentage of planned cost) concludes the results for the application of the second reallocation. The points on the graph represent the application of second reallocation on the 1st update after the application of the first reallocation, then the second point represent the application on the second update and so forth. Arrow on the line shows the direction of the application; with the point on the extreme right represent the last application of reallocation. Fig. 45 again confirms our previous findings that if the second reallocation is applied as soon as a problem arises, it reduces the final project duration though this is achieved at a higher cost. And in the later stages it can be seen from this figure that there is no use of this second reallocation as enormous amount of lateness adds up into the final duration.

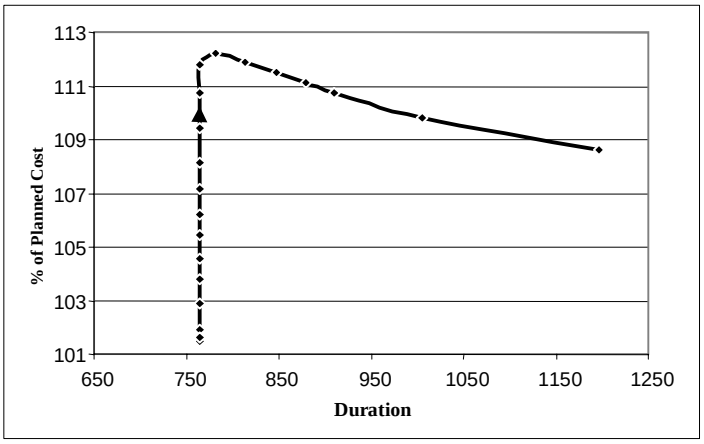

Figure 45. Results for second reallocation.

IV.3.8. Whether to use multiple Reallocations or not?

From the previous instances it can be inferred that if the SPI does not change then certainly there is no requirement for another reallocation. Besides if the SPI changes in such a way that the performance is degrading then another reallocation may help a manger pulling out the project before it goes out of control.

IV.6. CONCLUSION

This chapter presented the modeling, simulation and evaluation of the problem under study. First a numerical model was established for without redistribution and then with redistribution of workload.

Then a simulation model is programmed using VB Applications in MS Excel. Various instances of the problem were created for study by changing different variables in the program.

Three points that came up from the results are:

- Reallocation is the champion approach for these types of problems as compared to without reallocation projects.
- Reallocation if applied with $2/3^{rd}$ of the project duration passed will provide better results for both project duration and costs.
- If a need of a new country arises then it is beneficial to take this decision when $1/3^{rd}$ of the project duration has already passed, because it will provide a better compromise between project duration and costs.
- Apply the second reallocation, if required, as the half of the actual previewed project duration has passed.

CHAPTER V

DISCUSSIONS AND PERSPECTIVES

V. DISCUSSIONS AND PERSPECTIVES

Redistribution of work-load is a method if properly used minimizes project duration considerably. In this chapter we will discuss how this study was conducted, what was the research process and methodology. A presentation of the results will be followed by answering how the problem was changed for improving the results and how the results can still be optimized. Next we will discuss the benefits and contributions of this research in the field of industrial engineering. Perspectives and recommendations for further research will be presented en suite.

V.1. DISCUSSIONS

The problem studied is related to the pharmaceutical industry where new treatments or medicines are developed. The objective of a pharmaceutical firm is to convert a molecule into a blockbuster product. Drug development is a complex process involving numerous steps taking about 10 to 15 years and costing around $1 billion. Drug development follows: Pre-discovery, Drug Discovery, Preclinical testing, Clinical Trials, Review from the regulation authority, before starting the large scale manufacturing of the drug for treating a particular disease. As defined in previous chapters, Clinical trials has three phases, this study treats the third phase which involves the application of the treatment to a larger group of patients. A clinical trial consists of two stages: recruitment and treatment. This thesis focuses on developing a robust method for monitoring and forecasting the progress in a clinical trial TWLP, so that the project duration (time of clinical trials) is reduced and the objectives (goals of clinical study) achieved at a lower cost.

The reason why a TWLP is chosen for study is that mostly the pharmaceutical projects show characteristics similar to TWLPs for example the clinical trials project under study is a project where patients are interchangeable or transferable among different countries or sites. We are also interested in the monitoring and controlling of a globally distributed TWLP, which again defines a characteristic of a clinical trial project. This clinical trial TWLP is considered to be already started and is in the process of monitoring and control. Its recruitment planning has been generated from previous studies and experiences. The project is in the process of monitoring and control, where the status of the recruitment is established by comparing it with the plan.

The primary objective of this study is to optimize the project duration and for this *redistribution* of work-load is used as the focused method, in this globally distributed environment. A compromise between project duration and cost is treated as a secondary objective.

The recruitment follows a pattern described by the S-Curve or the learning curve, where working is at a slower pace in the start of the project and accelerates as the experience is gained, while the ending period shows retardation due to Parkinson’s Law or an intentional lowering of effort. There are two POIs, one at the end of the learning period and the other at the end of the working period. This learning curve or S-Curve is used extensively in this thesis with the postulate that the ending period along with the last POI will not be treated. That means the

working period will end the recruitment and there will be a POI manifesting the end of the learning period. POI is achieved after elapsing a pre-specified duration in this thesis, in lieu of the recruitment of a pre-specified number of patients.

With the simulation of an actual situation the problem was focused on answering: ***what is the best solution in terms of redistribution*** of the workload transferable between different partners in a project; when we see that the project is not behaving as expected. This redistribution corresponds to a transfer of workload from a less efficient partner to the one working faster. Another question was to know ***when such redistribution should take place***. It is also of interest to research ***when to add a new partner*** or country and what are its effects on our problem, in a situation where it's needed such as the shutting down of an existing partner due to an inevitable problem. ***Multiple redistributions*** present another avenue to discover.

V.1.1. RESEARCH PROCESS

The research process which was followed during this study will be defined here. First, research questions of interest were sorted out as in chapter two for study. Then literature was reviewed related to the questions under study. Theory was developed using the literature review process, which extends the understanding of the problem and this theory was then integrated with the experimental study of the problem. Theory development was completely structured which was presented in chapter two, i.e. how a particular field was inquired for finding information about the research question. It consisted of the literature review of old and current research. This literature review process was organized according to the objectives of our research. The review comprised of the areas such as: Project Management; Pharmaceutical Projects; Globally Distributed Projects; Forecasting; Drug Development.

V.1.2. RESULTS

Before discussing the results obtained, it is worthy to discuss the issue of linearity of data. The initial data were quasi-linear but certainly not linear. For solving the problem, linear regression was used on this data which then produces a linear model. This was done by considering the recruitment rate and the SPI to be constant throughout a period (learning or working), which is tough to obtain in reality.

For fulfilling the determined objectives a mathematical model of the pharmaceutical problem was established, which was then used for simulating the actual situations using a computer program. A *Linear Hypothesis* was developed which is a relationship used for the determination of recruitment rates or rhythms. The research process was greatly enhanced by the computer program, which aided in gathering important results for the study. A number of instances of the problem were generated with different values for the system variables, and which were used for generating results for the objectives defined. First redistribution is compared to no-redistribution for optimizing project duration, which depicted that redistribution or reallocation is the better approach.

As far as the time or project duration is concerned, the study shows the value of proceeding quickly to take the decision of redistribution as an answer to when to use redistribution. We have deliberately chosen, in our modeling, to await the passage of the POI so that we can do estimations for the later part of the project. The reliability of estimates is not ideal when estimated on the initial couple of updates after the POI; the reliability improves after some

time but as we go along the delays seen in some partners shall unfortunately be irreversible and difficult to catch up even by workload transfers.

The tool developed in this study aids a project manager to decide when to apply the redistribution with the project status visible. It also enables the manager to preview the future by inserting predictions about the behavior of a certain partner. A new site or partner is easily added as required using the computer program, and for this situation results were gathered which show that it is better to take this decision as soon as possible after the execution starts, as it does not optimize much the project duration also at a higher cost if the new partner is integrated for sharing the work-load in the later stages of a project.

After the application of redistribution, if some partners still show poor performance then the issue of multiple redistributions comes into play. Results were generated for a number of instances which manifest that second redistribution can not certainly minimizes the project duration lower than the one reached to by the previous reallocation. Besides an optimized project duration can only be maintained at a gradually increasing cost if the second redistribution is applied from one update to another, which directs the manager to take this decision without any further delays.

V.1.3. FINDINGS

Lessons learned from a project duration perspective (with the restrictive assumption that on the course of the project, the transfer of workload between partners can only be carried out once); there is evidence through this study for the need of searching a compromise between the reliability of forecasts of project completion and the irreversibility of delays accumulated. However, the assumption of the single application of work reallocation deserves to be discussed: for the reasons of organization, cost and simplification. It is obvious that opportunities to make these reallocations will be limited; we can consider the application of reallocation to two or three times - especially if the operation of certain partners is particularly disappointing.

From a cost perspective, the assumption we made of the reallocation cost being proportional to the number of patients "transferred" again penalizes our results; it becomes, from strictly economic aspect, more interesting to carry out the transfer as late as possible, when the remaining number of patients to be recruited (and therefore the number of times the application of reallocation) is reduced. This view is biased as the delays incurred by a partner or the whole project are not economically penalized.

Pharmaceutical industries today are under huge pressure as the production of new drugs is going down albeit R&D spending is going up, that illustrates the need for the development of innovative scientific and management techniques. For encountering this slow development, pharmaceutical companies are merging their efforts and knowledge. Along with this these firms are using extensive outsourcing for lowering costs and increasing work capacity. But poor project management shall undo the benefits gained by the above defined solutions. This thesis proposed a method for the management of the clinical trials, which will help in decreasing the drug development time as clinical trials are the longest phase in this development.

This work does not put less in evidence for the need to seek a compromise between on the one hand the perfect date for workload transfer (as pending reliable forecasts endangers the future ability to catch up the delays) and project costs. The study is continued for determining the ideal

number of such transfers if they are more than one, while continuing to show that these transfers represent a non-negligible cost. Our work will follow on the study of such compromise.

V.1.4. THE SIMULATION TOOL

This section discusses the benefits of the tool or software program prepared for the simulation of this pharmaceutical problem.

First results were gathered using data as it is, then linear regression is used on the same data for achieving linear data. Then results were collected for this linear data so that much more insight about the behavior of the system can be gained by this simplification. For more realistic effects the cost of transfer and the cost of the new country may be inserted by the manager rather than added directly by the program. The effect of the learning period, of the newly added country, is not incorporated for calculating the project duration; rather a fixed recruitment rate is required to be inserted for this new country by the user which becomes the basis of all the calculations. And thus two different recruitment rates, for learning and working periods respectively, may also be added which will provide a more realistic view of the problem to the manager for deciding whether to take this decision or not.

The tool presented in the previous chapter, with some screen views of a number of forms, gave the opportunity to simulate a pharmaceutical problem. This tool if used by following proper instructions, as described in this thesis, will hopefully not be difficult to use. It gives a user or more precisely a manager an acceptable level of flexibility to monitor and control the progress of the project along with previewing what will happen by the next update in terms of the duration of the project. A manager can preview what will happen by certain time with this program. It provides a good monitoring and controlling environment with graphical representation of the progress of each site or country. The options provided by the software program for controlling the project are considerably useful as a manager logically has a need for these options. Reallocation can be applied twice if required using this program. Though this tool requires improvements in various ways but it has an absolutely satisfactory performance as used for the completion of work in this thesis. Annex II will present the various programming blocks – procedures and function, used in the simulation of the problem.

V.2. PERSPECTIVES

In this section, the ambiguities, limitations along with the recommendations and perspectives of this research, will be discussed. Weaknesses will be translated into strengths and uncertainties into opportunities.

V.2.1. AMBIGUITIES AND LIMITATIONS

A lot of variables increase the complexity and ambiguity of the problem under study. That is why a number of assumptions were devised for simplifying the problem. An infinite number of situations are reachable by changing the variables but there were certain scenarios worth studying which were approached by fixing particular variables. Values of certain variables were known by experience and thus were used accordingly.

The planning data were the only data that were established by experience, thus this data have a solid base, while all other were generated using random number generation in VBA programming. This new data were generated using the pattern of the planned data and thus were used with conviction for reaching feasible and optimized solutions.

The problem under study was linked to various domains such as project management, life sciences, economics, pharmaceutical projects, technology management and statistics. This combination of study is certainly difficult to do, though in this research these multiple disciplines were approached as required. Researchers in these fields still have much to accomplish for optimizing the results of this problem.

The managerial part of the pharmaceutical problem was also not free from confusions as it is not a tangible part rather a theoretical aspect of the project. There is not much literature on the planning of TWLPs, so it is difficult to have a concrete guideline for the management of TWLPs. The limitation of literature, on the monitoring and control of TWLPs, was overcome gradually as the existing literature corrected and authenticated the initial ideas, which were also verified by the results generated using the modeling and simulation of the problem.

V.2.2. RECOMMENDATIONS FOR FURTHER STUDY

Several avenues are suggested for the extension of this study: a penalty for late project completion can be incorporated; transfer costs can be fixed or with a different cost coefficient for each treatment phase the transferred patient is in; negotiation costs can be added. Ending period can also be treated which was not studied in this thesis. Second POI along with its temporal effects can be added at the end of the working period in S-Curve. This will insert more variables to the problem making it more complex, thus simplifying assumptions may also be introduced accordingly.

Specific cases are also recommendable for future research where one partner may not continue with work-load can only be transferred towards limited number of partners, which are chosen by the project manager depending upon their performance. Adding the concept of negotiation costs here will also be suitable, as the less number of partners will be negotiated for this transfer, the less will be the negotiation costs.

In this study POI was taken as fixed and same for all countries or sites; as an extension to this thesis, it may be proposed to have different POI for each country. However, this change will increase the complexity of the problem though making it more realistic.

The problem is extendible towards finding the compromise between project duration and cost, i.e. how can this be achieved using redistribution. In the mathematical model this objective was touched, though detailed study is still required.

Not much attention has been given to the part of planning, for TWLPs in literature. For this study a selection of literature was studied, which either completely or partially is usable for extending the research on this topic. This also depends upon the new researcher's focus that may be more on the technical aspects of drug development, project management or philosophical aspects of globally distributed projects. Thus, every interest may follow the bibliographic review accordingly.

Our focus was on the monitoring and control of the pharmaceutical TWLPs, but the focus is extendable to other project management processes to have a global management package for

managing TWLPs. Relevant literature reviewed for each process may be helpful for this endeavor.

This work may be verified for industries other than pharmaceutical where the project managers may find it difficult to transfer work-load from one resource to another. Also, many projects involve activities with precedence relationships, which presents a more complex problem that the one studied in this thesis and thus provide an interesting problem.

The research may be verified by the use of a brochure or survey, and we will as an analysis of this study have an evaluation of the methods, results and findings by professional practitioners of the pharmaceutical industry by sending them a brochure or questionnaire. Due to the lengthy process of correspondence this action was not carried out.

Mature industries, by their use of Project management, can help less mature industries by benchmarking various processes, management techniques and practices. For better organization of these projects, the establishment of a multi-functional team shall also be effective in reducing project time and cost. The lessons learned may not be generalized but may be helpful in the realization of similar goals. This study is only a link in the long chain of on-going research and this unending chain is what matters.

CHAPTER VI

GENERAL CONCLUSIONS

VI. GENERAL CONCLUSIONS

Today, every industry faces a huge competition for developing products of superior quality and at the lowest cost. For this goal industries require sound techniques established in industrial engineering, project management and operations research. With the wide spread application of globalization and outsourcing, industries use project management methods for producing blockbuster products.

However there is still lot to do for establishing industry specific tools and techniques. The top project management references: IPMA, PMI and APM are general in nature. Every project is unique with its environment having a great effect on the project's performance, therefore the more certain and predictable the environment the more efficiently the project shall be managed. Project management is a growing field that aids us in solving problems encountered in every process of the project; major processes are: Initiating, Planning, Execution, Monitoring and Control, and Closing.

This study concentrates on the Monitoring and Control process group in the life-cycle of a pharmaceutical project, this process measures the project progress and devise a controlling action as required. Along with monitoring, this work also focuses on the forecasting and re-planning techniques. A special type of project is treated in this work that is called as the *transferable work-load project* (TWLP), which is a project where the work-load is transferable or interchangeable among different resources having similar competence. Thus, this thesis presents an opportunity to research a robust monitoring and forecasting method for a TWLP. This TWLP is a clinical trial project, which is the most important phase in the drug development process.

This research has a number of contributions:

- Monitoring and control of the performance of globally dispersed partners presents an interesting problem, which is not much studied. Thus, this study is an important contribution on this problem.
- Optimized project duration is attained by using redistribution as early as possible in the execution of the TWLP.
- Findings and results of this study provide an answer to our research questions which are vividly relevant to professionals in practice and academia.
- Literature relevant to our study was reviewed which became the basis for modeling and simulation.
- It is assumed that this study is well organized, more comprehensible, well presented and well informed theoretically on this multidisciplinary topic.
- The model presented in this thesis takes into account various situations achievable and thus models the real situation effectively, enabling us to study with confidence.
- The tool developed for the simulation of the problem, using VBA provides an opportunity to a project manager to monitor and control a clinical trial TWLP using the redistribution method.

- Researchers in the field of pharmaceutical project management and related domains can use the finding of this thesis for future research.
- Redistribution if used with proper understanding provides a better method for the optimization of project duration.
- This redistribution if integrated with a forecasting method becomes a complete monitoring and re-planning tool for controlling the project performance.
- This thesis is an important contribution to an area of research that heavily depends upon experience, personal acumen and imagination. Thus, adding ideas to the common sense of management.

A manager who is responsible for the completion of a clinical trial project, within planned duration and resources, may benefit from the results gathered. But it is very important to point out here that his or her job is not restricted to just moving from one MS Excel worksheet to another, rather he or she has a lot of managerial and administrative work to do for keeping all the communication channels alive so that each and every aspect affecting the project progress can be vigilantly watched. So that any problem before getting a big bottle neck can be avoided or a solution found out before hand.

Along with using the software program, the manager keeps in touch with different sites or countries for getting updates about the project progress through e-mails or telephones. The manager takes decision on the basis of the information he or she receives, that involves either to apply reallocation or to add a new country; the manager has to decide whether to apply the reallocation the second time or to just let the project progress as it is. In certain situations he or she has to personally visit the site for more information or providing guidance. Sometimes as the need arises the manager has to present the problem in front of the management for approval of certain actions depending upon the severity of the problem; high cost overruns, unacceptable lateness or an inevitable uncertainty can be those circumstances where a manager may present the status to the management. Also he or she has to attend or call meetings for analyzing various situations the project may encounter. Thus, this thesis along with the simulation tool can assist the manager in monitoring and controlling the project so that he or she can carry out the other aspects of managing the project, as defined above, effectively.

Globally, this work is a contribution to the ever important field of project management especially for the pharmaceutical industry. This work presented a method of optimizing and forecasting the project duration where the work-load is interchangeable among the different resources. It has taken into account various aspects affecting these projects and their environments.

RÉSUMÉ
(SUMMARY IN FRENCH)

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La redistribution de la charge de travail est une méthode qui peut réduire considérablement la durée d'un projet si elle est correctement utilisée. Dans ce résumé, nous commencerons par préciser comment cette étude a été entreprise, et quels ont été le procédé et la méthodologie de recherche. Suivra une présentation de notre démarche, et nous verrons comment le problème a été traité pour obtenir de meilleurs résultats, et comment ils peut l'être pour les améliorer encore. Nous discuterons ensuite des intérêts et des contributions de cette recherche dans le domaine du génie industriel. Des perspectives et les recommandations pour des recherches ultérieures seront ensuite présentées.

DISCUSSIONS

Aujourd'hui, chaque industrie fait face à une concurrence énorme pour des produits se développant vers une qualité accrue et des coûts moindres. Dans ce but les industries exigent des techniques saines, établies en génie industriel : la gestion des projets et la recherche opérationnelle. Avec la généralisation de la globalisation comme de l'externalisation du travail et des approvisionnements, les industries emploient de plus en plus les méthodes de gestion des projets pour concevoir et fabriquer des produits.

Il reste fort à faire pour établir des outils propres à l'industrie et aux techniques. Les références traditionnelles en matière de gestion des projets que sont : IPMA, PMI et APM, sont générales par nature. Chaque projet est unique, avec un environnement exerçant une grande influence sur son exécution. Donc plus l'environnement sera certain et prévisible, plus le projet sera contrôlé efficacement. La gestion des projets est un champ en pleine croissance qui nous aide en résolvant les problèmes issus de chaque processus du projet ; les processus importants sont : Lancement, planification, exécution / contrôle et clôture.

Cette étude se concentre sur le processus de contrôle d'un projet pharmaceutique, processus qui mesure l'avancement du projet et au besoin conçoit une action de contrôle. En parallèle avec la supervision, ce travail se concentre également sur les techniques de prévisions et de re-planification. Un type particulier de projet est traité dans ce travail, que l'on désigne comme « projet à charge de travail transférable » (PCT), qui est un projet où la charge de travail est transmissible ou interchangeable parmi différentes ressources ayant la compétence semblable. Ainsi, cette thèse présente une occasion de rechercher une méthode robuste de suivi et de prévisions pour un PTC. Le PCT – type que nous étudions ici est un projet de test clinique, qui est la phase la plus importante dans le processus de développement d'un médicament.

Le problème étudié est lié à l'industrie pharmaceutique où de nouveaux traitements ou médicaments sont développés. Il y a une concurrence énorme sur le marché pharmaceutique ainsi que de très lourdes contraintes réglementaires, et des techniques spécialisées sont ainsi exigées pour les issues scientifiques et gestionnaires liées au développement des produits. L'objectif d'une société pharmaceutique est de convertir une molécule en produit de production. Le développement d'un médicament est un processus complexe impliquant de nombreuses étapes prenant environ 10 à 15 ans et coûtant environ $1 milliards. Il a un environnement fortement

réglementé avec des autorités appropriées maintenant des normes dans diverses régions du monde. Le développement de médicament comprend le cycle suivant : Pré-découverte, découverte du principe actif, essais précliniques, tests cliniques, revue de l'autorité réglementaire, avant de mettre sur pied la fabrication à large échelle du médicament pour traiter une maladie donnée.

Les tests cliniques comprend trois phases, et l'objet de cette étude est la troisième phase qui implique l'application du traitement au grand groupe de patients (plusieurs milliers). C'est la phase la plus coûteuse et la plus longue ; elle est généralement appliquée dans différentes régions du monde, faisant que le projet est globalement distribué, et exige ainsi un suivi approprié. Un test clinique se compose de deux étapes : recrutement et traitement. Cette thèse se concentre sur le développement d'une méthode robuste pour surveiller et prévoir la progression du travail dans un test clinique (PCT), de sorte que la durée de cette phase (période des tests cliniques) soit la plus réduite posdsible, et que les objectifs (buts d'étude clinique) soit atteints au moindre coût.

La raison pour laquelle un TCP est choisi pour l'étude est que la plupart du temps les caractéristiques pharmaceutiques vues plus haut font de tels projets des TCP. Par exemple le projet de tests cliniques à l'étude est un projet où les patients sont interchangeables entre différents sites de traitement, parfois distribués en différents pays.. Nous sommes également intéressés à la surveillance et au contrôle d'un TCP globalement distribué, qui définit encore une caractéristique d'un projet de test clinique.

Ce test clinique dans le projet est considéré comme déjà commencé et en cours de contrôle. La planification du recrutement a été produite à partir des études et des expériences précédentes. Le projet est en cours d'exécution, où le statut du recrutement est établi en le comparant au plan. L'objectif est de traiter un nombre donné de patients qui sont répartis entre différents sites selon leur capacité de manipulation et le nombre de patients disponibles. Par ailleurs, on sait par expérience qu'un certain nombre de patients quitteront le système avant la fin de leur traitement : maladie, décès, crainte, désintérêt, … Ainsi davantage de patients sont recrutés que nécessaire pour le strict besoin statistique du traitement. Le traitement proporement dit se compose quant à lui de trois phases successives, chaque phase ayant un coût, une durée et une posologie spécifiques.

Le premier objectif de cette étude est d'optimiser la durée du projet et dans cette optique, mat en oeuvre une redistribution de la charge de travail restante. Un compromis entre la durée et le coût est traité comme second objectif.

Le recrutement suit un modèle décrit par la « Courbe en S », où le travail démarre à un rythme modéré dans le début du projet, et accélère ensuite quand l'expérience est acquise, alors que la période de fin montre un ralentissement, dû à un abaissement intentionnel de l'effort. Il y a deux points d'inflexion de la courbe en S, un à la fin de la période de démarrage et l'autre à la fin de la période de fonctionnement en régime permanent. Cette courbe en S est employée intensivement dans cette thèse avec le postulat que la période de fin (avec le second point d'inflexion) ne sera pas traitée. Cela signifie que le recrutement se maintient à pleine vitesse jusqu'à l'achèvement. Le point d'inflexion est supposé atteint après une durée préspécifiée dans cette thèse, au lieu du recrutement d'un nombre prédéfini de patients.

La surveillance et le contrôle est un long processus qui accompagne la phase d'exécution du projet. Les données réelles pour le test clinique dans ce processus sont produites en décrivant l'exécution dans les différents sites. À chaque mise à jour les données réelles sont comparées au

plan pour observer les écarts, et le directeur de projet a le choix d'appliquer ou non une redistribution des recrutements restants. Également, à chaque mise à jour, chaque site est payé selon le nombre de patients finissant une phase particulière du traitement.

Avec la simulation d'une situation réelle le problème a été concentré sur la réponse : ce qui est la meilleure solution en termes de redistribution de la charge de travail transmissible entre différents associés dans un projet, quand nous constatons que le projet ne se comporte pas comme prévu. Cette redistribution correspond à un transfert de charge de travail à partir d'un partenaire moins efficace que prévu vers un autre partenaire fonctionnant plus rapidement. Une autre question était de savoir quand une telle redistribution devrait idéalement avoir lieu. Il est également envisagé de rechercher quand avoir recours à un nouveau partenaire ou site non initialement planifié. Les redistributions multiples présentent une autre voie d'exploration.

PROCÉDÉ DE RECHERCHES

Le procédé de recherches qui a été suivi pendant cette étude sera défini ici. D'abord, des questions de recherches d'intérêt ont été triées comme en chapitre deux pour l'étude. Alors la littérature a été passée en revue. La théorie a été développée utilisant le processus de revue de littérature, qui prolonge la compréhension du problème et cette théorie a été alors intégrée avec l'étude expérimentale du problème. Les développements de la théorie ont été complètement structurés (présentation en chapitre deux), c'est-à-dire comment un champ particulier a été entrepris pour trouver des informations au sujet de la question de recherches. Il a compris l'examen de littérature de la vieille et courante recherche. Ce processus de revue de littérature a été organisé selon les objectifs de notre recherche. La revue consistée en les secteurs comme : Gestion des projets ; Projets pharmaceutiques ; Projets globalement distribués ; Prévisions ; Développement pharmaceutique. Ce processus a ainsi aidé en améliorant notre approche du problème et fourni ainsi un point de commencement de la modélisation et de la simulation.

RÉSULTATS

Pour réaliser les objectifs déterminés, un modèle mathématique du problème pharmaceutique a été établi, qui a été alors employé pour simuler les situations réelles utilisant un programme informatique. On a développé une hypothèse linéaire, qui est un rapport utilisé pour la détermination des taux ou des rythmes de recrutement. Le procédé de recherche a été considérablement augmenté par le programme informatique, qui a facilité en rassemblant des résultats importants pour l'étude. Un certain nombre d'exemples du problème ont été produits avec différentes valeurs pour les variables système, et qui ont été employées pour se produire résultent pour les objectifs définis. En premier, la redistribution est comparée à la non-redistribution, qui montre que pour ce qui est de la durée de réalisation du projet, la redistribution est la meilleure approche.

En ce qui concerne la durée de temps ou de projet, l'étude montre la marche à suivre pour prendre la décision de la redistribution. Nous avons délibérément choisi, dans notre modélisation, d'attendre le passage du point d'inflexion pour procéder à des réaffectation de charges, de façon à ce que nous puissions faire des évaluations pour la partie postérieure du projet. La fiabilité des évaluations n'est pas idéale une fois saisies les données des mises à jour après le point d'inflexion ; la fiabilité s'améliore ensuite pendant une certaine période, jusqu'à ce que des

retards constatés deviennent irréversibles et non rattrapables par simple redistribution du travail restant.

L'outil a développé dans cette étude des aides destinées à un chef de projet pour décider quand appliquer la redistribution. Il lui permet également d'anticiper sur le comportement futur en insérant des prévisions au sujet des performances de tel ou tel partenaire. Un nouveau site ou associé est facilement ajouté de la manière prescrite utilisant le programme informatique, et pour cette situation des résultats ont été rassemblés qui montrent qu'il vaut mieux prendre cette décision vers les débuts d'exécution, car elle n'améliore pas beaucoup la durée de projet et induit un surcoût sensible si le nouvel associé est intégré pour partager la charge de travail dans les stades avancés d'un projet.

Après l'application de la redistribution, si quelques partenaires montrent toujours la même dégradation de leurs performances, la question des redistributions multiples entre en jeu. Des résultats ont été produits pour un certain nombre d'exemples qui illustrent que la deuxième redistribution ne peut pas réduire la durée du projet par rapport à celle atteinte par la redistribution précédente. Sans compter qu' une durée optimisée pour le projet peut seulement être maintenue à un coût graduellement croissant si la deuxième redistribution est appliquée d'une mise à jour à l'autre, ce qui incite le responsable à prendre cette décision sans retards.

CONCLUSIONS

L'expérience acquise d'une perspective de durée de projet (avec la prétention restrictive que, au cours du projet, le transfert de la charge de travail entre les partenaires ne peut être effectuée qu'une fois seulement) ; il y a d'évidence selon cette étude le besoin de rechercher un compromis entre la fiabilité des prévisions sur le reste-à-faire du projet, et l'irréversibilité des retards accumulés. Cependant, l'acceptation de l'application simple de la redistribution de travail mérite d'être discutée pour les raisons d'organisation, de coût et de simplification. Il est évident que les occasions de faire ces redistributions seront limitées ; nous pouvons examiner la demande de la redistribution à deux ou trois reprises - particulièrement si le fonctionnement de certains partenaires est particulièrement décevant.

Du point coût, l'hypothèse que nous avons faite d'un coût de la redistribution proportionnel au nombre de patients « transférés » pénalise encore nos résultats ; cette redistribution devient, de l'aspect strictement coût, d'autant plus intéressante qu'elle survient tard, quand le nombre restant de patients à recruter (et donc à transférer) est réduit. Cette vue est biaisée car les retards encourus par un partenaire ou le projet entier ne sont pas économiquement pénalisés dans notre modèle.

Les industries pharmaceutiques sont sous une pression énorme aujourd'hui où la production de nouveaux médicaments diminue alors que la dépense de R&D augmente : cela illustre le besoin de développement des techniques innovatrices scientifiques et de gestion. Pour faire face à ce développement lent, les entreprises pharmaceutiques fusionnent leurs efforts et connaissances. En parallèle, ces sociétés recourent à l'approvisionnement à l'extérieur étendu pour abaisser les coûts et augmenter la capacité de travail. Mais une gestion des projets défaillante annulera les avantages gagnés par les solutions définies ci-dessus. Cette thèse a proposé une méthode pour la gestion des phases de tests cliniques, qui apporte des améliorations sérieuses en diminuant le temps d'élaboration des médicaments, car les tests cliniques sont la plus longue phase dans ce développement.

Ce travail ne met pas moins en évidence la nécessité de chercher un compromis entre d'une part la date idéale pour le transfert de charges de travail (attendre des prévisions fiables met en danger la future capacité de rattraper les retards) et les coûts du projet. L'étude est donc continuée par la détermination du nombre idéal de tels transferts s'il y en a plus d'un, tout en continuant à prouver que ces transferts représentent un coût non-négligeable. Notre travail se poursuivra donc par l'étude d'un tel compromis.

L'OUTIL DE SIMULATION

Cette section discute des avantages de l'outil ou du logiciel préparé pour la simulation de ce problème pharmaceutique.

Les premiers résultats ont été rassemblés en utilisant des données telles quelles, puis un modèle de régression linéaire est employé sur ces mêmes données pour fournir des données linéaires. Alors des résultats ont été rassemblés pour ces données linéaires de sorte que beaucoup plus de perspicacité au sujet du comportement du système peut être acquise par cette simplification. Pour des effets plus réalistes, le coût du transfert et le coût d'introduction d'un nouveau partenaire peuvent être fixés par le décideur, plutôt que directement imposés par le programme. L'efficacité de la période de l'étude, pour le site nouvellement créé, n'est alors pas incorporé pour recalculer la durée de projet ; plutôt, un taux fixe de recrutement est exigé, pour ce nouveau partenaire, de l'utilisateur, taux qui devient la base de tous les calculs. Et ainsi on peut également ajouter deux taux différents de recrutement, pendant les périodes d'apprentissage et de fonctionnement normal, respectivement, qui fourniront une approche plus réaliste du problème au décideur pour faire ses choix.

L'outil présenté dans le chapitre précédent, avec quelques vues d'écran d'un certain nombre de formulaires, a donné l'occasion de simuler un problème pharmaceutique. Il ne sera, si tout va bien, pas difficile à employer si utilisé conformément aux instructions appropriées détaillées dans cette thèse. Il donne à l'utilisateur, ou plus plus précisément au décideur un taux acceptable de flexibilité de surveiller et piloter la progression du projet, en visualisant ce qui vraisemblablement se produira lors de la prochaine mise à jour, en termes de durée du projet. Un chef de projet peut visualiser ce qui se produira, sur un horizon donné, avec ce programme. Il fournit un bon environnement de surveillance et de contrôle via la représentation graphique de l'avancement de chaque partenaire ou pays. Les options fournies par le logiciel pour paramétrer le projet sont considérablement utiles car un décideur a logiquement un besoin de ces options. La redistribution peut être appliquée deux fois s'il y a lieu en utilisant ce programme. Bien que cet outil exige des améliorations dans divers domaines, il a un fonctionnement absolument satisfaisant, comme vérifié pour l'accomplissement des travaux dans cette thèse. L'annexe II présentera les divers blocs de programmation - des procédures et fonction, utilisées dans la simulation du problème.

CONTRIBUTIONS

Cette recherche a un certain nombre de contributions :

- Le contrôle de l'exécution du travail par des partenaires globalement dispersés présente un problème intéressant, qui n'est pas beaucoup étudié. Ainsi, cette étude est une contribution importante sur ce problème.

- La durée optimale de projet est atteinte en employant la redistribution dès que possible dans l'exécution d'un PCT.
- Les résultats de cette étude apportent une réponse à nos questions de recherche, qui sont brillamment appropriées aux professionnels de la pratique comme au milieu universitaire.
- On a passé en revue la littérature concernée et référence pour la modélisation et la simulation.
- Le modèle présenté dans cette thèse prend en considération diverses situations réalisables, et modèlise ainsi fidèlement la vraie situation, nous permettant d'étudier avec confiance.
- L'outil développé pour la simulation du problème, utilisant VBA fournit une occasion à un chef de projet de surveiller et commander un test clinique PCT suivre la méthode de redistribution.
- La redistribution, si utilisée avec la compréhension appropriée, fournit une méthode efficace pour l'optimisation de la durée de projet.
- Cette redistribution, intégrée à une méthode de prévisions devient un outil complet de suivi et de re-planification pour piloter l'exécution de projet.

PERSPECTIVES

Dans cette section, les ambiguïtés, des limitations avec les recommandations et les perspectives de cette recherche, seront discutées.

AMBIGUÏTÉS ET LIMITATIONS

Beaucoup de variables augmentent la complexité et l'ambiguïté du problème étudié. C'est pourquoi un certain nombre d'hypothèses ont été formulées pour simplifier le problème. Un nombre infini de situations est accessible en modifiant des variables, mais certains scénarios intéressants à étudier ont été approchés en fixant des variables particulières. Des valeurs de certaines variables ont été connues par expérience et ont été utilisées ainsi en conséquence.

Les données de planification étaient les seules données qui ont été établies par expérience, ainsi ces données sont lues sur une base de données, alors que toutes les autres étaient produites en utilisant la génération à nombre aléatoire dans la programmation de VBA. Ces nouvelles données ont été produites utilisant le modèle des données prévues, et ont été employées ainsi pour atteindre des solutions réalistes et optimales.

Le problème étudié est relié à divers domaines, tels que la gestion des projets, les sciences de la vie, les sciences économiques, les projets pharmaceutiques, la gestion de la technologie et les statistiques. Il est certainement difficile faire cette compilation d'études, cependant dans travail, ces disciplines multiples ont été consultées. Les chercheurs dans ces domaines ont encore beaucoup à accomplir pour optimiser les résultats de ce problème.

La partie consacrée au traitement du problème pharmaceutique n'était également pas exempte des confusions car ce n'est pas une partie réelle mais plutôt un aspect théorique du projet. Il n'y a pas beaucoup de littérature sur la planification de PCT, ainsi il est difficile d'avoir une directive concrète pour la gestion des PCT. La littérature,initialement limitée sur le contrôle

de ces projets, a augmenté graduellement pendant la thèse, et cette nouvelle littérature corrigeait et authentifiait les idées initiales, qui ont été également vérifiées par les résultats produits en utilisant la modélisation et la simulation du problème.

RECOMMANDATIONS POUR LA POURSUITE DE CETTE ÉTUDE

Plusieurs voies sont suggérées pour la prolongation de cette étude : introduire des pénalité pour l'achèvement en retard du projet ; les coûts de transfert peuvent être fixes ou avec un coefficient différent de coût pour chaque phase de traitement du patient transféré ; des coûts fixes, représentatifs de coûts de négociation, peuvent être ajoutés. On peut également traiter la période de fin de la courbe en S, qui n'a pas été étudiée dans cette thèse. Le deuxième point d'inflexion, avec ses effets calendaires, peut être ajouté à la fin de la période de fonctionnement en régime permanent. Ceci introduira davantage de variables au problème, le rendant plus complexe, : la simplification de nos hypothèses peut également être envisagée en conséquence.

Des cas spécifiques sont également à recommander pour une poursuite de cette recherche. Le cas par exemple où la charge de travail d'un partenaire donné ne peut être transféré que vers un nombre limité d'associés, choisis par le chef de projet selon leur vitesse d'avancement. Ajouter également le concept des coûts de négociation interviendra opportunément ici, car moins les partenaires concernés par ce transfert seront nombreux, moindres seront les coûts de négociation.

Le problème de fond restant le compromis entre la durée de projet et son coût, c'est-à-dire comment un optimum peut être atteint en utilisant la redistribution.

Peu d'attention a été accordée à la partie de la planification pour les PCT dans la littérature. Pour cette étude un choix de la littérature a été étudié, qui est complètement ou partiellement utilisable pour prolonger la recherche sur cette matière. Ceci dépend également du nouveau centre d'intérêt de recherche qui peut porter plus sur les aspects techniques du développement de médicament, la gestion des projets ou sur les aspects philosophiques des projets globalement distribués. Ainsi, chaque intérêt peut suivre la revue bibliographique en conséquence.

Notre attention portait sur le contrôle des PCT pharmaceutiques, mais cette attention est extensible à d'autres processus de gestion des projets, pour avoir un paquet global de gestion pour le contrôle des PCT. La littérature appropriée passée en revue pour chaque processus peut être utile pour cet effort.

Les industries matures pour leur utilisation de la gestion des projets, peuvent aider des industries moins mûres par divers processus d'évaluation, techniques de gestion et bonnes pratiques. Pour une meilleure organisation de ces projets, l'établissement d'une équipe multifonctionnelle sera également efficace en permettant de réduire le temps et le coût du projet. L'expérience acquise ne peut être généralisée mais peut être utile dans la réalisation d'objectifs semblables.

Un directeur responsable de l'accomplissement d'un projet de test clinique, dans la durée et avec les ressources prévues, peut tirer intérêt des résultats rassemblés ici. Mais il est très important de préciser ici que son travail n'est pas limité au seul déplacement d'une feuille de calcul de MS Excel à l'autre … il a beaucoup de travail gestionnaire et administratif à faire pour maintenir toutes les voies de transmission actives de sorte que chaque aspect affectant la

progression du projet puisse être observé. De sorte que n'importe quel problème avant d'obtenir un grand cou de bouteille puisse être évité ou une solution a découvert avant main.

En employant ce logiciel, le directeur reste en contact par courriel ou par téléphone avec les différents partenaires du programme pour obtenir des information de mise à jour du projet. Le responsable du projet prend sa décision sur la base de l'information qu'il reçoit, décision qui peut être d'appliquer la redistribution, ou d'ajouter un nouveau pays ; qui peut être d'appliquer la redistribution la deuxième fois, ou bien juste laisser le projet progresser tel quel. Dans certaines situations il doit personnellement se rendre sur site pour plus d'information ou des conseils. Parfois au besoin il doit présenter le problème devant sa hiérarchie pour approbation de certaines actions selon la gravité du problème ; les dépassements de coût élevés, les retards inacceptables ou l'incertitude inévitable peuvent être des circonstances où un responsable doit présenter la situation et rendre des comptes. Il doit être également présent à des réunions pour analyser diverses situations que le projet peut rencontrer. Ainsi, cette thèse avec l'outil de simulation peut aider ce responsable pour le suivi et le pilotage du projet, de sorte qu'il puisse efficacement s'occuper d'autres aspects de la gestion du projet.

Globalement, ce travail est une contribution au champ toujours important de la gestion des projets, tout particulièrement pour l'industrie pharmaceutique. Ce travail a présenté une méthode de prévision et d'optimisation de la durée d'un projet où la charge de travail est interchangeable parmi différentes ressources. Il a pris en considération de divers aspects affectant ces projets et leur environnement.

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ANNEXES

ANNEX I: VARIABLES IN MODEL

ANNEX II: PROGRAM IN VBA

ANNEXES

ANNEX I: VARIABLES IN MODEL

j	=	No. of sites or countries
$N^0(j)$	=	Total planned patients required to be recruited by site "*j*"
N^0	=	Total planned patients required to be recruited by all sites
$T^0_f(j)$	=	Planned total or final duration for the site "*j*"
T^0_f	=	Planned total or final duration of the project
i	=	No. of stages in execution = 1, 2 (i.*e. learning and working*)
$s^0_l(j)$	=	Planned recruitment rate in stage "*l*" (learning period) for site "*j*" (*unit: patients/day*)
$s^0_w(j)$	=	Planned recruitment rate in stage "*w*" (working period) for site "*j*"
$s_l(j)$	=	Real recruitment rate in stage "*l*" (learning period) for site "*j*"
$s_w(j)$	=	Real recruitment rate in stage "*w*" (working period) for site "*j*"
SPI	=	Schedule Performance Index
$I^0(j)$	=	Date at which planned POI occurs for site "*j*"
$I(j)$	=	Date at which real POI occurs for site "*j*"
$n^0(t, j)$	=	Planned number of patients recruited from time = *0* to *t* for site "*j*"
$n(t, j)$	=	Real number of patients recruited from time = *0* to *t* for site "*j*"
k	=	No. of treatment phases = 1, 2, 3
C_k	=	Cost of the treatment phase "*k*" for a patient
$C^0_f(j)$	=	Planned final cost for treating patients at site "*j*"
$C_f(j)$ =		Actual final cost for treating patients at site "*j*"
C^0_f	=	Planned final cost of the project
C_f	=	Actual final cost of the project
C_N	=	Negotiation cost
C_T	=	Transfer cost
$\Delta t(j)$	=	Lateness after $T^0_f(j)$
W_{tc}	=	Remaining work to complete the project
D_{tc}	=	Remaining duration to complete the project

ANNEX II: PROGRAM IN VBA

```
                    ****************************
                    *      PROCEDURE # 1       *
                    * For Generating Real Data *
                    ****************************

Sub PharmacieProb()

    'For quick processing
    Application.ScreenUpdating = False

    'Definition
    Dim mws As Worksheet              'Main WorkSheet
    Dim pm As Worksheet               'Parameters WorkSheet
    Dim bws As Worksheet              'Scheduled Budget WorkSheet
    Dim c As Worksheet                'Country WorkSheet
    Dim i As Integer                  'ForNext Variable
    Dim j As Integer                  'Country #
    Dim k As Integer                  'Count how many times RecDate is called
    Dim l As Integer                  'For which country RecDate is called
    Dim ctr As Integer                'Counter
    Dim m As Integer                  'Month Update
    Dim p As Integer                  'Phase Counter
    Dim nbp As Range                  'No. of Patients for each country
    Dim rg1 As Range                  'Range/Column 1 i.e. Patient#
    Dim rg2 As Range                  'Range/Column 2 i.e. Random No.
    Dim rg3 As Range                  'Range/Column 3 i.e. Recruitment Date
    Dim rg4 As Range                  'Range/Column 4 i.e. Duration
    Dim rg5 As Range                  'Range/Column 5 i.e. Quit Date
    Dim rg6 As Range                  'Range/Column 6 i.e. Phase 1
    Dim rg7 As Range                  'Range/Column 7 i.e. Phase 2
    Dim rg8 As Range                  'Range/Column 8 i.e. Phase 3
    Dim sd As Range                   'Start Date of Project
    Dim ed As Range                   'End Date of Project

    'Initialization
    Set pm = ThisWorkbook.Worksheets(1)
    Set mws = ThisWorkbook.Worksheets(2)
    ctr = 0
    l = 1
    'If Option2 is selected > call XLFile procedure, Else Option1 is selected
    If Frm1.opt2.Value = True Then
        GetXLFile
        Set sd = mws.Range(Frm1.txtStartDt2.Value)
        Set ed = mws.Range(Frm1.txtEndDt2.Value)
    Else
        Set sd = mws.Range(Frm1.txtStartDt1.Value)
        Set ed = mws.Range(Frm1.txtEndDt1.Value)
    End If

    '_____________For Each Country_____________
    'Worksheets naming & creation
    pm.Name = "Parameters"
```

```
    mws.Name = "Main"
    Worksheets(3).Name = "Country 1"
    If (Frm1.txtNbrCtr.Value <> "" Or Frm1.txtNbrCtr.Value > 0) Then
        ctr = 2
        Do Until ThisWorkbook.Worksheets.Count - 2 = Frm1.txtNbrCtr.Value
            ThisWorkbook.Worksheets.Add
after:=ThisWorkbook.Worksheets(Worksheets.Count)
            Worksheets(Worksheets.Count).Name = "Country " & ctr
            ctr = ctr + 1
        Loop
        ctr = 0
    End If
    ThisWorkbook.Worksheets.Add after:=Worksheets(Worksheets.Count)
    Set bws = Worksheets(Worksheets.Count)
    bws.Name = "Sch. Budget"

    For j = 1 To (Frm1.txtNbrCtr.Value)
        Set c = ThisWorkbook.Worksheets(j + 2)
        'c.Name = "Country " & j
        m = Frm1.txtUpd.Value

        'Column Headings
        c.Range("B2").Value = "Patient"
        c.Range("C2").Value = "Random No."
        c.Range("D2").Value = "Rec Date"
        c.Range("E2").Value = "Duration"
        c.Range("F2").Value = "Quit Date"
        c.Range("G2").Value = "Phase 1"
        c.Range("H2").Value = "Phase 2"
        c.Range("I2").Value = "Phase 3"
        c.Range("B2").Font.Bold = True
        c.Range("C2").Font.Bold = True
        c.Range("D2").Font.Bold = True
        c.Range("E2").Font.Bold = True
        c.Range("F2").Font.Bold = True
        c.Range("G2").Font.Bold = True
        c.Range("H2").Font.Bold = True
        c.Range("I2").Font.Bold = True
        c.Columns.EntireColumn.AutoFit

        'Fills Columns
        If j = 1 Then
            If Frm1.opt1.Value = True Then
                Set nbp = mws.Range(Frm1.txtPtnCll1.Value)
            Else
                Set nbp = mws.Range(Frm1.txtPtnCll2.Value)
            End If
            Set rg1 = c.Range("B3")
            Set rg2 = c.Range("C3")
            Set rg3 = c.Range("D3")
            Set rg4 = c.Range("E3")
            Set rg5 = c.Range("F3")
            Set rg6 = c.Range("G3")
            Set rg7 = c.Range("H3")
            Set rg8 = c.Range("I3")
            k = 1
            For i = 1 To nbp.Value
```

```
        'Patient Column
        rg1.Value = i
        'Random No. Column
        rg2.Value = Rnd()
        'Rec Date Column
        rg3.Value = RecDate(mws, nbp, k, sd, m, l)
        k = k + 1
        'Duration Column
        If rg2.Value < (Frm1.txtQtPtn.Value / 100) Then
            rg4.Value = UnfmRndNbr(0, 364)
            ctr = ctr + 1
            c.Range("K3").Value = ctr
            c.Range("L3").Value = ctr / nbp.Value
        Else: rg4.Value = 365
        End If
        'Quit Date Column
        rg5.Formula = "=sum(R[0]C[-1],R[0]C[-2])"
        'Phase#1
        p = 1
        rg6.Value = PhaseCalc(rg3.Value, rg4.Value, rg5.Value, p)
        p = p + 1
        'Phase#2
        rg7.Value = PhaseCalc(rg3.Value, rg4.Value, rg5.Value, p)
        p = p + 1
        'Phase#3
        rg8.Value = PhaseCalc(rg3.Value, rg4.Value, rg5.Value, p)

        Set rg1 = rg1.Offset(1, 0)
        Set rg2 = rg2.Offset(1, 0)
        Set rg3 = rg3.Offset(1, 0)
        Set rg4 = rg4.Offset(1, 0)
        Set rg5 = rg5.Offset(1, 0)
        Set rg6 = rg6.Offset(1, 0)
        Set rg7 = rg7.Offset(1, 0)
        Set rg8 = rg8.Offset(1, 0)
    Next
    BudSch c, mws, pm, bws, Frm1.txtNbrCtr.Value, m, sd
Else
    Set nbp = nbp.Offset(0, 1)
    Set rg1 = c.Range("B3")
    Set rg2 = c.Range("C3")
    Set rg3 = c.Range("D3")
    Set rg4 = c.Range("E3")
    Set rg5 = c.Range("F3")
    Set rg6 = c.Range("G3")
    Set rg7 = c.Range("H3")
    Set rg8 = c.Range("I3")
    k = 1
    l = l + 1
    ctr = 0
    For i = 1 To nbp.Value
        'Patient Column
        rg1.Value = i
        'Random No. Column
        rg2.Value = Rnd()
        'Rec Date Column
        rg3.Value = RecDate(mws, nbp, k, sd, m, l)
```

```
                k = k + 1
                'Duration Column
                If rg2.Value < (Frm1.txtQtPtn.Value / 100) Then
                    rg4.Value = UnfmRndNbr(0, 364)
                    ctr = ctr + 1
                    c.Range("K3").Value = ctr
                    c.Range("L3").Value = ctr / nbp.Value
                Else: rg4.Value = 365
                End If
                'Quit Date Column
                rg5.Formula = "=sum(R[0]C[-1],R[0]C[-2])"
                'Phase#1
                p = 1
                rg6.Value = PhaseCalc(rg3.Value, rg4.Value, rg5.Value, p)
                p = p + 1
                'Phase#2
                rg7.Value = PhaseCalc(rg3.Value, rg4.Value, rg5.Value, p)
                p = p + 1
                'Phase#3
                rg8.Value = PhaseCalc(rg3.Value, rg4.Value, rg5.Value, p)

                Set rg1 = rg1.Offset(1, 0)
                Set rg2 = rg2.Offset(1, 0)
                Set rg3 = rg3.Offset(1, 0)
                Set rg4 = rg4.Offset(1, 0)
                Set rg5 = rg5.Offset(1, 0)
                Set rg6 = rg6.Offset(1, 0)
                Set rg7 = rg7.Offset(1, 0)
                Set rg8 = rg8.Offset(1, 0)
            Next

            'Calculates Scheduled Budget
            BudSch c, mws, pm, bws, Frm1.txtNbrCtr.Value, m, sd
        End If
    Next

    'Calculates the CUMULATE column in Sch.Budget Worksheet
    Cumul mws, bws, Frm1.txtNbrCtr.Value

    'Fills PARAMETERS sheet
    Parameters pm

    'Dereferencing
    Set mws = Nothing
    Set pm = Nothing
    Set nbp = Nothing
    Set rg1 = Nothing
    Set rg2 = Nothing
    Set rg3 = Nothing
    Set rg4 = Nothing

End Sub
```

```
                    ****************************
                    *      FUNCTION # 1        *
                    * For Returning Random No. *
                    ****************************

Function UnfmRndNbr(Low As Single, High As Single) As Integer
    UnfmRndNbr = Rnd * (High - Low + 1) + Low
End Function
```

```
                    ****************************
                    *      FUNCTION # 2        *
                    *  For Returning Rec. Date *
                    ****************************

Function RecDate(mws As Worksheet, nbp As Range, k As Integer, d As Range, m
As Integer, l As Integer) As Integer

    'Definition
    Dim d1 As Range                          'Last Update
    Dim d2 As Range                          'This Update
    Dim n1 As Range                          'Patients uptil last Update
    Dim n2 As Range                          'Patients uptil this update

    'Initialization
    Set d1 = d
    Set d2 = d.Offset(m, 0)
    Set n1 = d.Offset(0, l)
    Set n2 = n1.Offset(m, 0)

      'Changes the above initialization for d which has to be StartDate, if
      'reallocation is done more than once
    If ThisWorkbook.Worksheets(2).Name <> "Main" Then
        Set d = ThisWorkbook.Worksheets("Real Rec").Range("B3")
    End If

    'Indicates the correct point of start for date values for the new country
If NC = True And l = ThisWorkbook.Worksheets("Parameters").Range("C3").Value
Then
        Set n1 = Update.Offset(0, l)
        Set n2 = n1.Offset(m, 0)
        Set d1 = n1.Offset.End(xlToLeft)
        Set d2 = d1.Offset(m, 0)
End If

    'Fills RecDate Column
    Do Until n1.Value = nbp.Value
        If k > n1.Value And k <= n2.Value Then
  RecDate = UnfmRndNbr(CSng(d1.Value - d.Value) + 1, CSng(d2.Value - d.Value))
        End If
        Set n1 = n1.Offset(m, 0)
        Set n2 = n2.Offset(m, 0)
        Set d1 = d1.Offset(m, 0)
        Set d2 = d2.Offset(m, 0)
```

```
        'Checks if No. of patients n2 is empty
        If (mws.Name = "Real Rec" And IsEmpty(n2)) Then
            Set d2 = d1
            'Set n2 = n1.End(xlDown)
            Set n2 = n1
        End If
        If (mws.Name = "Real Rec" And IsEmpty(n1)) Then
            Exit Do
        End If
    Loop

    'Dereferencing
    Set d1 = Nothing
    Set d2 = Nothing
    Set n1 = Nothing
    Set n2 = Nothing
End Function
```

****
* **FUNCTION # 3** *
* For Returning Phases *
****

```
Function PhaseCalc(rd As Integer, dur As Integer, qd As Integer, p As Integer)
As Integer

    'Definition
    Dim p1 As Range                                 'Phase#1
    Dim p2 As Range                                 'Phase#2
    Dim p3 As Range                                 'Phase#3

    'Initialization
    Select Case p
        Case 1                                      'Completed or not Phase1
            If dur < 122 Then
            PhaseCalc = 0
            ElseIf dur >= 122 Then
            PhaseCalc = rd + 122
            End If
        Case 2                                      'Completed or not Phase2
            If dur >= 244 Then
            PhaseCalc = rd + 244
            Else
            PhaseCalc = 0
            End If
        Case 3                                      'Completed or not Phase3
            If dur = 365 Then
            PhaseCalc = qd
            Else
            PhaseCalc = 0
            End If
    End Select
End Function
```

```
                    ********************************
                    *         PROCEDURE # 2        *
                    *  For Estimating Sch. Budget  *
                    ********************************

Sub BudSch(c As Worksheet, mws As Worksheet, pm As Worksheet, bws As
Worksheet, nbc As Integer, m As Integer, sd As Range)

    'Definition
    'nbc is No. of Countries
    Dim sr As Range              'Searching Range
    Dim ins As Range             'Insert in this range
    Dim d1 As Range              'Last Update
    Dim d2 As Range              'This Update
    Dim ctr As Integer           'Counter
    Dim i As Single              'ForNext Variable
    Dim j As Single
    Dim d As Date                'Keeps the date for MONTHS column's expansion

    'Initialization
    Set ins = bws.Range("B2")
    Set sr = c.Range("G3")
    Set d1 = bws.Range("B3")
    Set d2 = bws.Range("B3")
    ctr = 0

    'Calculates Scheduled Budget

    'Column Headings
    ins.Value = "MONTH"
    ins.Font.Bold = True
    For i = 1 To nbc
        Set ins = ins.Offset(0, 1)
        ins.Value = "COUNTRY " & i
        ins.Font.Bold = True
        bws.Columns.EntireColumn.AutoFit
    Next
    Set ins = ins.Offset(0, 1)
    ins.Value = "CUMULATE"
    ins.Font.Bold = True
    bws.Columns.EntireColumn.AutoFit

    'Months clumn copy-pasted & expanded
    mws.Activate
    mws.Range("B:B").Select
    Selection.Copy
    bws.Activate
    bws.Range("B:B").Select
    ActiveSheet.Paste
    bws.Range("B:B").NumberFormat = "mmm-yy"
    bws.Range("B:B").Font.Size = 8
    bws.Range("B:B").Font.Name = "Comic Sans MS"
    Set ins = bws.Range("B3")
    Do Until IsEmpty(ins)
        d = ins.Value
        Set ins = ins.Offset(1, 0)
```

```
Loop
'For generating 13 months of treatment of the last patient
For i = 1 To 15
    d = DateAdd("m", 1, d)
    ins.Value = d

    Set ins = ins.Offset(1, 0)
Next

'Generates ScheduledBudget for a country
For i = 1 To 3
    j = 0

    'Locates SearchRange according to the Phase
    If i = 1 Then
            Set sr = c.Range("G3")
        ElseIf i = 2 Then
            Set sr = c.Range("H3")
        Else
            Set sr = c.Range("I3")
    End If
    Set d1 = bws.Range("B3")                    'Back to starting point
    Set d2 = bws.Range("B3")                    'Back to starting point

    'Locates cell to insert budgetary data according to the country
    Set ins = bws.Range("C2")
    Do Until Right(ins.Value, 1) = Right(c.Name, 1)
        Set ins = ins.Offset(0, 1)
    Loop
    Set ins = ins.Offset(1, 0)

    'Checks if QuitDate is within d1 and d2 then insert budgetary data
    Do Until IsEmpty(d2)
        Do Until IsEmpty(sr)
    If sr.Value > CSng(d1.Value - sd.Value) And
    sr.Value <= CSng(d2.Value - sd.Value) Then
                ctr = ctr + 1
            End If
            Set sr = sr.Offset(1, 0)
        Loop
        j = j + 1
        If i = 1 Then                       'SearchRange at starting point
                Set sr = c.Range("G3")
            ElseIf i = 2 Then
                Set sr = c.Range("H3")
            Else
                Set sr = c.Range("I3")
        End If
        If j > 1 Then Set d1 = d1.Offset(m, 0)
   'So that it starts offsetting with 1 lag with d2
        Set d2 = d2.Offset(m, 0)
        If i = 1 Then
   'Payments according to completed Phase
                ins.Value = ins.Value + (ctr * CLng(Frm1.txtPh1))
            ElseIf i = 2 Then
                ins.Value = ins.Value + (ctr * CLng(Frm1.txtPh2))
            Else
```

```
                    ins.Value = ins.Value + (ctr * CLng(Frm1.txtPh3))
                End If
                Set ins = ins.Offset(m, 0)
                ctr = 0
            'Counter is restarted for the next d1 and d2
            Loop
        Next

End Sub
```

```
                    ****************************************
                    *            PROCEDURE # 3             *
                    *  Decision Making Options after POI   *
                    ****************************************

Private Sub cmdRR_Click()

    Dim rg1 As Range
    Dim rg2 As Range
    Dim rg3 As Range
    Dim ctr As Integer                                  'Counter

    If Frm2.optReqRR.Value = True Then
    'ReqRR is selected it will change the RecRate to what is required to
    'achieve the No. of patients
        Module3.UpdateReal reqdRR, Frm1.txtNbrCtr.Value, Frm2.cmbxChart.Value

    ElseIf Frm2.optInsertRR.Value = True Then
    'InsertRR is selected and it will change the RecRate to what is inserted
    Module3.UpdateReal (1 / Frm2.txtInsertRR.Value), Frm1.txtNbrCtr.Value,
Frm2.cmbxChart.Value

    ElseIf Frm2.optLP.Value = True Then
        Module4.manLP

        Frm2.Hide
'hides Form2 until LP is completed & then will be visible for real budget

    ElseIf Frm2.optNC.Value = True Then
        'Insert a procedure here to add a slot for a new country in manLP with
        'a previewed RR (inserted in text box)
        'and then use manLP for distributing the work acc. to RRs to end the
        'work on the same date
        NC = True
        Module4.addNewCountry
        Module4.manLP

        Frm2.Hide       'to hide Form2 till the LP is completed and then will
        'be visible for final real budget

    End If

    Set rg1 = Application.ThisWorkbook.Worksheets("Real Rec").Range("B3")
    Set rg2 = rg1.End(xlDown)
    Set rg3 = rg2.Offset(0, 1)
```

```
   'For locating the end of the project and saving the duration in expDuration
    ctr = 1
    Do While IsEmpty(rg3.Value)
        ctr = ctr + 1
        Set rg3 = rg3.Offset(0, 1)
        If ctr > Frm1.txtNbrCtr.Value Then
            Set rg2 = rg2.Offset(-1, 0)
            Set rg3 = rg2.Offset(0, 1)
            ctr = 1
        End If
    Loop
    expDuration = (rg2.Value - rg1.Value)

        'Deletes the "Rough" worksheet
    For ctr = 1 To ThisWorkbook.Worksheets.Count
        If ThisWorkbook.Worksheets(ctr).Name = "Rough" Then
            Application.DisplayAlerts = False
            ThisWorkbook.Worksheets("Rough").Delete
            Application.DisplayAlerts = True
        End If
    Next

    Frm2.cmdRR.Enabled = False
End Sub
```

****
* **PROCEDURE # 4** *
* Adds Chart Object *
****

```
 Sub AddChartObject(dur As Integer)

    'Definition
    Dim myChtObj As ChartObject
    Dim chrt As Worksheet          'Chart Worksheet
    Dim i As Integer               'For loop variable
    Dim NbCtr As Integer           'No. of countries
    Dim rg As Range                'For keeping a range
    Dim sel As Range               'Selection of Source Data
    Dim ws As Worksheet            'For checking if Chart sheet already exist
    Dim ttl As Range               'For keeping the title of the chart

    'Initialization
    Set ttl = ThisWorkbook.Worksheets("Main").Range("B2")

    'Adds worksheet for keeping Charts if it doesn't already exist
    On Error Resume Next
    Set ws = ThisWorkbook.Worksheets("Charts (Real)")
    If ws Is Nothing Then              'i.e. if ws doesn't exist then creates
        ThisWorkbook.Worksheets.Add
after:=ThisWorkbook.Worksheets(Worksheets.Count)
        Set chrt = ThisWorkbook.Worksheets(Worksheets.Count)
        chrt.Name = "Charts (Real)"
    End If
```

```
    'Adds charts of Real Rec Data for each country
    ws.Activate
    NbCtr = ThisWorkbook.Worksheets(1).Range("C3").Value
    Set rg = ThisWorkbook.Worksheets("Real Rec").Range("C3")
    For i = 1 To NbCtr
        'Deletes the previous Charts if any exist
If Not Worksheets("Charts (Real)").ChartObjects("Country " & i) Is Nothing
Then
            Worksheets("Charts (Real)").ChartObjects("Country " & i).Delete
        End If
        'Creates the updated charts
Set sel = ThisWorkbook.Worksheets("Real Rec").Range(rg.Address, rg.Offset(dur,
0).Address)
        Set myChtObj = ActiveSheet.ChartObjects.Add(Left:=100, Width:=375,
Top:=75 * i, Height:=225)
        myChtObj.Name = "Country " & i
        myChtObj.Chart.ChartType = xlXYScatterLines
        myChtObj.Chart.SetSourceData Source:=sel

        'Gives title to the chart
        Set ttl = ttl.Offset(0, i)
        myChtObj.Chart.ChartTitle = ttl
        myChtObj.Chart.HasTitle = True
        myChtObj.Chart.ChartTitle.Text = "Country " & i

        Set rg = rg.Offset(0, 1)
    Next

    'Dereferencing

End Sub
```

****
* **PROCEDURE # 5** *
* Update Real Data *
****

```
Sub UpdateReal(NewRR As Single, NbCtr As Integer, CtrN As String)

    'Definition
    Dim i As Integer      'For loop variable
    Dim rg1 As Range      'For keeping No. patients rec to Update
    Dim rg2 As Range      'For keeping total No. of patients to be rec
    Dim dt As Range       'For keeping the update Dates
    Dim ins As Range      'Insert the new No. of patients in this cell
    Dim d1 As Range       'Date 1
    Dim d2 As Range       'Date 2
    Dim dur As Long       'Remaining duration to achieve total No. of patients
    Dim rrws As Worksheet 'RR work sheet

    'Initialization
    Set rrws = ThisWorkbook.Worksheets("Real Rec")

    'Generate acc. to Reqd RR the data till total no. of patients to be rec
    'are achieved with dates
```

```
    For i = 1 To NbCtr
        If CtrN = "Country " & i Then
            Set rg1 = Update.Offset(0, i)
            Set rg2 = ThisWorkbook.Worksheets("Main").Range("B2")
            Set rg2 = rg2.End(xlDown)
            Set rg2 = rg2.Offset(0, i)
            Set ins = rg1

            dur = Round(NewRR * (rg2.Value - rg1.Value), 0)
            'Remaining duration

            Set d1 = Update
            Set d2 = Update.Offset(1, 0)

            Do Until (ins.Value = rg2.Value)

                'Fills the MONTHS column to the end
                If IsEmpty(d2) Then
                    d2.Value = DateAdd("m", 1, d1)
                    rrws.Range("B:B").NumberFormat = "mmm-yy"
                    rrws.Range("B:B").Font.Size = 8
                    rrws.Range("B:B").Font.Name = "Comic Sans MS"
                    rrws.Columns.EntireColumn.AutoFit
                End If

         'Fills the column with No. of patients recruited monthly till the end
                Set ins = ins.Offset(1, 0)
                ins.Value = Round((d2.Value - d1.Value) / NewRR, 0)
                ins.Value = ins.Value + rg1.Value
                Set rg1 = rg1.Offset(1, 0)
                If ins.Value > rg2.Value Then
                    ins.Value = rg2.Value
'Deletes any other values in the column under the row of total No. of patients
Set rg1 = ThisWorkbook.Worksheets("Real Rec").Range(ins.Offset(1, 0),
ins.End(xlDown))
                    rg1.Value = ""
                End If

                Set d1 = d1.Offset(1, 0)
                Set d2 = d2.Offset(1, 0)
            Loop
        End If
    Next

    'Dereferencing
End Sub
```

****
* **PROCEDURE # 6** *
* Prepares Data for LP *
****

```
Sub manLP()

    'Definition
```

```
    Dim rg1 As Range            'Range object
    Dim rg2 As Range            'Range object
    Dim rg3 As Range            'Range object
    Dim rg4 As Range            'Range object
    Dim rg5 As Range            'Range object
    Dim rrws As Worksheet       'RealRec worksheet
    Dim pm As Worksheet         'Parameters worksheet
    Dim i As Integer            'For loop variable
    Dim tpt As Integer          'Total Patients
    Dim rr() As Single          'Rec. Rate Array

    'Initialization
    Set rrws = ThisWorkbook.Worksheets("Real Rec")
    Set pm = ThisWorkbook.Worksheets("Parameters")
    Set rg2 = Update.Offset(0, 1)
    ReDim rr(Frm1.txtNbrCtr.Value)
'Dimension Rec. Rate array of size of No. of countries

    'Create data for doing LP

    '1. Delete all real rec. data from this update onwards
    For i = 1 To pm.Range("C3").Value
        'Fills empty cells with " 0 + last No. of rec. ptns."
        Set rg1 = Update.Offset(0, i)
        If IsEmpty(rg1) Then
            Set rg5 = rg1.Offset.End(xlUp)
            Set rg5 = rg5.Offset(1, 0)
            Do While IsEmpty(rg5) And rg5.Address <> rg1.Address
                rg5.Value = rg5.Value + rg5.Offset(-1, 0).Value
                Set rg5 = rg5.Offset(1, 0)
            Loop
            rg1.Value = rg1.Value + rg1.Offset(-1, 0).Value
        End If

        Set rg1 = Update.Offset(1, i)
        Do Until IsEmpty(rg1)
            rg1.Value = ""
            Set rg1 = rg1.Offset(1, 0)
        Loop
    Next

    ''2. Calculate Rec. Rates for each country after the pt. of inf.
    On Error Resume Next
    For i = 1 To pm.Range("C3").Value
        Set rg1 = Update.Offset(0, i)
'No. of Patients rec. till this update
        Set rg2 = rrws.Range(PtInf(i)).Offset(0, i)
        Set rg3 = rrws.Range(PtInf(i))

        If NC = True And i = pm.Range("C3").Value Then
'If this is the new country then
            rr(i) = Frm2.txtNCRR.Value
        Else
     rr(i) = Round((Update.Value - rg3.Value) / (rg1.Value - rg2.Value), 2)
'Fills the Rec. Rate array
        End If
    Next
```

```
    '3. Put data in Parameters worksheet for LP
    pm.Activate
  'Fills the Tot. Patients to be recruited according to the countries involved
 Set rg1 = ThisWorkbook.Worksheets(2).Range(Frm1.txtEndDt1.Value).Offset(0, 1)
    pm.Range("B5").Value = "Tot. Patients"
    tpt = 0
    'For i = 1 To pm.Range("C3").Value
    '    tpt = tpt + rg1.Value
    '    Set rg1 = rg1.Offset(0, 1)
    'Next
    tpt = rg1.Offset.End(xlToRight).Value
    pm.Range("C5").Value = tpt
            'Headings
    pm.Range("D2").Value = "Planned Dur."
    pm.Range("D2").Font.Bold = True
    pm.Range("E2").Value =
(ThisWorkbook.Worksheets(2).Range(Frm1.txtEndDt1.Value).Value -
ThisWorkbook.Worksheets(2).Range(Frm1.txtStartDt1.Value).Value)
    pm.Range("B6").Value = "Est. Duration"
    pm.Range("B7").Value = "Country #"
    pm.Range("C7").Value = "Rec. Rate"
    pm.Range("D7").Value = "Patients Rec."
    pm.Range("E7").Value = "Remaining Pat."
    pm.Range("F7").Value = "Est. Duration"
    pm.Range("B4").Value = "Tot. Duration"
    pm.Range("D4").Value = Update.Value
    pm.Range("E4").Value = rrws.Range(Frm1.txtStartDt1.Value).Value
    pm.Range("C4").Formula = "=R[0]C[1] - R[0]C[2] + R[2]C[0]"
    pm.Range("C7:F7").Font.Bold = True
    pm.Range("B2").Value = "Elapsed Duration"
    pm.Range("C2").Formula = "=R[2]C[1] - R[2]C[2]"
'Fills column-B with Country Nos., column-C with the respective Rec. Rate and
'column-F with the formula for Est. Duration
    Set rg2 = pm.Range("B8")
    Set rg3 = pm.Range("C8")
    Set rg4 = pm.Range("F8")
    For i = 1 To pm.Range("C3").Value
        rg2.Value = "Country " & i
        Set rg2 = rg2.Offset(1, 0)

        rg3.Value = rr(i)
        Set rg3 = rg3.Offset(1, 0)

        rg4.Formula = "=(R[0]C[-3] * R[0]C[-1])"
        Set rg4 = rg4.Offset(1, 0)
    Next
            'Fills column-D with No. of patients rec. till now
    Set rg2 = pm.Range("D8")
    For i = 1 To pm.Range("C3").Value
         Set rg1 = Update.Offset(0, i)

        If NC = True And i = pm.Range("C3").Value Then
'For putting 0 patients rec. at the new country
            rg1.Value = "0"
        End If
```

```
        If IsEmpty(rg1) Then
'Checks whether rg1 is empty or not, if yes then search for the last row
'having data for Rec. Patients uptil now
            Set rg1 = rg1.End(xlUp)
        End If

        rg2.Value = rg1.Value
        Set rg2 = rg2.Offset(1, 0)
    Next

    'Checks if reallocation is already applied......if yes then changes the
    'value of cells E2 in Parameters
    If ThisWorkbook.Worksheets(2).Name <> "Main" Then
        Set rg1 = ThisWorkbook.Worksheets("Main").Range("B3")
        Set rg2 = rg1.Offset.End(xlDown)
        pm.Range("E2").Value = (rg2 - rg1)
    End If


    pm.Columns.EntireColumn.AutoFit

    'Dereferencing

End Sub
```

PROCEDURE # 7

Linear Prog. Macro

```
Sub LinProg()

' LinProg Macro
' Keyboard Shortcut: Ctrl+p

    SolverOk SetCell:="$C$6", MaxMinVal:=2, ValueOf:="0", ByChange:= _
        "$E$8:$E$12,$C$6"
    SolverAdd CellRef:="$C$5", Relation:=2, FormulaText:="sum($D$8:$E$12)"

    SolverAdd CellRef:="$C$6", Relation:=3, FormulaText:="$F$8"
    SolverAdd CellRef:="$C$6", Relation:=3, FormulaText:="$F$9"
    SolverAdd CellRef:="$C$6", Relation:=3, FormulaText:="$F$10"
    SolverAdd CellRef:="$C$6", Relation:=3, FormulaText:="$F$10"
    SolverAdd CellRef:="$C$6", Relation:=3, FormulaText:="$F$11"
    SolverAdd CellRef:="$C$6", Relation:=3, FormulaText:="$F$12"

    SolverOk SetCell:="$C$6", MaxMinVal:=2, ValueOf:="0", ByChange:= _
        "$E$8:$E$12,$C$6"
    SolverDelete CellRef:="$C$6", Relation:=3, FormulaText:="$F$10"
    SolverOk SetCell:="$C$6", MaxMinVal:=2, ValueOf:="0", ByChange:= _
        "$E$8:$E$12,$C$6"
    SolverSolve userFinish:=True
    Range("G13").Select
End Sub
```

```
                        **************************
                        *      PROCEDURE # 8     *
                        *  Adds Transfer Costs   *
                        **************************

Private Sub addTransferCosts()

'Definition
Dim pws As Worksheet                                'Parameter WS
Dim mws As Worksheet                                'Main WS
Dim rg1 As Range                                    'Range
Dim rg2 As Range                                    'Range
Dim rg3 As Range                                    'Range
Dim rg4 As Range                                    'Range
Dim rg5 As Range                                    'Range
Dim rg6 As Range          'Range for No. of transferred patients after Realoc2
Dim rg7 As Range          'Range for No. of transferred patients after Realoc1
Dim i, j As Integer                                 'For loop variables
Dim totRec As Integer                               'Total Rec. patients
Dim trPtnCost() As String                           'Transfered patients

'Initialization
Set pws = ThisWorkbook.Worksheets(1)
Set mws = ThisWorkbook.Worksheets("Main")
Set rg1 = pws.Range("D8")
Set rg2 = pws.Range("E8")
Set rg3 = mws.Range("C3").End(xlDown)
Set rg6 = pws.Range("C20")
Set rg7 = rg6.Offset(0, -1)
ReDim trPtnCost(pws.Range("C3").Value)

    '1. Calculates totRec and then compares it with the planned rec i.e. rg3
For i = 1 To pws.Range("C3").Value
    If IsEmpty(rg1.Value) Then
        Exit For
    ElseIf NC = True And i = pws.Range("C3").Value Then 'Changes total planned
rec. for new country = 0
        Set rg3 = rg1
    End If

    totRec = Round((rg1.Value + rg2.Value), 0)
    If ThisWorkbook.Worksheets(2).Name = "Main" Then
        If totRec > rg3.Value Then 'If total rec. ptns are greater than
planned then charge transfer fees i.e. 10% of total cost
            trPtnCost(i) = (totRec - rg3.Value) * (CLng(Frm1.txtPh1.Value) +
CLng(Frm1.txtPh2.Value) + CLng(Frm1.txtPh3.Value)) * 0.1
        Else
            trPtnCost(i) = 0
        End If
    Else                        'Means reallocation is applied more than once
        Set rg4 = ThisWorkbook.Worksheets("Old Plan").Range("B3").End(xlDown)
'Old planned rec patient for the country
        Set rg4 = rg4.Offset(0, i)
        Select Case totRec
            Case Is > rg3.Value
'Case where Rec. Patients > What was Planned
```

```
'Patients after 2nd reallocation will cost 20% more
trPtnCost(i) = (totRec - rg3.Value) * (CLng(Frm1.txtPh1.Value) +
CLng(Frm1.txtPh2.Value) + CLng(Frm1.txtPh3.Value)) * 0.2
                rg6.Value = totRec - rg3.Value
                If rg3.Value > rg4.Value Then
'Adds the cost of transfered patients from the last reallocation
 trPtnCost(i) = trPtnCost(i) + (rg3.Value - rg4.Value) *
(CLng(Frm1.txtPh1.Value) + CLng(Frm1.txtPh2.Value) + CLng(Frm1.txtPh3.Value))
* 0.1
                    rg7.Value = rg3.Value - rg4.Value
                End If
            Case Is < rg3.Value
'Case where Rec. Patients < What was Planned
                trPtnCost(i) = 0
                rg6.Value = 0
                If totRec > rg4.Value Then
'Adds the cost of transfered patients from the last reallocation
trPtnCost(i) = trPtnCost(i) + (totRec - rg4.Value) * (CLng(Frm1.txtPh1.Value)
+ CLng(Frm1.txtPh2.Value) + CLng(Frm1.txtPh3.Value)) * 0.1
                rg7.Value = totRec - rg4.Value
                End If
        End Select
    End If

    Set rg1 = rg1.Offset(1, 0)
    Set rg2 = rg2.Offset(1, 0)
    Set rg3 = rg3.Offset(0, 1)
    Set rg6 = rg6.Offset(1, 0)
    Set rg7 = rg7.Offset(1, 0)
Next

    '2. Adds the transfer fee of additional patients to the recruiting country
Set rg4 = ThisWorkbook.Worksheets("Act. Budget").Range("B3").End(xlDown)
If IsEmpty(rg4.Offset(0, 1).Value) Then
    Set rg4 = rg4.Offset(0, 1).End(xlUp)
'locates the last recruitment cost on the actual budget sheet
Else
    Set rg4 = rg4.Offset(0, 1)
End If
Set rg5 = rg4.End(xlToRight)
'locates the cumulative cell for this last recruitment cost row
rg5.Font.Bold = True
rg5.Value = rg5.Offset(-1, 0).Value
For i = 1 To pws.Range("C3").Value
    rg4.Value = rg4.Value + trPtnCost(i)
    'Adds aditional cost of adding a new country
    If NC = True And i = pws.Range("C3").Value Then
        rg4.Value = rg4.Value + 10000
    End If
    rg5.Value = rg5.Value + rg4.Value           'Cumulates the values
    Set rg4 = rg4.Offset(0, 1)
Next


'Dereferencing

End Sub
```

```
                    ********************************
                    *         PROCEDURE # 9        *
                    *  Prepares for Re-Planning    *
                    ********************************

Private Sub cmdRP_Click()

    'Defintion
    Dim pm As Worksheet     'Parameters WS
    Dim mws As Worksheet    'Main WS
    Dim rr As Worksheet     'Real Rec WS
    Dim ch As Chart         'Charts WS
    Dim r1 As Range         'Range 1
    Dim r2 As Range         'Range 2
    Dim i As Integer        'For loop variable
    Dim j As Integer        'For loop vairable
    Dim ctr As Integer      'Counter

    'Initialization
    Application.DisplayAlerts = False       'Disables the delete WS dailog box

    'Changes Names of WS i.e. the Real Data becomes Planning for Re-Planning
    'and Deleting useless WS
    ThisWorkbook.Worksheets("Main").Name = "Old Plan"
    ThisWorkbook.Worksheets("Real Rec").Name = "Main"
    ThisWorkbook.Worksheets("Sch. Budget").Name = "Old Budget"
    ThisWorkbook.Worksheets("Act. Budget").Name = "Sch. Budget"
    ThisWorkbook.Worksheets(Array("Country 1", "Country 2", "Country 3",
"Country 4", "Country 5", "Charts (Real)")).Delete
    Set pm = ThisWorkbook.Worksheets("Parameters")
    Set mws = ThisWorkbook.Worksheets("Main")

    'Creates new WS naming "Real Rec", then place all data from Main into it.
    ThisWorkbook.Worksheets.Add
after:=ThisWorkbook.Worksheets(Worksheets.Count)
    ThisWorkbook.Worksheets(Worksheets.Count).Name = "Real Rec"
    Set rr = ThisWorkbook.Worksheets("Real Rec")
    mws.Columns("B:G").Copy
    rr.Columns("B:G").Select
    rr.Paste
    'Removes Dates/Months from the first column of Main after the EndDate
    Set r1 = mws.Range("B2")
    Set r1 = r1.Offset.End(xlDown)
    Set r2 = r1.Offset(0, 1)
    Do While IsEmpty(r2.Value)
        r1.ClearContents
        Set r1 = r1.Offset(-1, 0)
        Set r2 = r1.Offset(0, 1)
    Loop
    'Removes Dates/Months from the first column of Real Rec after the EndDate
    Set r1 = rr.Range("B2")
    Set r1 = r1.Offset.End(xlDown)
    Set r2 = r1.Offset(0, 1)
    Do While IsEmpty(r2.Value)
        r1.ClearContents
        Set r1 = r1.Offset(-1, 0)
```

```
        Set r2 = r1.Offset(0, 1)
    Loop

'____1. Call Form2, But there is no need of the top frame to be Enabled_____
'____2. Also as the POI has already reached so enable the lowest frame________
'____3. Then make the objects in lowest frames to work properly_______________
'____4. Determine the last point where reallocation was applied_______________
'____5. Add Chart WS and Charts for each country till the reallocation update_
'____6. Delete the useless fields from Parameters WS__________________________
'____7. Then show Form 2 and start from the last reallocation Point___________

        'Fills PointOfInflexion array
        ReDim PtInf(pm.Range("C3").Value)
        For i = 1 To pm.Range("C3").Value
            PtInf(i) = "B12"
        Next

        'Adds charts WS and charts till the first update for avoiding errors
        Module3.AddChartObject (1)

        'Calls Form2
        Frm2.Hide

        'Disables the objects in Frame1 & 3
        Frm2.Frame1.Enabled = False
        Frm2.cmbxNbrCtr.Enabled = False
        Frm2.txtCtrRt.Enabled = False
        Frm2.cmdCtrRt.Enabled = False
        Frm2.lblUpdMon.Enabled = False
        Frm2.lblMonths.Enabled = False
        Frm2.txtUpdMon.Enabled = False
        Frm2.cmdReal.Enabled = False
        Frm2.Frame3.Enabled = False
        Frm2.cmbxInf.Enabled = False
        Frm2.lblInf.Enabled = False
        Frm2.cmdInf.Enabled = False
        Frm2.txtInf.Enabled = False

        'Enables the objects in Frame2
        Frm2.Frame2.Enabled = True
        Frm2.cmbxChart.Enabled = True
        Frm2.Image1.Enabled = True
        Frm2.cmdChartUpdate.Enabled = True
        Frm2.Frame4.Enabled = True

        'Enables the objects in Frame4
        Frm2.optContinue.Enabled = True
        Frm2.optInsertRR.Enabled = True
        Frm2.optReqRR.Enabled = True
        Frm2.optLP.Enabled = True
        Frm2.optNC.Enabled = True
        Frm2.lblContinue.Enabled = True
        Frm2.lblInsertRR1.Enabled = True
        Frm2.lblInsertRR2.Enabled = True
        Frm2.lblReqRR.Enabled = True
        Frm2.lblLP.Enabled = True
        Frm2.lblNC.Enabled = True
```

```
        Frm2.cmdRR.Enabled = True
        Frm2.txtInsertRR.Enabled = True
        Frm2.txtNCRR.Enabled = True
        Frm2.optContinue.Value = False
        Frm2.optInsertRR.Value = False
        Frm2.optReqRR.Value = False
        Frm2.optNC.Value = False
        Frm2.txtInsertRR.Value = ""

        'Fills the ComboBox Chart with Country Nos.
        Frm2.cmbxChart.Clear
        'Clears if any data is already present in the combobox
        For j = 1 To pm.Range("C3").Value
            Frm2.cmbxChart.AddItem ("Country " & j)
        Next
        Frm2.cmbxChart.ListIndex = 0

        'Sets the Update (global variable) to the cell of the Update
        '& Counts the No. of rows to reach the update for Chart Creation
        ctr = 1
        Set r1 = rr.Range("B3")
        Set r2 = r1.Offset(1, 0)
        Do Until ((r2 - r1) = pm.Range("C2").Value)
            Set r2 = r2.Offset(1, 0)
            ctr = ctr + 1
        Loop
        Set Update = r2

        'Creates the Charts WS and creates charts till the reallocation update
        Module3.AddChartObject (ctr)
        Frm2.AddPPChart (ctr)

        'Shows Country1 Chart in Image1 object on the form
        Set ch = Worksheets("Charts (Real)").ChartObjects("Country 1").Chart
        ch.CopyPicture Appearance:=xlScreen, Format:=xlPicture, Size:=xlScreen
        Set Frm2.Image1.Picture = modPastePicture.PastePicture(xlPicture)

        'Deletes the useless fields from Parameters WS for LP to work
        Set r1 = pm.Range("E8")
        Set r2 = r1.Offset.End(xlDown)
        pm.Range(r1.Address & ":" & r2.Address).ClearContents
        pm.Range("C6").ClearContents

        'Disables This Re-Planning button
        cmdRP.Enabled = False

        'Calls Form2
        Frm2.Show


    'Dereferencing

End Sub
```