Business Process Re-engineering and Information Technology in the Clinical Research CRO Business.

by
Ezra Bar

Dissertation project submitted to Leicester University
in partial fulfilment of the requirements for the degree of
Master of Business Administration.

Submitted in March 2002.

Table of Contents.

Acknowledgement.

I have chosen for my MBA dissertation project a business and a topic that I believe are of high challenge. My previous knowledge of the pharmaceutical industry in general and the clinical research business in particular were very limited, so I could truly be considered as a prejudice-free consultant with an outsider's viewpoint.

The firm, at which my project is aimed, allowed access to information that already had been publicised, for either internal or external audiences. Access was in principle limited to the top management, for both telephone calls and on-site interviews. However, the firm considers the information as business confidential, and has requested that its identification will not be disclosed. For university purposes, the firm's name is known from my dissertation proposal, and it will not be mentioned anywhere in this paper, but as the artificial name "**ACROF**" (for: **A CRO F**irm).

The name ACROF has been given to the organisation, since I believe this company reflects the average midsize CRO (Clinical Research Organisation) firm, by means of business processes and information technology being used. For the same reason the title of my work is "Business Process Re-engineering and Information Technology in the Clinical Research CRO Business" in general, rather than "at ACROF" in particular.

The objective of this project is to examine the information technology in the context of the business processes, in the CRO business. Both business processes and information technology will be presented and analysed in this paper. For the purpose of this work, no confidential business data was needed at all, so the restrictions on access to the data at ACROF has not had any influence on the project's quality.

Executive Summary.

The pharmaceutical industry has developed substantial entry barriers, which result in a profitable and stabile industry. The clinical research is among the businesses operating within the pharmaceutical industry. Therefore, clinical research is either carried out in-house by the pharmaceutical firms, or outsourced to contracting companies, known as Contract Research Organisations (CRO). The USA based, ACROF, is relatively a small CRO firm, competing with about 1,000 other companies, for a worldwide market of US$4.5 billion annually. The Massachusetts based company has undergone impressive growth and quite radical changes since it was established in 1970. Recently, ACROF has been friendly merged into a US-based international pharmaceutical company.

The objective of this dissertation project is to study the company's business-processes and Information Technology, and to examine ways of improving its stand by implementing BPR and IT initiatives. Among the sub-processes of the parent clinical research process, I chose the clinical trial one, which I believe, is a core-process at any CRO firm.

Among the BPR schools of thoughts, I believe that the one with holistic approach, presented by Michael Hammer and other advocates, is the one that can produce the best, organisational-wide, long-standing results [Hammer, 1990], [Davenport, 1993], [Hammer & Champy, 1993], [Hammer, 1996]. This approach is aimed at transforming the organisational structure from the hierarchical structure to the Process-Centred horizontal one [Hammer, 1996].

BPR and IT can be seen as Siamese-twins, in the way they are dependent on each other. Wherever the project is initiated at, would it be BPR or IT, it will eventually result in a simultaneously business-processes and information technology development. It is true, to a greater extent, for the CRO business, which is very much related to IS/IT.

The as-is processes are hierarchically presented by using a process-tree, as well as IDEF (**I**ntegrated **DEF**inition language) charts. These are followed by textual analysis, and suggesting improved processes and IT. Developed conclusions and recommendations, which are briefed here, end this paper.

Information and knowledge sharing between study-team members, between study-teams and between organisation's sites is essential for time and cost reduction, and for overall quality increase. The women dominated CRO business is very likely to be a perfect ground on which process-centred team working can be nurtured. IT can improve information and knowledge sharing at all levels, by adopting the comprehensive GroupWare concept, which should include the pharmaceutical companies (clients) and the investigator sites (data suppliers), too. Top management should deal with organisational culture more seriously, and develop such a culture that will encourage employees to make decisions and take calculated risk. It will build quality into the real process, rather than being a process by itself.

Sharing activities and processes between ACROF's branches is to be encouraged. European and Asian parent company's subsidiaries should be integrated into ACROF. Current differences between offices and branches in regard to capabilities, culture and efficiency/ performance are a great stumbling block in the way of equalising workload and sharing tasks and processes between study teams and sites.

The concept of capturing data once and at the source should lead to abandoning the data-entry and the double-data-entry, and investigator sites should enter data directly onto the computerised system. GroupWare and sophisticated IT can play a major role in achieving this objective. Only those investigator-sites that economically and technologically worth it, should be invested in.

ACROF must perceive itself as an Information Processing company, operating in the clinical research business. For being competitive in the future it must build up it core competencies, and these are heavily based on IS/IT.

The clinical research process is a flexible process, and flexible tools should be used in carrying it out. These include the recommended "Frame-processes" from which individual ones are derived, the Dynamic Systems Development Method (DSDM) and Joint Applications Development/ Design (JAD).

At the end of this executive summary I would like to focus on the short questionnaire presented to ACROF's top management, asking them to rate BPR initiatives according to given 24 key words. At that questionnaire, IT should had been rated much higher above its 17th place, because ACROF is still operating old IT systems based on primitive IS conceptions. The same is said about cultural change, which is rated at the bottom of the list. ACROF has a significant organisational culture problem, and any BPR initiative must face it and take it into account.

1. Introduction:

1.1. The Pharmaceutical Industry:

A broad characterisation of the pharmaceutical industry can be drawn from articles in the 1999 Strategic Management Journal ([Cool *et al*, 1999], [Roberts, 1999], [Yeoh and Roth, 1999] and others). The pharmaceutical industry has developed substantial entry barriers as a result of large initial investments in product development, great financial effects from registered new drugs, long new product development processes (thus payback time), and a considerable degree of institutional and governmental interaction. Because of its structure, the pharmaceutical industry is among the most profitable and stable industries. The ever-growing demand for its products keeps this industry growing. The long process-time of a new drug development (with the average of 8.5 years from concept to marketing) provides the industry with a high level of stability. Global economy downturns, even recession periods, do not influence the pharmaceutical industry very much, as can be seen during the current global recession period.

The pharmaceutical industry is described as "*A combination of a university and a hospital, in its day-to-day activities*" [Styhre *et al*, 2001]. In their study, they refer to the industry as one that "*operates as a nexus between applied academic research, the health care sector, and the service sector*".

The process of bringing a new drug to the market is shown from two viewpoints: annex C represents the FDA's viewpoint, and "A-1" process-map is my interpretation to this high level process, using the IDEF tool. This process is made of three major phases: (1) Laboratory research produces a product that aims to have desirable effects on the human body, (2) Pre-clinical research tests the new "drug" on animals, and (3) Clinical research phase tests the drug on diversified population of patients, aiming to prove that the new drug delivers the desirable results, while not having any severe adverse effects.

1.2. Clinical Research and the CRO Business:

This paper covers the third major phase of the new drug development process, as described above, known as clinical research. The complete new drug development process, consisting of up to three pre-approval phases and a post-marketing surveillance phase, is the ultimate responsibility of the pharmaceutical firm developing the new drug (also called the Sponsor). Each phase can be carried out by either the pharmaceutical company itself, or by outsourcing and contracting some, or all, of the activities in that process.

Clinical research may include up to thousands of patients, be carried out in many regions and countries, and could last for a number of years, depending on the developed drug. Therefore, the clinical research phase is very expensive, and may constitute a significant part of the total development cost to the pharmaceutical firm.

The CRO business (Contract Research Organisation) is highly fragmented and can be identified as a free-competition market. There are about 1,000 CRO firms worldwide, whilst market leaders have less than 40% of the market share. The clinical research outsourcing is estimated US$4.5 billion per annum. CRO firms work under heavy pressure from the sponsors to reduce time and cost. They also work in an environment characterised by tight constrains of rules, regulations and standards, to which they must abide. Along with time, cost and regulation constrains, the quality plays a major role in the CRO business.

The pharmaceutical industry plays two roles at the CRO business: on one hand it is the major (some argue ***the only***) customer and researches' sponsor, while on the other hand it is a major competitor to CRO firms. The big pharmaceutical firms have in-house clinical research departments, and some own CRO firms. This structure provides the pharmaceutical industry with a great power over the CRO firms, which are very much dependant on it. My research does not deal with the internal clinical research departments, but only with CRO firms.

The Critical Success Factors in the CRO business are: (1) Time and cost reduction through ongoing efficiency improvement, (2) High effectiveness of the clinical research process, by providing the desired results and products, (3) Ongoing improvement of the quality, both input to and output of the process, (4) Adding value to the sponsor, as a by-product of the process.

For a CRO firm to possess these critical success factors, there are three elements that must be embedded in it: (1) Professional project management, (2) Process-Centred working teams, and (3) Information technology, which is used in an efficient, effective manner. The last two elements are the heart of this work.

Yet, there is another characteristic of the CRO business that distinguishes it from the laboratory research and pre-clinical research phases [Styhre *et al*, 2001]. They argue that the clinical research activities, no matter that they constitute a very significant part of the total new drug development budget, are the least prestigious, therefore the least favourite activities in the pharmaceutical industry. These activities might be thought of as merely aimed at delivering credible evidence that the new drug provided the desirable effects. The CRO business is seem to be the tedious processing of information that had already been collected. From my viewpoint, this argument implies that the CRO business could be seen as a player in the information processing field, therefore heavily relying on information technology.

Another important finding is that most of the employees in the clinical research in general, and in CRO firms in particular, are women [Styhre *et al*, 2001]. They argue that women perceive team working and their role as team members in a different way from the one of men's worldview.

1.3. "ACROF" - A CRO Firm:

As explained above, the firm's identity is not to be revealed in this paper. Nevertheless, the information, which is important for better understanding its stand, is outlined here. As mentioned, this picture, for a great extent, describes the average CRO firm, as well.

ACROF was established in 1970 in Massachusetts, USA. It started with clinical trial monitoring, and in late 1980s added the integration of data management and bio-statistics. Following, ACROF expanded its core business to include comprehensive project management, and entered into alliances with other clinical research companies. In 1997 it marked a significant milestone by achieving an ISO 9002 certification. Geographically expansion was the next step, by opening offices in California and Toronto. In 1999 ACROF was acquired by a US-based international pharmaceutical firm. ACROF, with the annual revenue of US$30M, which is about 0.67% of the market share, is a small player in the CRO business. Yet, the small CRO firms have benefited from the market structure and used it as a leverage for their ongoing growth. By pursuing a 'differentiation strategy" as identified by Michael Porter, ACROF has been able to grow and increase the performance and the profit alike [Porter, 1980].

ACROF satellite branches, in California and Toronto provide mere Clinical Data Management, and there is an intent to expand their capabilities so to include Bio-Statistics and Project Management. The parent's European Clinical Division provides clinical monitoring, data management, bio-statistics and project management. Its Asian capabilities are being developed, using China as an operating base. At the moment the parent company does not intent to bring all these clinical research businesses, including ACROF under a common umbrella.

ACROF covers all phases of clinical trials, and offers its clients a full-service trial. However, most of the projects carried out by ACROF are not full-service covered, and the clients (sponsors) decide what parts of each trial process to perform in-house (or by other CRO firms). For example, Protocol can be developed either by ACROF or by the sponsor itself. The same can be said regarding Trial Monitoring.

1.4. Project's Objectives and Boundaries:

What has been examined, and widely covered by the BPR theorists and practitioners are the processes, which I call "peripheral" business activities. Such activities, functions and processes include the sales & marketing, finance & accounting, procurement, packaging & shipment and customer service. It must be said that my identification of peripheral versus core activities is not in line with the definition of main versus supportive activities made by Michael Porter, in his Value-Chain theory [Porter, 1985]. This thesis work does not deal with a "peripheral" activity/ department, but examines the fundamental, professional, core-business activities of ACROF, meaning the Clinical Trial Process. More generally, ore processes are defined as those that: *"The business's strategic thinking has identified as critical to excel at, to meet or beat the competition. They make up part of the company's set of core competencies"*. [McHugh *et al*, 1995].

This work is aimed at examination of IT as part, and in the context, of the clinical trial process. General principles in these two disciplines are analysed, and the extent to which it is practical to implement them is developed.

BPR advocates identify three phases for a re-engineering project: Learning phase, Design phase and Transition phase. This paper does not include the transition (implementation) phase. Moreover, this work is not aimed at being implemented by ACROF, and is more theoretical than practical.

As explained earlier, there is a wide range of service packages, offered by CROs, starting with merely trial monitoring and up to a full-service clinical trial. Though most of the studies carried out by ACROF are of partial-service, the Full-Service Clinical-Trial process is examined and analysed for this re-engineering project.

1.5. Collecting Information for the Study:

The study of the pharmaceutical industry and the CRO business has been mostly done by reading relevant documents, books and case studies. The Internet was found to be very helpful, and among the useful web sites are those of "Good Clinical Practices" [GCP, 2001] and the "US Food and Drug Administration" [FDA-CDER, 2001]. The book of Eleanor McFadden [McFadden, 1998] was found to be a good source of study of the business and some of its core-processes. Among the articles and case studies which I used as references are [Cool *at al*, 1999], [Roberts, 1999], [Styhre *et al*, [2001] and [Yeoh and Roth, 1999]. The Society for Clinical Data Management Journal's articles and Internet web site, [SCDM, 2001], shed more light on the CRO's processes, and in particular in the area of data management.

My study of the firm is based on non-confidential published documents, such as ACROF's Annual Business Review 2001, ACROF's Internet web site and the one of its parent company. In addition, several telephone calls and few on-site interviews with top management and IT manager have been carried out, for information gathering and verification.

2. BPR and IT Theories, Principles and Tools:

The objective of this project as mentioned above, is to examine the information technology in the context of the business processes in the CRO business. For doing it, methodologies and tools from different disciplines have been used. These include BPR methodologies and principles, tools for process mapping as well as theories and practices about the role that IT should play and its relationship with BPR initiative.

2.1. BPR Definitions and Principles:

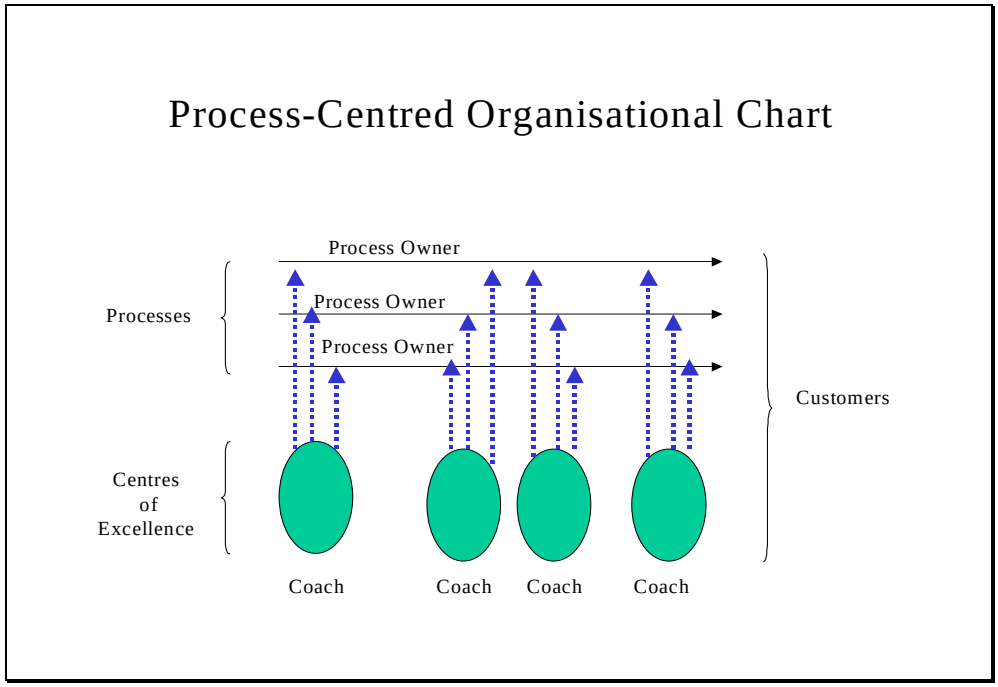
Michael Hammer is considered the "father" of the re-engineering movement, launched in late 1980s. He identifies Business Process Re-engineering (BPR) as: "*The fundamental rethinking and radical redesign of business processes to achieve dramatic improvements in critical, contemporary measures of performance, such as cost, quality, service and speed"* [Hammer and Champy, 1993].

However, there are other, different worldviews of BPR, expressed by theorists and practitioners. [Davenport and Short, 1990] perceive BPR as being "*The analysis and design of workflows and processes within and between organisations*".

Yet, another school of thought emphasises the technology enabling, and describes BPR as "*The use of evolutionary tools/ techniques combined with enabling technologies to provide an explosive mix to make dramatic change throughout the organisation*" [Parker, 1993].

[Hewitt and Yeon, 1996] put these differences under the spotlight, and present them as a question in their research paper: "*Is BPR a tool-based methodology, analogue to Operations Research; or a management philosophy, comparable to Scientific Management Theory; or is it something else, a discrete and temporary activity, analogue to a performance improvement project?*".

According to Michael Hammer, implementing Re-engineering will change the entire organisational structure from the hierarchical structure to the Process-Centred horizontal structure, as shown in the following illustration [Hammer, 1996].



2.2. IT Principles and Practices:

Technology in general and Information Technology in particular, play a significant role in any re-engineering initiative, whether it is a re-design project of certain process or processes, or an organisation-wide re-engineering programme. Probably the most known part of IT in relation to re-engineering, is having it as an enabler for the organisational and processes re-design. BPR advocates suggest that the availability of new technologies can enable the organisational re-invention, while unavailability or pre-mature technologies can be a high barrier for any innovation implementation [Hammer, 1996], [Hammer & Champy, 1993], [Davenport, 1993].

Until the late 1980s organisations had undergone through projects of "automation of activities", "organisational/ departmental computerisation", "strategic computerisation plan" and alike. Many organisational changes had been triggered and initiated by IS/IT needs, and were a by-product of IS/IT requirements. BPR changed the direction, and made IS/IT changes as a subsequent and by-product of process re-invention. However, I have noticed during the last years a trend for mutual adaptation of BPR and IT, in a manner that the "master-follower" relations do not exist to the same extent. *"BPR offers one potential and increasingly influential solution to the requirements problem in software engineering by focusing on core processes"* [Crabtree *et al*, 2001].

Information Technology projects may become very complex, even regardless of their relationship with BPR. Dorothy Leonard-Barton argued that *"Technology implementation is innovation"*, and suggested that *"Because technology will never exactly fit the user environment, there is always a need for a carefully managed "beta site", i.e., experimental introduction into the user environment with the intent to learn*" [Leonard-Barton, 1988].

Systems development methods have been shifting during the last years from the traditional Structured method toward the Dynamic one. The basic SSADM (Structured Systems Applications Development Method) consists of well-identified sequential tasks and milestones along the project's lifecycle. SSADM is considered to be a rigid method, and best fits hierarchical organisations, operating in a steady and well-predictable environment, and providing them with an efficient tool for controlling over the development process. DSDM (Dynamic Systems Development Method) is the new trend emerging in the IS/IT industry. This flexible method is used in a rapidly changing environment, and enables adjustments and learning during the development and implementation process.

A survey at British Airways shows that IS/IT projects carried out by using DSDM instead of SSADM were significantly improved, by several factors [British Airways, 2000]. Average time to delivery reduced to 4-6 months from 18-24 months, average team size was 5 instead of 11, while percentage of completed projects rated good to excellent increased from 77% to 87%. One of the core concepts of DSDM is called "time-boxing", and is seen to be in contrast with a project's critical-path. Geoff Randall, a DSDM strategy & Innovation Director at IBM, described DSDM and the concept of "time-boxing": *"Companies are business focused, demand rigid deadlines and work within constrained resources and cost limits. They need regular refinement of their direction and need to prioritise and compromise. The same is true of people in their daily lives. We are constrained by fixed appointments and deadlines, constantly re-appraising and re-prioritising the next action while accepting that what can't be achieved within the available time must be either rescheduled or dropped. However, even in this environment of compromise, essential things obviously must be done".*

2.3. Tools for BPR and Process-Mapping:

There are several tools developed for presentation and analysis of processes. The most known and widely used are Data-Flow Diagrams and Workflow Charts. Among the new generation of tools for BPR is the Unified Business Process Modelling, as part of the **U**nified **M**odelling **L**anguage (UML). UML is a comprehensive CASE (Computer Aided Software Engineering) tool, covering all phases of the systems development, therefore the Unified Process Modelling is ideal for projects that are intended to be followed by design, coding and testing.

However, for the process mapping I decided to use the IDEF (**I**ntegrated **DEF**inition language) methodology. I found the IDEF as an ideal tool for process mapping, since it enables to focus on the control to the process, which is separated form other inputs. In addition, there is a complete separation of organisation and function: The tool provides the analysis of functions and processes, regardless of the organisation, and the process purpose statement defines the function's purpose and not the organisation's objectives. IDEF is described as a "*combination of graphic and narrative symbols and rules designed to capture the processes and structures of an enterprise*" [Hunt, 1996].

More details about the IDEF concepts are presented in annex B.

3. As-is Processes and IT in ACROF:

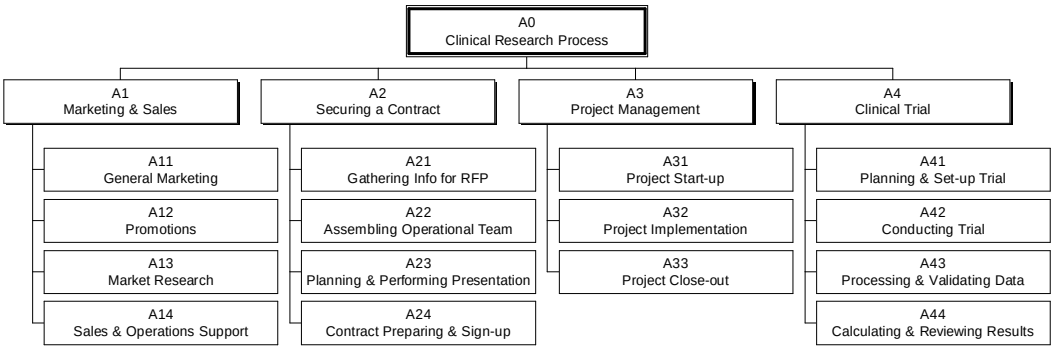
3.1. As-is Process-Maps:

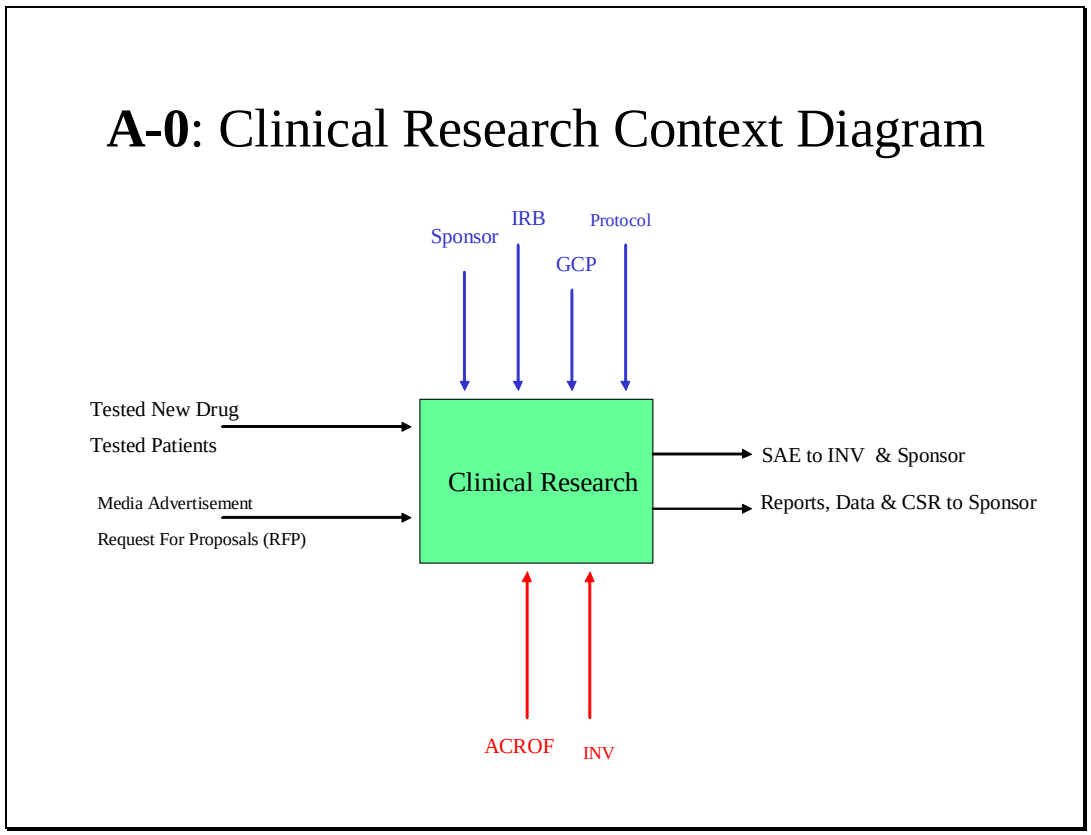
In their book, Carr and Johansson refer to as-is process-maps as Quickmaps, and define them as: *"The first-cut representations of current business processes. They provide the big-picture of the processes in a macro sense, thereby defining the internal and external connections and boundaries between processes, and the workflow characteristics and controls placed on each process"* [Carr and Johansson, 1995]. Regarding the extent to which processes should be detailed, they suggest that: *"Process maps should be detailed enough to break a process down into more manageable units for team to work on redesigning… You usually don't need to map the most minute level of detail, but rather should stop at least one step above that level – the activity or transaction level"*. They argue that *"Quickmaps lie at the core of Business Process Re-engineering"*.

As-is processes at ACROF are presented by using the IDEF method for process mapping. Based on limitations on access to detailed data and information, thus detailed processes and activities, my process maps stop at a greater step above the activity/ transaction level, and is followed by textual analysis of the current state. As a result, there are no to-be process maps, but high level of principles for improved IT and processes, the barriers to implementing/ achieving them, and conclusions/ recommendations.

Preceding the as-is process maps is the process-tree. Clinical Trial Process, "A4" is the process that is developed. IT is embedded into the most of "A4" processes. For presentation of IS/IT and data processing, I am using the flowcharts, which follow the A4 process map. These flowcharts are based on ones provided by ACROF.

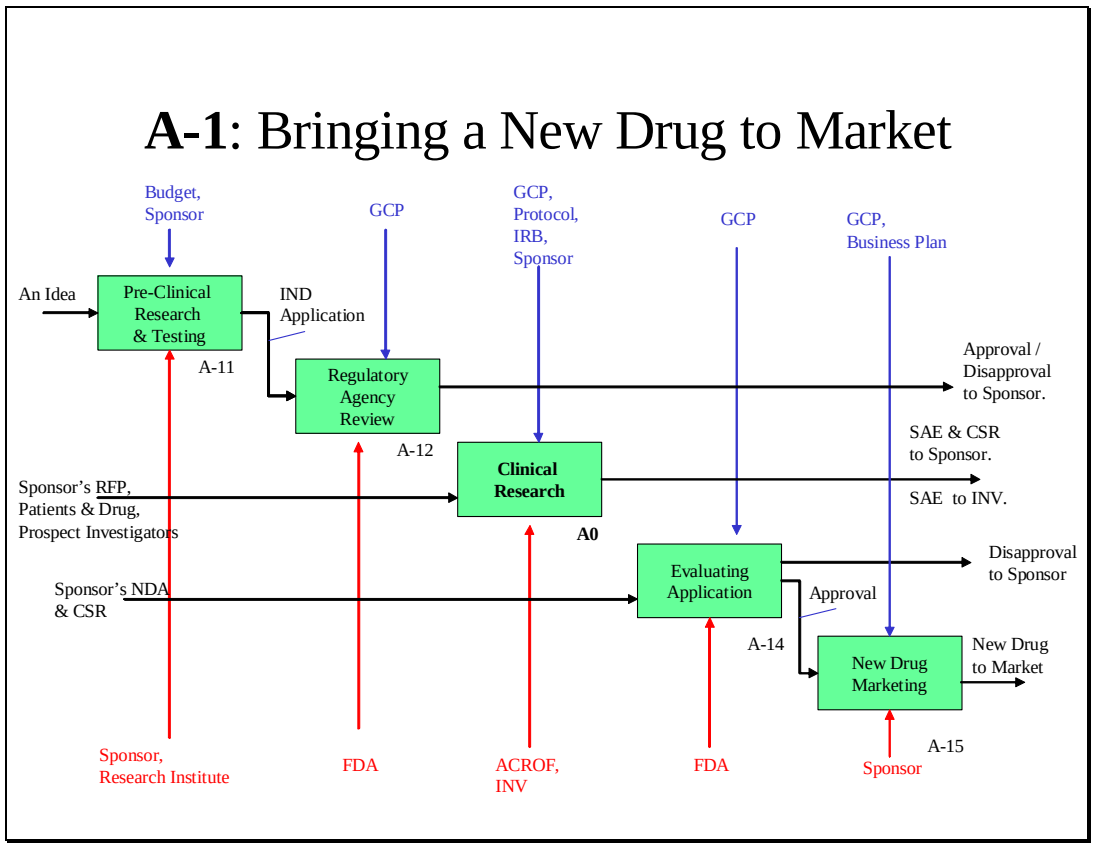
The Clinical Research Process-tree

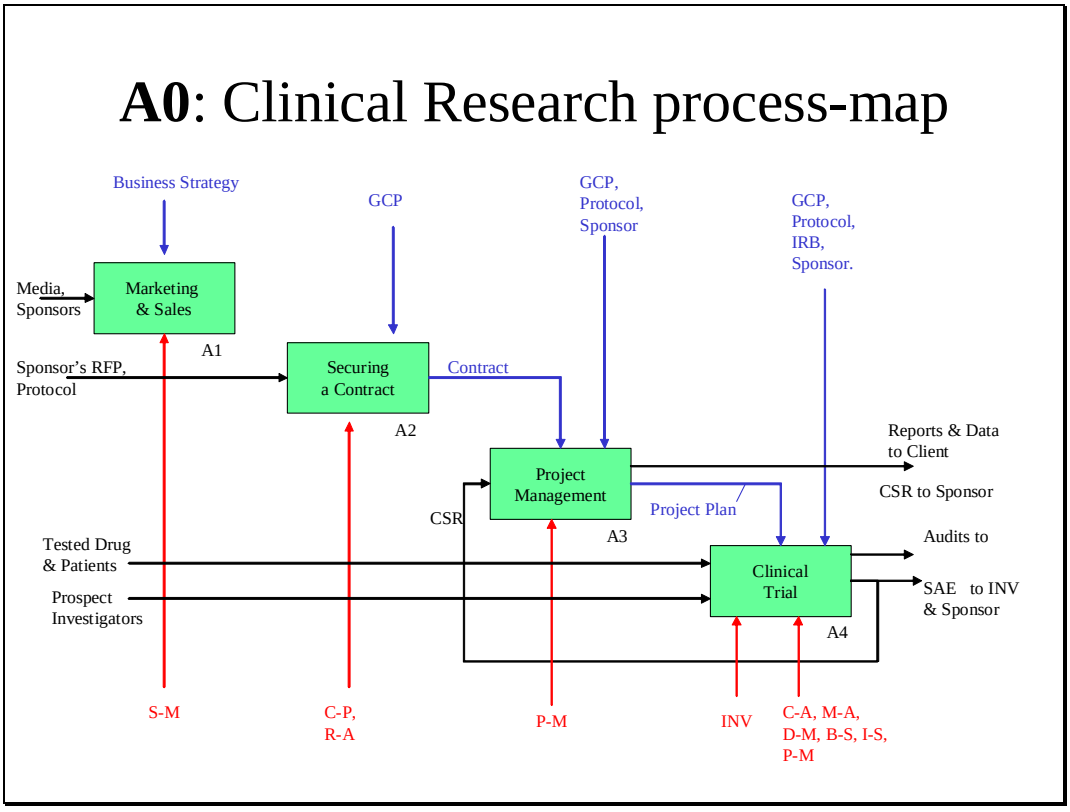


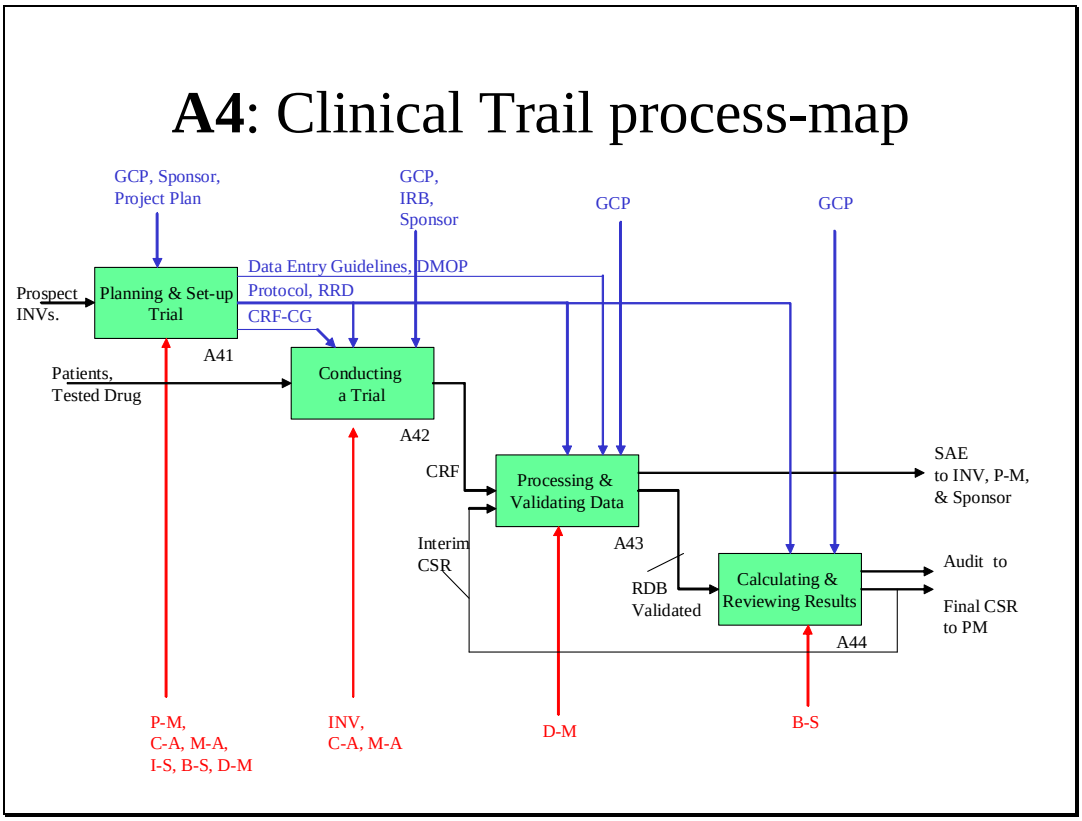


Process Purpose: As an essential part in the new drug development process, clinical research's purpose is to make sure the drug is safe and effective, that during the course of the trial participating persons' safety is tightly kept, the quality of raw and processed data is high and that the process is performed in most efficient and effective manner.

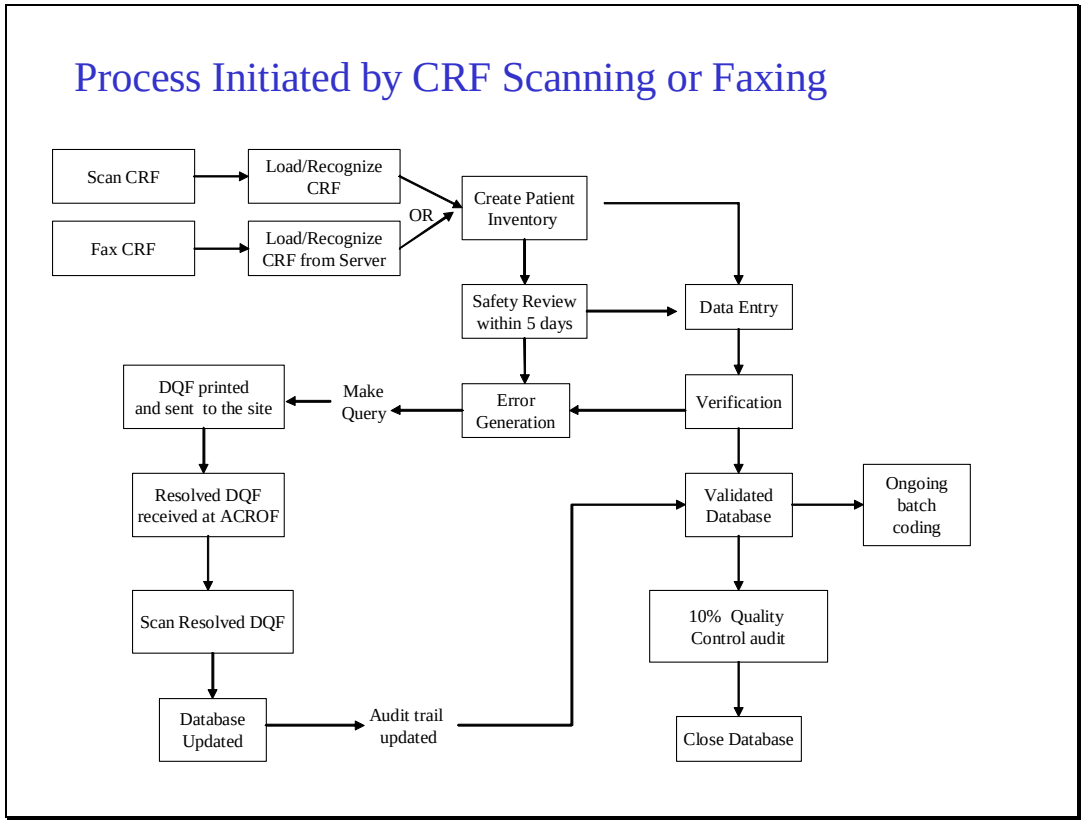
Process Viewpoint: Business Process Re-engineering Consultant.


A-1: Bringing a New Drug to Market
Budget, Sponsor
GCP
GCP, Protocol, IRB, Sponsor
GCP
GCP, Business Plan
An Idea
Pre-Clinical Research & Testing
IND Application
A-11
Regulatory Agency Review
A-12
Approval / Disapproval to Sponsor.
SAE & CSR to Sponsor.
Clinical Research
A0
SAE to INV.
Sponsor's RFP, Patients & Drug, Prospect Investigators
Disapproval to Sponsor
Evaluating Application
Approval
Sponsor's NDA & CSR
A-14
New Drug Marketing
New Drug to Market
A-15
Sponsor, Research Institute
FDA
ACROF, INV
FDA
Sponsor


A0: Clinical Research process-map
Business Strategy
GCP
GCP, Protocol, Sponsor
GCP, Protocol, IRB, Sponsor.
Media, Sponsors
Marketing & Sales
A1
Sponsor's RFP, Protocol
Securing a Contract
Contract
A2
Project Management
Reports & Data to Client
CSR to Sponsor
CSR
Project Plan
A3
Tested Drug & Patients
Prospect Investigators
Clinical Trial
Audits to
SAE to INV & Sponsor
A4
S-M
C-P, R-A
P-M
INV
C-A, M-A, D-M, B-S, I-S, P-M

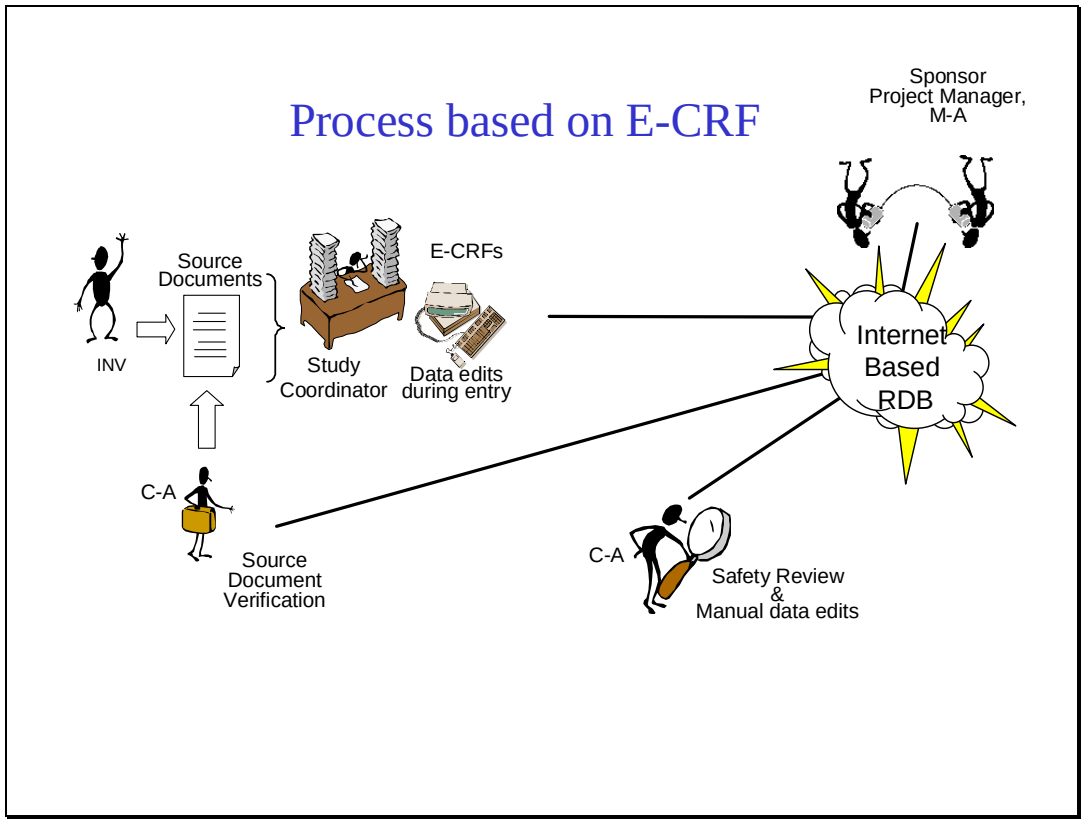

A4: Clinical Trail process-map
GCP, Sponsor, Project Plan
GCP, IRB, Sponsor
GCP
GCP
Data Entry Guidelines, DMOP
Protocol, RRD
CRF-CG
Prospect INVs.
Planning & Set-up Trial
A41
Patients, Tested Drug
Conducting a Trial
A42
CRF
Processing & Validating Data
SAE to INV, P-M, & Sponsor
Interim CSR
A43
RDB Validated
Calculating & Reviewing Results
Audit to
Final CSR to PM
A44
P-M, C-A, M-A, I-S, B-S, D-M
INV, C-A, M-A
D-M
B-S

A43: Processing and Validating Data - Workflow.



CRFs are either faxed at the site directly into ACROF's database, or mailed to an ACROF office for manual scanning. In either process, CRFs are saved into the study database as images. Later, each CRF is linked to a textual and coded file, including patient's history.

Using the Internet as a vehicle and a medium for GroupWare and integrated process, is in its very early stage, and is being developed these days. The chart below outlines the design of future work process and IT, as seen by ACROF.



Statistics at ACROF show that by scanning CRF it takes 13 days to database lock (on average), and by faxing CRF the time is reduced to 11 days, while web-based process is to be completed in 9 days. The new technology based process will save more than 30% of the processing time, compared to the old paper process (mailing and scanning). It might, as well, influence other areas of the process, and significantly shrink overall time.

3.2. Analysis of Existing Processes and IT:

Leading UK practitioners were asked to rate 24 given key words by the way they perceive their importance to BPR [Hewitt and Yeon, 1996]. At the top 5 were rated cultural change (96%), process (96%), customer satisfaction (92%), competitiveness (88%) and profitability (85%). Breakthrough (42%) and starting over (35%) were rated at the bottom of the list. However, for my dissertation at the area of BPR and IT, it is interesting to find that IT was rated ninth of 24, with 77% of citation.

Top management at ACROF was asked to rate the same list of key words. Annex D presents the survey's results in a graphic way. Customer satisfaction led the list, followed by competitiveness, profitability and quality. In their words: *"improving customer service and quality, while cutting costs and overall process time"*. IT rated as low as 17th of 24, based on the belief that IS/IT at ACROF is already a 'state-of-the-art', and there is little room for significant revolutionary improvements. ACROF top managers also categorise BPR as a project, with start and end, objectives, budget, milestones, project manager and alike. Just for a reference, they perceive the TQM (Total Quality Management) as an ongoing, organisation-wide programme at ACROF. Another important finding at ACROF is that BPR projects have been initiated and directed by its CEO (who is now a VP of the parent company). These findings increase the commitment of the company to any BPR initiative.

The Clinical Trial process (process "A4") is performed by a project team (also called study team), organised around any individual drug study. In reality, these study teams are quite artificial, and do not really work as close teams. Team members come from different disciplines, which could be excellent, if only they worked as a team, and were able to perform each other's tasks. Each team member comes with their knowledge base, depending on the discipline they come from, and there is a little incentive to share this knowledge with other team-mates.

To make it even worse, the level at which the organisational hierarchy is flattened, and study teams work as homogeneous teams, is different at the firm's branches. This is very much related to the differences in organisational culture between these offices. While Toronto office is rated high at this scale, resulting in a high performance, Massachusetts home-office is associated with most of the social and performance problems. It causes a great deal of hostility and distrust toward the recently established, women dominated, Toronto office.

As described earlier, capabilities of ACROF's branches are not equal, and they do not carry out the same processes, nor they possess the same knowledge. Even though there are organisational-wide procedures and standard processes for study works conducting and information handling (i.e. gathering, processing and disseminating), variances have been found between study teams and, to a greater extent, between branches. These variances, combined with inequality of capabilities, are among the causes resulting in different performances at ACROF's branches.

The clinical research business is among the very few ones that use a highly sophisticated IT, while at the same time, and in the same processes, a primitive and outdated technology is still in use. At ACROF there is (what its management perceives as a 'state of the art' IT) a quite sophisticated information system, being used at the clinical data management processes. In parallel to it, there is still a great deal of data entry, while the source is either mailed or faxed. The industry and the regulatory authorities keep sticking to the rule of "double-entry" for better data quality, just because there is still data entry in the process.

4. Improved IT-Enabled Processes:

4.1. Principles for Improved IT-Enabled Processes:

I believe that the holistic approach to BPR, as presented by Michael Hammer and other BPR advocates, is the one that can produce the best, long-standing results, for the entire organisation [Hammer, 1990], [Hammer, 1996], [Hammer & Champy, 1993], [Davenport, 1993]. These BPR and IT principles are examined below, in the context of ACROF and the CRO business in general.

Treat geographically dispersed resources as though they were centralised. ACROF should treat its branches and headquarters office as a single unit, conducting the same processes (or at least same frame-processes). Raising the capabilities at the branches to a more uniform level will allow sharing work between them. As a result of this flexible work sharing between branches, a more balanced workload and higher performance will be reached at all branches. Moreover, the European and Asian subsidiaries of the parent company should be merged with ACROF as a consolidated international CRO firm.

Put the decision point where the work is performed, and build control into the process. One of the corner stones of a process-centred-team is the empowerment of team-members toward decision-making and risk taking. This concept has been adopted by ACROF (at least officially), as part of its TQM initiative. Nevertheless, there is still some level of hierarchy within the study teams, including supervisor roles and reporting procedures. For better decision making, open information system is required, and a free flow of information and knowledge is essential. This is extremely related to the organisational culture, which should be watched closely and developed.

Capture information once and at the source. In other words, data-entry should be dropped at all, and the person who produces the data (at the investigator's site) should be the one who enters it directly to the database. Site co-ordinators should be trained to enter the data directly to computerised database. It could be done either by typing onto an on-screen CRF, or using sophisticated handwriting and voice recognition software. Transformation of data from source files to CRFs should be eliminated, therefore would be the double data entry practice, too. The web-based data processing and validating system is the right direction toward achieving this principle, yet I am not sure there would be a total elimination of CRF filling by hand from sources at the patients' files.

Simplify and annihilate processes, so to reduce cycle-time and cost. Efficiency of the clinical research process at all, in terms of time and cost, is one of the key determinants in the CRO business. The great buyer-power and competition-power of the pharmaceutical industry over the CRO firms magnifies the need for high efficiency even more. Simplification of processes, and trying to carry out as many as possible in parallel, rather than in sequence, will result in shortened cycle-time and reduced costs. In the process of clinical trial, processing and validating data could and should be conducted in parallel, to a greater extent than it is done now. CRFs should be fragmented to smaller batches, and be dealt with immediately upon entering the system. Work sharing between ACROF's branches and different teams on their availability, will boost the cycle-time reducing.

Keep only these processes that will add more value than if they were outsourced. The CRO business is a contracting business, so it already gets whatever the pharmaceutical companies decide to be less value adding for them when carried out in-house. Yet, a contractor can decide to sub-contract some of its activities and processes (pre-approval by the sponsor is required). Moreover, a firm may not bid all the processes offered by the sponsor, but only those it believes to be competitive and outperforming at. At ACROF, some processes and activities should be carried out at other, better performing branches. Activity-Based Costing/ Management (ABC/M) is among the useful tools for deciding what activities are value-adding and what are not-value-adding [Leahy, 2001]. Leahy also suggests that those activities, which do not add value to the organisation, should be outsourced, so to better balance overall workload.

Set out-of-reach, not out-of-sight targets. New vision as related to re-engineering is rated as low as 22nd of 24 by ACROF's top management. Even though BPR is perceived as a project, not as an ongoing organisation-wide programme, it should be envisioned and linked to firm/ branch/ department objectives. Each and every BPR project should have its qualitative goals and quantitative measurable targets.

Re-think functions and processes. Distinguish between Value-Adding, Non-Value-Adding and Waste activities. Try to obliterate non-value-adding and waste activities. In the highly regulated CRO business, it is not always simple to "break the rules" and rethink functions and processes. However, it is not impossible, either, and there are cases of firms that has changed their industry structure. For example, highest quality of data is, indeed, a top goal for a CRO firm. But how to achieve this goal should be open to debate, and revolutionary solutions must be welcomed. The double data entry can and must be questioned, amongst other non-value-adding and waste activities.

Use IT as an enabler. *"The use of IT to automate existing business processes had often fallen short of the expected results"* [Hammer, 1990]. Information Technology does not and should not stand by itself, in any organisational change initiative. IT must be perceived as part-and-parcel of BPR projects/ programmes. The new web-based data processing and validating system is basically aimed to automate existing processes. In contrast, the process should have been questioned and assessed, resulting in a new IT aided process. New technology, such as voice and handwriting recognition can be used as enablers at the re-designed processes.

And probably above all – challenge outdated organisational principles, question fundamental assumptions and underlying operations.

Knowledge, according to [Styhre *at al*, 2001], includes not only the formal and informal tangible information used in organisations, *"but also the tacit knowledge that cannot easily be transcribed, codified, stored and disseminated"*. They argue that *"there is no knowledge per se in organisations, but the construction of knowledge, determined or affected by certain worldviews, perspectives, and favoured modes of thinking that define what legitimate and useful knowledge is"*. In their study, they found that *"Men were claimed to be more focused on results and output, while women were identified as having a proclivity towards democratic decisions that took all team members' views into account"*. The women-dominated clinical research study-team is a perfect intimate-cell, where experience and knowledge of all forms could and should be shared. Since women employees' turnover rate is lower than men's rate, the knowledge is more likely to be better retained in the organisation, as well.

Sharing information and knowledge between different study teams is even more difficult than within an individual team. Small CRO firms, like ACROF, are more successful at sharing information and knowledge between study-teams, since the same employees work at several studies at a time. It is even magnified by the fact that those specialists, who possess valuable knowledge, are few in numbers (sometimes only one at the firm), so they participate in most of the studies.

As described earlier, sharing information and knowledge between sites of ACROF is a real problem. Virtually no valuable information flows between its offices, and knowledge sharing between branches is out of consideration.

Cultural change rated by ACROF's top management as low as 14th of 24, according to its importance to BPR initiatives. Based on the organisational culture problems found at ACROF, I believe it should be ranked much higher, and rated near the top of the list. This issue should be dealt with much more seriously at ACROF.

Processes, according to Hammer, not only cross functional departments within the organisation, but also should break away from the organisation's boundaries and include customers and suppliers, as if they were part of the organisation. A process has been started before the organisation is involved, and will probably be continued by the customer. This is very relevant to the CRO business, which is virtually dependent on the long relationship with pharmaceutical firms, where the clinical research process starts. Tight connections and linkages between processes and systems at ACROF, and those at the pharmaceutical companies should be developed. This may be initiated either by ACROF or by the pharmaceutical industry. On the other side, the investigator sites can be seen as ACROF's users and data suppliers, so providing them with the tools to better manage their "supply" is of the interest of ACROF. It may result in computerising these sites, not only for supporting ACROF's processes, but for benefiting the sites themselves, too.

In the CRO business, each study (project) is unique and has its tailored process, as reflected in the Protocol, the Contract and the POP (Project Operational Plan). For coping with such a flexible environment, a "flexible process" is required. It might be called "Frame process", "Umbrella process" or "Template process" from which specific processes can be derived for each study. For example, scanned and faxed initiated data processing are very similar processes, with the only difference at their start. Now these are two separated processes, and should be consolidated into a one flexible process (as shown in the flowchart of process A43).

DSDM (Dynamic Systems Development Method) is not only used in the systems development process, but is also a good fit for business development in general. This flexible method even better fits the piecemeal implementation that has been adopted by ACROF for BPR projects. Rather than making top management sign off the project's milestones, which freeze and imprint the past assumptions - thus analysis and design products of BPR – to the following phases, the JAD (Joint Application Development/Design) method should be adopted. During JAD cross-functional team sessions, where all stakeholders are represented, a free discussion is followed by a win-win decision making, based on the broadest possible consensus. The project manager should be the JAD sessions' facilitator, who is in charge of preparing and managing these meetings. During a JAD session each of the members can raise issues for discussion and decision, and the course of the project may be changed, regardless of the approved analysis and design documents and the overall project plan. DSDM and JAD will best suit the women dominated project teams at ACROF.

"For firms to consistently outperform others, only pursuing a clear generic strategy within their industry (such as low cost/ low price strategy) will not be enough, and the corporation's core-competencies building for the future is a must" [Prahalad and Hamel, 1990]. In the case of ACROF, it means building IT capabilities that are part and parcel of its business core competencies. These will be difficult to copy by others, at least in the short time, and will provide the company with the advantage of first runner. Obviously, the Internet is the vehicle on which future application systems will be based. It will allow the GroupWare and enable many other simplified, improved, with higher quality and less costly business processes. For being competitive in the future, a CRO firm will have to possess the Internet based technology, either in-house or as an alliance partnership with an IT company that already owns these capabilities.

4.2. Analysis of Barriers to Implementation of these Principles:

When dealing with implementation of BPR and IT combined initiatives, I like to bring the case of the public sector, at which a "successful failure" is examined [Kock and McQueen, 1996]. In their case study, they describe an attempt to re-engineer a large state-owned civil engineering company in Brazil. *"As a result of the re-engineering attempt, the organisation had its IT infrastructure significantly improved… The CEO believed he had taken over an old-fashioned organisation and turned it into a modern one, with the use of 'state-of-art IT'… However, no radical changes in the organisation's business processes had resulted…Even though some processes had been automated, almost no staff reduction was affected…It meant that the increase of efficiency in those processes, which by no means was radical, was not realised"*. However, they agree that *"Only slight changes in the process could really be implemented, without making the process prone to be contested by lawyers"*. I believe that, to a great extent, this problem characterises the re-engineering attempts of the clinical trial process, which is highly regulated. Radical change of processes requires re-design of the industry structure, as a pre-condition for success.

As mentioned, the CRO business is highly regulated, in a way that some regulations may prevent the obliteration of non-value-adding and waste activities. But, in reality, no re-engineering initiative is absolutely free from external influences and environmental barriers. These should be anticipated and carefully studied by the re-engineering agent, and the organisation's executives should be consulted, so to find ways to cope with them, if it is not possible to curb or change them. Leading pharmaceutical firms, as well as regulatory agencies should be involved in the process of consulting, in an attempt to make them accept the revolutionary re-designed processes.

"Successfully initiating and well planning a project might be a difficult task, but implementing it and keeping everyone's support is a much more difficult and sometimes frustrating job" [Yeates and Cadle, 1996]. It is true in particular when changes are organisational, and significantly affect employees' and managers' role. Changing organisational structure from functional to process-centred one (as explained earlier) is the most radical change an organisation may ever undergo. Flattened organisation is not in the interest of middle management, which will be the "victims" of this new structure. Change management advocates list three conditions that will create significant resistance to change: when people are comfortable with the status quo, when they do not understand why the change is desirable and when they have doubts about the firm's ability to achieve the desired change. The latest merger could be a trigger to justify radical change and persuade staff members to collaborate. Top management on-going commitment to the BPR project, which is required for its successful development and implementation, exists at ACROF (at least officially). Sincere and intensive communication of the re-engineering purpose to staff members at all levels of the organisation, along with implementation of a re-engineering radical change in a piecemeal manner, and using a pilot method will, most likely, reduce the level of uncertainty and consequential resistance. Incentive methods, based on efficiency and effectiveness (personal and team's) rather than on amount of work done, will likely to promote the idea of Process-Centred team working organisation and decrease front-line employees' resistance.

Differences between ACROF's offices in regard with capabilities, culture and efficiency/ performance is a great stumbling block in the way of equalising workload and sharing tasks and processes between study teams and sites. This barrier can be, and should be removed, as a precondition for GroupWare and process-centred organisation setting. Having that will inevitably increase information and knowledge sharing and decrease the level of hostility and distrust between the firm's branches.

BPR is perceived and managed as a project, by ACROF's top management. This highlights another prospective barrier to BPR initiatives: the financial justification. Projects, and especially large ones, are measured by means of cost and benefits, and must meet shareholders expectations and approval. BPR and IT expenditures are difficult to quantify in term of cash flow. However, a BPR/ IT project should be perceived as a long-term investment, rather than a project that will result in immediate performance improvement and yield higher profits. Activity-Based Costing/ Management (ABC/M) is one way companies can better understand these costs, over the project's lifetime [Leahy, 2001]. The Balanced Scorecard (BSC) theory is another good way, in which a re-engineering programme can be justified, by showing that eventually it will contribute to the firm's financial performance, too [Kaplan, 1992]. The BSC theory consists of four perspectives for firm's performance measurement. These are internal business, innovation & learning, customer, and financial perspective. An organisation undergoing business process re-engineering, and during the transition to a Process-Centred organisation, beefs up and strengthens the first three components of BSC. Achieving the BPR objectives and other three components of the BSC will contribute indirectly to the financial performance, too.

Firms can find that the most efficient and effective processes and IT solutions they designed cannot be implemented because they do not fit the customers' needs or users' abilities. In the GroupWare concept, supported by web-based technology, the investigator sites play a major and significant role, are deeply involved in the process, and indeed, should be an integral part of it. Persuading doctors and nurses to enter data directly to the computerised systems, instead of handwriting it to the patients' files, won't be an easy task. The re-designed processes and IT must fit the site needs and capabilities, and benefit them too. Should these processes consume more time, sites should be compensated accordingly. However, not all sites will accept that level of enforced change, even if it benefits them eventually. In complement, carefully segmenting and analysing sites by needs, will help to reduce the impact of such a problem. If ACROF were free to choose the sites with which to work, it should have built strategic partnerships with those selected ones, and that would have helped to ensure effective design of processes, of which sites will be part. It must be noted that some sites, in particular the smaller ones, are selected by the sponsor for a single study, and in which the clinical research is just a side activity of a regular small medical centre. Investing in these sites is very likely to be unworthy, by economical and technological means.

BPR and IT are dependent on each other, and the best way to illustrate it is by the inter-dependencies of hens and eggs. Many re-engineering programmes require technical improvements or breakthroughs in order to realise their full potential. Technical shortcomings can stop a radical re-engineering programme. Successful implementation of the GroupWare requires the deployment of highly sophisticated IT. This may include, but not limited to, clinical Expert-Systems, voice recognition and handwriting recognition software, highly secured network and alike. Careful technology monitoring, planning and forecasting by the re-engineering agent is very central to IT-enabled re-engineering programmes.

5. Conclusions and Recommendations:

Clinical research activities are described as *"based on a number of skills, know-how, and capabilities that are employed throughout the clinical phase. The ability to initiate, start up, administrate and organise, and finally to submit a new drug application to the medical authorities such as the FDA requires the orchestration of a multiplicity of skills and experiences"* [Henderson and Cockburn, 1994]. My study of the clinical research process, and the clinical trial process (A4) in particular, carried out at ACROF, brings me to the following conclusions and recommendations, most of which are true for the CRO business in general, too:

Information and knowledge sharing between study-team members, between study-teams and between organisation's sites is essential for time and cost reduction, and for overall quality increase. This goal can be achieved by developing and implementing "items" from different disciplines. The women dominated CRO business is very likely to be a perfect ground on which process-centred team working can be nurtured. IT can improve information and knowledge sharing at all levels, by adopting the comprehensive GroupWare concept, which should include the pharmaceutical companies (clients) and the investigator sites (data suppliers), too. Top management should deal with organisational culture more seriously, and develop such a culture that will encourage employees to make decisions and take calculated risk. It will build quality into the real process, rather than being a process by itself. These conclusions and recommendations are developed in the following paragraphs.

IT and BPR can be both initiators and means for better long relationships between ACROF and its clients in the pharmaceutical industry. Business processes should regard the client's ones as an integrated part of them, and IT should enable and enhance these tight relationships. The fact that ACROF is now owned by a pharmaceutical company is a great benefit, since its parent company can be used as a pilot system.

Outsourcing and selecting tenders for bids must be well entrenched in the process of securing a contract (process A2). Not all activities of the clinical research ought to be bided for, but only those that the company believes to be competitive and outperforming at. Other, not-value-adding activities, may better be outsourced and sub-contracted.

Nevertheless, sharing activities and processes between ACROF's branches is to be encouraged. For that matter, European and Asian parent company's subsidiaries should not be excepted, but integrated into ACROF. However, current differences between offices and branches in regard to capabilities, culture and efficiency/ performance are a great stumbling block in the way of equalising workload and sharing tasks and processes between study teams and sites. ACROF has successfully undergone significant changes since it was established, including the latest adoption of TQM. I believe that the barrier of inequality can be forestalled, as part of establishing a Process-Centred organisation and GroupWare with a strong organisational culture. Having that will inevitably increase information and knowledge sharing and decrease the level of hostility and distrust between the firm's branches, too.

Investigator sites are the source of raw clinical data, on which the entire clinical trial process is relying. The concept of capturing data once and at the source should lead to abandoning the data-entry, therefore the double-data-entry. GroupWare and sophisticated IT can play a major role in achieving this objective. Incentives to the investigator sites should be developed and offered, too, as a means of encouragement and compensation. ACROF should carefully monitor the investigator sites, and choose only those that economically and technologically worth the investment and effort.

ACROF must perceive itself as an Information Processing company, operating in the clinical research business. It should be a source of pride to its employees, rather than a low professional self-esteem. For being competitive in the future it must build up its core competencies, and these are heavily based on IS/IT. These unique capabilities can be either possessed in house, or be acquired through strategic alliances with companies that already own them.

The clinical research process in general, and the clinical trial one in particular, are, to a great extent, flexible processes. For carrying out flexible processes, flexible tools should be used. These include the recommended "Frame-processes" from which individual ones are derived. Dynamic Systems Development Method (DSDM) and Joint Applications Development/ Design (JAD) are recommended for project management at the clinical research process. Project managers must be trained at using these new methods and tools.

Core-competencies include revolutionary processes, as well. ACROF is a small player in the CRO business, though, yet it is owned by an international pharmaceutical company. It provides ACROF with the power to try and change the industry structure, so to accept new innovative processes. It is hard, probably extremely hard, but not impossible, and many innovative ideas emerged from front the line player companies, rather than top regulatory agencies.

The short questionnaire presented to ACROF's top management brought onto the surface some problems and misconception of the BPR initiative. IT should be rated much higher above its 17th place, and ACROF must understand that it still operates old IT systems based on primitive IS conceptions. The same is said about cultural change. ACROF has a significant cultural problem, and any BPR initiative must face it and take it into account.

References:

British Airways (2000). ***British Airways IM Department, Newcastle, England.*** Publicised by DSDM Consortium Ltd.

Carr, D.K. and Johansson, H.J. (1995). ***Best Practices in Re-engineering: What Works and What Doesn't in the Re-engineering Process.*** New-York: McGraw-Hill.

Cool, K., Roller, L.H. and Leleux, B. (1999). "The relative impact of actual and potential rivalry on firms profitability in the pharmaceutical industry". ***Strategic Management Journal***. (1999), Vol 20, pp. 1-14.

Crabtree, A., Rouncefield, M. and Tolmie, P. (2001). "There's something else missing here: BPR and the Requirements Process". ***Knowledge and Process Management.*** (2001) Vol. 8 Num. 3 pp. 164-174.

Davenport, T.H. And Short, J.E. (1990). "The New Industrial Engineering: Information Technology and Business Process Redesign". ***Sloan Management Review***. (Summer 1990). Pp. 11-27.

Davenport, T.H. (1993). ***Process Innovation.*** Boston: Harvard Business Press.

FDA-CDER (2001). "Food and Drug Administration, Centre for Drug Evaluation and Research". ***Internet***: www.fda.gov/cder. Visited October 30th, 2001.

GCP (2001). "Good Clinical Practices – Consolidated Guideline". ***Internet***: www.ncehr-ncerh.org/english/gcp. Visited October 30th, 2001.

Hammer, M. (1990). "Re-engineering Work: Don't Automate, Obliterate". ***Harvard Business Review.*** (July-August 1990), pp.104-112.

Hammer, M. and Champy, J. (1993). ***Reengineering the Corporation: a Manifesto for Business Revolution.*** New York: Harper Collins.

Hammer, M. (1996). ***Beyond Reengineering: How the Process-Centred Organisation is Changing Our Work and Our Lives.*** New York: Harper Collins.

Henderson, R. and Cockburn, I. (1994). "Measuring competence? Exploring firm effects in pharmaceutical research". ***Strategic Management Journal.*** (1994) Vol. 15 pp. 63-84.

Hewitt, F. and Yeon, K.H. (1996). "BPR Perceptions, Practices and Expectations – A UK Study". ***Business Change and Re-engineering***. (1996) Vol. 3 Num. 3 pp. 47-55.

Hunt, V.D. (1996). ***Process Mapping: How to Reengineer Your Business Processes***. New York: John Wiley & Sons.

Kaplan, S.R. (1992). "The Balanced Scorecard – Measures that drive Performance". ***Harvard Business Review***. (January 1992).

Kock, N.F. and McQueen, R.J. (1996). "Is Re-engineering Possible in the Public Sector? A Brazilian Case Study". ***Business Change and Re-engineering.*** (1996) Vol. 3 Num. 3 pp. 3-12

Leahy, Tad (2001). "When Activity-Based Management Meets IT". ***Business Finance Magazine.*** (April 2001). Also in http://www.BusinessFinanceMag.com/archives/appfiles/article.cfm?IssueID=347

Leonard-Barton, D. (1988). "Implementation as mutual adaptation of technology and organisation". ***Research Policy*** (North Holland). February 1988, #17, pp.251-267.

McFadden, E. (1998). ***Management of Data in Clinical Trials.*** New-York: John Wiley & Sons.

McHugh, P., Meril, G. and Wheeler, W.A. (1995). ***Beyond Business Process Reengineering: Toward the Holistic Enterprise.*** New-York: John Wiley.

Parker, J. (1993). "An ABC Guide to Business Process Re-engineering". ***Industrial Engineering***. (May 1993). Pp.52-53.

Porter, E.M. (1980). ***Competitive Strategy: Techniques for analysing industries and competitors***. Free-Press.

Porter, E.M. (1985). ***Competitive Advantage.*** Free-Press.

Prahalad, C.K. and Hamel, G. (1990). "The core competence of corporation"***. Harvard Business Review.*** May-June 1990.

Roberts, P.W. (1999). "Product innovation, product-market competition and persistent profitability in the US pharmaceutical industry". ***Strategic Management Journal***. (1999), Vol 20, pp. 655-670.

SCDM (2001). ***The Society for Clinical Data Management Journal.*** Also the organisation's ***Internet*** web site: http://www.scdm.org visited September 20th, 2001.

Styhre, A., Ingelgard, A. and Roth, J. (2001). "Gendering Knowledge: The Practices of Knowledge Management in the Pharmaceutical Industry. Case Study". ***Knowledge and Process Management.*** Vol. 8 No. 2 (2001) pp.65-74.

Yeates, D. and Cadle, J. (1996). ***Project Management for Information Systems***. Second Edition. Prentice-Hall.

Yeoh, P.L. and Roth, K. (1999). "An empirical analysis of sustained advantage in the US pharmaceutical industry: impact of firm resources and capabilities". ***Strategic Management Journal***. (1999), Vol 20, pp. 637-653.

Annex A: Glossary, Abbreviations & Acronyms.

Audit Trail	A component of the Quality Control System. The record (electronically stored or on paper) of any change in the data, including the date, reason for, and the name of the person who made the change.
B-S	Bio-Statistics
C-A	Clinical Affairs
C-P	Contracts and Proposals (Organisational Unit).
CRO	Contract Research Organisation. A firm that a sponsor hires to carry out some of his clinical trial duties.
CRF	Case Report Form. A document tailored to a study, developed by ACROF/ Sponsor, and aimed to collect relevant data about each Subject. Relevant data is transformed from the original patient's records to CRF at the site.
CRF-CG	CRF Completion Guidelines.
CSR	Clinical Statistical Report. The final statistical report, analysed according to the Protocol, as specified by GCP and as required by the Regulatory Agencies.
D-M	Data Management
DMOP	Data Management Operational Plan. An internal document, tailored for a study and describing the data management activities during the trial.
Double Data-Entry	The data from CRF is entered to the database twice, by independent persons. In the First-Pass data from CRF is entered as-is. During Second-Pass discrepancies between the two entries are immediately flagged by the system, allowing the second operator to select the correct entry.
DQF	Data Query Form. A form used for sending queries and receiving answers.
F-A	Finance & Accounting (Organisational Unit).

FDA	Food and Drug Agency (Federal USA). The US regulatory agency that evaluates and monitors the safety, effectiveness and quality of drugs. The FDA division performing it is **CDER** – the Centre for Drug Evaluation and Research.
GCP	Good Clinical Practice. An international regulations and guidelines for conducting clinical trials on human subjects.
H-R	Human Resources
ICH	International Conference of Harmonisation. Consolidated guidelines on GCP, and other guidance topics.
INV	Investigator. Refers to the clinical trial site and the physician conducting the trial.
IRB	Institutional Review Board. (Also **IEC**: Independent Ethics Committee). A formal institution reviewing medical research on human subjects. The IRB approves the Protocol before conducting the study, and its main objectives are to ensure that risk to Subjects is minimal, and the anticipated benefits of the treatment outweigh that risk.
I-S	Information Systems (Organisational Unit).
M-A	Medical Affairs
M-W	Medical Writing
NDA	New Drug Application.
P-M	Project Management
POP	Project Operational Plan.
Protocol	A study document that outlines scientific rationale for study, details the treatment plan, identifies patient population and defines criteria for assessment. Also includes the statistical methods to be used in the study.
Q-A	Quality Assurance
RDB	Research DataBase.
R-A	Regulatory Affairs

RFP	Request for Proposal.
RRD	Required Regulatory Documents.
SAE	Serious Adverse Event. Also: Serious ADR – Serious Adverse Drug Reaction. Any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity. Or is a congenital anomaly/birth defect.
S-M	Sales & Marketing
SOP	Standard Operational Procedures (Corporate/ Division guidelines).
Sponsor	The pharmaceutical firm that develops the new drug.
Subject	A person (volunteer/patient) who is a subject of a clinical trial.

Annex B: IDEF mapping Methodology and Concepts.

For the process mapping I decided to use the IDEF methodology, which characteristics and concepts are described in this annex. [Hunt, 1996] describes IDEF as a *"combination of graphic and narrative symbols and rules designed to capture the processes and structures of an enterprise"*. IDEF techniques were derived from the Integrated Computer-Aided Manufacturing (ICAM) programme sponsored by the US Air Force. The acronym IDEF was formed from the term **I**CAM **DEF**inition language. Today it has been renamed and stands for **I**ntegrated **DEF**inition language.

There are several IDEF process map concepts and rules, which are designed to enhance communication:

- Diagrams based upon very simple box and arrow graphics.
- Plain text specifying meanings of box (function or process) and arrow (data or objects).
- Gradual exposition of process detail, featuring a hierarchy with major functions at the top and successive levels of sub-function processes, revealing well-bounded detail process breakout.
- Arrows include Input, Control, Output and Mechanism (ICOM) to and from process boxes.
- All functions/ processes require at least one control.
- Each process-map should have purpose and viewpoint.

In contrast to workflow charts and data-flow diagrams, the IDEF is an ideal for process mapping, since it enables to focus on the control of the process, which is separated form other inputs.

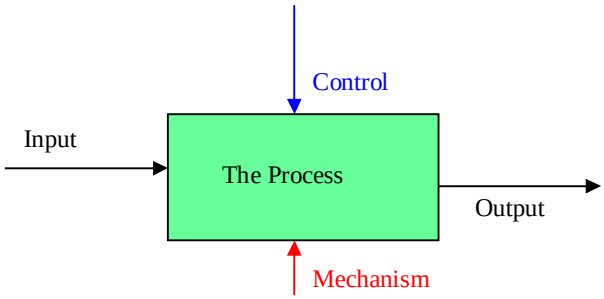
There is a complete separation of organisation and function. The tool provides the analysis of functions and processes, regardless of the organisation. The process purpose statement defines the function's purpose and not the organisation's objectives.

Context Diagram, also called **"A-0"** Diagram (pronounced A-minus-zero), represents the entire process-map by a single box and its bounding arrows.

Zero-Level Process Map, called **"A0"**, includes the main sub-processes and the connections between them. These main sub-processes are numbered 1,2,3... Process #1 will be detailed as process map "A1", #2 as process map "A2", and so on. Process "A1" will then be detailed as process maps "A11", "A12" and so on, until the bottom level of the processes is reached.

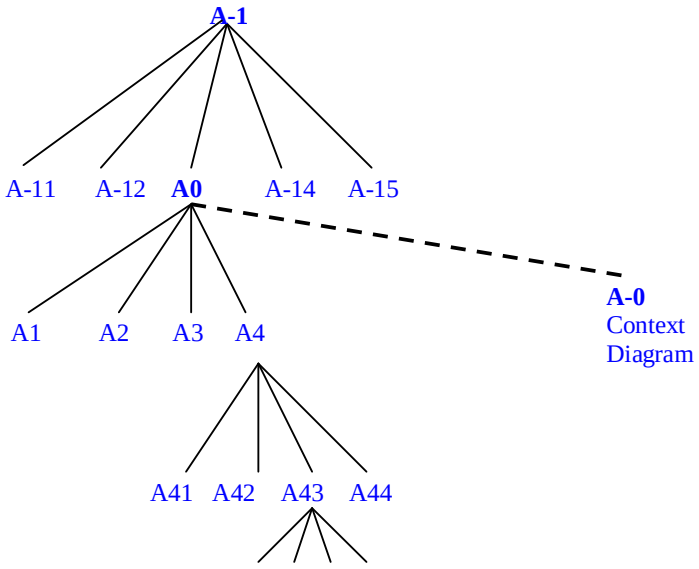
The Process-Tree (also called Node-Index or Process-Index) is a placement of the diagrams in hierarchical order, so to give an overall view of the process, and to allow access to any portion of the process map. The view can be either graphical or textual (the graphical view is shown below and in the paper itself).

An example of **"A-0"** Context Diagram:

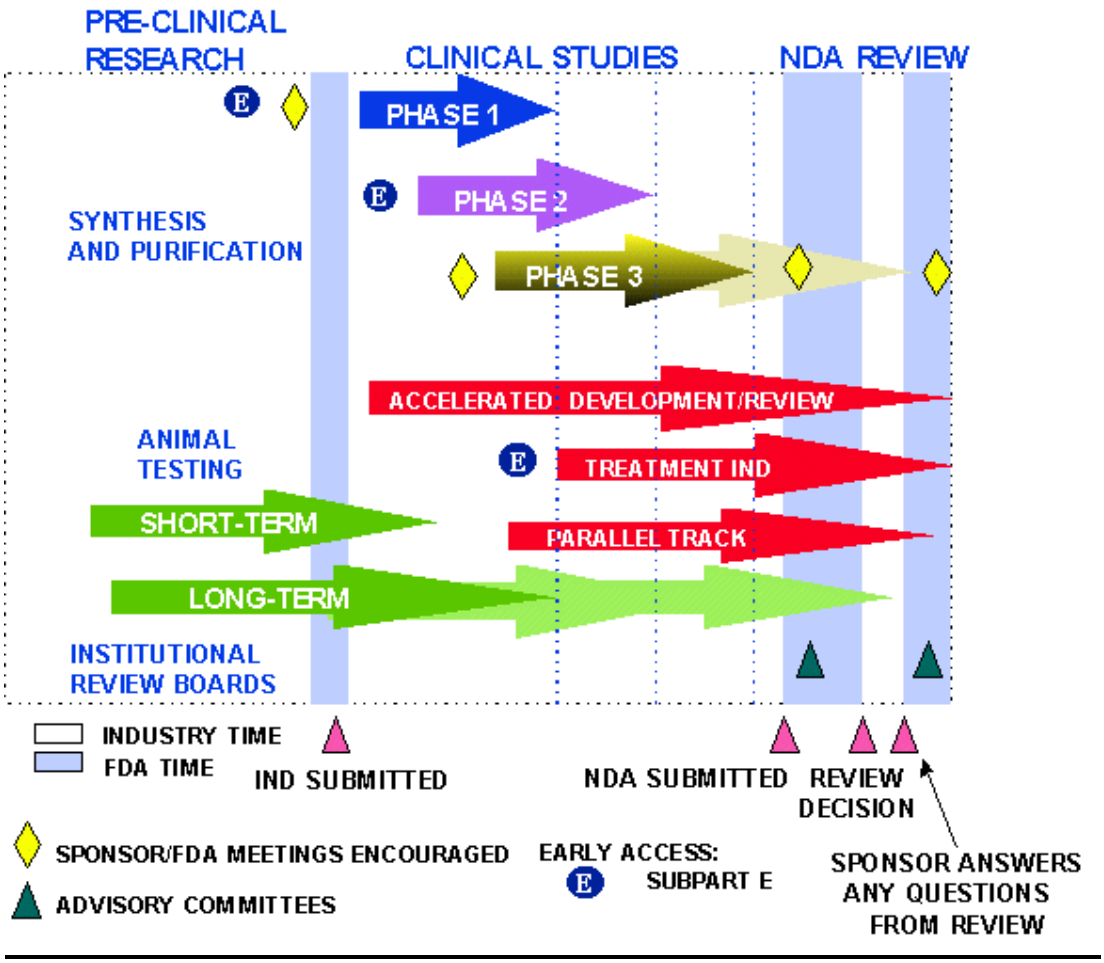


High-Level Context map, also called "A-1", is aimed to show the broader context of processes in which our Zero-Level "A0" process is carried out, and the connections to them.

An example of **Process-Tree Diagram**, starting from "A-1" level:



Annex C: FDA's Viewpoint of New Drug Development Process.



- The diagram was copied from FDA-CDER's web site: http://www.fda.gov/cder/handbook

Annex D: How is BPR Perceived by ACROF's top management?