Performance Evaluation of Management Information Systems in Clinical Trials: A System Dynamics Approach

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Abstract

The complexity and characteristics of the pharmaceutical firm present an intriguing context for underlying information management issues during clinical trials for new drug development. This paper reports on the evaluation and performance of MIS for information management in clinical trials in new drug development. The main objective of the study is to examine the economic and business impacts of automating that process, to enhance our understanding of informational stakes involved, using a system dynamics (SD) model. The SD method is enriched in this paper with other conceptual frameworks such as Alter's (2001) Work Centered Analysis (WCA) and the activity diagram offered by the Unified Modeling Language (UML). Results of the simulations for alternative sensitivity analyses on errors rates in data transmissions, that is, on alternative error-rate specifications, do not necessarily influence project delay, but rather work intensity. A discussion details the usefulness of enriching the SD modeling process with alternative conceptual frameworks in the problem definition in such complex settings.

Keywords: information systems, information management, clinical trials, project management, performance measurement.

Introduction

The pharmaceutical industry, one of the largest manufacturing sectors worldwide with annual sales of US$ 300 billions, is well known for its intense R&D spending (Santos, 2003). Even though its activities are focused on the research, the development and the commercialization of new drugs, time-to-market is slow (somewhere between 8 to 12 years) and expensive (about US$ 800 millions per new drug), in part, due to the complexity of the process and heavy regulation.

Several steps are required for a new drug to reach the market. The process involves a series of trials, known as pre-clinical and clinical trials required for approving and commercializing a new drug. These clinical trials are divided into four main phases (Alshawi, 2003). The phase I involves tests on an important number of voluntary healthy patients. The effectiveness and side effects are then assessed on these voluntary patients in phase II clinical trials. The purpose of phase III clinical trials is to verify and confirm results of this assessment on a larger number of voluntary patients. Finally, in phase IV trials, a regulatory agency (such as the Food and Drug Association (FDA) in the US, or Health Canada, in Canada) reviews and approves the development process and the final product (drug) for commercialization.

Knowledge and information management are key to success for firms involved in clinical trial studies. Pharmaceutical firms, looking to lower R&D costs and time-to-market, turn to information systems (IS) to improve the management and guarantee the flow of information during the many clinical trial phases. Thus, automating the clinical trial process through IS is a means for these firms to meet project performance goals, that is to keep cost, time delay, and data quality in check, notably during the more extensive clinical trial phases II, III, and IV, where many events take place for which a large quantity of data are gathered, processed, and analyzed.

This paper looks into measuring how IS can improve the execution of a complex information management process within the R&D process of clinical trials for new drug development. The objective of this research is to highlight the impact of automating information management during clinical trials through the use of a system dynamics (SD) model. The results generated by the model can help firms involved in that process determine the economic value associated with software investment decisions, in conjunction with their business objective. The remainder of the paper is organized as follows. The next section introduces some issues associated with IT and health care. Then, the research methods followed during the course of this research are presented. An emphasis is placed on the research steps followed. The model is applied and some sensitivity analyses are conducted and illustrative results are presented. Finally, a conclusion follows where some learning points and the contribution of the research are emphasized.

IT and health care

Information technology (IT) is becoming ubiquitous to health care and related activities. For instance, Anderson (2002) analyzes the impact of information systems (IS) on the organizational context in which it is implemented, notably on health (medical) services. These highly dedicated IS have enabled medical decision-making in hospital settings, and also have helped uncover and lower the number of medical errors.

Augen (2002) emphasizes the important role of IT in the drug discovery process. Over the past 25 years, the drug discovery process, coupled with IT, has evolved to become inseparable components of the product life cycle, or of the "drug discovery pipeline" (Augen, 2002). Hence, the contribution of IT to the drug discovery process is a critical strategic element for firms involved in these activities. Information management during clinical trials relies on specific software, technology that often are critical to the economic and business livelihood of that process due to the complexity and hurdles associated with the project management of clinical trials and strict deadlines associated with the process (Rowe et al., 2002). The negative impact of such time delays on the drug discovery process is easily foreseen, as firms want to rush the product to market. Furthermore, stricter regulation has pushed, over the last ten years, to double the number of patients required to complete a clinical trial study (Rowe et al. 2002), thus increasing data management requirements. These constraints have pushed firms towards automating data extraction and processing with the end goal of reducing time delays, costs and information risks.

Over the past 20 years, the pharmaceutical industry has witnessed a large portion of its clinical trial activities outsourced to specialized clinical research organizations (CROs), more specifically to conduct phases II to IV of clinical trials. Large pharmaceutical firms, that outsource some of these activities, are more able to focus on their core capabilities, to gain in flexibility and effectiveness in their R&D activities, to improve internal capabilities, and to gain superior access to technology, knowledge and competencies (Piachaud, 2002). The number of CROs worldwide is estimated to be about 1,300 firms and the market value of these activities at US$ 8.8 billion (Piachaud, 2002). This is a support activity to an industry that has experienced a 20% growth rate over the last few years (Azoulay, 2003).

In health care related activities, most studies that use SD address specific problems, such as: the diffusion of medical technology, the flow of patients in an establishment, etc. (McDonnell, 2004). Anderson (2002), who contributed significantly to this field, has shown how with many simulation methods, it is possible to represent and evaluate decision-making processes using IS in a healthcare environment. Indeed, the health care system is complex, and issues associated with it should be treated accordingly (Gloubermann and Zimmerman, 2002). Researchers in this field are hence increasingly tackling research questions related to health care management with flexible approached such as SD. As stressed by McDaniel and Driebe (2001), several characteristics of health care organizations are amenable to this type of analysis using approaches such as the ones found in complexity science. This interdisciplinary approach, based on the notion of nonlinear dynamics, and on the management of interactions/feedback loops, enables a better understanding and the potential for learning about complex systems (Sterman, 2000). Other authors also insist on the benefits of simulation, one of the quantitative methods contiguous to the approach (Wiendahl and Worbs, 2003; Morecroft et al., 1991). Anderson (2002) notes that with SD, changes envisioned to a system, or process improvement, may be tested risk-free before engaging or continuing on a given project effort (Davidson, 1994). The future behaviour of a system structure is thus anticipated under various conditions without disturbing the actual system. According to Wiendahl and Worbs (2003: 30), computer simulation "*offers the possibility to describe and analyze the behavior of existing systems under changing conditions and different parameters*". These methods facilitate the generation of quality data for scenario building

(Wiendahl and Worbs, 2003). This set of principles and methods have long been used to evaluate the performance of IS (Wolstenholme et al., 1993).

Several studies focus on IS use in health care, and very many few have used SD methods. However, given that drug development and clinical trials are an extreme case of information flow management, the paucity of IS research in this area using SD is surprising

Research method

The management of information intensive processes carried out during clinical trials can be generalized through a dynamic set of interrelations in a specific timeframe. This process is basically akin for all firms in a clinical trial context, and similar constraints (rules and norms) pressure information management within these firms. In order to support the management of information, alternative software technology is available on the market. This research focuses on a case study in which a generic information management simulation model was designed. The objective of the model is to represent in a generic structure the results of this research, so that it can be applied to other organizations involved in clinical trials.

The case study was realized within a contract research organization (CRO) in the pharmaceutical sector. A Canadian-based CRO has contributed to this research effort by making available all expertise and data required to develop a SD model, and more importantly, by allowing one of the team's researchers to participate in the day-to-day activities of the firm to gain an intimate understanding of the work methods, information management needs, business objectives; and to provide data on information management activities and processes. The research context provided by the CRO was appropriate due to the fact the firm, at the time, faced an IT investment dilemma in its clinical trial infrastructure. The automation level of its processes being limited, the firm could not address its market growth potential, given available resources. Semi-structured interviews were conducted at every two or three weeks with the three main respondents who participated in the data collection effort over a seven-month period: the business manager, the IT manager and the financial officer. The data collected were synthesized from the firm's experience with four previously completed projects. These projects were conducted for Phase IV clinical trials, the most frequent type of projects conducted by the CRO. Moreover, a secondary information source was required from software providers, on the availability of different product offerings; as well as their characteristics and functionalities. The analysis of several documents and brochures was first conducted to understand product availability on the market. To obtain more detailed information, this documentation was further enriched by attending product demonstration and holding meetings with software providers such as ClinTrial, Datafax, Oracle Clinical and Teleform. The results from the case study along with the analysis of the IS were used to elaborate the SD model. The complexity of the information management process, and of the context in which it is carried out, prompted the use an approach which is more structured than the ones typically suggested in the SD literature. The framework employed in the study is generically based on Sterman's (2000) "Steps of the Modeling Process" to structure the research sequence of the study. This provided a generic research framework that allowed to stock and manage the information required for the development/evaluation of the level-rate model.

In a first step, the definition of the problem and model's objectives were clarified. The information management process was represented using the Unified Modeling Language (UML). The actual process represents the case of low IT support, and the improved work process, that is with the use of a performing IS, was represented using activity diagrams. Then, to develop or improve the IS supporting the process within the firm, Alter's (2001) Work Centered Analysis (WCA) was applied to analyze the process. This approach has allowed for a better understanding of the business process to be automated, while providing a link between the system and the information treatment service offered to clients. Five perspectives were treated, with respect to the WCA framework: clients, products and services, business processes, clinical trial participants and IT infrastructure.

The second step involved the development of influence diagrams that represent the dynamic hypothesis of the interacting feedback loops within the information management process. The third step included the design and calibration of the SD level-rate model using the Powersim software. The level-rate model was then assessed, in a fourth step, by evaluating whether its behavior over time was similar to the real system's behavior. The fifth and final step focused on the scenario building to analyze future business strategies with the analysis for software decision.

Information management in clinical trials

The information management process for clinical trials amounts to a set of information exchanges between the organization in charge of clinical trials, physicians who meet with patients, and the regulatory agency. Clinical trials involve the testing of new drugs on a certain number of patients in good health or matching a specific criterion. The firm conducting clinical trials receives forms that contain data relative to clinical tests that it treats and analyzes. It is important to note the data can be collected internally, using a call center, or can originate from physicians external to the firm. The information to treat is mainly external to the firm and the data treatment process differs little between clinical trial phases.

The first important step of that process is the definition of a clinical trial protocol. This is a document that determines the basis of the clinical study to execute and indicates the number of physicians to recruit, the number of patients to enroll, the number of visits for each patient, the contents of data fields to fill up on the form, etc. When physicians are recruited and the forms (questionnaires) are ready for distribution to physicians, the study can begin. The forms, referred to as Case Report Forms (CRF), are then completed by the physicians recruited following a patient's "visit". These forms contain entry fields such as the name, blood or other test results, the comfort level of the patient, etc. The external physician can transmit one or many forms with the required data entries completed. Forms are typically transmitted by fax. The faxed data are treated upon receipt, in other words, verified, corrected and then, stored. If the CRF contains errors (non-evident error in data or missing entry on the form), a form listing these error entry data is generated and will be faxed back to the physician for correction or completion. This form is called a Data Clarification Form (DCF). When all the required visits are completed, that is when the study has met its target, the stored data is analyzed, and a statistical report analysis is generated.

This data management process is represented using a Unified Modeling Language (UML) as shown in figure 1. The UML approach is convenient to illustrate this business process, and more generally, the activity diagram (OMG Unified Modeling Language Specification, Version 1.5, 2003) models data and control flows, and explicitly displays the role of actors involved in the set of activities. This is a useful means to show the dynamic aspects of the information management process at a general level.

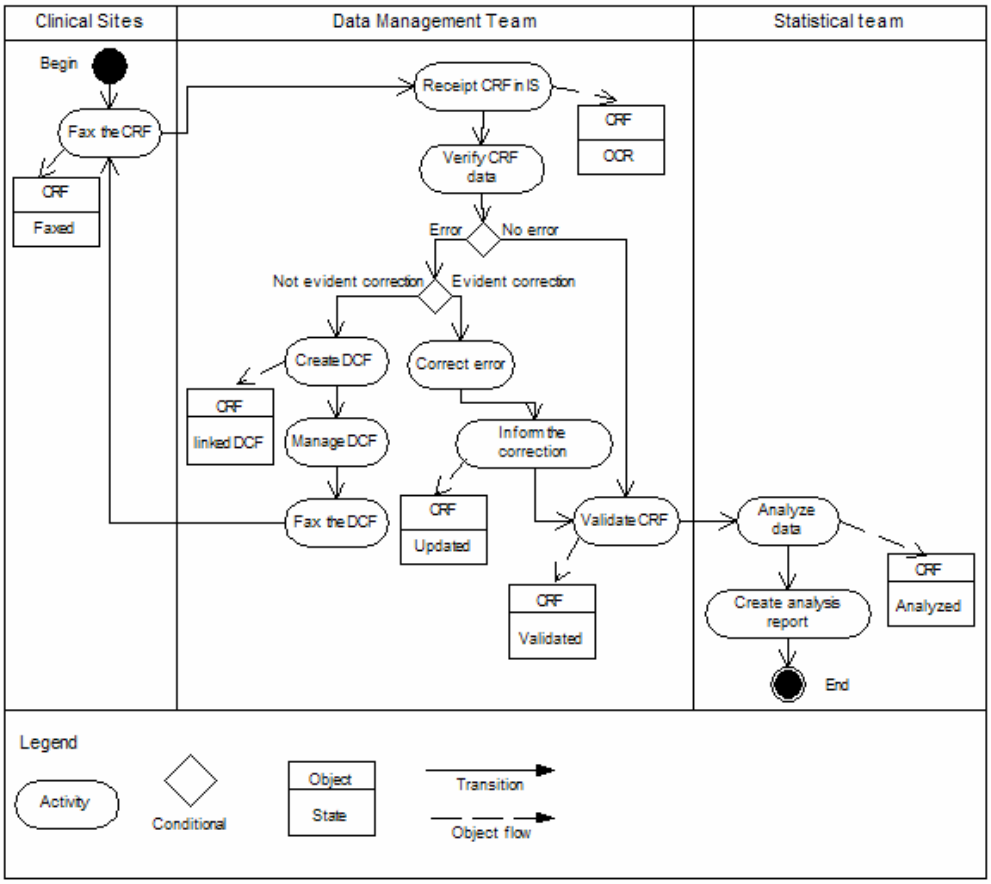

Figure 1 – UML activity diagram

In this context, the main role of an IS, in addition to support project management, is the reception of forms by fax, optical character recognition or OCR (conversion of data from a paper to an electronic format), data control, fax and error tracking, and finally the archiving of data for further consultation and analysis. These functionalities may vary from one software to another. The different software available on the market do not always offer the same set of functionalities, and functionalities may vary as to their performance levels. Furthermore, the information management need differs amongst firms. For example, according to organizational objectives (some prefer speed in information treatment, others favor 100% error free), or to financial resources (a small or medium size CRO can invest a more limited amount into its hardware and software). The problem selection relates to the choice of an IS appropriate for the specific criteria of the clinical trial process and firm policies.

As seen in figure 2, this information management system includes a number of balancing feedback loops. Feedback loops B1, B2, and B3 relate to the generation visits. First, these require the enlistment of patients, which is function of a target stated in the protocol, that is, for the "enrollment objective". The greater is the enrollment objective, the greater will be the enrollment. This has for consequences to increase in the number of "enrolled patients" and to reduce the objective of patients to enroll, as seen in the balancing loop B1. However, a number of patients already enrolled are suppressed from the study, because a portion of patients give up on the study or because it fails to meet a criterion. The rejection rate, directly linked to the number of enlisted patients, negatively impacts the number of patients to visit, as seen in the balancing loop B2. The balancing loop B3 concerns the generation of the number of visits, and depends on the number of patients to visit, and these visits require a certain time delay for completion.

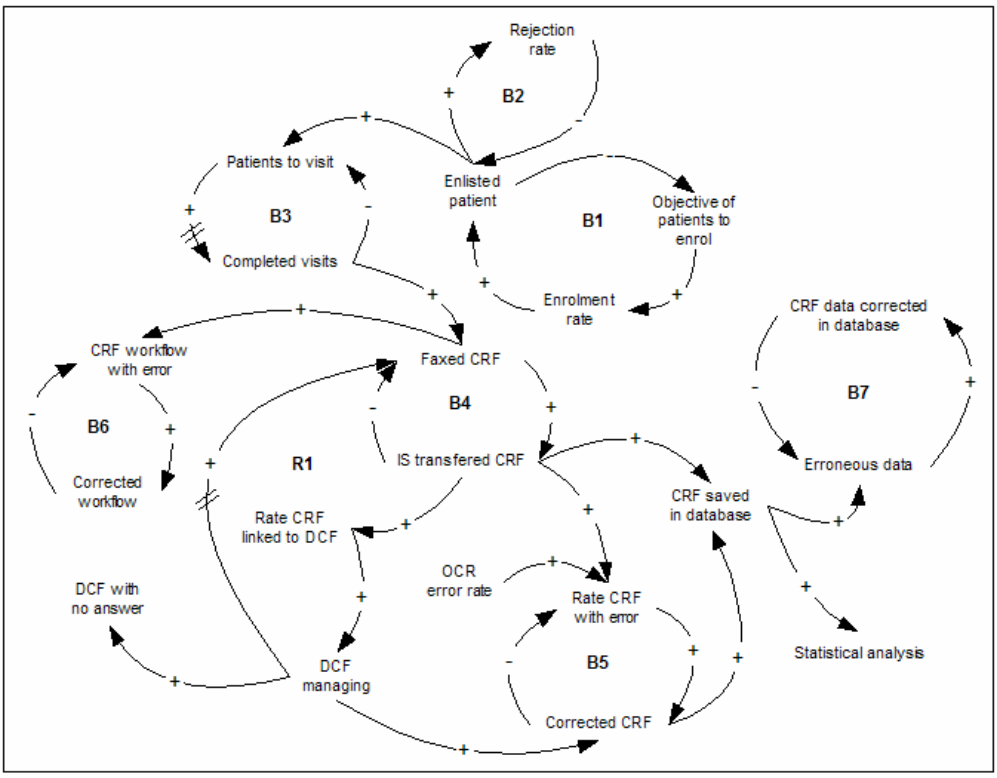

Figure 2 – Influence diagram of information management process

The generation of visits leads to the transmission of CRFs. As seen in the balancing loop B4, these CRFs are transferred upon receipt to the IS, and this, through the OCR functionality of the information system. These CRFs can then be directly stored in the database, which may require some manual intervention for the fixing of any error, or lead to the generation of a DCF. In the case of a DCF, the rate of a CRF linked to a DCF determines the number of DCF to be generated. As seen in the reinforcing loop R1, following the issuance of a DCF, the initial CRF can be manually fixed or at times, a new CRF is faxed back to a physician, following a certain time delay. It is important to note that some CRFs will remain unanswered by physicians and, thus, the corresponding CRF will never be treated or analyzed. The number of outstanding CRFs depends in part on whether the IS can manage DCFs. For the specific case of the CRO under consideration, the return fax of the DCF back to physicians was not automated, which may lead

to a time delay in the execution of the task, leading to a non-response on the part of physicians for returning the DCF. The CRFs requiring a manual correction are a function of the CRF rate to correct, which depends, among other things, on the performance of the IS relative to the OCR, and this will eventually impact the number of corrected CRFs. This will allow the reduction in the rate of CRFs to correct. This sequence is shown in the balancing loop B5. It is important to note that some software can support only to a limited extent the error correction process, and this will have an impact on the time it takes to treat CRFs. Finally, the corrected CRFs can be saved in the database and a statistical analysis will be performed.

Two other feedback loops are shown in this diagram. The balancing feedback loops B6 and B7 are related to the tracking of CRFs and to data quality. Indeed, errors can crop up, when for example, when the CRF status is conferred (B6), or fields have missing or false entries in the database itself (B7). Information systems that manage CRFs with strong data control functionalities can help avoid this type of error. However, this was not the situation for the case under study and an additional effort was required on the project management front.

The main feedback loops that have been emphasized from the modeling effort lead to the quantitative representation of the model structure. The data collected to build the model (CRO or software suppliers), have been used to calibrate this model, with the quantification of the level-rate model, and associated parameters. The general structure of the model is shown in figure 3.

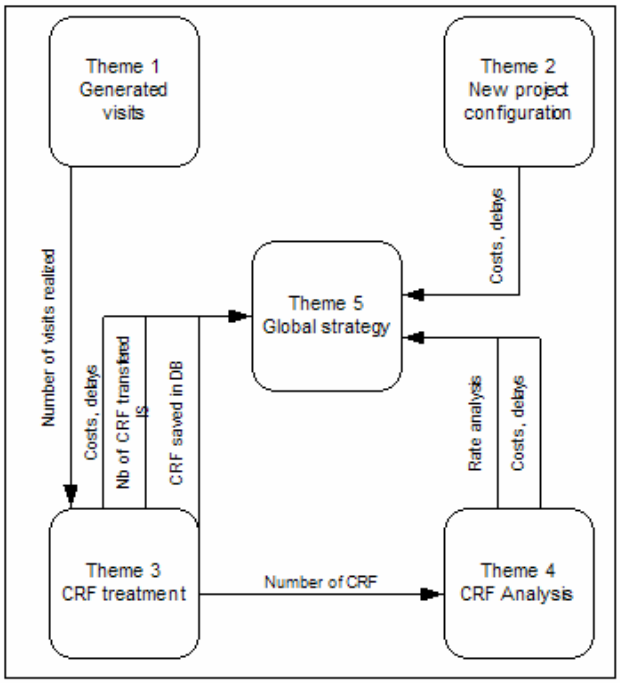

Figure 3 – General structure of the model

This process can be analyzed using five themes to which correspond five level-rate sub-models linked up with interacting variables. These themes are:

1) Visits generated by physicians, linked to the characteristic of the study, that are linked to the size of the study;

2) New project configuration to which are related the required configuration for each new project, and that includes all preliminary steps prior to begin the information management process;
3) The treatment of CRFs, that is the data, at the center of information management during the clinical trial process;
4) The statistical analysis of CRFs; and
5) The general strategy of the organization that underlies the study and orients the many actions.

The model is a detailed representation of the management structure of clinical trials supported by an IS. It takes into account parameters that represent both organizational and technological dimensions of clinical trials management. This model includes 44 level variables and 49 parameters, and a large number of balancing feedback loops.

The complex structure of clinical trials makes it difficult to fully understand this system. The application of Alter's (2001) WCA or the process modeling using the UML language, have been key elements to structure the simulation model. The use of these approaches have helped delineate the clinical trial process, to represent the key feedback loop structure at a level general enough to justify a generic SD model. The use of these descriptive frameworks is treated only to a limited extent in the literature, and this further justifies the interest in the proposed research.

Results

Sterman's (2000) research process has contributed to the structuring and design of the many analytical components, such as: the formulation of a new strategy and the evaluation of simulation results. The simulation model was examined using the analysis of alternative specification for sensitivity analyses on a parameter linked to the use of an IS, like variations in the business throughput (that depends, among other things, on the treatment capacity of the IS in terms of volume), error rates relative to the performance of the optical recognition (OCR) of the IS, or even, the number of human resources on the IT team. The results presented examine the main impacts of the automation of the information management process during clinical trials, by parameterization of alternative software functionalities. The software functionalities and specifications were obtained from dedicated products commercially available on the market.

This section presents some illustrative results of sensitivity analyses conducted on error variation linked to optical recognition. This choice is motivated by the fact this parameter is directly linked to the performance level of one of the functionalities of the IS. Indeed, the basic required automation in information management during clinical trials requires the optical character recognition (OCR) to electronically read the information received by fax from the physicians. However, some errors can be linked to the OCR, which is translated into an "OCR error rate", thus in the percentage of forms for which one or more fields on the form are not appropriately recognized. The error rate is mainly linked to the performance of the IS implemented but also to the readability of the fax itself. Readability originates both from the layout of the form (space between fields) and from the physician's handwriting. Initially, the OCR error rate is set at 15% (base case specification, or specification 1), the error rate is then set to 0% (specification 2), 50%

(specification 3), and 70% (specification 4). Thus, the impact on the process performance associated with the OCR and efforts on improving the form layout are measured with the results obtained from the specification 1.

The impacts of such a variation in error have first been examined for a single project. It is important to note that a clinical trial project can last over a year. From the calculated means of data from several Phase IV projects from the CRO under study, the different specifications have been tested on the basis of 1,000 patients enrolled by project, with three required visits per patient. The initial number of CRFs to be treated is 6,000, and the total revenue generated amounts to $180,000.

The results show that the variation in the OCR error rate has a direct impact on the number of CRFs to correct, either higher or lower, according to the variation in that rate, CRFs treatment activities, and project costs. In table 1, the results show a variation according the rate of error.

Table 1 – Impact of alternative OCR error rate specifications

Specification	**1**	**2**	**3**	**4**
Error rate due to OCR	15	0	50	70
CRF to correct due to the number of OCR errors	900	0	3000	4200
CRF processing (number of days)	185	176	207	220
Costs associated with CRF processing ($)	14 815	14 056	16 586	17 597
Gross benefit margin per project (% of revenue)	40,9	41,3	40,1	39,6

It appears that an error-free OCR rate would lead to a 20% cost reduction relative to a 70% error rate. Relative to the base case, with a 15% error rate in the OCR, the CRF treatment costs would increase by $1,770 for specification 3 and close to $2,800 for specification 4. This due to a variation in the duration of activities for the treatment of CRFs: the number of days allocated for the treatment of CRFs increases with the number of errors. For the base case, the number of days is 185 and decreases to 176 in the error-free case, and the number of days would be 207 and 220 with a 50% and 70% error rate, respectively. The gross benefit margin is impacted by this error rate but the variations in margins are the highest at 41.3%, with an error-free specification, and are lowered to 39.6% with an error rate of 70%. However, it remains true that an error-free situation does not depict a real life situation, and is virtually impossible.

It can be assumed that the smaller the number of CRFs to correct, the more rapidly the project will be completed. However, as seen on figure 4, this is not necessary the case. This result is shown on the flow of archived CRFs in the database, and available for analysis at the end of the process. Even though CRFs can be saved more rapidly, the analysis of the data only takes place in month 13, and this, no matter the scenario under consideration. One can understand this phenomenon by looking at figure 5, where the dynamic paths show CRFs are corrected over the same period, and this, no matter the number of CRFs to be treated. The organization actually corrects more CRFs in the case of specifications 3 and 4, but uses the same time interval to get the work completed as in the specifications 1 and 2. It is important to note that even in the case of specification 2 (error-free) the number of CRFs to be corrected is not entirely zero. This is because errors other than from the OCR can occur.

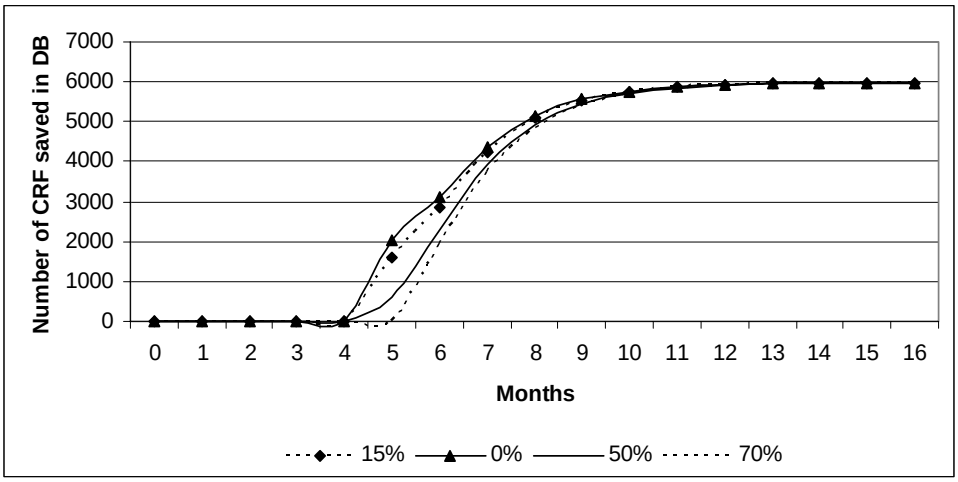

Figure 4 – Impact of the OCR error rate specification on project duration and intensity

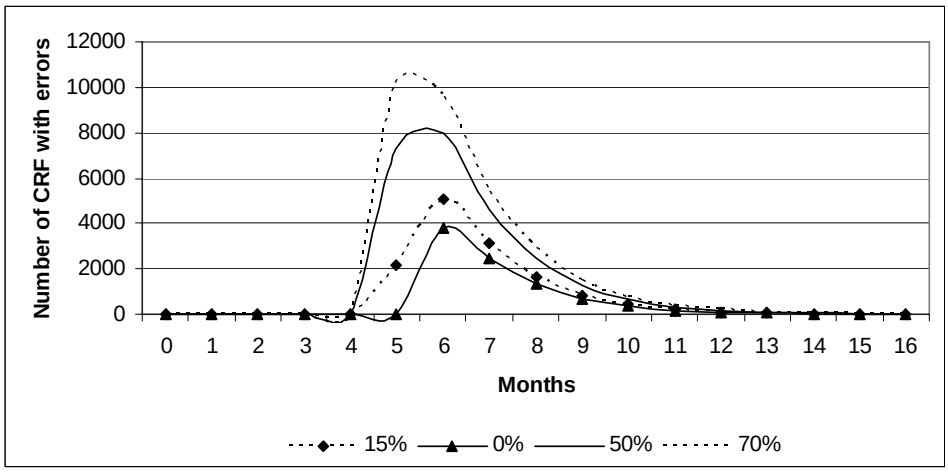

Figure 5 – Impact of OCR error rate specification on the number of CRF with error

To sum up, it is important to note that the error variation in the OCR error rate has almost no impact on the duration of the project. Indeed, no matter the strategy adopted, the time delay associated with the treatment of CRFs, that is, of the project, is much more dependent on the velocity of patient enrollment and on the frequency of visits that follow, than factors exogenous to the information management process. Thus, increases and decreases in the number of CRFs to correct have only a minimal impact on the project execution.

The results emphasize that errors rates impact costs, but also the human resources efforts required for fixing these errors. The rate of errors from OCR should have a real impact in multi-project situations, while resources can be allocated to other tasks if error rates are low. The capacity to conduct several projects simultaneously is a source of competitive advantage. For the case under study, and given available capacity in resources, only the equivalent of two large scale projects can be conducted over a year. The selection on an IS, that could support the execution of several projects by limiting the data correction effort, could play a greater role in a business growth strategy.

Conclusion

This paper was concerned with the IS performance evaluation of information management for drug development, and more specifically in clinical trials. The approach taken to research this question was SD. The purpose of the model designed was to examine the repercussions of automating the process and to capture the informational issues that must face organizations involved in clinical trials. The analysis of the information management process during clinical trials, and its modeling, has stressed how complex is such a system. Indeed, it is characterized by a number of interrelated mostly negative feedback loops that generate non-linear behavior. The resulting dynamics make it difficult to structure an understanding of the actual and future behavior of the system. To accomplish this, the WCA and the UML were used as complements to help scope the research problem. The resulting model has helped realizing a comparative analysis of software technologies, and in addition, alternative scenarios were proposed. A few sensitivity analyses were conducted on the error rate, and these results were presented in the paper. The results of the research emphasize that since the IS has no real impact on the duration of a project, the choice of an IS should favor multi-project execution.

The conceptual framework brings a genuine contribution in terms of the modeling process, while following the general SD modeling process (Sterman, 2000). The proposed model in this complex context is even more interesting, as the advantages that SD can bring to decision-making are emphasized.

Given the generic nature of clinical trial projects, the management needs and constraints in clinical trials management may differ from one organization to another. Applying this model to other CROs would be interesting to evaluate the generic model and confirm some conclusions. It would also be interesting to include a parameterization of biopharmaceutical firms, which have not been included in this research. Large pharmaceutical groups, or smaller biotechnology firms, may possess characteristics that differ from CROs.

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