
UNIVERSITY OF NORTH TEXAS
HEALTH SCIENCE CENTER AT FORT WORTH
1970

CLINICAL INTERNSHIP WITH THE ANTERIOR SEGMENT CLINICAL DIVISION AT ALCON LABORATORIES, INC.: ELECTRONIC DATA CAPTURE (EDC) APPROACH VS. PAPER-BASED APPROACH TO DATA MANAGEMENT

THESIS

Presented to the Graduate Council of the

Graduate School of Biomedical Sciences

University of North Texas

Health Science Center at Fort Worth

In Partial Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE

By

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Fort Worth, Texas

November 2003

CLINICAL INTERNSHIP WITH THE ANTERIOR SEGMENT CLINICAL DIVISION AT ALCON LABORATORIES, INC.: ELECTRONIC DATA CAPTURE (EDC) APPROACH VS. PAPER-BASED APPROACH TO DATA MANAGEMENT

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ACKNOWLEDGEMENTS

First and foremost, I would like to extend all praises to my heavenly Father who has given me the strength to overcome yet another challenge. Also, I would like to say 'thanks' to Alcon Laboratories, Inc. for lending me their facilities, instruction, and their dynamic personnel. It was more than a pleasure to work with the Anterior Segment Group of the clinical research and development division. Words can not express the gratitude I have for all the individuals at Alcon who welcomed me with open arms, took the time to enhance my learning experience, and shared their personal experiences with me. There would not be enough room to personally name everyone who made an impact on me during my time there, but I am sure they know who they are. Special thanks to the representatives of the various Alcon departments that gave of their time so freely to be interviewed and provide me with feedback.

To my Alcon internship mentor, Judy Vittitoe, thank you for toiling with me to make this project a success! Judy has my everlasting gratitude for creating a well-rounded internship that exposed me to many facets of clinical research. I appreciate the countless hours of instruction on the roles and responsibilities of a clinical research scientist, the numerous ideas and assistance on developing a career in clinical research. I would also like to thank my Alcon committee member, Terri Pasquine, for such a provocative thesis project idea and continuous intervention in its development. It is truly a compliment that she believed in my abilities and chose me to become a part of their team. Another sign of genuine appreciation is extended to Kym Cowart for exposing me to actual monitoring visits and providing me with industrial contacts.

My admiration also goes out to my other committee members who provided me with input on my thesis. Dr. Rouel Roque, my major professor, gave me encouragement and novel perspective. The expertise I received from Dr. Atiles, another committee member from MedTrials, Inc., was invaluable in providing me the proper guidance for an inclusive thesis. I must also express my gratitude to Dr. Simecka for his aid in the development and organization of my thesis presentation. His input helped to enhance my presentation to provide a more dynamic effect. Furthermore, I must express my appreciation to Dr. Victoria Rudick for her guidance, honesty, and reliability. From day one, she has been a pillar of strength and encouragement as I pursued this degree.

Last, but definitely not least, I must thank all of my family and close friends for their unwavering support as I completed this milestone. To my father, Danny Crout, I can never thank you enough for every sacrifice and every word of advice you have provided me throughout my life. Thanks for the spiritual foundation and constant support, both financially and emotionally, that you always gave without hesitation. Daddy, I love you and I hope that I have made you as proud of me as I have always been of you!

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CHAPTER I

INTRODUCTION

The process of developing a test article and subsequently gaining approval to market it involves a long, tedious chain of events. One of the most critical parts of the development process is the coordination and implementation of clinical trials. Clinical trials are defined as the systematic study of a test article in one or more human subjects with the intention of discovering or verifying the clinical, pharmacological, and/or pharmacodynamic effects of an investigational product while identifying any adverse reactions (13). Clinical research, which encompasses the various stages of clinical trials, is a requirement by the United States Food and Drug Administration (FDA) to provide hard, quantifiable data about the safety and efficacy of a test article's interaction within the human population.

The clinical research team

The clinical research team of a trial is central to the execution of the clinical trial and includes several disciplines and functions. Although the monitor is the primary contact regarding the progression of a study, there is an assortment of entities, both in-house at the sponsor and outside the sponsor company, involved in evaluating and validating clinical data. Departments within Alcon Research, Limited that are part of the sponsor's clinical team include clinical science, clinical data management (CDM), clinical applications, biostatistics, finance, regulatory affairs, and last, but definitely not least, product safety (PS) (fig. 1). For the purpose of the remaining pages, Alcon Research, Ltd. will be referred to as Alcon.

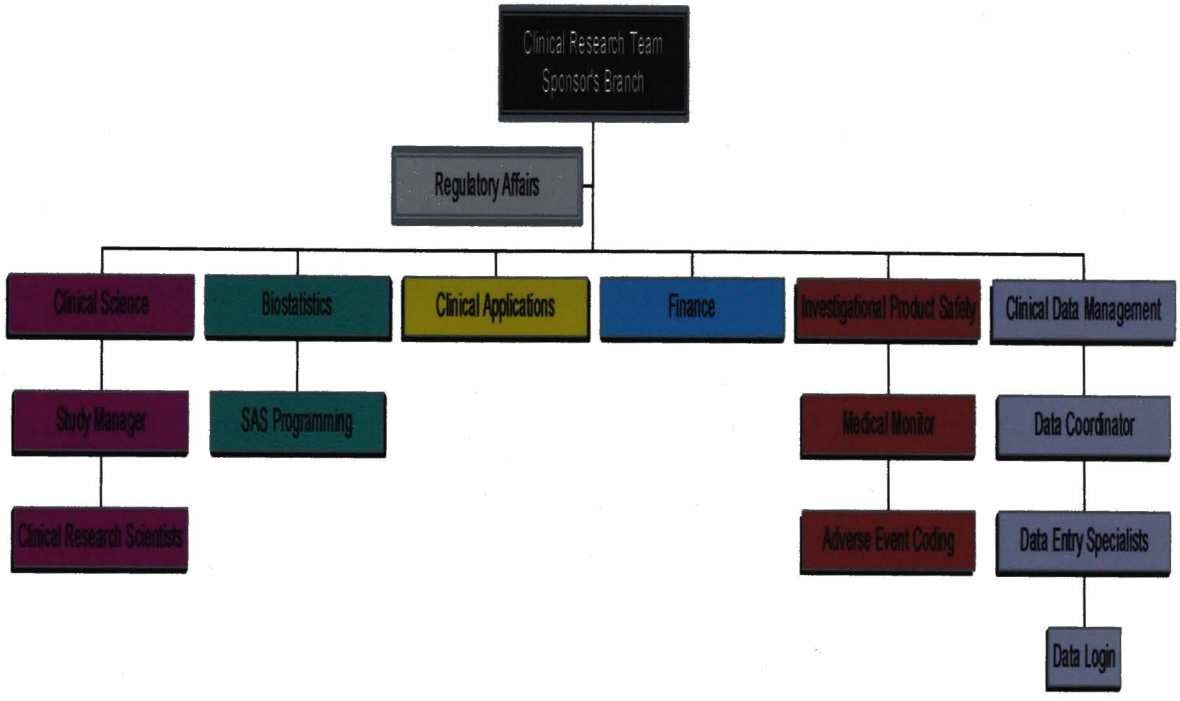


Figure I: Illustration of the organization of the clinical research team within Alcon

On the other hand, outside the company are the investigative sites, the institutional review boards (IRBs) and the regulatory agencies, such as the FDA. The investigative sites are the backbone of any study because this is where the data are generated although without contributions from each of the previously listed entities, the study would not be all embracing to the diverse issues that arise.

Roles and responsibilities of the sponsor's clinical research team

The clinical science department houses the clinical study managers/directors and the clinical research scientists (CRS), also referred to as clinical research associates (CRA) or study monitors. The study manager is a CRS that has been assigned a lead role in the overall

Roles and responsibilities of the sponsor's clinical research team

The clinical science department houses the clinical study managers/directors and the clinical research scientists (CRS), also referred to as clinical research associates (CRA) or study monitors. The study manager is a CRS that has been assigned a lead role in the overall responsibility for the conduct of a clinical investigation although many of their duties may be delegated (3,13). Responsibilities of the study manager include, but are not limited to:

- the overall design/development of the clinical protocol
- implementation of the protocol
- conduct of the study
- reporting of the study results
- preparing the protocol, case report forms (CRF), clinical investigators brochure (CIB), and the final clinical study report
- ensuring adherence to good clinical practices (GCP) and sponsor standard operating procedures (SOP)

The CRS has the responsibility of monitoring a clinical investigation and performing the day-to-day activities related to the study (3,13). Specific duties of a CRS involve the following:

- overseeing the study progress to assure adherence to timelines

- ensure compliance from investigative sites with government regulations, GCPs, SOPs, and the protocol
- ensure supplies and equipment are adequate
- ensure clinical data are verified, including adverse events
- ensure informed consent forms are adequately written and signed in accordance with regulatory guidelines
- ensure CRFs are complete, accurate, and legible
- ensure patient eligibility/recruitment is compliant with the protocol and within the specified timeframe
- ensure other related information, such as IRB correspondence, are monitored

Regulatory affairs is the interface between the sponsor and the regulatory agencies such as the FDA, and is responsible for ensuring that clinical protocols are designed to fulfill the regulatory agencies' requirements for demonstrating the efficacy and/or safety of the test article (25).

Clinical data management (CDM) is the department responsible for handling and processing of the clinical data once it is received from the investigative site. Within Alcon, there are three key branches under the overall heading of CDM: data login, data entry, and data processing (23). Data are first viewed 'in-house' by the login personnel who is responsible for stamping the pages with a date and time of arrival at sponsor,

thereby verifying receipt of the CRFs. The next stop for the original CRF data is at data entry. At this point, the individual data on the pages are transcribed from the paper form into the computer for entry into the protocol's database by a double entry system, also called a second-pass system. After passing the data entry 'checkpoint', the data reaches the data coordinator who must merge the data into the complete database. Once the data are merged, it is available for the clinical team to access it, review it, and clarify any discrepant data (23).

Clinical applications encompass the information technology personnel. Overall, Information technology (IT) is responsible for the design and validation of a database. Within this department, the clinical data entry systems that are used in the conduct of clinical trials at Alcon are developed. Additionally, they provide support with the Integrated Adverse Event System, which Product Safety uses to aid them in safety reporting.

Biostatistics is the department that provides the statistical rigor on a study for significance of the benefits and risks in order to prove, or disprove, one's hypothesis about the test article's performance. Under the heading of biostatistics are the SAS programmers. The SAS programmers are responsible for the database capabilities, including what type of data can be accepted, the maximum characters allowed in the data, and what format the data must be entered in. These individuals specify all the capabilities of a protocol's database, including pre-programmed edit checks, via specialty programs.

Finance gives the final authorization and approval of check requests based upon the overall study budget. This department is also responsible for tracking and reporting financial disclosures from investigators that report financial interest in the outcome of a trial (13).

The last department includes the medical monitors as part of the personnel that works together to evaluate and ensure the safety of the test article both during the trial and post-study. Within the product safety personnel, there is an individual responsible for coding an adverse event (AE). Coding an adverse event is simply assigning a number based on pre-established guidelines about a reaction that a study subject may have to a test article. Overall, product safety is responsible for reviewing all reported adverse events and meeting regulatory requirements of reporting such events. The medical monitor and the investigative site's PI are the primary decision-makers about a product's safety. These individuals must make a determination based on his/her medical knowledge and experience about whether the test article has caused the AE. The medical monitor determines the reasonable risks for use within the study population and whether a test article should subsequently be discontinued from development consideration.

Timeline Activities in a Clinical Trial

The general timeline of activities within a clinical trial are typically consistent despite the area of concentration. At the forefront of any study, there must be FDA clearance and IRB approval to begin the initial proceedings relating to the clinical trial (5). The first milestone of a clinical trial is the planning period. Planning includes many

activities such as meeting with the various departments that will comprise the project team, preparing the clinical protocol, requesting clinical supplies, preparing the grants to request the funding for the study, establishing timelines, deciding on investigators to conduct the protocol, and most importantly, getting the protocol approved (5). One's planning period is simply the initial internal procedures and thoughts to getting a clinical study project 'up and running'. Once the planning period has run its course, the next sequential step is the initiation of the trial. The initiation period can be described as the time that the final, approved protocol is signed to the date of the last site initiation visit. The date the final, approved protocol is signed is a good starting point for the initiation period because prior to getting a confidentiality agreement, which will protect the sponsor's intellectual rights and proprietary secrets, the study manager must have their 'road map' in place. Alcon requires the site initiation visit before shipment of the test article to the investigative site (6). Once the site is initiated and test article is shipped, technically, the study conduct has begun, thus, ending the trial's initiation period. Ideally, in tandem with the initiation period, the database is being set up, validated, and released although realistically, these events most often do not occur until after trial subjects have been enrolled (12). During trial conduct, there are major milestones used to monitor the study's progression, such as first subject enrolled, first data merged to the system, last patient exited, and ultimately, the date of database lock. Although many other milestones are noted, sponsors care most about the speed of database lock because in theory, the faster the lock, the faster the results of the study are available and the data can be submitted to the appropriate regulatory authority for approval (20).

Data Collection Tools

Two main data collection tools within clinical research are the source documents and the CRFs. The source documents are the primary reference point of all data relating to the study patient. Many things can serve as the source document, ranging from a simple note pad to a complex medical chart, as long as it is the first place that data are recorded. For clinical studies, in order to capture all the data requested by the sponsor, the source documents can be designed and formatted by the sponsor and provided to the investigator. The primary way of transmitting the data to the Sponsor Company is via the CRF. A CRF is a data collection tool designed to draw key elements of data from the study subject's medical record into a consolidated database, and hence, must be provided by the Sponsor Company (13). CRFs can be presented in either electronic form using electronic data capture (EDC) or as a paper-based hard copy (13). Data points that are solicited should be an exact replica of the information within the source documents.

CHAPTER II

BACKGROUND

Traditionally, the data generated through the implementation of clinical trials are collected solely using paper. The workflow processes regarding paper-based trials have been fine-tuned constantly over the years, recently spawning a novel process of data management at Alcon while yielding the initial process to extinction. The initial data management process will be referred to as the 'traditional data management process' and the newer process will be referred to as the 'revised data management process.' The basic problem with paper-based clinical trials is that the paper medium requires a huge processing effort, provides delayed access to the data generated and is vulnerable to human error, which ultimately decreases efficiency (15).

The General Scheme of a Paper-Based Trial's Data Management

Over the years, the process of data management with paper case report forms has been tried and perfected several times over establishing two current systems of data management in Alcon: the traditional and revised data management processes. The primary difference between the two paper-based processes is in how discrepant or illogical data is questioned. Hence, there are many identical steps within the traditional data management workflow and the revised data management workflow that must be sequential for its proper execution. Once the final protocol has been approved, the clinical data specialist and the clinical study manager collaborate to design the paper case

report form (pCRF) (4). The design is then circulated amongst the necessary personnel at the sponsor company, such as clinical science, biostatistics, information technology (IT), clinical data management (CDM), and product safety (PS). If any department believes the pCRF design needs changes, the clinical data specialist must draft another prototype for re-circulation to the various departments until the pCRFs gain everyone's approval. Once all departments agree that the pCRF design is acceptable, it is ready for production (4). Traditionally, the pCRFs are printed on two-part non-carbon reporting (NCR) paper in booklet form for each patient. Once the CRF design has been accepted, clinical applications can begin designing and setting up the actual database that will accept the data solicited by the pCRFs (12). The approved pCRFs provide a framework as to what data the database needs to be able to receive before programs can be brought to fruition. Approved pCRFs are forwarded to the investigational sites for commencement of the study conduct (fig.2a).

Within the workflow of the sites' study conduct, the personnel must document any procedures solicited by the study or routine check-ups into a medical chart, which serves as the source document (8). Following examination of the patient, the exam results are transcribed into the pCRF, usually by the study coordinator at the site. When the study monitor from the sponsor company visits the site to review the data, they will compare the data in the pCRF to the data in the source document. If there is discrepant data, the study monitor will query the data by communicating with the appropriate party verbally or in the form of written communication indicating what the problem is and requesting a resolution. The site personnel may find that the data was simply a

transcription error or an oversight of the data from the medical chart. Once all data is cleared to the study monitor's satisfaction, the investigator must review and sign the pCRFs to acknowledge the data or any corrections made to the data (7). The investigative sites must finally send their completed pCRFs to the sponsor via mail, courier, or by the CRS in order to receive payment (fig.2b). Payments are typically generated with receipt of completed CRFs. The original (top) pages of the pCRFs are sent to the sponsor and the copies remain at the site. Paper CRFs require more responsibility regarding handling, transcription, copying and storage. Case in point, when the pCRFs are sent to the sponsor by courier or mail, no one knows what takes place while the documents are in-transit. Some of the pages of pCRFs may be lost or examined by an unauthorized individual, which could jeopardize confidentiality.

When the completed pCRFs are received at Alcon, the first stop is log-in (17). These forms must be time and date-stamped to show when they were received from the site. Following log-in of the originals, the individual who logs the pages produces two to three copies of each page for distribution to the entities needing them (8). For instance, regular pCRF pages would typically only be copied for clinical science and CDM, whereas, AE forms would have to be copied for these two departments, as well as product safety (fig.2c).

CDM uses a system of double data entry to a master clinical database to serve as a checkpoint tool (17). In theory, the second-pass system should eliminate the occurrence of data entry errors by having the data inputted by two individuals who are blinded to

each other and who enter the data at different times (fig.2c). During the first-pass, the individual will go through the pCRFs and those having illegible handwriting or illogical data will be flagged 'unenterable' to be forwarded back to clinical science. As noted in a case study, twelve-percent of sites within a study have illegible pCRFs (15). The illegibility of these documents will inevitably slow the process of entering the data because of the extra time it will take to clarify the data due to the fact that handwriting can not be left to chance or assumptions. Meanwhile, the first individual will enter all data fields from the acceptable pCRFs into the computer software and then return them to the data coordinator that will then forward them on to the second individual in the double entry process. The same data is entered into the computer again during the second-pass to key verify that the data is read and entered consistently. After entry into the computer system, the data is compared to locate any discrepancies that may have inadvertently occurred during the chain of data entry's events (8). If, the data entry workforce is not large enough, bottlenecks in the process may delay data entry for days or weeks. On average for paper-based trials, it takes 125 days to enter and merge 89% of the data (28). Merging the data means that any newly inputted data will be combined with previous data into a consolidated database specific for the protocol.

When the data are compiled into the protocol's database, also referred to as merging the data, the CRS may retrieve the data via a program called I-Review (8). I-Review is data management software that allows clinical science or any other department to generate reports and query any questionable data. If the information in the database is consistent with the data on the pCRF and it is logical, a successful round of data

management is complete. However, if there are discrepancies or illogical data, the discrepant information must be clarified by the clinical team and the investigative site. Subsequently, the most time-consuming application of clinical trials that uses pCRFs is the verification of the data to ensure 'clean data' (i.e. correct data), which takes a mean of 149 days to completely clean the database (28). Due to this extended period of time to get the queries resolved, a survey revealed that approximately 11% of sites with data query forms resulting in 'clean data' are not source verified by the sponsor's monitor. On the other hand, another 18% of the sites simply do not make the required correction (15).

With paper-based trials, product safety receives notification of the AEs only after the forms have been logged and entered through data management. Upon log-in and entry of an AE by data management, a medical monitor form is automatically generated (10,17,23). The medical monitor form will go to product safety for coding of the adverse event and to the medical monitor for his/her assessment regarding causality. Coding of an adverse event entails reviewing the symptoms and placing them in a category primarily based on body systems. After categorizing the adverse event, there will be a universal number using specific software to identify that body system's reaction. Upon completion of the two parts on the medical monitor form, the form will be sent back to data management to be logged in once more, entered, and merged with the database (fig.2d). It is at the query workflow that one begins to see the marked difference between the traditional data management process and the revised data management process.

Query Process within the Traditional Data Management's Workflow

The query process for the traditional data management workflow entails many steps that are implemented either before or after the data is entered into the protocol's database. First and foremost, CDM produces photocopies of the pCRFs as a means for the CRS to review and begin clarifying the data (8). The goal of distributing photocopies is to combat the possibly significant lag period that could occur between the time the data first comes in-house to the time it is put into the database for review and analysis, hence they are often termed 'working copies.' After the photocopies have been made, the original pCRF goes to Archives, where all the authentic data are stored and available for regulatory agencies during sponsor audits (17). The CDM workflow continues by passing the photocopies on to the data entry personnel.

Within the traditional query process, the study monitor will contact the site by phone, fax, or e-mail. If the correction can be made by clinical, the CRS will make it in red ink on the working copy so that data management can quickly recognize it as a modification (8,23). The corrected working copy is then sent back to data management where the process of log-in, entry, and merging repeats itself. In addition, the study monitor must still notify the site of the data change so that they may make the same correction in their CRF copy and in the source document, if needed (8,17). Likewise, a modification that can only be done by the site must be sent to the site for correction. Once the correction is made, the copied pCRF will be sent back to the study monitor at Alcon. Again, the study monitor will need to make the correction on the 'working copy' in red

ink. Once the discrepancy is resolved, the study monitor must confirm the correction with the site to ensure consistency (fig.2e).

Query Process within the Revised Data Management's Workflow

From the side of the revised data management process, the query process appears less strenuous. Prior to the start of study using this new process, clinical science, data management, biostatistics, and other relevant parties will sit down and decide on edit check specifications and allowable self-evident corrections (10). The self-evident corrections must be pre-determined modifications to the data that are documented prior to study start (2). Edit check specifications is a document that lists a question or statement to the database for verification of an item to ensure validity and accuracy of the reported value (2). There are three types of queries that stem from the early meeting: the OK query, the COR query, and the SEND query.

An OK query is one in which a particular discrepancy is raised for review, but supporting information elsewhere indicates the response is correct (2).

A COR query stands for 'correction needed.' The COR queries are due to data entry errors or corrections that apply to discrepant data identified by a rule in the self-evident correction document that will allow for the correction to be made by clinical data management (CDM) personnel (2). COR queries are commonly generated from numbers that are transposed or dates that are illogical. As with the earlier example, if the date on the CRF reads January 2002, but the study did not begin until November 2002, it is obvious that the date should be January 2003. Hence, data management can make that

correction to the year if that is something that was previously identified as a possible problem.

A SEND query is an edit check that is triggered during data entry that requires the pCRF to be sent outside of the data management department. When CDM cannot resolve the query based on the available information provided in the pCRFs, these queries would be a 'SEND' for clinical science to review and resolve with the site (2). Once the problem is forwarded to clinical, the study monitor must evaluate if that is a problem they can clear up without the site's input or if the query must be sent out to the investigator to handle directly.

The SEND and COR queries do not obliterate the possibility of a MANUAL query, however MANUAL queries in this process may duplicate efforts. Because the pre-programmed edit checks are not activated until data entry occurs, if data entry is backed up, the monitor may see data needing correction and manually query the site. However, once the data are inputted, an identical query will be generated, regardless if it was previously identified, unless the MANUAL query is answered and forwarded to data management before data entry begins. Generally speaking, the workflow of this process is sequential for the most part, however, when data are being entered, the database is being 'cleaned' at the same time to clarify or eliminate any incorrect data while validating the other data. With the exception of the COR query, all query types must be clarified on a data clarification form (DCF) (fig.2f).

Storage of Paper CRFs

Regarding paper CRF storage, imagine companies, like Alcon Research, Ltd., that have been involved with clinical trials for numerous years. The stacks and stacks of pCRFs that these established companies in the field of clinical research have to store is surreal, which inadvertently compounds the financial responsibilities of sponsor companies because they must pay for adequate, secure storage of this sensitive information. The complexities of paper-based trials extend far beyond the previously mentioned points; however, 96% of clinical trials are still using a paper-and-pen approach to collecting data (4). Why, you ask? The fear of the unknown is the simplest answer, but within this response the particulars are far more complex.

History and Evolution of EDC

EDC has been available in some form or another for almost two decades although the electronic CRF tools have only been available for approximately ten years (7,10). The former approaches to this electronic process, EDC, which included fax, optical character recognition, intelligent character recognition, interactive voice response, and speech recognition fell short of their goal because there were no provisions made to implement quality processes of data collection and cleaning (11). Due to the disappointments of these earlier advances, most companies overlooked the claim that the EDC trial time would be reduced because the shortcomings overshadowed the benefits. The first spin-off of the earlier options was termed remote data entry. Remote data entry was a process where the data entry application was developed at the sponsor company and then loaded onto a laptop computer (14). The laptop computer was then sent out to the investigative

site for the study coordinator to enter the data and following the last data entry, the laptop would be sent back to the sponsor. Although remote data entry can be used for any clinical trial, it typically works best when only a limited number of sites are used (14). Still, after uphill improvements to the technology, only a 'mere four-percent' of clinical trials within ten of the top fifteen pharmaceutical companies currently utilizes it (4). There are numerous culprits that account for the sluggish uptake of EDC. The first reason is rooted in the fact that several large pharmaceutical companies are traditionally quite conservative and naturally want to evaluate the best system before employing a relatively new concept such as EDC on a broad scale. Secondly, sponsors have concrete concerns regarding the security of data. Last but not least, many of the solutions that are available lack a direct link to the sponsor's in-house clinical data management systems, making it difficult to run paper-based and EDC-based parts of a trial alongside each other (12). This last point is the most important aspect of choosing a vendor to initiate a pilot trial, but the software must still be readily accepted by the initial users which will be the personnel at the investigator site and the data monitors. As stated in a report addressing the user-friendliness of an EDC software, 'EDC should help facilitate the site's responsibilities for the study conduct, but should not dominate the data collection routine because workload reduction is the true value of EDC to the sites and data monitors' (9). When there is inadequate training or help with the software, the perceived ease of EDC will be totally overshadowed by the user's frustration with the system. There are two main ways in which EDC software can be applied, including via a web-enabled system or a web-based system. A web-enabled system is not generally accepted as being the most efficient way

to conduct an electronic-based trial. Studies using the web-enabled approach require that software be loaded onto the local computer, which would need to be compatible with the computer system (15). The software can be used through the web so that newly entered data may be 'uploaded' into the database. Uploading refers to the process of sending the data through the web, whereas, the actual entry of the data is performed offline (not connected to the web). The current description of a web-based EDC system is one in which the data entry application is developed and is accessible via a web browser using an internet connection which consequently allows for entry to be performed at investigator sites using browser-based software (14). A 'true web-based' system is completely dependent upon the available technology of the Internet in order to function. The speed at which the web-based system operates is contingent not upon the Internet availability, but upon the type of Internet connection the individual sites and sponsor company uses. For instance, an individual that uses a cable modem versus a telephone modem will undoubtedly have a quicker response time navigating within the Internet.

Workflow of an Electronic-Based Trial Using EDC

Before adopting the new technology involving EDC, it has been an accepted practice within the pharmaceutical industry to conduct a 'pilot' project, or 'trial run.' Although EDC pilot projects have been rampant for several years, 'the pharmaceutical industry still sees EDC as something new.' Pilot projects educate and demonstrate at the same time. It is during a pilot project that the workflow of a new process is learned. During the course of a pilot project using EDC, the staff must learn to accept new roles that may require new skills. Bunn states that personnel involved in programming,

designing, and building an eCRF now need a much greater understanding of how the scientific staff actually work at the investigator site when using EDC (6). In addition, monitors have to become evangelists of EDC to help persuade site staff to make the change from paper to electronic data entry (6). This new process still keeps many of the same elements of a paper-based trial, such as the design stage of eCRFs and the database, the sites' study conduct, the in-house study conduct, and the product safety process.

A major learning curve associated with the implementation of EDC is a new custom-made regulation regarding electronic records and signatures, United States Code of Federal Regulations Title 21 Part 11. The scope of the stated regulation applies to "..records in electronic form that are created, modified, maintained, archived, retrieved or transmitted, under any records requirement set forth in agency regulations. This part also applies to electronic records submitted to the agency under requirements of the Food, Drug and Cosmetic Act... even if such records are not specifically identified in agency regulations (8)." Despite the written manuscript submitted by the FDA, the industry continues to grapple with the interpretation of this regulation. However, the interpretation of this law is 'Alconized' to demand validation of a system to ensure accuracy, reliability, consistent performance, and the ability to discern invalid or altered records (1). A validated system per Alcon's interpretation must be able to 1) generate accurate and complete copies in both human readable and electronic form 2) protect the records throughout their retention period and 3) limit access (1). This expectation demands that any designated site or sponsor personnel with access to the data have a personal username and unique password. The investigator must also have a personal username and unique

password to fulfill his/her duties because his/her electronic signature is still required on all eCRFs following the last entry or modification to data.

Before an eCRF can be designed, there must still be an approved, final protocol in place. Once the eCRF is designed, including the possible layout of data fields on a computer screen, the sponsor's clinical team personnel, such as biostatistics, clinical science, product safety, information technology, and data management must review the prototype (11). If there are changes recommended, the review cycle continues until everyone has incorporated changes and accepts the design. Otherwise, the database is designed and set up for testing and edit check programming (12). The last step in the design stage is the actual testing of edit checks using artificial data (fig.2g).

At the investigative site, the study coordinators must have access to a personal computer (PC) to participate in an electronic-based trial. The study site personnel, usually the investigator, will conduct an exam as usual and document the procedures into the source document (8). The study coordinator, investigator, or other designated personnel must then enter the data into the eCRF, which is accessible via a standard Internet browser. As soon as the data are entered, the site personnel will simultaneously engage in the cleaning of the data they enter. Because edit checks have been programmed into the database, anyone entering data will be notified if a query exists immediately (24,28). The program will instantaneously generate a pop-up message letting the user know if there is a problem with the data, such as the data being out-of-range, incomplete, or otherwise. The ability to continuously monitor data allows the study monitor to manually generate a query if he/she recognizes something questionable by simply typing a note into the eCRF

from his/her personal computer (21,28). Once the query is placed into the database, the site may go in and answer the query on the spot without the need for a CRS to take a monitoring visit directly to the site (fig.2h).

In theory, the data and audit trail are immediately available to anyone in the sponsor's clinical team with access to the database (14,21). Real-time notification of the data also enhances the workflow of product safety and the medical monitors. When the site enters an AE, product safety receives an e-mail notification of the event upon the site personnel's submission of the electronic form. The AE coder and the medical monitor can immediately address the AE that requires attention and a response. The AE can be coded on the computer and assessed by the medical monitor as to the causality and relationship to the test article within minutes in no sequential order (fig.2i).

Because EDC provides continuous access to the data for monitoring, less monitoring trips are expected. However, when a trip is taken to the site, the query process is still done by inputting the discrepancy into the database from a PC. Once all the data are acceptable and there are no more queries, computer-generated or study monitor-generated, the CRS will 'freeze' the eCRF with a few clicks from the computer, meaning that none of the data within that frozen eCRF can be changed by the site. Product safety reviews all the data when the clinical science department decides that the study procedures are complete and all outstanding issues and queries at the site are resolved (9). If product safety finds a problem with data anywhere within the electronic casebook, the study's monitor must unfreeze the eCRF and query the discrepancy online. The site must go back to the database for the study and address the query. Conversely, if product safety

reviews the data and everything looks appropriate, CDM is sanctioned by clinical science to lock the eCRFs so that neither the study monitor nor the site can change the data (fig.2j).

CHAPTER II ILLUSTRATIONS

PAPER-BASED WORKFLOW

ELECTRONIC-BASED WORKFLOW

Fig. 2a

Paper-Based Trials: Alcon's CRF Design Process

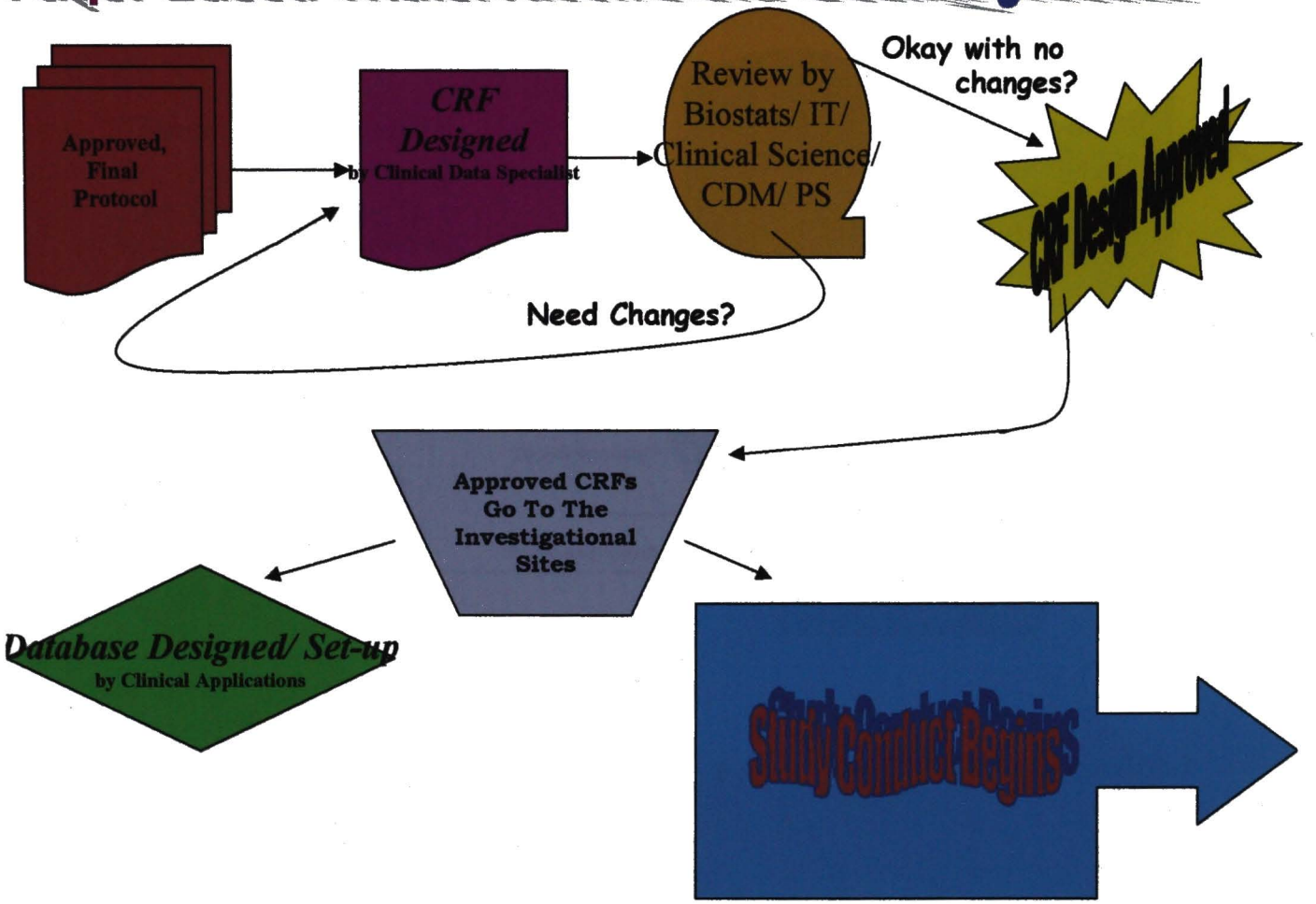


Fig. 2b

Paper-Based System: Site's Study Conduct

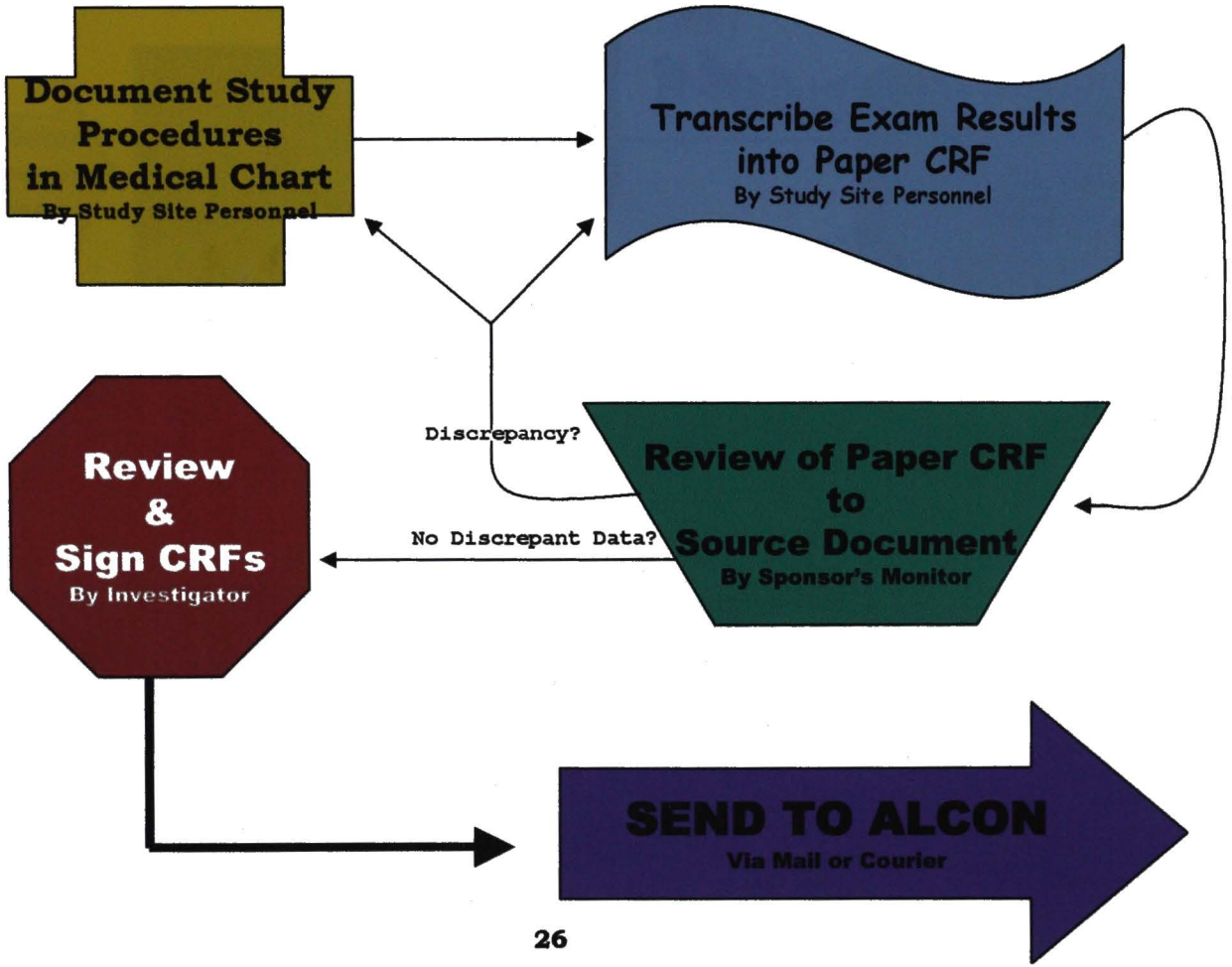


Fig. 2c

Paper-Based System: Alcon's General In-House Scheme

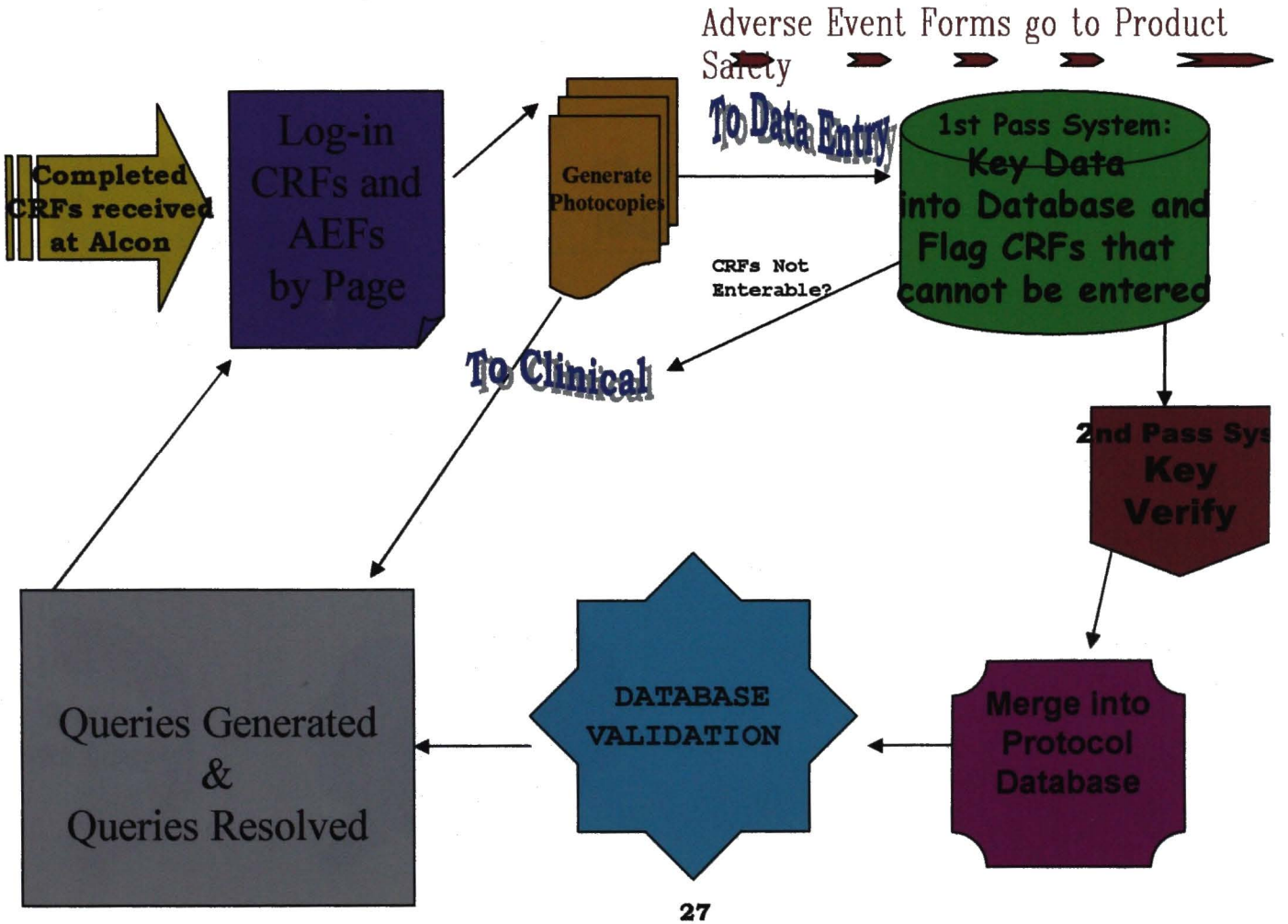


Fig. 2d

Paper-Based System: Alcon's Product Safety Process

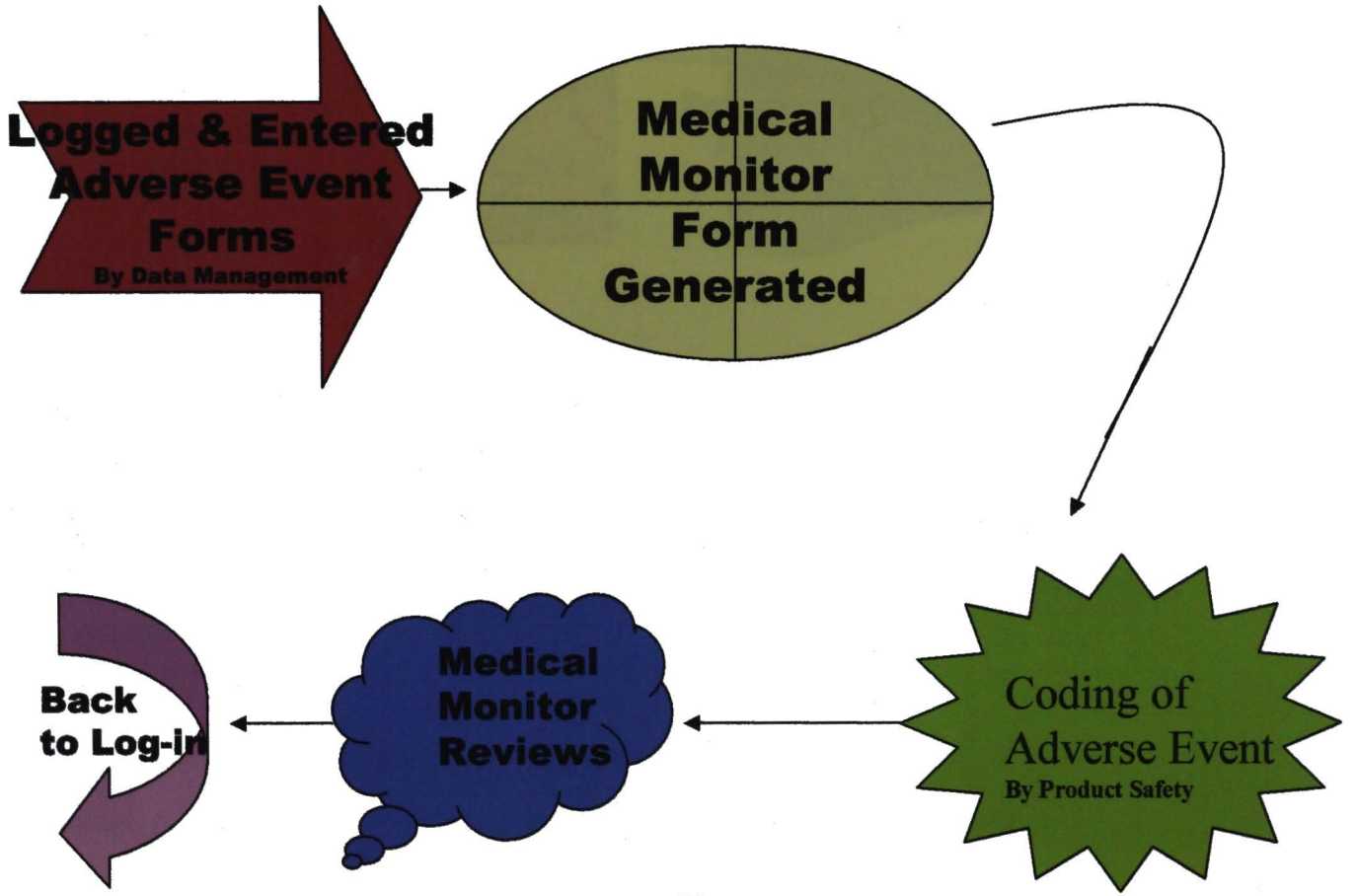


Fig. 2e

Paper-Based System: Alcon's Traditional Query Process

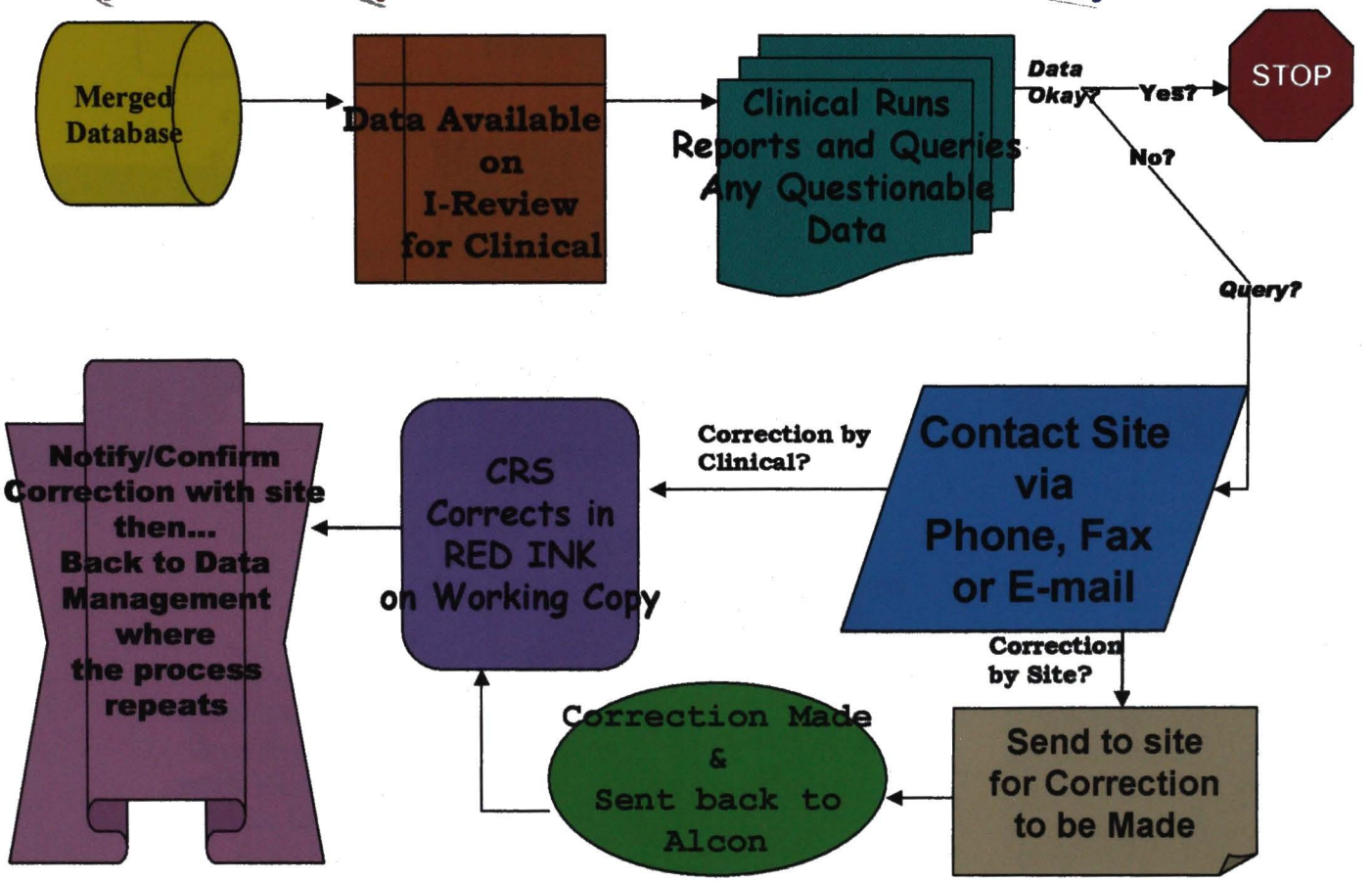


Fig. 2f

Paper-Based System: Alcon's Revised Query Process

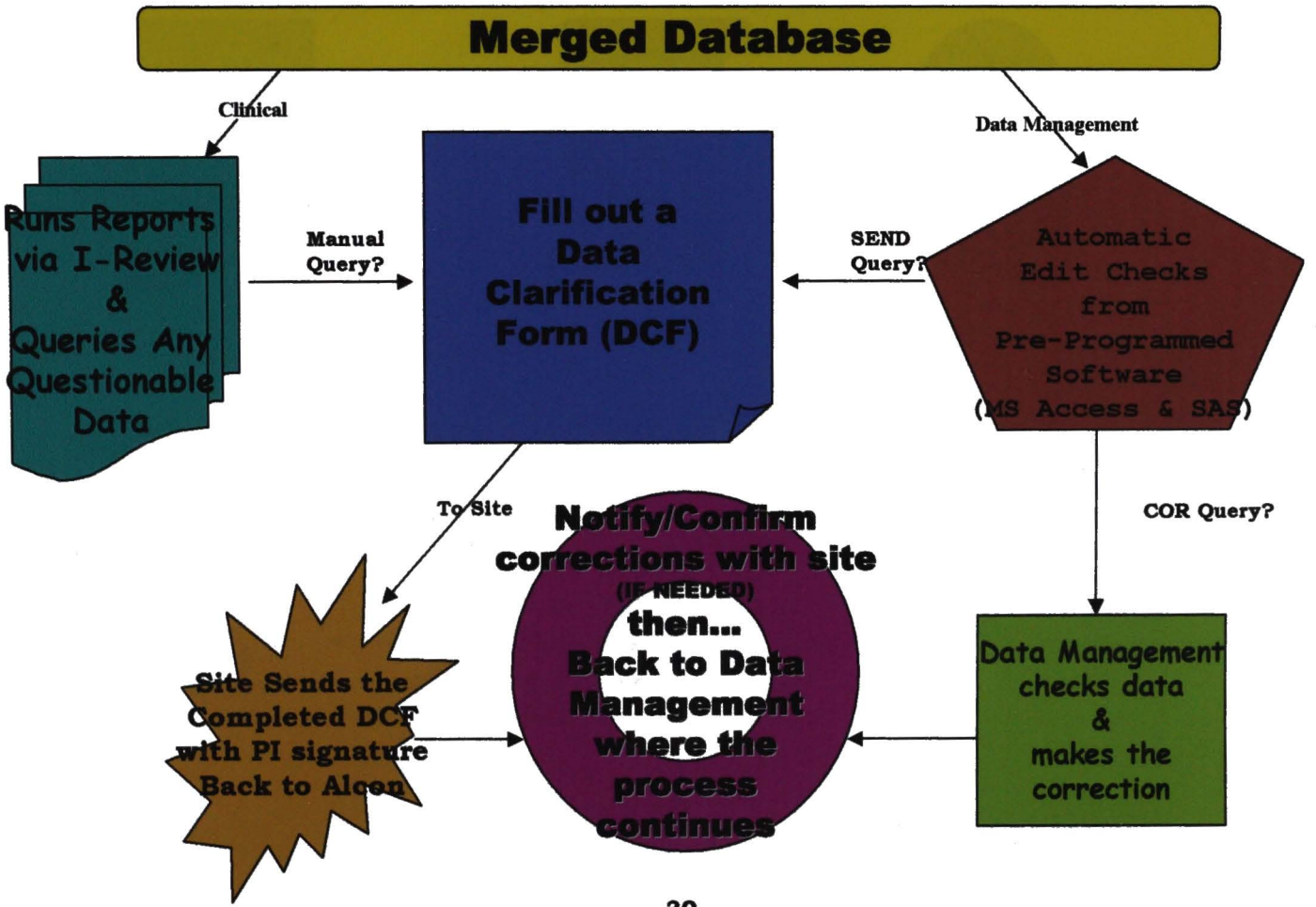


Fig. 2g

Electronic -Based Trials: eCRF Design Process

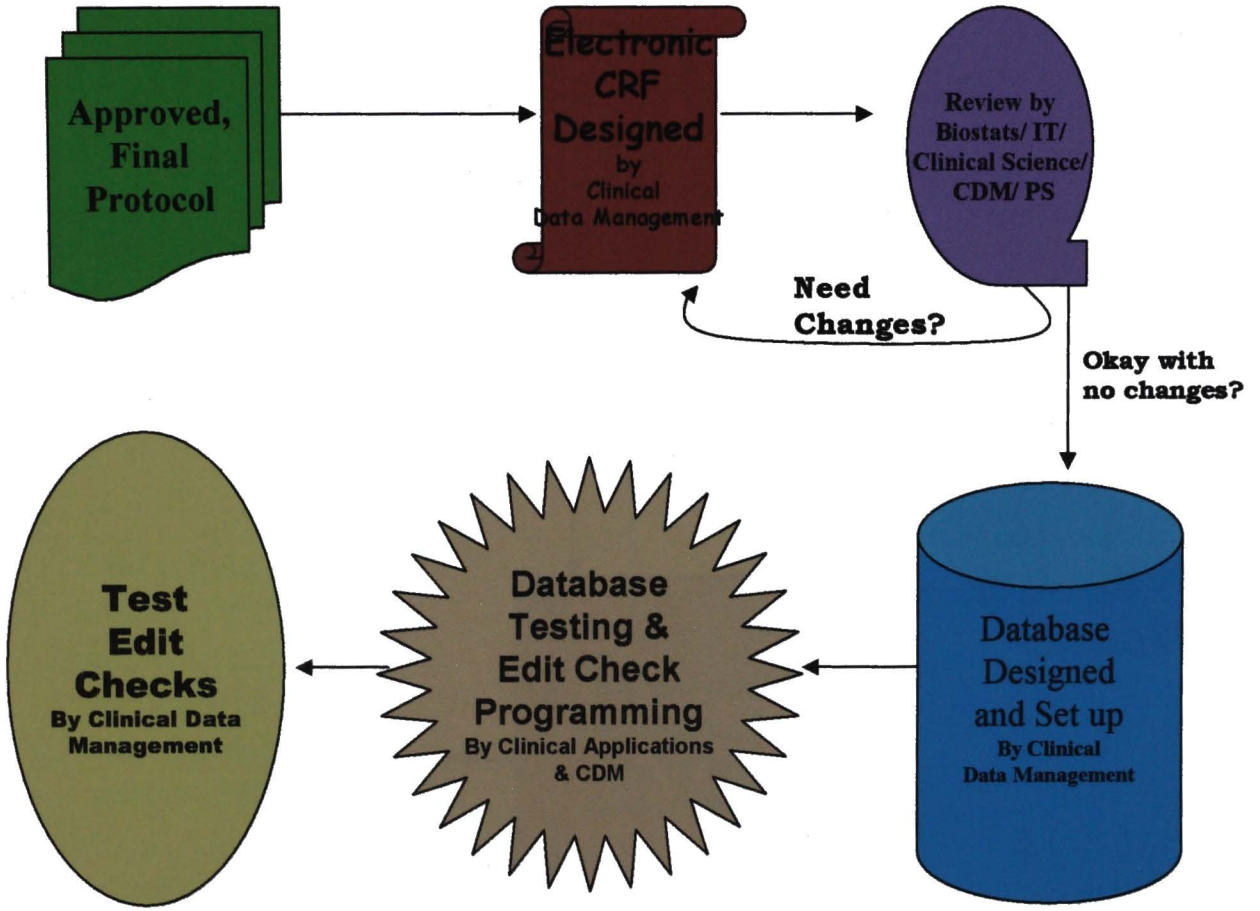


Fig. 2h

Electronic-Based System: Site's Study Conduct

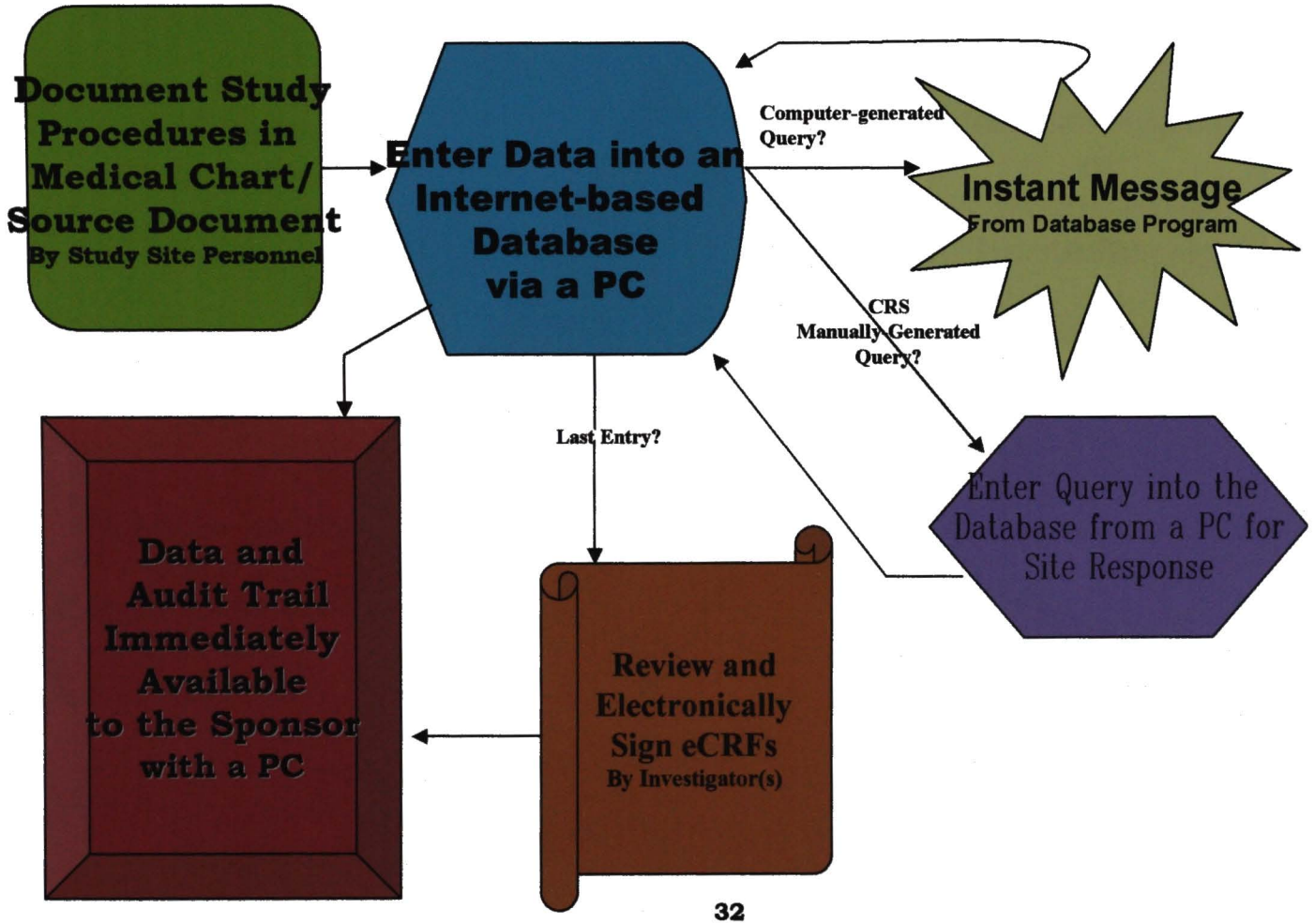


Fig. 2i

Electronic-Based Trials: Alcon's Product Safety Process

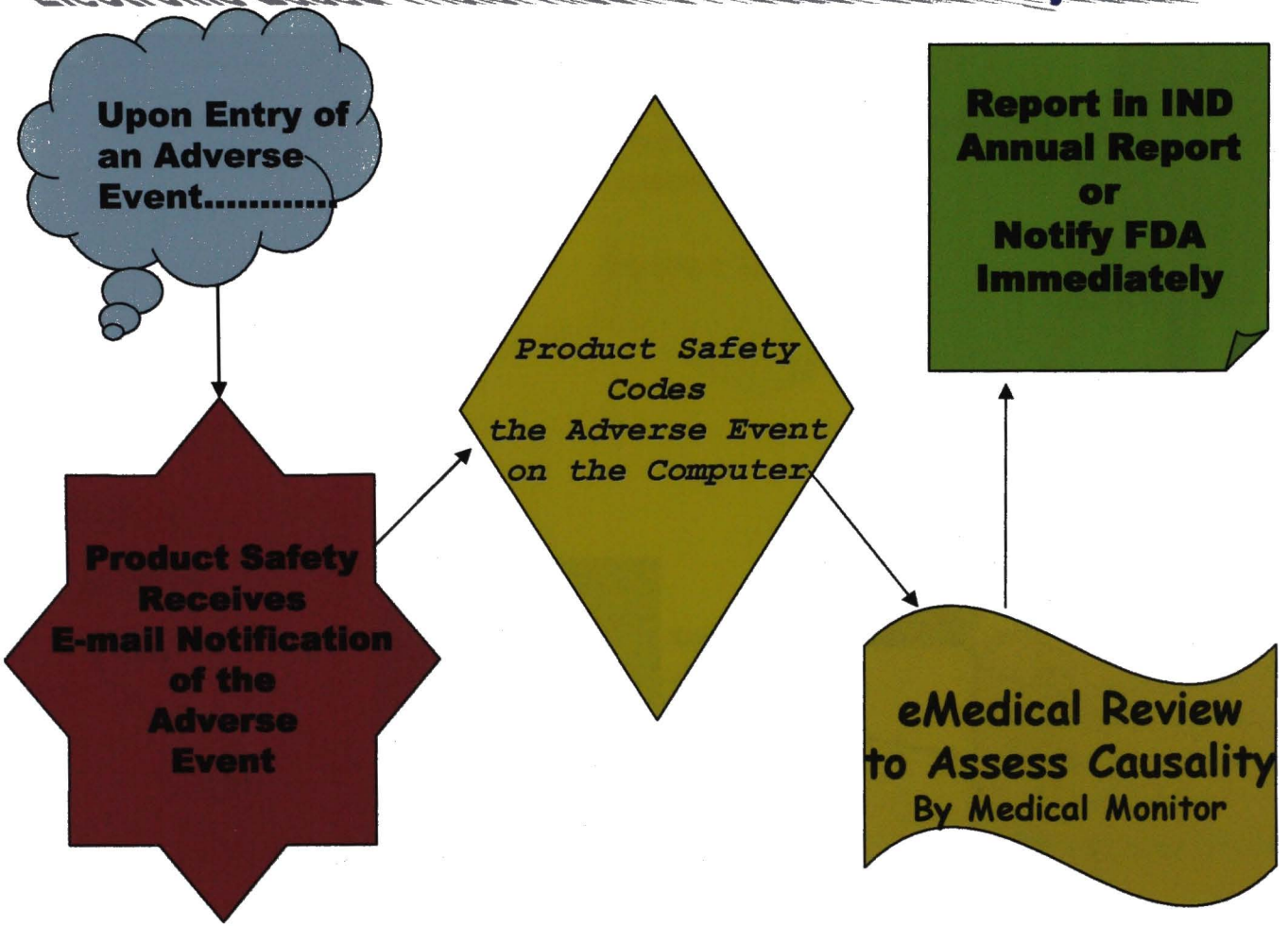
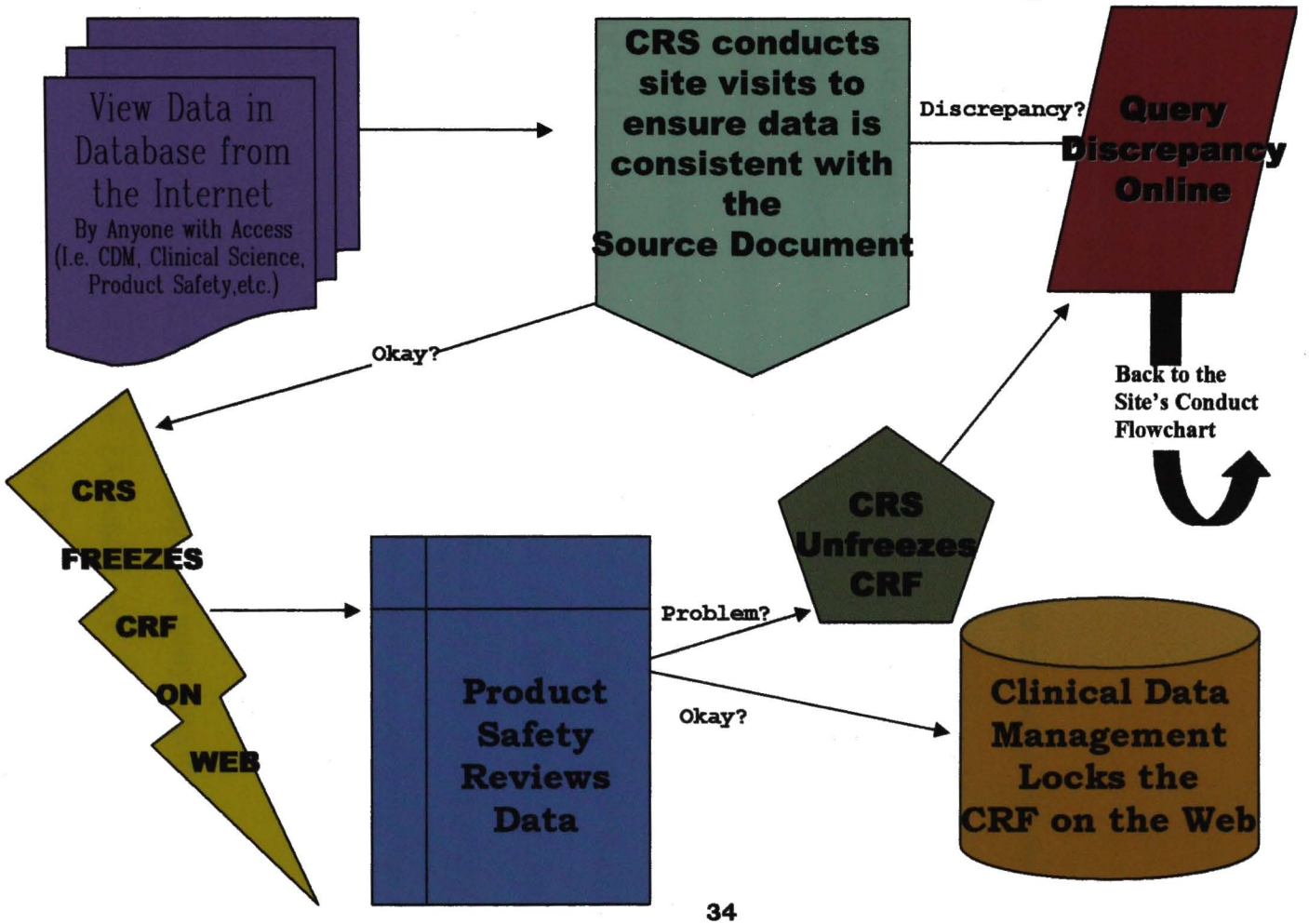


Fig. 2j

Electronic-Based Trials: Alcon's In-House Study Conduct



CHAPTER III

METHODOLOGY

Thesis Objectives and Projections

My thesis project was based on a five-month clinical internship with the anterior segment clinical division at Alcon Laboratories, Inc. The internship practicum was designed to give students supervised, practical application of the theoretical principles of Clinical Research Management that was learned during classroom instruction. During this five-month internship, I gained valuable on-the-job training in addition to the data needed for my project's topic. Based on the literature reviewed about electronic data capture (EDC), I formulated my hypothesis that the total number of queries would be less than with paper-based trials. Furthermore, although this was Alcon's first time using EDC in the conduct of a trial, I believed that all queries would be resolved quicker, which would add to a more timely and efficient database lock. It was also my belief that study coordinators would positively accept EDC technologies.

On-The-Job Training

During the course of the internship, I engaged in many activities far beyond the simplistic on-the-job training experience (Appendix A). I performed observational interim site monitoring and closeout visits for both paper-based and electronic-based ophthalmic clinical trials, which included source document review and comparison to an eCRF or pCRF, drug accountability and reconciliation, and regulatory binder review.

Monitoring also further familiarized me with the regulatory documents required for an U.S. conducted trial. My duties for my thesis project included a review of historical timelines and tasks for previous and current data management processes, as well as a pilot electronic data capture system, to provide a comparison for future applications within Alcon.

Source of Evaluation

For this project, I used three separate clinical studies as a foundation for the evaluation of data management options. From the available three options of data management, each study used a different process to gather and manage data from the study's conduct. Two studies were related to dry eye syndrome and the third study was related to glaucoma, but all had a patient population of approximately 100 subjects. Each of the three studies examined only one drug during the second phase of clinical trials. Two of the studies were evaluated by taking a retrospective look at the databases and the working files. The evaluation of the traditional data management process took considerable effort to manually hunt through the working copy files to track the date and time stamps to get the query metrics. Being that the queries for the revised data management process is a function of the computer software, gathering the query metrics was very straightforward. The clinical study utilizing EDC has only recently been completed. Specific metrics related to the EDC study had to come from Phase Forward, the EDC system's vendor, as a custom report that would be generated as a result of programs written to achieve one's desired parameter. To get a visual picture of the

duration of the entire study conduct, the study milestones were put on a timeline that was constructed to depict each of the data management alternatives.

At the start of this project, I did an extensive literature review on EDC. I also spoke with members of the process improvement team (PIT) that conducted the initial research on EDC before the pilot began. The interaction with the PIT members gave me the foundation I needed to understand Alcon's approach to begin this revolutionary idea.

Development and Distribution of a Survey

In order to gain the information needed for my project, one of my tasks was to develop and distribute a survey consisting of close-ended and open-ended questions to assess the study coordinators' views on EDC. Within this study, there were ten sites, which gave me a sample size of ten coordinator surveys. Specifically, the survey was developed to ascertain the following: study coordinator's overall experience and knowledge level within the field of clinical research, their general knowledge of EDC, their perceptions of positive or negative characteristics, as well as recommendations for improving the current EDC system, and their foresight for future applications of EDC on a wide scale. In order to focus the study coordinators' assessments, the five-page survey was broken down into four separate sections: I. Demographic Data, II. Experience/Familiarity with EDC, III. Current Perceptions of EDC in relation to this study, and IV. Future Promise of EDC (Appendix B). There are two ways that the survey was distributed to the study coordinators. They received a hard copy of the survey, which was mailed to them, along with an electronic version of the survey, which I developed as

a form to e-mail to them. These results were either faxed or e-mailed back to me and I used them to evaluate EDC from the standpoint of a study coordinator.

Interviews with the Sponsor's Clinical Team

Another task to assess the change in staff roles and project the impact of EDC on Alcon's business practices that I executed was to interview the sponsor's clinical team members on this project. I interviewed the senior CRS for this study in clinical science, clinical data management personnel, clinical applications personnel, product safety personnel, biostatistics personnel, and regulatory affairs personnel to get their comments, opinions, and projections about EDC and Alcon's paper-based data management processes. A list of questions was developed to ask specific questions related to the advantages and disadvantages of the data management processes, their process preference, and the impact of EDC on their duties (Appendix C). As an added bonus, the Alcon personnel that worked on the pilot project of EDC was afforded the time to give me their recommendations and projections regarding this new option for the company.

CHAPTER IV

RESULTS

Impact on the Drug Development Timelines

The manner in which the sponsor's goal is achieved is the greatest impetus for a company to explore new possibilities. A couple of major questions that come into play when evaluating new possibilities are 1) Will it help the company get the test article to market sooner? and 2) Will it provide reliable data to ensure efficacy and safety of the product? Because 'time is money', one of the most telling signs of a viable process within a company is the impact that it makes on reducing the time to get a product to market. One of the driving principles and theories behind EDC is that it allows for reduction in the drug development timeline based on the timeliness of database lock. Interestingly enough, in this EDC pilot, EDC did not have as great an impact on decreasing the drug development timeline as projected. On the surface, comparisons of all the available processes here at Alcon indicates that the revised data management process is most efficient with respect to decreasing the days between study conduct commencement when the final protocol is signed and trial completion upon database lock. The timeline depicting the revised data management workflow shows 110 days until database lock, which greatly exceeds the EDC timeline showing a total of 280 days for study completion, however, the traditional timeline comes in a close second taking only 135 days from start to finish (figs.4a, 4b,& 4c). Preliminary reviews of these numbers demand a closer look at the data. When the entire timeline is segmented by periods, the numbers

illustrate a more inclusive explanation. The overall drug development timeline was divided into smaller increments based on the initiation period, the observation period, the patient enrollment period and the closing period. The boundaries of the initiation period has previously been stated to be the time from when the final protocol is signed to the date of the last site's initiation. This period of enrolling sites to gain study subjects took longer to complete for the EDC pilot than any of the other two trials (fig.4d). Time used to complete the initiation period for the EDC trial spanned almost 4 months which was much longer than with the trials using the traditional and revised data management processes. With the EDC pilot, the last site was not initiated to enroll patients until April 1st, almost four (4) months after the final protocol was signed. In comparison, the paper-based trial using the traditional process only had a lapse of a little over a month although the trial under the auspice of the revised process had the shortest time lapse with only fifteen (15) days for its initiation period. The observation period entails the time from the patient's first visit to the patient's last visit. Within the EDC trial, the observation period was two times longer than the trial using the revised data management process and three times longer than the traditionally conducted study (fig.4d). Additionally, the patient enrollment period is defined as the total time that all patients, from the first patient's first visit to last patient's last visit, were enrolled and participating in the study. The patient enrollment period in the EDC trial had the longest duration spanning a total of 228 days (fig.4d). Once the last patient has had their last visit, closing procedures are implemented beginning the process of eliminating any outstanding issues with the data in the database so that it may be locked for complete analysis. The closing period did not show a marked

difference like the numbers from the initiation and observation periods. Among the three processes, the traditional CDM process allowed the study to be locked quickest taking only eleven days from the last patient visit to the date the database was locked. EDC consumed 29 days of the total timeline in preparation for database lock, which is only eight days longer than what was required to lock the database that used the revised CDM process (fig.4d). Compounded by the conflicting internal processes, there were many other factors beyond Alcon's control that contributed to EDC's extended drug development timeline, such as the delay in releasing the database and the edit checks.

Query Metrics

The paper-based trials evaluated in this project had a dramatically lower total amount of queries that were addressed during the study conduct compared to the 2,113 total queries handled during the EDC pilot. Each trial using a paper-based process kept the total number of queries below 150 with the revised data management workflow totaling only 119 modifications. Alternatively, the traditional process of data management had a slightly greater number of total queries at 141. Although the study using the traditional process of data management had the greatest total number of queries among the two paper-based trials, the traditional data management process had the shortest overall time from the date of the first query resolved to the date of the last query resolved (fig.4c). Using the traditional process of data management, there was only a lapse of ten (10) days between the resolution of the first query and the resolution of the last query, whereas the other paper-based process coursed 31 days for the same interval (figs.4a&4c). However, the most obvious variance was with the EDC-based trial, which

consumed 114 days from when the first query was resolved to when its last query was complete (fig.4b). These results suggest that the traditional data management process resolved queries most quickly out of the three available options, which should indirectly ensure its database to lock quickest. However oddly enough, the database was not locked quicker with the traditional data management process. As stated before, the revised data management process allowed the database to be locked about 25 days sooner than the database using the traditional workflow.

Assessment of Data Reliability with EDC

Considering that the reliability of data is contingent upon the actions of investigative sites and their project team during the conduct of a study, it seems logical to assess their opinions about the efficiency of the clinical trial. Overall, 40% of the study coordinators surveyed disagreed that EDC helped the conduct of the trial to be more efficient while only 30% agreed that the clinical trial was more efficient with EDC compared to paper-based trials (fig.4e). The three remaining study coordinators were divided between a neutral opinion and total disagreement about the statement. Two of the coordinators (20%) were neutral with the statement that the EDC increased the trial's efficiency communicating that they did not see any obvious impact, good nor bad, but one study coordinator blatantly disagreed indicating that there was an unfavorable impact (fig.4e). Although EDC delivers both system-generated and CRS-generated queries, an equal number of study coordinators have the opinion that overall the amounts of queries are reduced versus not being reduced (fig.4f). Consequently, there was a divided response when asked if EDC reduced follow-up questions from the sponsor. Forty percent (40%)

of study coordinators neither disagreed nor agreed that the follow-up questions were reduced. Likewise, another 40% agreed that the questions were reduced, leaving only 20% discrepant with the fact that follow-up questions from the sponsor was reduced due to the EDC system (fig.4g). At the conclusion of the clinical trial, 40% concurred that EDC ensured more accurate data from the sites, but five (5) of the ten (10) study coordinators surveyed were neutral and could not agree that EDC actually did make the data more accurate (fig.4h).

Impact of EDC on the Study Coordinators at the Investigative Sites

Because EDC has long been examined from the sponsor company's stance, study coordinators have had little, if any input in the feasibility of this technological revolution. Many would wonder how any individual could dislike technology, but with the steady rise of computer-use and elimination of people-driven jobs, it is not astounding for one not to favor advancing knowledge. However, when the technology does not eradicate one's job, but instead ameliorates their duties, I alleged that all its progeny, including EDC, would be positively accepted. Based on the fact that nine of the ten study coordinators recommend that Alcon and other companies use EDC in the conduct of clinical trials, it appears that my hypothesis was correct (fig.4i). Theoretically, EDC offers many benefits that should place it in a class of its own. Based on the different literature reviewed, some of the commonly desired benefits are 1) a reduction in the amount of coordinator involvement 2) cleaner data 3) fewer queries 4) fewer follow-up questions from the sponsor and 5) a reduction in the time the CRS spends at the investigative site (3,4). Among the ten study coordinators that were involved in Alcon's

pilot of EDC, six (60%) of them had seven or more years of clinical research experience (fig.4j). Although this was Alcon's first time using EDC, 70% of the coordinators had previous experience with EDC in the conduct of another clinical trial for some other company (fig.4k). Of the seven polled study coordinators, who previously used EDC, 57% have worked with EDC on clinical studies three or more times (fig.4l). These numbers clearly demonstrate that the results of this survey are formulated from experience and comparative perceptions. The study coordinators were allowed to check as many of the expected benefits that they perceived EDC would bring to the trial conduct. Out of the five previously listed theoretical benefits, eight study coordinators believed that the data would be cleaner with EDC, while the next popular benefit expected was fewer queries claiming seven picks (fig.4m). Prior to study start when the coordinators were asked if they believed 'EDC would make their duties easier and more timely,' 40% agreed that it would, whereas, only two (20%) thought that the technology would make their duties more complex, in turn, slowing them down. Despite the fact that Alcon was using EDC for the first time, four of the ten coordinators did not believe that their duties would be affected in any way (fig.4n). At the completion of the EDC pilot, when posed with the statement, 'EDC reduced the amount of time I spent recording data for this study,' seven of the coordinators (70%) disagreed. This was an increase in the number of negative perceptions about EDC from the baseline number of only two prior to experiencing the system. Having had the opportunity to use the EDC system, only two coordinators agreed that the amount of time they spent recording data for the trial was reduced (fig.4o). The earlier supposition that EDC would make one's duties easier and

timelier was disproved. Although the majority of study coordinators believe that Alcon and other companies should use EDC in the conduct of clinical trials, only a mere four individuals said they would do another EDC trial using Alcon's recent system (fig.4p). The other six vowed that they would not do a trial with the system as is. Given some substantial modifications, ranging from changes in the software design to changes in the eCRFs and source documents, all of the coordinators who were disappointed with the current system said that they would perform another EDC trial once the modifications have been implemented. In the study coordinator's opinion, the area of EDC needing the most improvement is the software design of Phase Forward's InForm 4.0 system (fig.4q). Many coordinators complained that the design is too cumbersome because too many clicks are required for submitting data and navigating through the system. With patients waiting on service and sponsors demanding data, many study coordinators say that having to wait for the 'form submitted successfully' prompt each time was very time-consuming. Conversely, one of the positive aspects of EDC is the transmission of data to the sponsor. The majority of study coordinators agree that data transmission to get the information where it needs to go is the area of EDC needing the least improvement (fig.4r).

Impact of EDC on Staff at the Sponsor Company

The staff involved in this pilot had mixed reactions about EDC's feasibility within an Alcon environment. In each of the interviews I conducted with the individual clinical team members, I inquired about which process they preferred. There were split numbers between choosing either system or the EDC system; 42% for each of the previous options

(fig.4s). Despite familiarity with the paper processes, there were more advantages noted for EDC than for the paper-based trials. The advantages and disadvantages of paper-based trials and EDC, ranging from issues related to the environment to its function, are summarized in a table (table 1). As stated in an article entitled "Scaling up EDC," an EDC trial will require that the staff acquire new skills (13). However, the increase in personnel duties did not deter the clinical team from keeping an open mind to EDC. As stated by a member of product safety, 'In my opinion, although EDC makes my job more difficult, it is the best process for the company.' Similarly, 73% of the clinical trial staff at Alcon notice that their duties expand with an EDC trial (fig.4t). Product safety (PS), clinical data management (CDM), clinical applications, and clinical science felt the workload increased with EDC. During the EDC pilot, personnel in CDM had the added responsibility of coordinating with the vendor, Phase Forward. This change required CDM to work with multiple departments within Alcon, such as clinical science, product safety, SAS programmers, R&D Legal, etc., and also with multiple departments within the vendor company, such as the project sales manager, project coordinator, eCRF designer engineer, and sponsor advocate. CDM and clinical science also had to work in collaboration on getting the sites trained, lengthening their list of duties as well. The data coordinator reported that she had to devote about 6 hours per day for 3 weeks to the EDC trial at start up because she was aiding sites in getting trained and passing the required test. Within clinical science, EDC added considerable time to the usual interactions with the site. Because many of the investigators were resistant to the online test given by Phase Forward, the CRS had to walk them through the test to ensure that they passed.

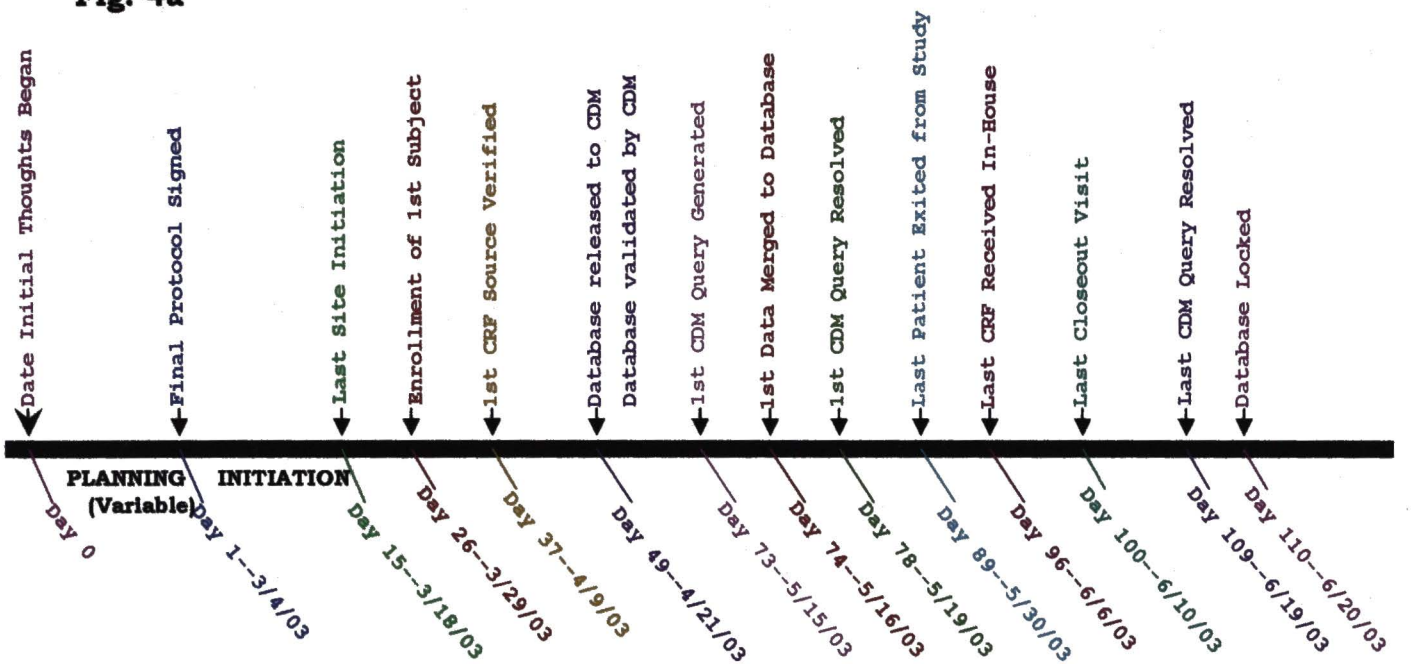
Furthermore, without I-review being available for this trial, review of trends and the data as a whole picture was delayed until clinical applications had the resources available to produce the requested reports. Clinical Applications complained most about the workload increase to simply understand the data structure and field names of Phase Forward. One programmer substantiates that her workload experienced a significant increase of about three times because programming tools had to be developed from scratch because there was none previously developed that would be applicable to the EDC data structure. Product safety's duties were expanded with this pilot of EDC so that it was the duty of the individual coding the AE to also assign a tracking number to the incident. In one person's opinion, 'EDC will require the addition of more staff in product safety because the limited personnel was not sufficient for the database to be continuously monitored for new or modified AEs.'

The staff at Alcon encountered and overcame many changes in their duties and processes. As a result, the staff had many recommendations to improve future applications of EDC within Alcon (table 2). However, in order 'to take EDC towards the eClinical vision and realization of its benefits, the staff, a company's internal processes and one's habits must be revolutionized.

CHAPTER IV ILLUSTRATIONS

CHAPTER IV CHARTS AND GRAPHS

Fig. 4a

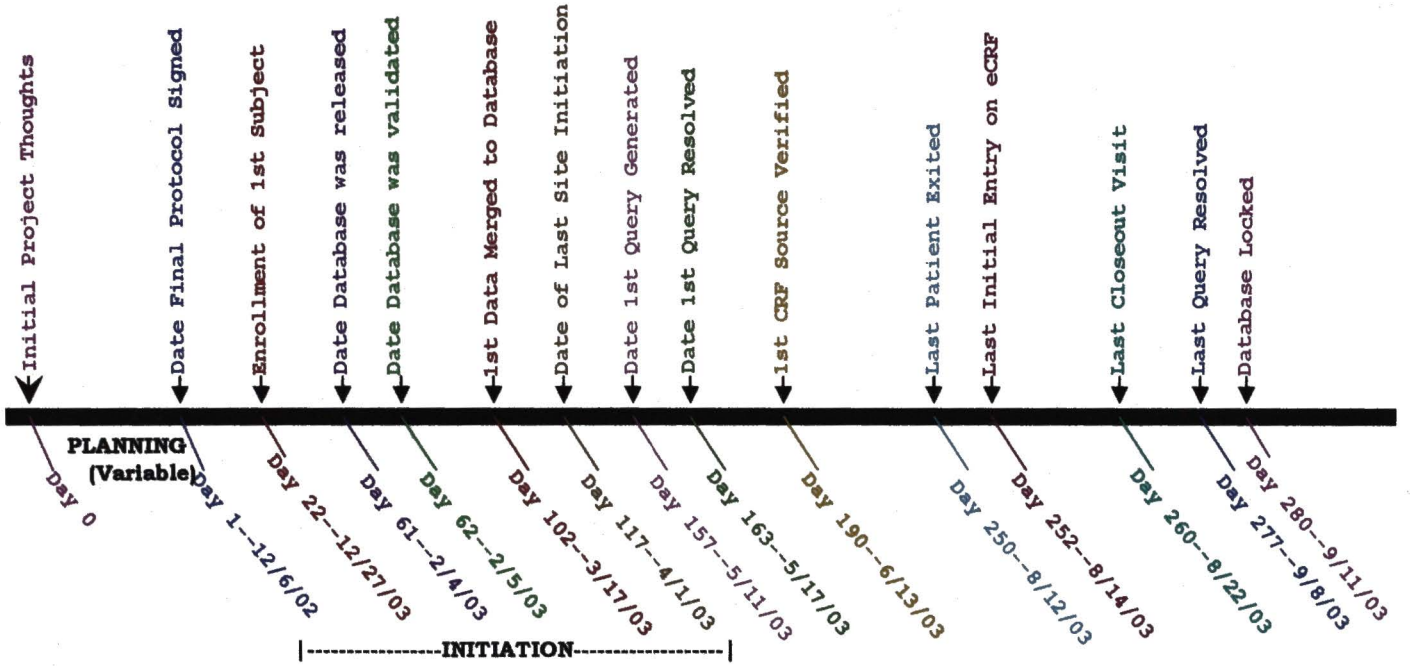


Timeline for a Paper-Based Trial

Using Data Management's Revised Query Process

Total Queries During Study Conduct = 119

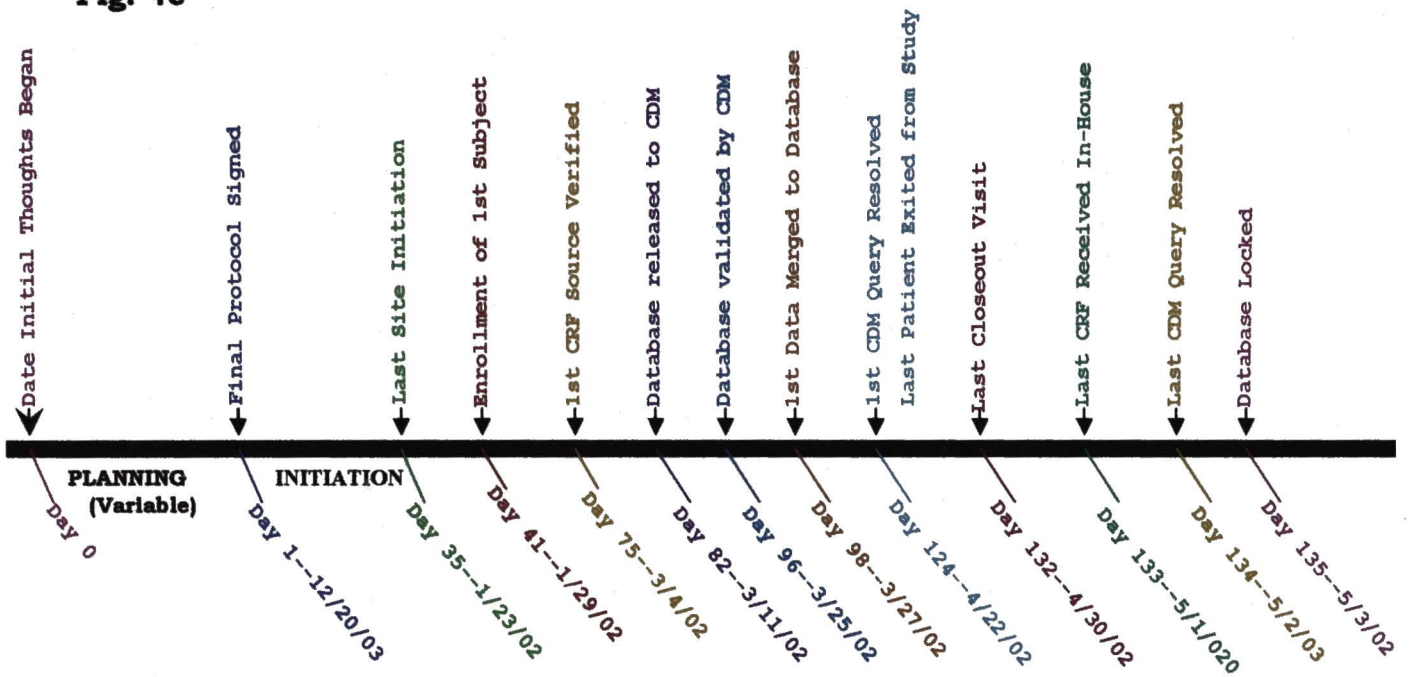
Fig. 4b



Timeline of the Electronic-Based Trial

Total Queries During Study Conduct = 2,113

Fig. 4c



Timeline for a Paper-Based Trial

Using The Traditional Data Management Process

Total Queries During Study Conduct = 141

Fig. 4d

Within the Drug Development Timelines...

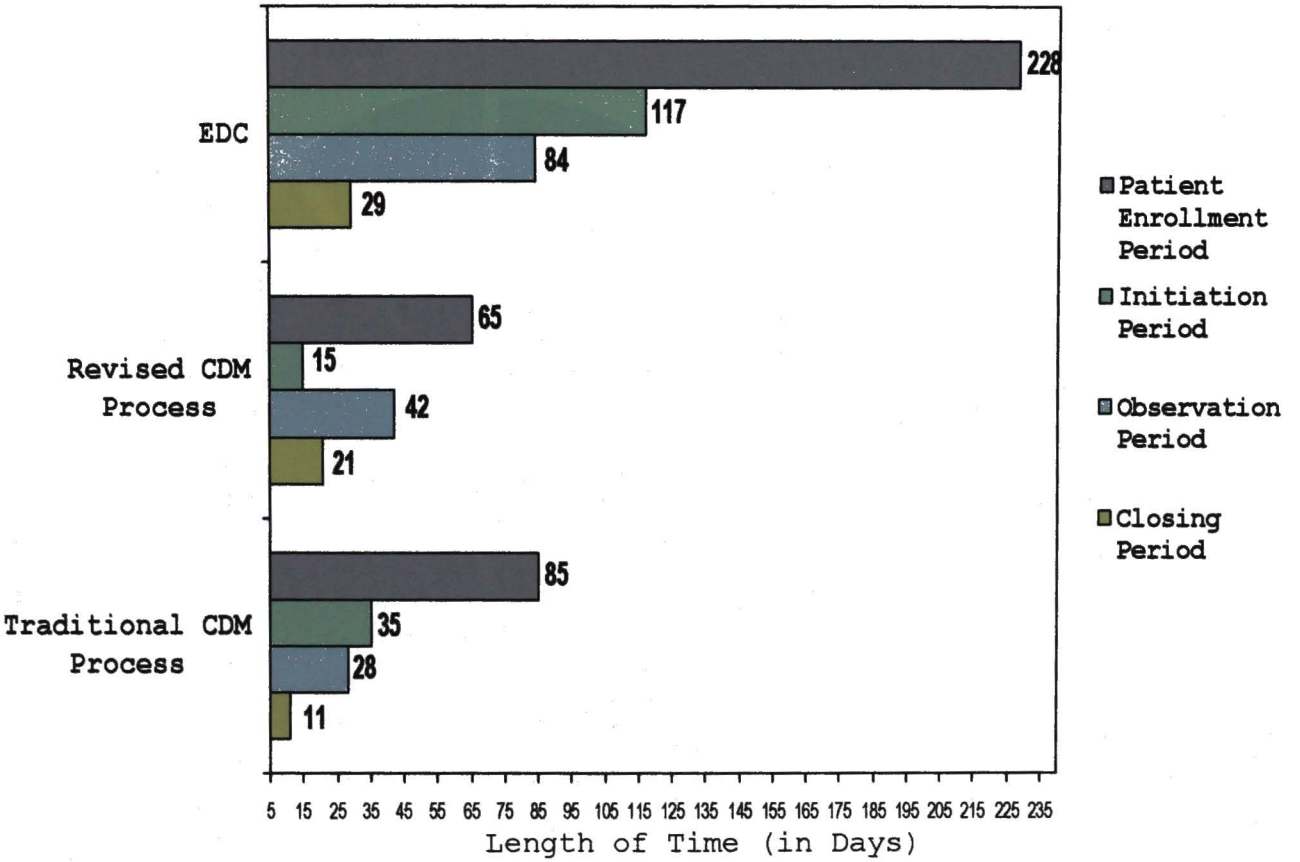


Fig. 4e

Overall, the Conduct of the Trial is More Efficient...

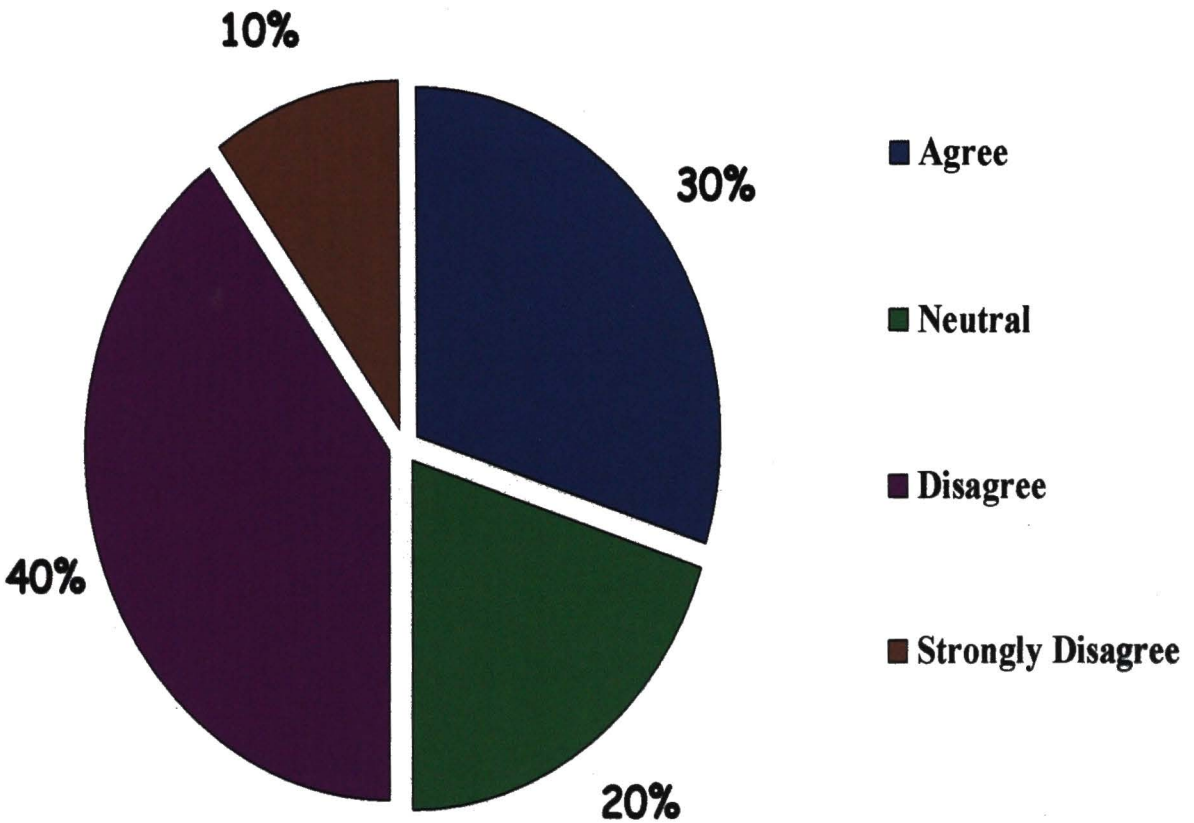


Fig. 4f

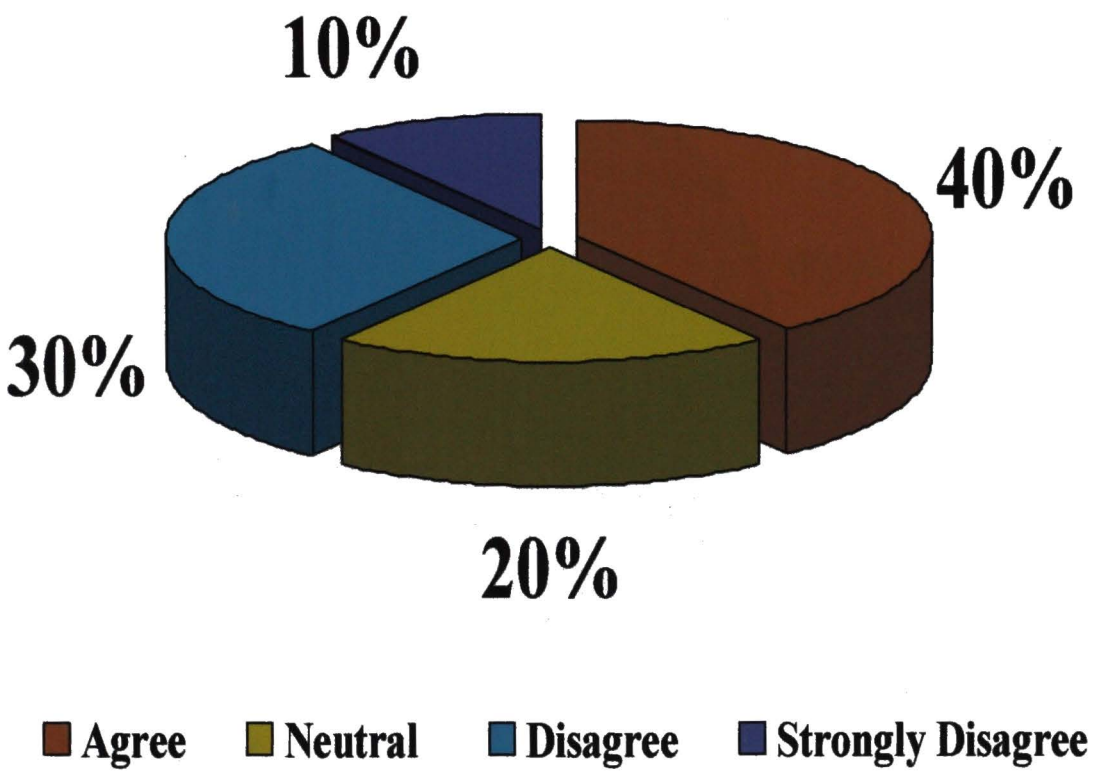

EDC Reduced the Amount of Queries...
10%
40%
30%
20%
Agree
Neutral
Disagree
Strongly Disagree

Fig. 4g

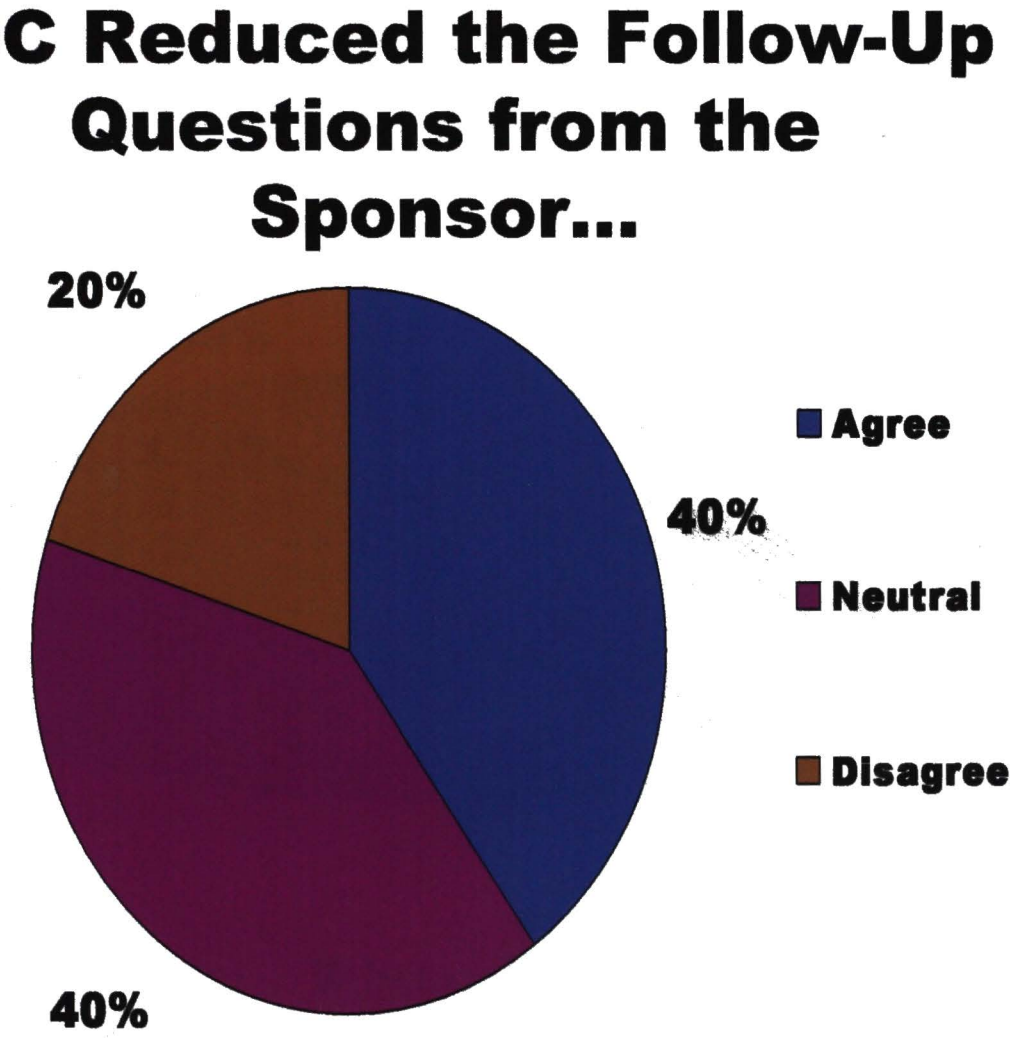

EDC Reduced the Follow-Up Questions from the Sponsor...
20%
40%
40%
Agree
Neutral
Disagree

Fig. 4h

EDC Ensures More Accurate Data from the Investigative Sites....

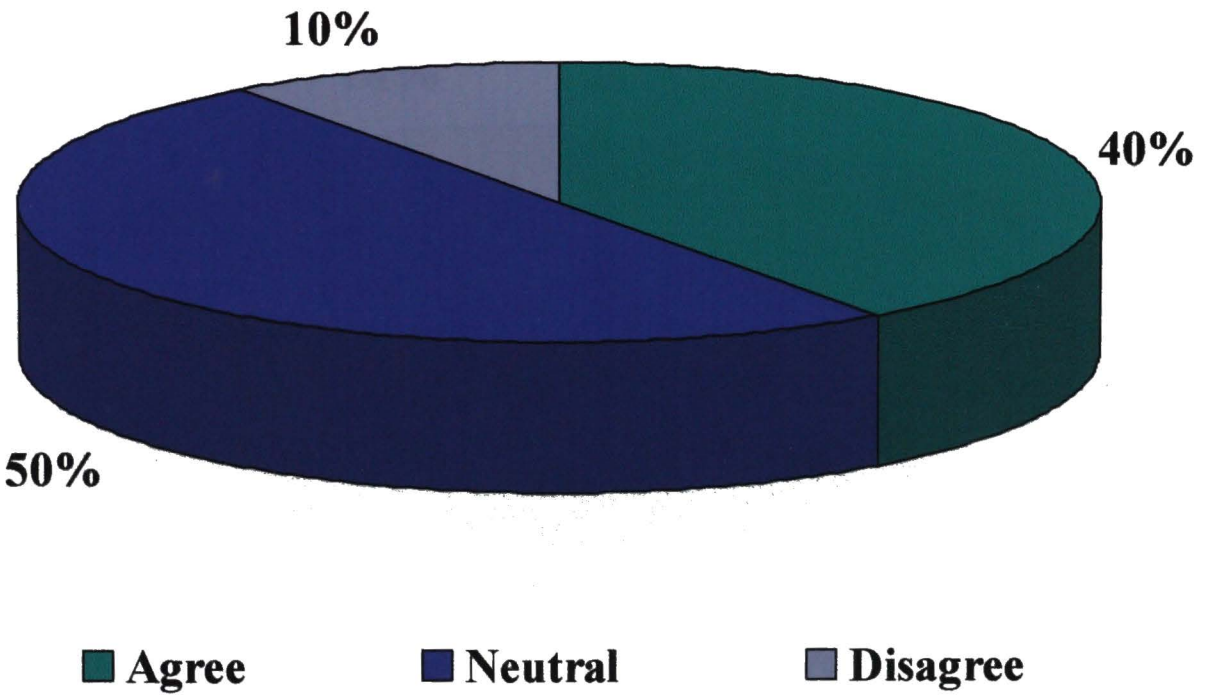


Fig. 4i

Do Study Coordinators Recommend Alcon and Other Companies Use EDC?

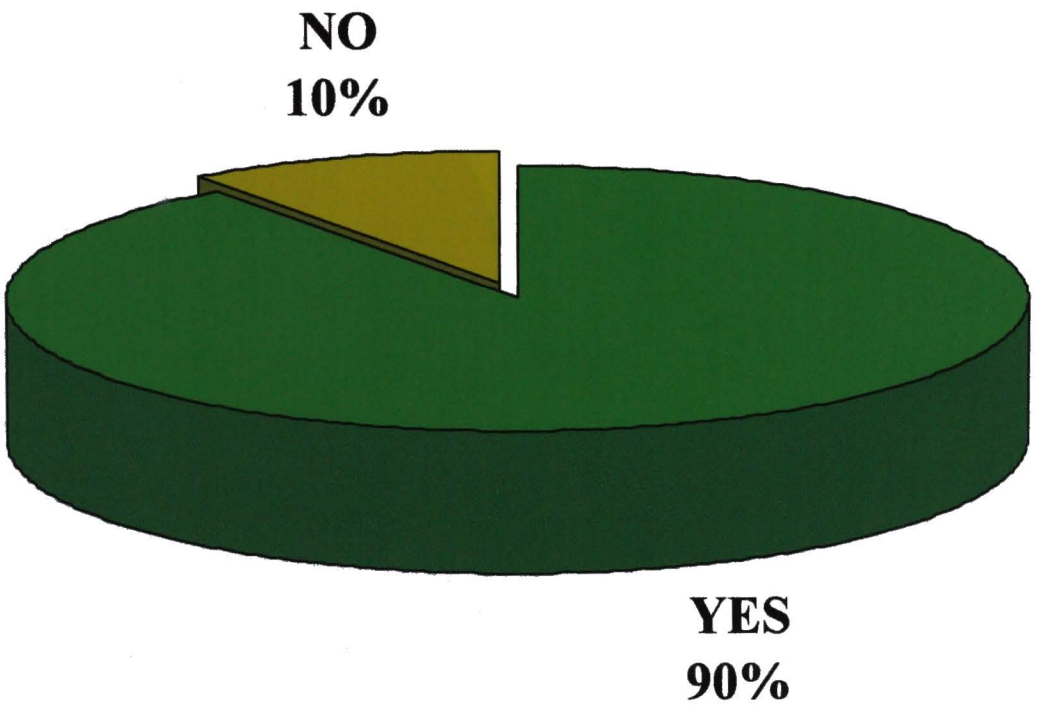


Fig. 4j

Coordinators' Clinical Research Experience

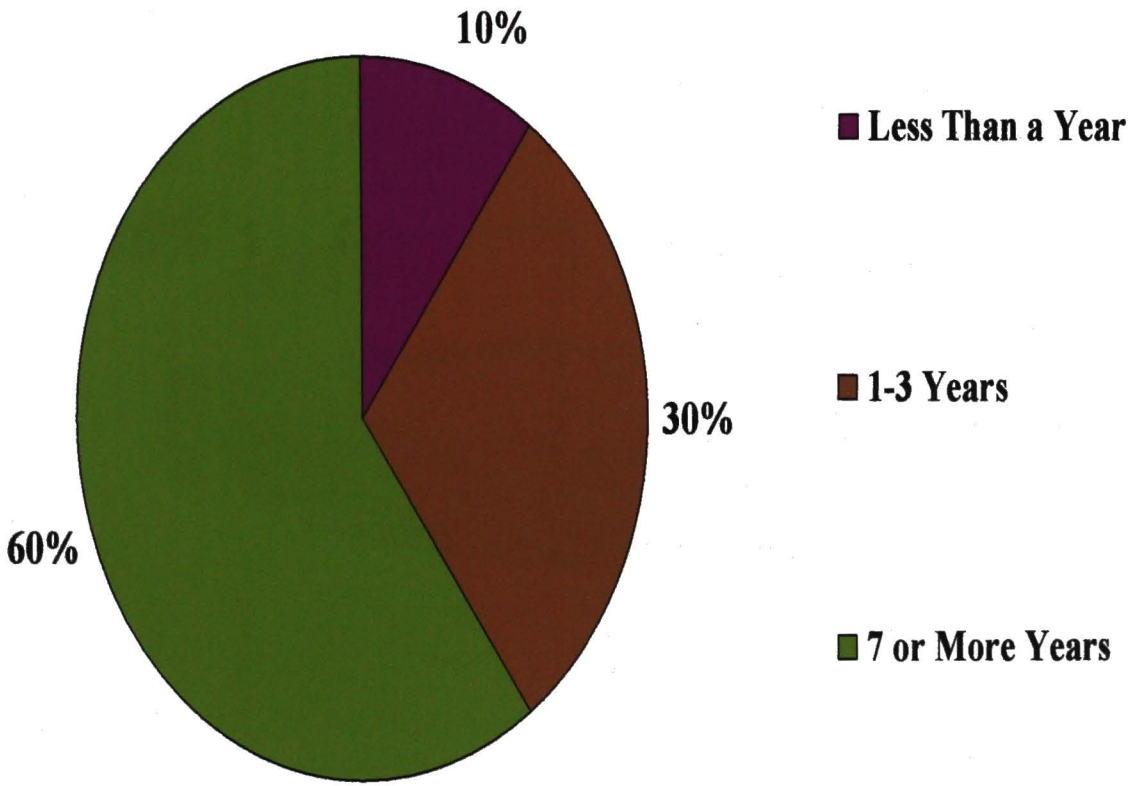


Fig. 4k

Study Coordinators Having Previous Experience Using EDC in Another Clinical Trial

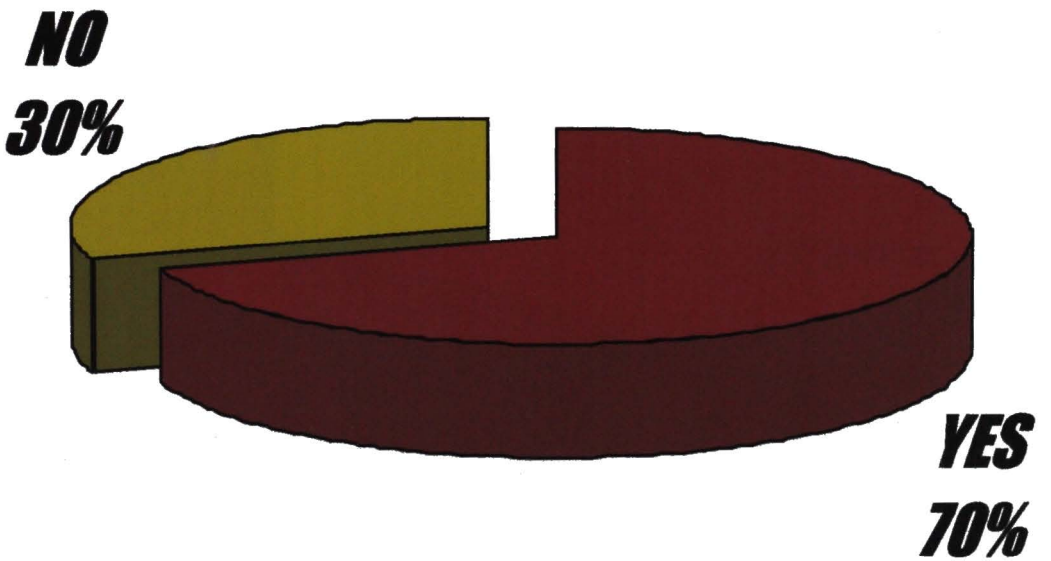


Fig. 41

How Many Times Has EDC Previously Been Used By the Study Coordinators?

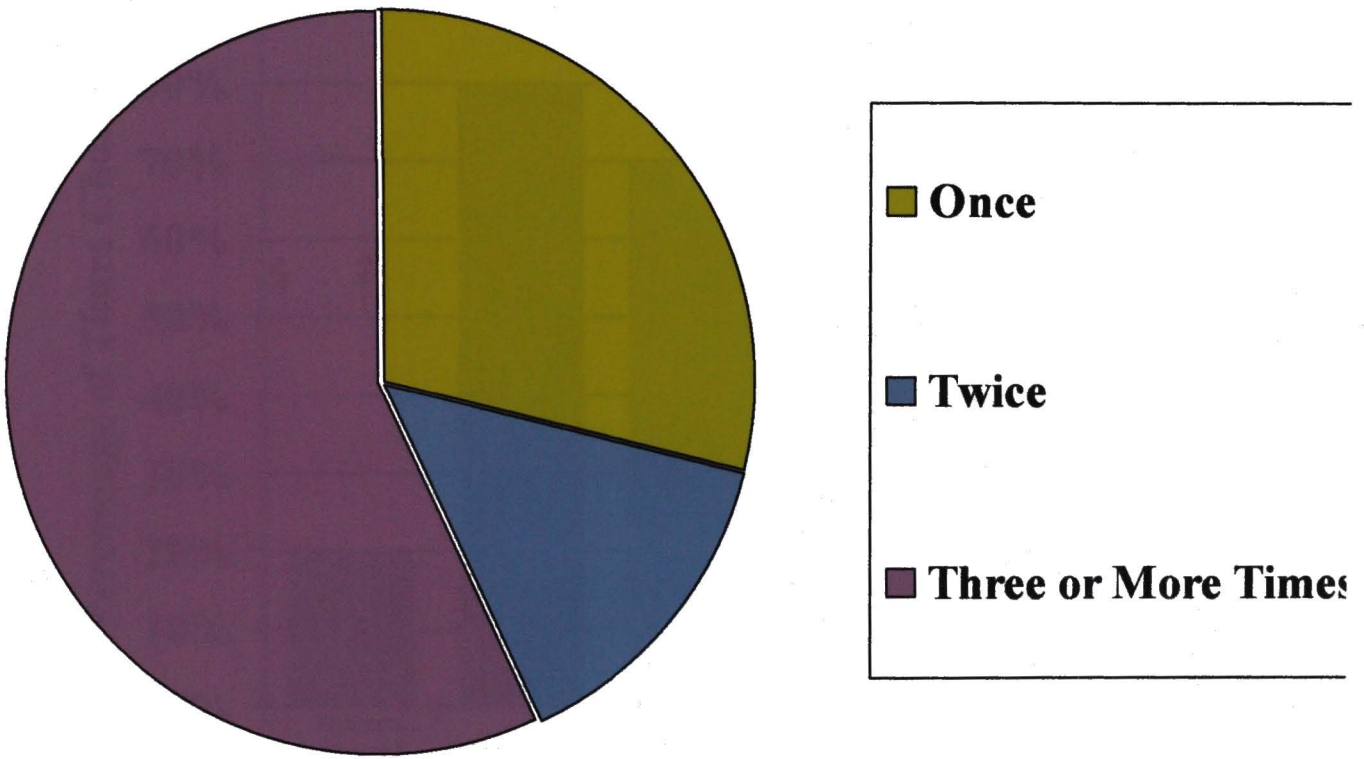


Fig. 4m

Expected Benefits of EDC

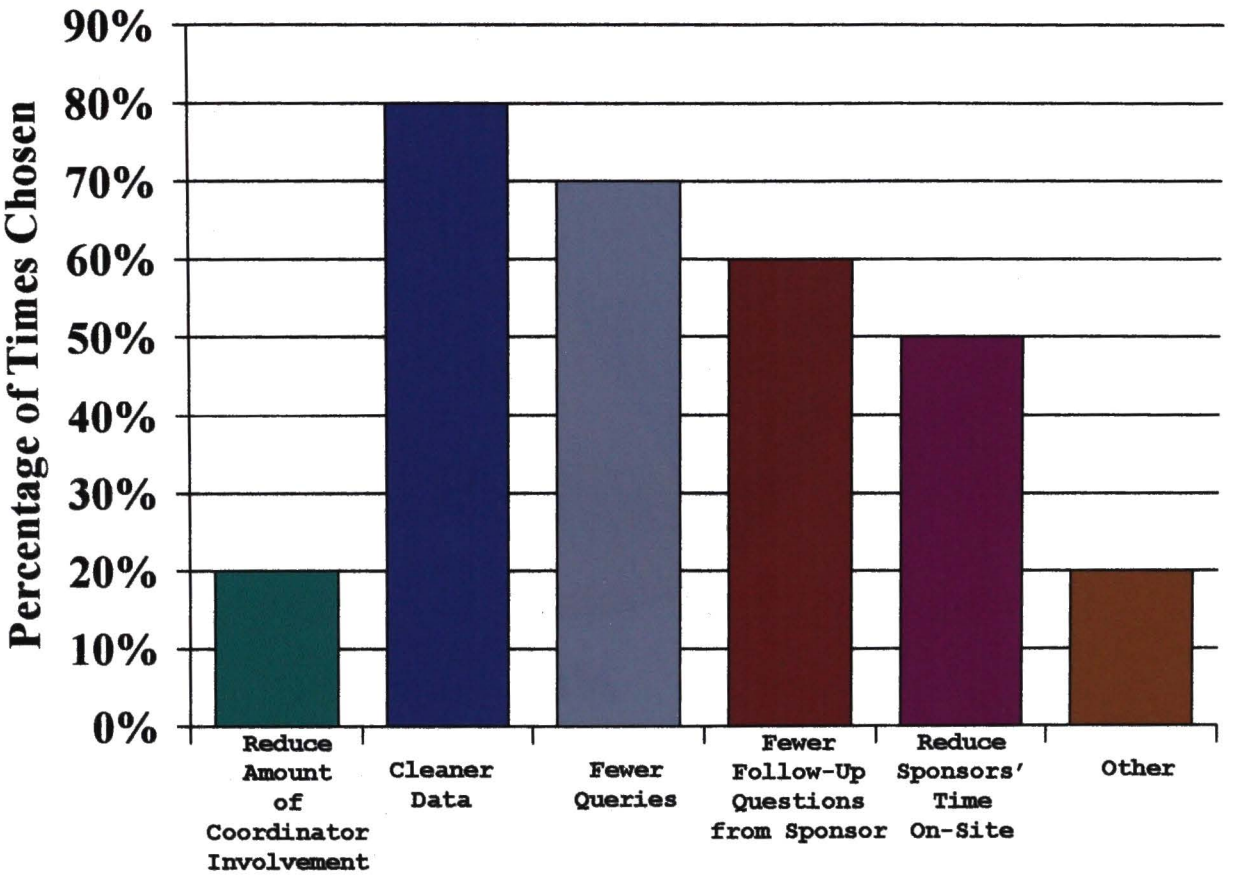


Fig. 4n

Prior to Study Start, How Did Study Coordinators Feel EDC Would Impact Their Duties?

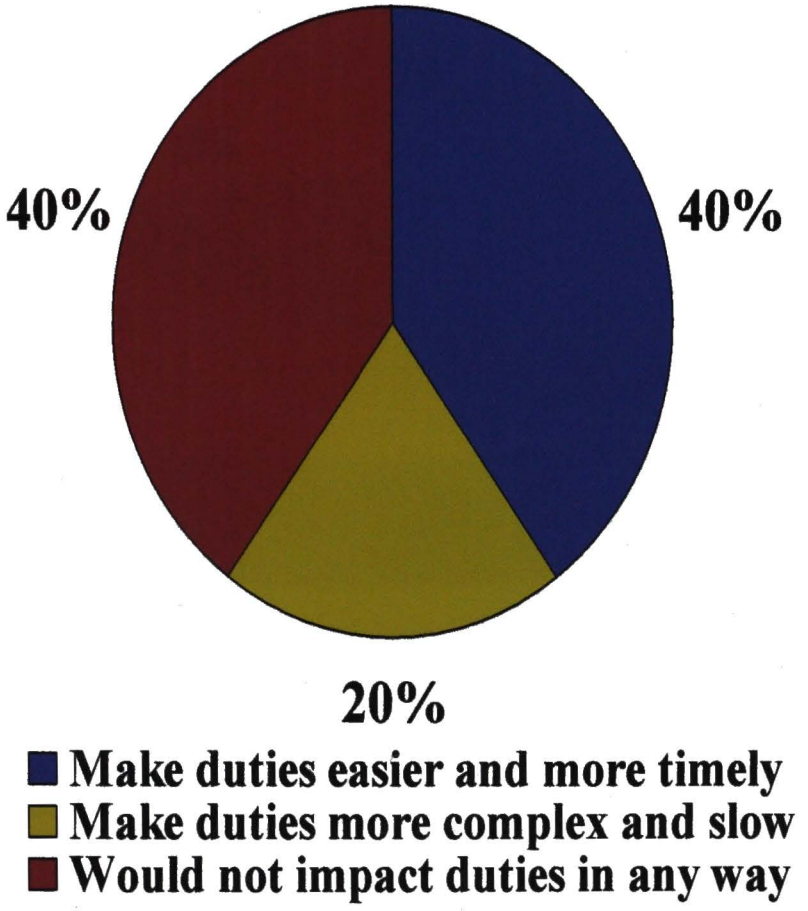


Fig. 4o

EDC Reduced the Amount of Time I Spent Recording Data For This Study....

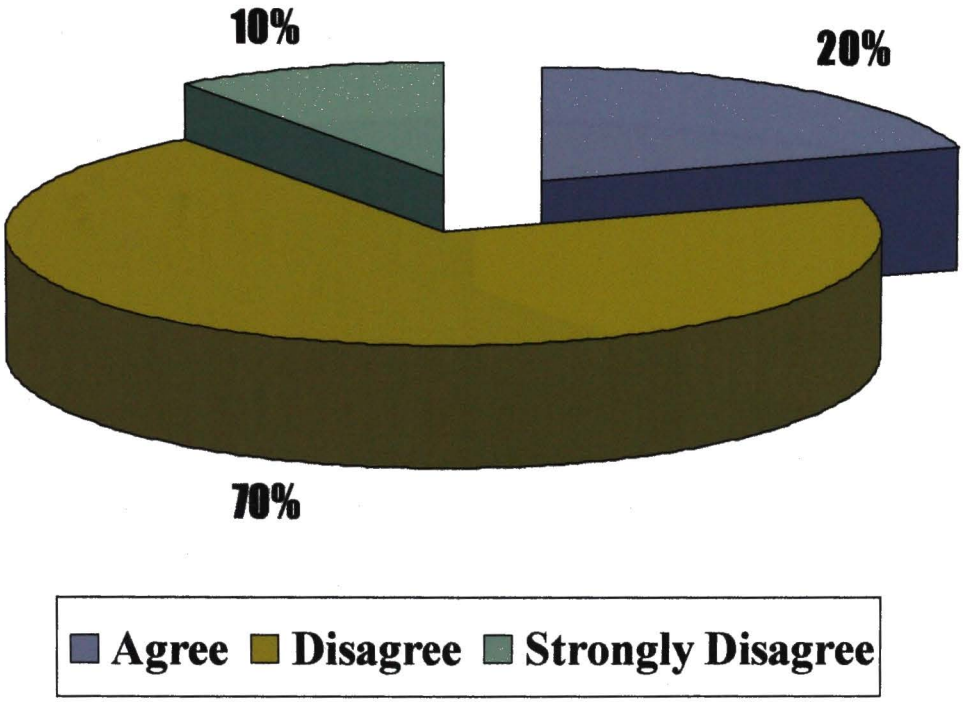


Fig. 4p

Based on the Current EDC System at Alcon, Would Study Coordinators do another EDC trial?

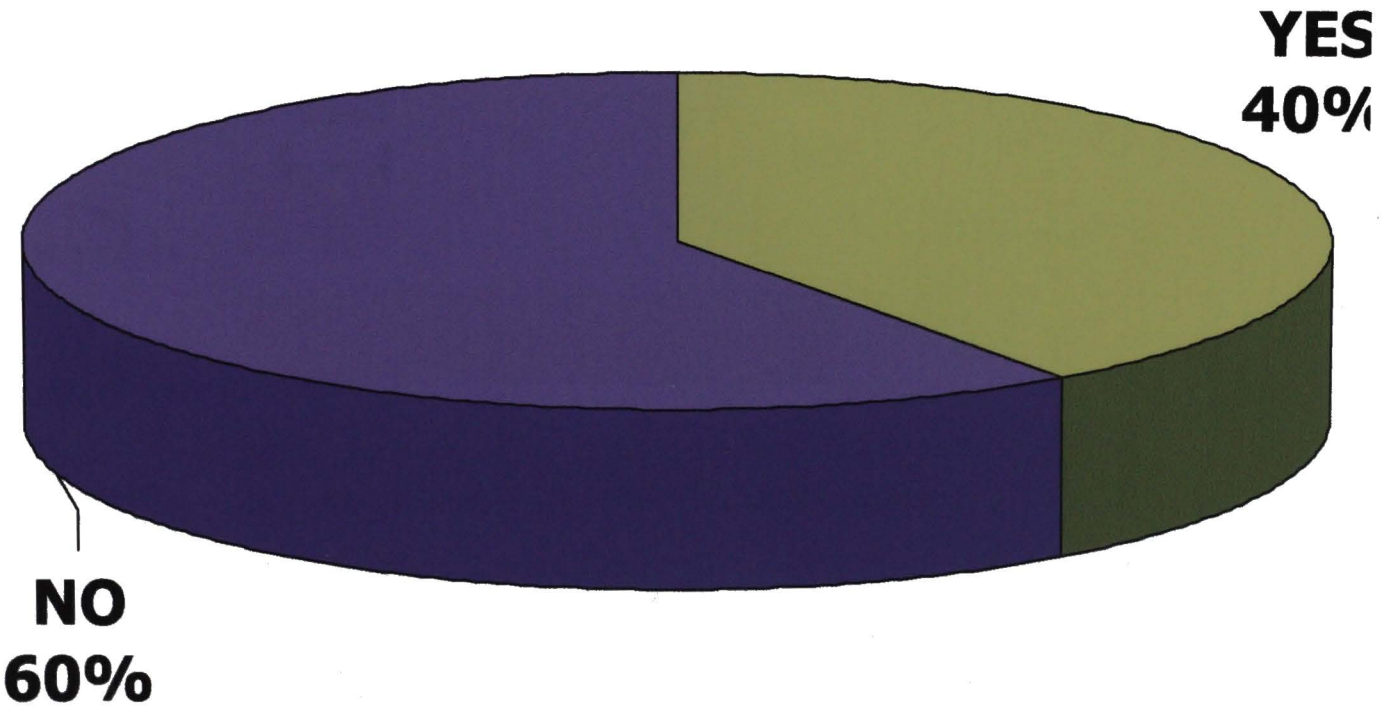


Fig. 4q

Areas of EDC Needing the Most Improvement...

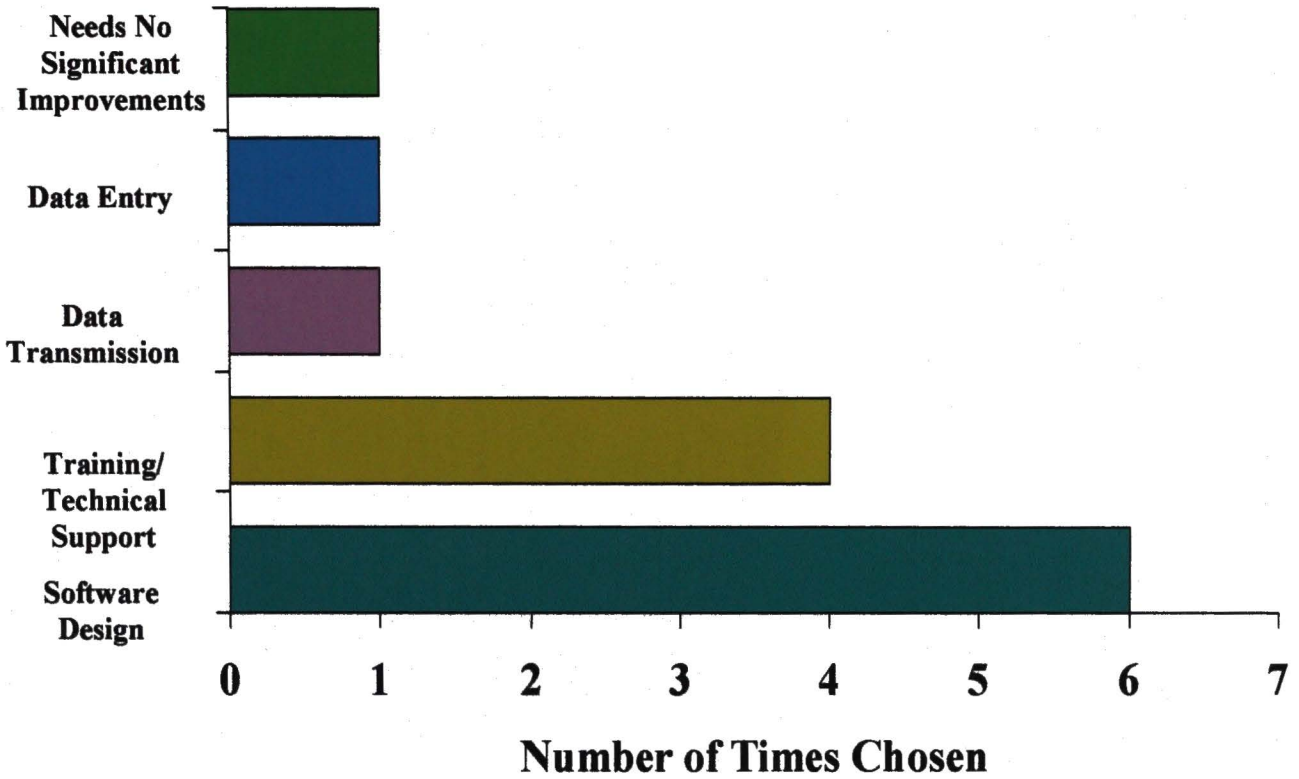


Fig. 4r

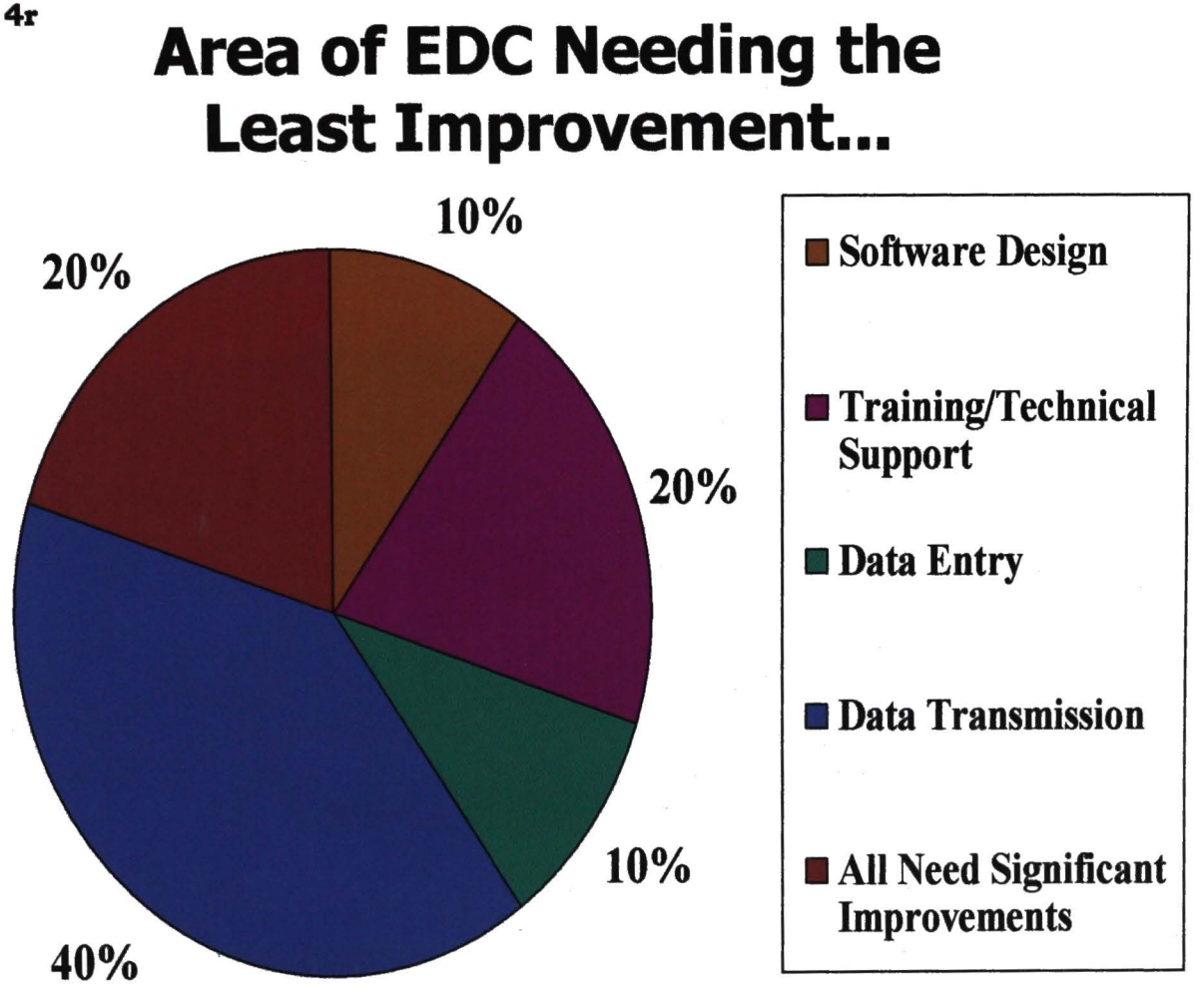

Area of EDC Needing the Least Improvement...
10%
20%
20%
10%
40%
Software Design
Training/Technical Support
Data Entry
Data Transmission
All Need Significant Improvements

Fig. 4s

Process Preference of the Sponsor's Clinical Team

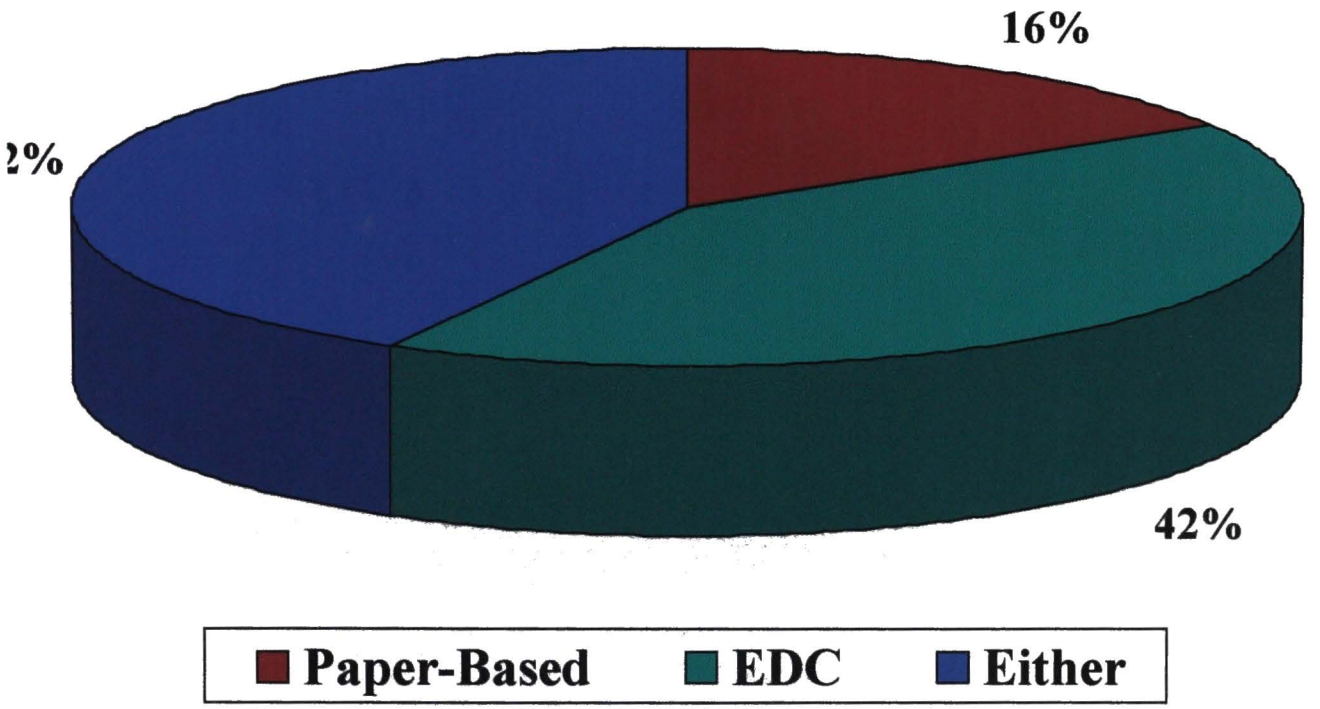
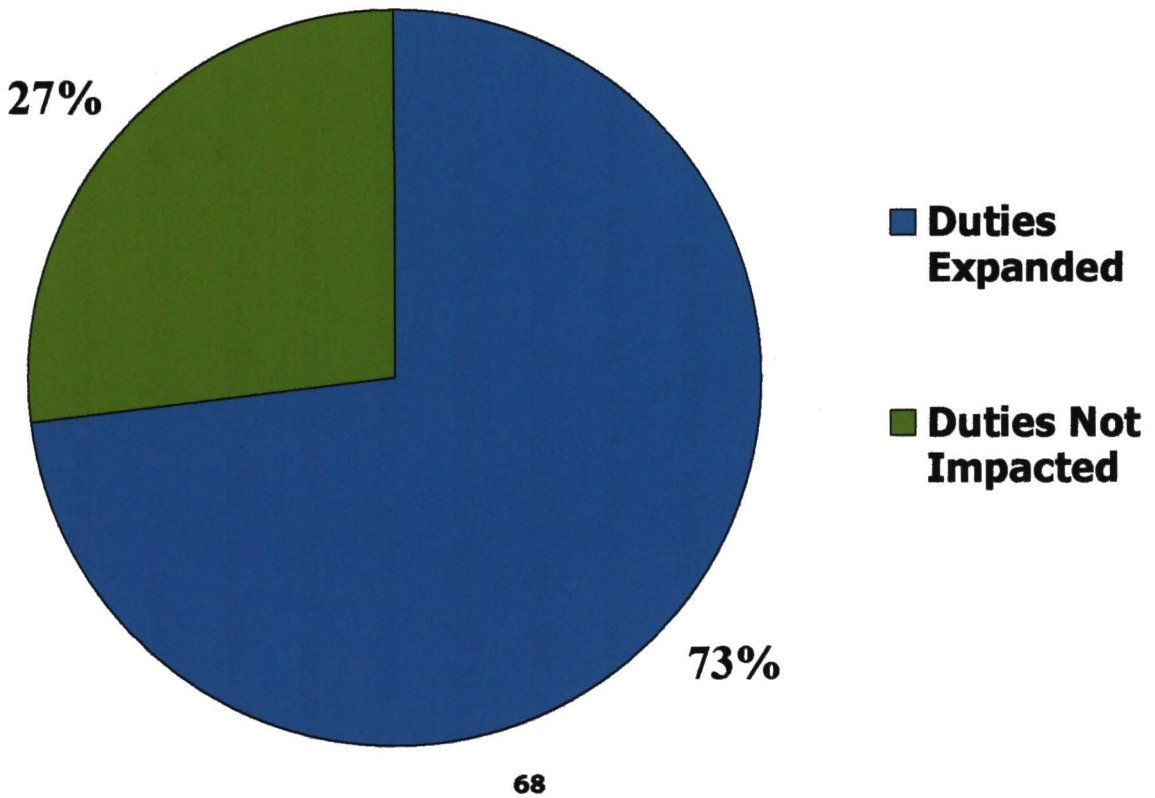


Fig. 4t

EDC's Impact on Duties of the Sponsor's Clinical Team



CHAPTER V

DISCUSSION

Although electronic data capture (EDC) has been available for 20 years or more, companies have remained hesitant about its applicability to enhance clinical trial conduct. Before any company adopts a process that is new to their organization, the procedures and regulations must be practiced and perfected. Pilot trials are developed to gain more knowledge and ease about the proposed process change. Already this year, the clinical data management (CDM) department reported that they have processed over a quarter-million paper case report forms (pCRFs). CDM is an integral component in maintaining clinical trial databases to be used during FDA submissions for approval to market a test article, therefore, data management processes are constantly improved while options are cyclically evaluated. EDC has been recently recognized within Alcon as a possible alternative to improving the efficiency of data collection while simultaneously decreasing data processing time. As a result, this prospective option was compared against the two processes of data management that Alcon currently uses with paper CRFs.

Analysis of Timeline Results

Examination of the results, with respect to the timelines, indicates that the revised data management process, which uses data clarification forms (DCFs) and pre-programmed edit checks that are fired-off during in-house data entry, had the shortest drug development timeline among the three processes. There were less days with the revised process between the date the final protocol was signed, which marks study

commencement, and the date the entire database was locked, which indicates trial completion. Although the EDC-based trial took considerably longer to complete, there were many factors that distorted the numbers.

The data entry process is very diverse between paper-based trials and electronic-based trials. Paper CRFs (pCRFs) accumulate until they are received at the sponsor company for input into the protocol's database. Because data entry does not occur until the pCRFs reach the sponsor company, it is not required for the database to be completed prior to study commencement. On the other hand, with EDC, it is ideal for a database and/or server to be developed and functional by the time the first patient is enrolled. Data collected at any visit, screening or otherwise, must be entered directly into the database by the investigative site's personnel. With this EDC pilot, the database was not developed and released until March 17th, over three months after the trial began. In turn, the amount of data to be inputted accumulated on top of the incoming data and monitoring of sites was also held up because there was no database to receive the data.

Even after release of the database, the system was not complete. The edit checks that were supposed to be used to correct or validate the data were not released with the database. Edit checks were not released until May, two months following the database release. Since the final edit checks were not in place at the time the database was released, the system was generating queries that were not supposed to be queries, causing the coordinators to revisit and correct previously entered data. Coordinators had to answer all those queries that were generated inappropriately by the system, then the CRS had to go into the system and close them.

Perhaps, the most significant impact on the EDC drug development timeline was the extended initiation period the trial experienced, which is primarily dependent on the type of study being executed. Getting adequate study volunteers for the dry eye patient population is very difficult, which caused some sites to be dropped for no enrollment. Because a new site had to be added as a replacement, the last site initiation visit was not done until April 1st, almost four months after the final protocol was signed. As a result, the patient enrollment period was also extended during this EDC pilot. The study using the traditional data management process only had a lapse of a little over a month between the date the final protocol was signed to the last site's initiation visit. With the trial that used the revised data management process, all the sites used in the study were initiated in less than a month. The initiation period was different for each of the studies evaluated, which clearly plays a role in the variations between the drug development timelines.

All of Alcon's Standard Operating Procedures (SOPs) were written with the intention of using paper medium. Many of the steps within EDC require a new approach to usual processes. Case in point, EDC theoretically works optimally when CDM locks casebooks by patient rather than by study, but the procedures within Alcon are written so that the study is locked at the end all at once. EDC affords CDM the opportunity to lock by patient, instead of by study as it is usually done. However, with this pilot project, the option to lock by patient, which is really where EDC shaves time off the closing period, was not totally realized because of conflicting internal processes. CDM has used paper-based procedures since the company's inception so the steps are well known for precise execution.

The learning curve associated with new processes undoubtedly affected this metric because the components and parameters needed in an EDC database were not lucid. Because there was no expertise among the Alcon personnel, they expected more coaching from the vendor, Phase Forward. However, coaching by Phase Forward was minimal so the clinical team simply had to learn by experience and implement options in a 'trial and error' fashion. A lot of parameters can be blamed for the longer timeline from the EDC trial conduct. Consequently, now that there are some precedents to be followed, the process will steadily be improved to accurately show the significant impact EDC could have in managing clinical trial data.

Analysis of the Total Amount of Queries During Study Conduct

The total number of case report forms (CRFs) per patient, regardless of whether it is paper or electronic, will undoubtedly affect the query metrics. The fact that the trial using EDC technologies had 16 more CRFs per patient than the paper-based trial having 46 CRFs per patient communicates a lot more about the variability of the query metrics (fig.5). When there are more forms to be filled out, it is understandable that there will be more potential for error. EDC had far more total number of queries than the paper-based trials, which follows the previously stated logic of the more CRFs per patient, the more queries.

Furthermore, the query numbers obtained from the paper-based trials only takes into account the queries generated after the sponsor's data entry workforce has entered the data into the database. The manual queries generated by the CRS during site visits or

telephone conversations prior to entering the data into the database are not included in the previously reported numbers.

Within paper-based trials, monitoring visits are taken more frequently and corrections made in-person at the site are never tracked. Therefore, during the monitoring visit, numerous queries can be generated and resolved prior to the CRFs being brought in-house where the modifications are tracked so the number obtained is not inclusive. Prior to reaching the sponsor company, there is no data in the database, only on the paper, which can be changed multiple times, but never realized.

With EDC, queries are generated and often resolved instantaneously upon the coordinator's entry of the data. The initial learning curve experienced with EDC also possibly inflated the total number of queries. The immediate feedback gained with EDC is a positive despite the total number of queries exceeding 2,000. The coordinators' earlier entries could have had many queries over a short time period until they learned the data structure requirements and demands of the EDC system specific for this trial. Because data is going directly into the protocol's database, any change, regardless of how minor or how quickly it is resolved, will be documented electronically to show the audit trail. Over time, there is a greater chance that the queries declined as the coordinators became more well verse with the organization of the eCRFs and the format required of the data for entry. EDC has a more inclusive metric, but there is no assurance that the study using the revised process of data management had the least amount of total queries because all the queries can not be accounted for.

Another factor contributing to the higher number of queries with EDC was the initial error made by Phase Forward in programming the edit checks. The edit checks are meant to decrease problematic data being entered into the database, but in this case the edit checks was not written with the correct specifications. All the sites had hundreds of additional queries not based on their individual error, but on the system error.

Analysis of Resolution Time for All Queries

The total number of queries will definitely impact the total time it takes to lock the database. Because queries help to make the data more accurate, or 'clean', the database can not be locked until all outstanding issues and/or discrepancies are settled. The lag time for resolving a single query is partly a function of how difficult the query is to resolve and it is not dependent on the type of process used. For instance, if the site has to locate a patient who has completed treatment to confirm or question data, it will likely take much longer to get this issue resolved than would be needed to check a box that was an oversight by the site's personnel. Technology also added unexpected delays with EDC in getting data to the sponsor. Some sites had problems with their Internet service, such that they could not access the Internet for days, further delaying data transmission and query resolution. Once the queries were finally answered, the completion of the query process was dependent on the workload of the study monitor. The CRS must go into the database, see if the coordinator's answer satisfies the request, and then close each of the queries. There was only one CRS initially on this trial so even after queries were answered, the time he could spend reviewing the database to close the queries were very limited. Furthermore, if the response given by the coordinator did not satisfy the question

posed by the system or the CRS, that one query could remain open for an extended period of time until there was an answer to satisfy the request. Aside from the issues related to the system, the study design itself affected the metrics. Because the observation period of the EDC trial was longer than the comparators, queries were submitted over a wider range of time. Hence, the time from the first query's resolution to the last query's resolution was innately going to be longer.

Analysis of the Reliability of Data with EDC

Data reliability is a major issue for sponsor companies because it is an inherent code of ethics that will escalate industry and consumer confidence in one's products and illustrate how efficient quality systems are. There is no concrete way of determining whether the data from sites are reliable except by getting the assessment directly from the source. Study coordinators were polled about the reliability of data from the EDC pilot based on their opinion regarding the overall efficiency of the trial's activities. Even though a large number of study coordinators believed that follow-up questions were reduced, still the majority did not believe that the data was more accurate. When evaluating this parameter, it seems implausible that the sponsor's reduced follow-up would not indicate that the data were more reliable. Furthermore, although there was a split decision that the overall amounts of queries are reduced with EDC, still the majority disagreed that the conduct of the trial was more efficient. These results suggest that there is no association between queries and trial efficiency in the minds of study coordinators. Indeed, reducing the number of queries do not automatically predispose the trial to be more efficient if the study design and efficacy parameters are not distinctive enough.

Nevertheless, when the CRS does not follow-up as much as expected, it is a good indication that the data provided is not significantly flawed.

Analysis of the Sites' Study Coordinators Acceptance of EDC

As expected, study coordinators positively accepted EDC. Although there were obvious disappointments about the expected benefits of EDC, people like to experience new things, which spurred the coordinators' enthusiasm towards EDC. Because most of the coordinators are experienced in the field of clinical research, they most likely welcome a change to combat some of the monotony of their job duties. Many of the polled study coordinators from Alcon's EDC pilot had some considerable previous experience, which biased their review of Alcon's EDC system and processes. Because Alcon's personnel was not very familiar with the specifications of the EDC system, the system did not operate at an optimal level, which explains the negative feedback on Alcon's current system as is. The only plus of Alcon's current system reported by coordinators was the reliability that the data will be transmitted to the sponsor although many complained that the speed was sub-par.

The benefit most expected by study coordinators was that the data would be cleaner, but at the trial's conclusion, the majority did not agree that the data was cleaner with the EDC system. This discrepant evaluation could be due to the lack of experience by Alcon with designing the database. In view of the fact that the study coordinators were more familiar with the capabilities of EDC due to previous knowledge from other systems they've used, it is probable that their expectations for this system's performance prior to using it was higher than what the system actually delivered.

My previous explanation is further solidified when examining the responses before and after the trial regarding the belief that 'EDC would make their duties easier and more timely.' More coordinators believed that the duties would be easier with EDC, but that is because they expected the data to be cleaner, thereby lessening the time they must spend on queries and conversing with the CRS. However, the time coordinators devoted to this study was not reduced more than likely due to the fact that there were a lot of unfamiliar steps with EDC that neither Alcon nor some sites were aware of. For example, a major issue that surfaced just days, or hours in some cases, prior to the locking of the database was the electronic signature required from the investigators. The sites that did not have previous experience with EDC were not aware of the complexities related to electronic signatures. Each time a query was answered that resulted in a data change, the investigator would need to go back into the database and electronically sign the eCRF to acknowledge that he/she was aware and in agreement with the modification. Therefore, the study monitors spent numerous hours calling and e-mailing the site coordinators to get this issue resolved, which increased the amount of time the coordinators had to devote to this trial.

In relation to Alcon's EDC system, coordinators complained of many technical issues, such as the software's lack of ability to link related eCRF pages within a casebook and to show specific pages that are frozen without having to go into the time and events schedule within the casebook. On the contrary, all the study coordinators recommended that Alcon and other companies use EDC. If the system is improved, coordinators, and myself alike, prefer this electronic-based option. Additionally, when the study

coordinators who had previous use of EDC were initially asked to rate their earlier experience, there were no negative assessments. The study coordinators who have used a system like this before have more background and confidence in EDC than what was communicated in this pilot. It is more than likely understood that because this is Alcon's first time implementing EDC technologies in their trial conduct, the true value of its benefits would not be appreciated to the fullest extent. There should have been more input from the vendor company, Phase Forward, at the study initiation to combat the 'slippery slope' of the unknown in hopes of reducing some of the technical complaints that arose during the conduct of the trial. Perhaps then, the coordinators would not have chosen the software design of InForm 4.0 as the area of EDC needing the most improvement.

Projected Impact of EDC on Alcon's Business Practices

EDC can be a very positive alternative within the Alcon environment, but it must be accompanied by many changes in the business procedures. The staff will have to be open to duty changes and technology. The numbers of staff at the sponsor company that would be willing to use EDC are positive, which shows the progressive thinking of individuals at Alcon. Most of the team's workload increased with this pilot of EDC compared to their usual load in the conduct of paper-based trials, but that can be attributed to the time and effort required to understand the structure of this electronic-based trial. There was loads of reference material that had to be continuously accessed and read to learn what symbols meant or to learn how to navigate through the system. With paper-based trials, the steps and options are so well understood that the tasks can be

completed without having to refresh the information or question the help desk. Nevertheless, as the company gets more and more well versed in the execution of an electronic-based trial, the methods will be perfected more and more to become as painless as the methods used with pCRFs. The primary hurdles with EDC at Alcon stemmed from the internal processes that are followed for a paper-based trial. Utilization of EDC requires the advent of standard operating procedures (SOPs) specific for the demands of EDC. Furthermore, the workforce is rooted in the current procedures. Yet, EDC is best executed with continuous monitoring, whereas paper-based trials can be monitored in one lump amount by viewing the data a few times so it is logical that either the budget for hiring more personnel must be increased or the allocation of resources must be modified. To address the issues related to software design, I propose that Alcon eventually develop their own server and database for EDC trials. Although it will take a tremendous amount of resources and finances to accomplish this feat, developing one's own system for EDC trials could possibly be the best alternative to outsourcing the database's development. Emotions were mixed amongst the staff about the responsibility of the database's development because of the lack of knowledge about what it entails to develop it and the steps in its development. First, I would suggest the company begin by developing their own software and loading it onto laptops to be distributed to the investigative sites. Once the software is proven to be functional in the field and in-house, Alcon should further develop the infrastructure around the program to include establishment of an internet connection, construction of a server, and availability of some personnel around the clock to serve as the help desk. In my opinion, although literature affirms that the most

expensive part of EDC technologies is the development of the database, it will be better to pay for the database development to ensure that it is comparable to the data structure that the company is accustomed to. Ensuring that a familiar program is built will help with the uneasiness of trying a different option because there will be peace of mind that programmers are accessible to manipulate and fine-tune any problems in the database. On the other hand, with an outside vendor, the sponsor company must accept the structure they use and any manipulation suggested to the system will result in an extra fee assessed, which will overshadow the perceived savings that EDC has been professed to provide. As one senior staff member stated, 'for Alcon to develop their own database for EDC, it will require a significant infrastructure.' There will need to be more technical personnel with a diverse knowledge about software development, database development, server maintenance, and a host of other parameters surrounding EDC technologies. Initially, the elimination of the data entry workforce will not save any money for a company looking to develop their own EDC system because it will simply be a trade-off for a larger workforce within clinical applications.

Limitations and Recommendations

The results of this pilot project nullified all but one of my hypotheses. I was correct in my projection that study coordinators would positively accept the EDC technology despite some negative assessments recording the selected EDC system used to execute Alcon's pilot study. However, many of my expectations related to the query metrics and impact of EDC on timelines were not realized. At the conclusion of the EDC trial, instead of there being a reduction in the number of queries produced, there were

more. There are many reasons that explain the shortcomings of my hypotheses, such as my initial oversight of the diverse approach to electronic-based and paper-based trials.

Within the field of clinical research, as with any job, the outcome is what one makes of it. Individual work habits and preferences will undoubtedly shape the evaluation of the CDM processes. Although all the studies evaluated were in phase two of clinical development, all three of the studies used for evaluation had a different duration of observation, which has limited the acceptance of the query metrics obtained. Case in point, protocols without long-term duration should have less queries overall and should require less time to resolve them. The numerous variations in style, approach, and mental reasoning compound the limitations of comparing three separate processes. For example, the CRS whose trial used the traditional process of data management said that he had a customary way of resolving queries so that all of them are brought to the investigative site during his monitoring visit(s). Alternatively, another CRS may send the queries to the site to be resolved as they are generated. Differences in the way queries are handled by the CRS definitely influence the metrics.

Comparing three different data management processes from three different studies is very difficult. A generalization can not be accurately made because of the differences in the design of the CRF and available patient population. Dry eye studies and glaucoma studies seek different patient populations naturally, but the strict inclusion and exclusion criteria can make finding suitable patients very tedious. However, because glaucoma is a specialized disease that has been elucidated more in recent years, there are more

specialists that deal specifically with glaucoma adverse to dry eye. Many people do not realize they have dry eye, so a physician often never examines people who may be suitable patients. Aside from the patient availability, most glaucoma test drugs seek to lower intraocular pressure, whereas, a dry eye test drug will focus on increasing the tear film break-up time. Therefore, the data points solicited on a CRF, whether paper or electronic, would be widely varied across the two areas of study.

Even the overall rating of EDC from study coordinators was biased. For the study coordinators experienced with EDC technologies, their individual perceptions and preferences about systems used in the past contributed to their acceptance of Alcon's EDC system. Majority of the coordinators had some experience with EDC so despite issues with Alcon's pilot system, their overall acceptance of the technology was influenced by the promise of EDC which they may have experience with another system. Therefore, the result of this parameter was primarily subjective.

The learning curve associated with a company's pioneer project also skewed the data, but a major drawback to achieving a more conclusive evaluation stemmed from the vendor company's lack of timeliness and attentiveness in producing customized reports to break the total number of queries down to specific categories. In order to evaluate the actual time saved from the last patient's visit to database lock, a custom report was requested to give the total number of queries during that time period, but it was not provided. The assumption that EDC allows for the data to be cleaner due to the numerous

queries generated and resolved throughout study conduct could not be objectively evaluated.

If I were to redesign this project, I would seek to control more of the variables to get an accurate assessment of each process's effect on the handling of data. Because of the significant differences in the study designs, their endpoints, and their personnel, these results can not serve as a standard. The number of queries that were resolved by the CRS at the site during the paper-based trials' monitoring visits were not accounted for, which could drastically alter the end conclusions about which process actually had the most queries generated. At the start of the project, the methods I employed to test the reduction in total queries generated did not take into ac count that the frequency of site visits would cause such an impact on the 'real' numbers. There are two plausible ways that the sponsor company could design a study to compare and contrast the efficiency of an EDC trial and a paper-based trial: in parallel or sequentially. To sequentially test the different processes, one would need to repeat the same study three times using a different process each time. By employing this technique, there would be less variables to control and the likelihood of a result being due to chance should be reduced. For example, there would be no difference in skill level or monitoring approaches across the monitors because it will be the same individual each time the trial is executed. The drawback with executing a trial three times is that it could become very expensive when you include the staff labor, materials, etc. In lieu of this downside, a parallel study appears to be a more attractive option. Paralleling the processes within one trial eliminates the added cost that would be incurred for the second and third execution. I suggest that the sites be evenly divided

amongst the study monitors, assigning one group to utilize paper CRFs to collect their data while the other group utilizes electronic CRFs as one of their data collection tools. This should provide more accurate measurements if all queries are documented in the same way.

I recommend that Alcon continue to do pilot studies with other EDC technologies. However, revision of current internal processes or development of different internal processes that are specific for EDC should be evaluated before another trial is implemented. Studies should be done to take a closer look at the financial impact of each process. For example, Alcon should consider evaluating how much each case report form costs to process, including the labor costs, supplies, and any other miscellaneous expenses. Once that figure is obtained, deduce the total amount required for management of all the CRF data related to one study by multiplying by the total number of CRFs acquired during study conduct. Then, compare that amount by the amount required to establish the EDC database, plus any labor incurred during the data cleaning process, to evaluate which process actually saves on financial expenses from a data management perspective. Additional studies should focus on evaluating whether there would be a substantial difference in the margin of profit between outsourcing the development of an EDC system and developing the system in-house. In order for a recommendation to be made of which system is better, in lieu of all the uncontrolled variables, it is suggested that one study be implemented three times with a different process each time. Repetitive execution of a trial using the different processes will reduce the number of variables

impacting the outcome to allow a true representation of the benefits afforded by the varied data management processes.

Eventually, I believe that it would be beneficial for Alcon to develop its own system for EDC trials. I propose starting with the development of custom-fitted software by our internal clinical applications personnel. I agree with the suggestion made by one of the sponsor's clinical team members for development of software. 'The software can be built in modules so that it can be easily adapted for any ophthalmic trial, thereby eliminating the need to reinvent what's already been invented.' Once the software has been built, tested, and improved, give it a go in the field by loading it onto portable devices, such as laptops or personal data assistants (PDAs), and delivering the pre-packaged software to the sites for the duration of a trial. Although internalizing a new way of doing things is often expensive and frustrating, the gratification the company's courage is sure to bring should remind them of the famous quote by Robert Frost: 'I took the road less traveled by, and that has made all the difference.'

DISCLAIMER: THE PROCESSES DESCRIBED IN THIS PAPER ARE SPECIFIC TO ALCON RESEARCH, LIMITED. AS A RESULT, THE FINDINGS PRESENTED MAY VARY ACROSS SPONSOR COMPANIES.

CHAPTER V ILLUSTRATION

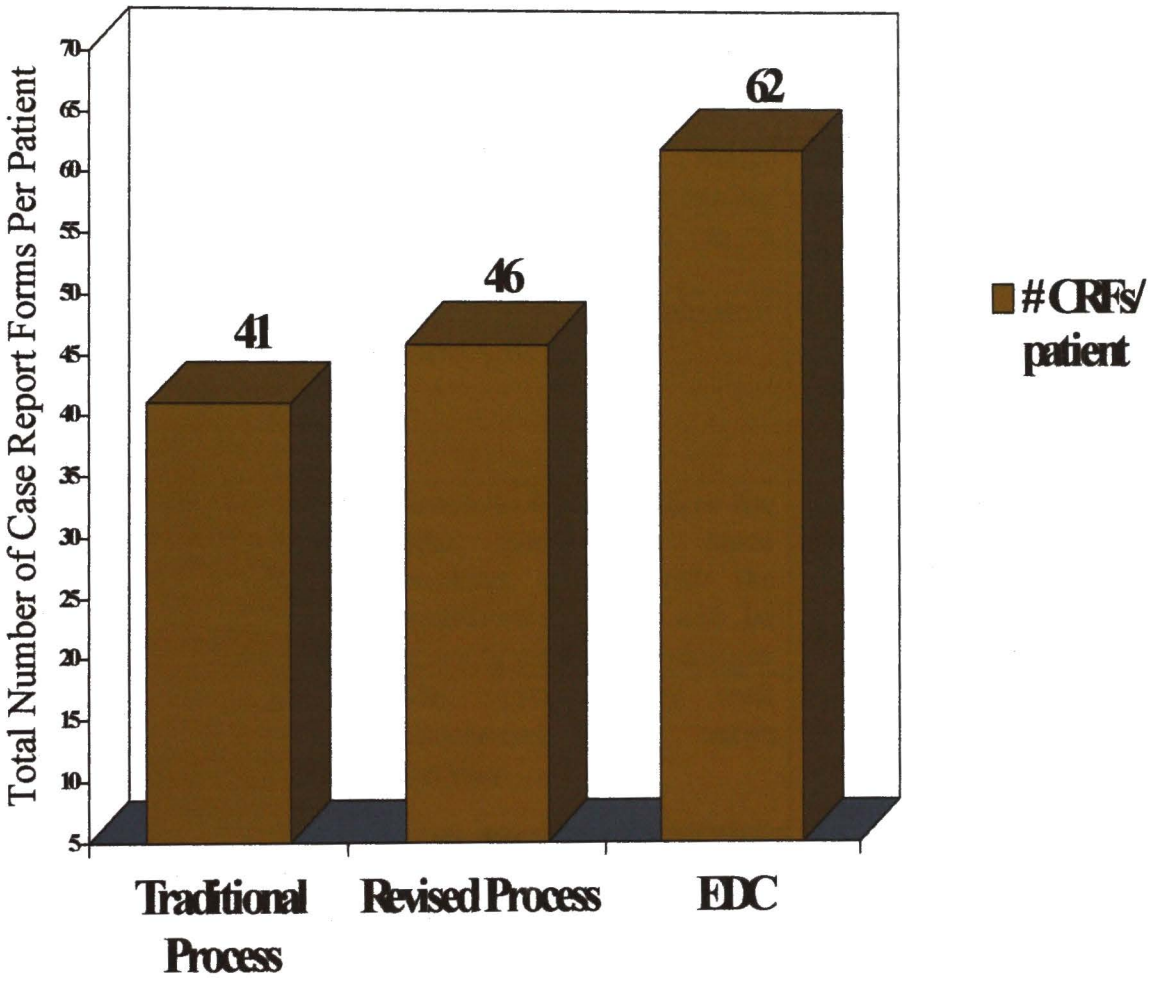


Figure 5: Total number of CRFs per patient by study

Table One: Summary of Advantages and Disadvantages of Paper-Based Trials and EDC

	Advantages	Disadvantages
Paper-Based Trials	Physically have the entire document in front of you so scrolling is not necessary and reviewing is quicker	Only one person can do their job at a time in sequential steps
	Can quickly and easily access a file without having to wait to log-on to a computer	Uses more file space and more office area
	Easier to track the physical paper CRFs	More people handle the pCRF so if anything goes wrong in the exchange, the paper can be misplaced and the lag time is increased
	Easier to identify where the data issues are since working copies with the traditional process will be given to request the changes	Negative impact on the environment
	The processes are well understood and more familiar	Must ensure CDM and clinical science are working with the most recent copy of the pCRF
		With the DCFs, chances of making an error when doing modifications are much greater
		DCFs are hard for CDM to track and keep up with
		Errors are not caught until they reach Alcon's CDM and by then the sites could have made the same error on other patients
		Must watch the data entry staffing because it is unpredictable when data will come in for a protocol
		Paper takes a lot of

		processing time (i.e. source to pCRF, shipment of pCRFs from site to sponsor, pCRF to data entry)
		Many issues with data may not be identified until the database is about to lock
Paper-Based Trials...cont.	**Advantages**	**Disadvantages**
		Receipt of AE and MM forms depends on how back logged CDM is at the time
		With the revised system of data management, the set up time for the edit check specifications is lengthy
		Data cleaning is very time consuming
EDC	Receive 'real time' e-mail notifications about AEs	More time consuming to understand the data structure
	Individuals can work independently of one another therefore some tasks do not have to be sequential	Software has cumbersome features
	Can store more data using less space	Switching between forms and panels is very slow
	Reduces the amount of paper used	E-mail notifications are not specific enough to quickly access the data
	Has less hands handling the data	Requires an increase in product safety personnel to continuously monitor the data
	Pre-programmed system edit checks to validate data as it is entered	Possible for a computer virus to prevent access to the data
	Eliminates the demand on data entry workforce	Numerous technical issues (including hardware and software problems)
	There is little, if any, transcription error	User awareness is low so training is difficult

	Gives the site immediate feedback so 'problems fix themselves quickly early on in the process'	The vendor's database not being set up to be compatible with Alcon's traditional database
	Better capacity to pick up problems and trends because the data is immediately available	Difficult to validate the sites and sponsor personnel for access to the database
	More likely to get cleaner data with EDC	Some of the investigators are unwilling to utilize a computer
	Decreases the number of database issues found at the sponsor company	Software performance varies from location to location
EDC...cont.	**Advantages**	**Disadvantages**
	Can ideally lock per patient instead of per study	Having to wait for the computer to start and log on to access the data
	Allows for continuous monitoring	Automatic log off/ idle time is too short
	Complete duties from any PC	

Table Two: Recommendations from the Sponsor's Clinical Team Members for EDC

ITEM:	RECOMMENDATIONS:
COMPUTER EQUIPMENT:	➢ Larger screen (~22" wide) for more visibility of the eCRF ➢ Provide 'ready-to-use' laptops or PDAs
SOFTWARE:	➢ Faster, more user friendly EDC system ➢ Option to split the screen to view multiple documents ➢ Make the action buttons more ergonomically spaced ➢ Compatible data structure with existing databases ➢ Alcon develop an in-house software in modules ➢ Ability to generate more helpful custom reports
AE NOTIFICATIONS:	➢ Specify whether it is an addition modification to the data ➢ Include a hyperlink to the system
TIMELINES:	➢ More preparation (~4 months prior to trial start)
DATABASE:	➢ Test field and panel set-up more ➢ More User Acceptance Testing
TRAINING:	➢ Simplify the training ➢ Eliminate the test to gain certification
INTERNAL CHANGES:	➢ Create standard operating procedures (SOPs) specific for EDC prior to another pilot ➢ Evaluate the mode of transmission at sites for study participation
DEPARTMENT BUDGETS:	➢ Increase the budgets to hire extra personnel and for specific training with EDC

APPENDIX A

INTERNSHIP EXPERIENCES

APPENDIX A

INTERNSHIP EXPERIENCES

Monday, June 9,2003—Received topic of thesis/research project and attended training sessions in the following areas:

1) Training Orientation
2) Legal Basics
3) Archives and Tour
4) Test Article Label Basics
5) Diseases and Alcon Products

Tuesday, June 10, 2003—Began search on electronic data capture (EDC) and compiling lists of contacts. Attended training sessions in the following areas:

1) IRB/IEC Basics
2) Research and Development (R&D) Systems and Organization and Program/Project Development

Wednesday, June 11, 2003—Continued literature searches on EDC and attended training sessions in the following areas:

1) Financial Disclosure Basics
2) Introduction to Alcon Clinical Research
3) Overview of Clinical Data Processing
4) Initiating Studies Basics

Thursday, June 12, 2003—Began to compile preliminary finding about EDC and streamline research goals and attended training sessions in the following areas:

1) Clinical Monitors Basics

2) Informed Consent/Assent

3) Study Management Planning

Friday, June 13, 2003—Met with T. Boyer from the library to see what data and resources they have available for my project. Drafted element one of the research proposal, summary, and attended training sessions in the following areas:

1) AE Basics

2) Final Clinical Data

Monday, June 16, 2003—Worked on "specific aims and significance' section of research proposal. Continued literature searches on EDC for thesis and research proposal and attended a training session on case report form (CRF) basics.

Tuesday, June 17, 2003—Attended an all-day training session on Introduction to Clinical Research Level I where we covered the following topics:

1) Investigational Product Development

2) Ethics, Research and the Law

3) Roles and Responsibilities

4) Clinical Study Design

5) Initiating Clinical Studies

Wednesday, June 18, 2003—Attended an all-day training session on Introduction to Clinical Research Level I where we covered the following topics:

1) Monitoring Basics I

2) Monitoring Basics II

3) Monitoring Workshop

4) Adverse Event Reporting

Thursday, June 19, 2003—Attended a welcome reception hosted by Alcon R&D for the clinical interns. Had an extensive meeting with on-site advisor, Judy, about proposal and revisions. Attended training sessions in the following areas:

1) Test Article Shipment/Return Basics
2) Study Files Basics
3) Report Completion Basics
4) Clinical Forms Basics

Friday, June 20, 2003—Attended training sessions in the following areas:

1) Introduction to Quality Management Systems
2) Marketing
3) International Clinical Development

Monday, June 23, 2003—Scheduled a meeting of committee members and Dr.Rudick for thesis project clarification. Went to the Health Science Center's library to search for journals needed. Got final signatures from Dr.Roque and Dr.Rudick on the Designation of Advisory Committee and Degree Plan forms and brought them to the Graduate School office for Dr.Yorio's signature and subsequent filing. Attended training sessions in the following areas:

1) Site Audit Basics
2) Introduction to Clinical Quality Assurance Unit (CQAU)

Tuesday, June 24, 2003—Met with the clinical team members on my project, including data management, adverse event coding, biostatistics, and SAS program manager. Scheduled first monitoring visit to Baylor Medical Center in Houston, TX. Attended training sessions in the following areas:

1) Health Economics (HE) Basics

2) Introduction to Biostatistics

3) Introduction to Global Regulatory Requirements

Wednesday, June 25, 2003—Met with on-site advisors, Judy and Terri, to brainstorm and finalize meeting agenda for committee member meeting this afternoon. Prepared packets for committee meeting and met with them (Dr. Bens attended as Dr.Atiles' representative) along with Dr.Rudick to discuss project and thesis expectations. Attended training sessions in the following areas:

1) Investigational Device Manufacturing/Pilot Line Tour

2) Monitoring Basics

Thursday, June 26, 2003—Worked on and completed research proposal and then submitted proposal to on-site advisors for reviewing. Signed up for Concur training class on 7/18/03. Attended a training session on the Eye Clinic.

Friday, June 27, 2003—Worked on the development of the survey that will be distributed to site coordinators and received input from advisor on survey. Received comments back on research proposal and began to correct proposal. Attended last day of three-week boot camp training on Introduction to Clinical Supplies Manufacture and Distribution.

Monday, June 30, 2003—Submitted corrected research proposal to on-site advisor. Reviewed clinical protocol, clinical investigator's brochure (CIB), source documents, and diaries/questionnaires in order to prepare for site visit on 7/3/03. Attended a training session on Clinical Data Management (CDM) Standard Operating Procedure (SOP) training.

Tuesday, July 1, 2003—Met with advisor to discuss site visit tasks, forms, etc. Read reference materials, including test article accountability, International Conference on Harmonization (ICH) guidelines, Clinical Trial Monitoring (Study Closeout), and the Ocular Glossary, to prepare for site closeout visit. Familiarized myself further with the protocol's study visit flowchart, forms to be used during closeout visits, and SOPs regarding closeout. Copied Quality Record Documents, including any correspondence, curriculum vitaes (CVs), licenses, etc., to bring to the site for review of regulatory binder.

Wednesday, July 2, 2003—Accessed our protocol's electronic case report forms (eCRFs) via the Phase Forward InForm database to familiarize myself with navigation through the data panels. Prepared packet to take with me on the site visit which included SOPs, reference information, forms, Code of Federal Regulations (CFR) booklet, notepad, and Phase Forward folder with instructions on the system.

Thursday, July 3, 2003—Went to clinical site in Houston (Baylor Medical Center). Observe on-site advisor's steps in closing out the site. Completed 100% source document verification against the eCRF on the computer while filling out a monitoring report as we proceeded. Completed test article accountability, checked and inserted documents into the regulatory binder. Reconciled the site documents in the investigator's study file to Alcon's file then caught flight back to Fort Worth.

Monday, July 7, 2003—Received on-site advisors' comments on research proposal and made the necessary corrections to it. Worked on drafts of flow charts for inclusion in the thesis. Went to Alcon's library where I did the following:

1) Cleared up misinformation that they had the Drug Information Journal when they did not.

2) Completed self-training requirements, which included Dolphin Material Safety Data Sheet (MSDS) web version, hazcom for employees, emergency evacuation, R&D environmental policy, control of non-critical electrical consumption, and tornado emergency.

Tuesday, July 8, 2003—Completed the last self-training item, waste minimization, and sent in training form to Quality Systems. Attended a clinical team meeting to discuss the requirements to lock the database for the study project I am evaluating. Met with Dr. Roque at University of North Texas Health Science Center (UNTHSC). Worked on the questions I will ask the clinical team members from the various departments within Alcon to evaluate their role differences between the two systems. Received input back on survey and incorporated the changes. Read protocol for a comparator study that uses paper CRFs.

Wednesday, July 9, 2003—Sent final draft of survey to committee members for review. Gathered required committee signatures for approval of the final draft of the research proposal. Received input on questions to the clinical team for revisions and continued to work on paper system flowcharts.

Thursday, July 10, 2003—Started trying to convert survey to an electronic format with the help of Linda Jones. Draft a cover letter to be included with the survey when sent out. Prepare another draft of questions for the clinical team. Read presentations about the Query Management Process. Spoke with Tracy Wu in data management about the current paper-based systems and received her input on the flowcharts that are done. Continued working on thesis flowcharts and called site coordinators to introduce the purpose of my survey and myself.

Monday, July 14, 2003—Received survey back in electronic form from Linda Jones. Made changes to survey letter per Judy's suggestion and new format. Worked on flowcharts per data management discussion and requested changes. Attended meeting for clinical's review of presentations to be given at the 'All Clinical Meeting.' Go to UNTHSC to do the following activities:

1) Pick up the journal articles I ordered
2) Return lab access card
3) Speak with Dr.Roque
4) File research proposal at the Graduate School

Tuesday, July 15, 2003—Got trained by Cullen on the following computer programs:

1) E-Z Web
2) Clinical Information Management Systems (CIMS)
3) Concur Express

Got passwords for the preceding programs and spoke with Cullen about data management (DM) systems. Read journal articles on EDC.

Wednesday, July 16, 2003—Followed-up on phone calls made to study coordinators about the survey who I did not reach initially. Sent out electronic copy and hard copy of survey to Baylor Medical Center's study coordinator and made spreadsheets to track surveys and interviews. Continued to read journal articles for thesis literature search. Received survey back from Baylor's coordinator.

Thursday, July 17, 2002—Received feedback from Cullen in clinical about current flowcharts (pack no.3) and modified them based on the comments. Began drafting the

background portion of the thesis. Started searching for metrics on a comparator study. Sent first packet of paper-based system flowcharts to on-site advisor for review.

Friday, July 18, 2003—Attended training for Concur CXS System and completed my July expense report. Compiled a packet of information for Judy to review and continued working on background information for thesis. Read more journal articles on EDC.

Monday, July 21, 2003—Changed the thesis layout and prepared an outline. Met with the data manager/ coordinator assigned to my department to confirm and gather metrics for thesis. Searched for metrics on a comparator study that used Alcon's traditional paper-based process and received patient listings about my study from on-site advisor.

Tuesday, July 22, 2003—Made an eCRF data-tracking sheet regarding availability and association between adverse events (AEs) and Concomitant medications. Worked more on thesis and read more information about EDC from a process improvement team (PIT) member, Tolgar B.

Wednesday, July 23, 2003—Worked on thesis more and completed spreadsheet for tracking the data on eCRFs. Gave advisor patient listings back along with the spreadsheet. Began looking for another comparable study that used the traditional paper-based process to compare the different systems of data management.

Thursday, July 24, 2003—Worked on thesis introduction and completed this section. Made changes to flowcharts based on advisor's suggestions and read the Code of Federal Regulations about 21 CFR Part 11 a little.

Friday, July 25, 2003—Made more progress on thesis. Attended an 'All Clinical Meeting' where the topics were:

1) Clinical Data Management Update

2) Drug Information Association (DIA) Trip Reports

3) CDM Clinical Experiences

Tuesday, July 29, 2003—Worked on thesis and prepared for site visit in San Antonio to experience monitoring a paper-based trial by doing the following:

1) Read Protocol to Gain an Overview of Study Procedures

2) Pack Refresher Materials and Forms that may be needed

Flew to San Antonio.

Wednesday, July 30, 2003—Went to site for interim monitoring visit. Observed a colleague, Kym, and completed 100% source verification of all patient charts (~18). Went through all queries with coordinator and got them resolved. Got the principal investigator (PI) to sign exit forms that were not done and flew back to Dallas.

Thursday, July 31, 2003—Worked on thesis a little more and updated resume'. Began copying site files for closeout visits to be sent to site for reconciliation with Investigator Study Binder. Spoke with a study coordinator about study survey for follow-up and sent the electronic format of survey and the hard copy to Dr.Berdy's study coordinator.

Friday, August 1, 2003—Continued and completed copying of files for closeout visits. Mailed study survey to next coordinator that will have site closed next week, 8/6. Read through thesis for general errors and e-mailed the thesis draft to Dr.Atiles.

Monday, August 4, 2003—Mailed hard copy of survey to Dr.Friedlander's office. Made changes to thesis per on-site advisors' comments and made an organizational chart of jobs as an appendix to the thesis. Explored within InForm to see what was the status of the site's conduct.

Tuesday, August 5, 2003—Worked on thesis more and redone questions to ask team members during interviews. Received feedback from a colleague on thesis flowcharts and continued to create flowcharts for electronic-based system.

Wednesday, August 6, 2003—Received the coordinator's completed survey from Dr.Berdy's office. Went through more background information on EDC, which was sent by Andy Richardson and mailed hard copy of survey to Dr.Baumgartner's office. Looked up the metrics on a comparator study, C-01-86, which used the traditional paper-based system.

Thursday, August 7, 2003—Made a spreadsheet/document to compare the data points for my timeline on two studies using different data management process, traditional paper process and a revised paper process. Attended a teleconference on the EDC-based trial and went to UNTHSC to give Dr.Rudick some paperwork and to pay for journal articles. Mailed the coordinator survey to Dr.Small's office and e-mailed electronic survey to Dr.Friedlander's office. Received patient listings from Judy to find various data such as:

1) Ocular History
2) Blepharitis History and Medications Used to Treat It
3) Primary Diagnosis

Made notes on the assignment to give to Judy for review.

Friday, August 8, 2003—Completed journal entries for the week and prepared hard copy of survey to bring with me to Dr.Sall's office. E-mailed electronic surveys to both Dr.Baumgartner's and Dr.Sall's study coordinators. Received completed survey from study coordinator at Dr.Baumgartner's office and worked on initial slides for the EDC process.

Sunday, August 10, 2003—Fly to Long Beach, CA for closeout visit.

Monday, August 11, 2003—Went to site to begin activities for closeout. Reviewed regulatory binder and reconciled investigator binder with Alcon's study binder to prepare site for a FDA audit. Observed advisor, Judy, and colleague, Kym, do 100% monitoring of eCRFs to source, including patient diaries. Made sure that the study coordinator had answered the queries generated during monitoring.

Tuesday, August 12, 2003—Flew back to DFW.

Wednesday, August 13, 2003—Mailed hard copy of surveys to Condemi and Kivitz and e-mailed electronic version of survey to Dr.Sall's office. Received completed surveys from study coordinator at Dr.Friedlander and from study coordinator at Dr.Small's office. Corrected questions for clinical team interviews and reviewed sites eCRFs on InForm who previously omitted Dry Eye or KCS from the patients ocular medical history. Requested patient listings of primary diagnosis from the data manager, Marla.

Thursday, August 14, 2003—Updated survey tracking sheet and made resume' changes per Judy's suggestions. Met with Judy about organization of discussion section in thesis and scheduled meetings with all clinical team members.

Monday, August 18, 2003—Confirmed meeting with IT/Programming representative, Anne Malloy. Brainstormed about how to present survey results within the thesis. Faxed survey to study coordinator at Dr.Scherrer's office. Began typing internship experience section of the thesis. Prepared for tomorrow's interview.

Tuesday, August 19, 2003—Met with Dr.Gross, Medical Monitor, for interview on EDC. Attended an 'All Employee' meeting with Dr.Cagle and other key Alcon personnel. Continued typing internship section of the thesis. Cancelled interview with Anne Malloy

and just sent her the questions to answer. Called to confirm tomorrow's interview with Mary-Lou Keating, data coordinator. Went to UNTHSC to meet with Dr.Roque to do the following:

1) Review and Sign the Faculty Assessment Form
2) Complete my 'Intent to Graduate' Form
3) Discuss the progress of my thesis

Wednesday, August 20, 2003—Interviewed Mary-Lou about traditional and current data management systems along with her perceptions on EDC. Confirmed interview with Greg in Product Safety. Got patient listings for primary systemic diagnosis to compare with non-ocular medical history and make sure the diagnosis is listed on the medical history. Created a spreadsheet for patients whose non-ocular medical history did not contain the listed primary systemic diagnosis. Turned in spreadsheet to Judy to continue the process of 'cleaning' the database and evaluating patients ability to be evaluated in the final statistical analyses.

Thursday, August 21, 2003—Interviewed Greg Sullins in Product Safety to capture his perceptions on EDC and paper-based trials. Received more patient listings from Judy to aid in the 'cleaning' process for the database. Looked at patients who took excluded medications and found at what visit the medication was started and dropped to see what visits would be evaluable. Made a report of the excluded medications and the associated visits. Revised the electronic system's flowcharts per Greg's suggestion on the Product Safety Workflow to include their reporting in an annual safety report or immediately to the FDA. Began generating a timeline for one of my comparator studies that uses the

revised data management workflow process. Began a spreadsheet for the study coordinator's responses to my survey.

Friday, August 22, 2003—Began generating prototype graphs for the survey responses and continued with developing the timeline illustrations. Made a document to track the patients that were screen failures after the receipt of vehicle along with the reason for failure. Revised the excluded medication sheet based on Dr.Gross, medical monitor, comments, which included deleting some patient visits altogether so that they will not be included in the efficacy statistics. Sent Dr. Roque examples of the data, including a bar graph and a timeline.

Monday, August 25, 2003—Scheduled a Committee Meeting for October 8, 2003 and waiting for responses. Continued to work on timeline for revised data management system. Typed responses from Greg's (Product Safety) interview. Called and confirmed tomorrow's interviews with Gary and Diane, SAS Programmers, and with John, Sr. CRS. Organized surveys and reviewed the responses to see what questions needed follow-up. Called the study coordinators whose answers were vague or incomplete.

Tuesday, August 26, 2003—Interviewed Gary and Diane about their job as a SAS Programmer in relation to the paper-based and EDC systems and received general recommendations and comments on EDC and its effect on their workload. Rescheduled meeting with John, the Senior CRS on this study, for after database lock due to the lack of his time. Began generating the pictorial timeline for the comparator study that used the traditional paper-based data management process with the working photocopies of CRFs. Worked more on the draft of the thesis. Looked on E-Z Web to get some dates for the protocol done with working copies such as the final date the protocol was signed, etc.

Wednesday, August 27, 2003—Completed the timeline for the revised data management process with paper-based trials. Drafted a plan for reporting results and data for the thesis, outlining the goals to prove/disprove from the proposal and the ideas to reach that goal. Submitted timeline for review to onsite advisor on traditional processes. Listened to Dr.Gross's interview, wrote his responses down to type up, and typed his responses into a Word document. Listened to, wrote Gary and Diane's comments (SAS programmers) from the interview, and typed up their responses into a Word document. E-mailed Dina, biostatistics, and Darell, biostatistics and data management supervisor to confirm tomorrow's interviews.

Thursday, August 28, 2003—Interviewed Dina and Darell on their perceptions and outlook regarding EDC and the paper-based processes. Continued typing up the internships activities section of the thesis and began gathering timeline data points for C-02-42. Received last study coordinator survey from Dr.Condemi's office. Attended a weekly teleconference with the data manager, Phase Forward, and other clinical team members.

Friday, August 29, 2003—Began placing the dates for C-02-42 into a timeline. Interviewed Fred Schneiweiss, Product Safety AE Coding, about EDC and paper-based data management processes. Began listening to Dina and Darell's interviews to type up on the computer. Revised PowerPoint slides with flowcharts per Darell's suggestions and continued proofing the thesis up to this point. Assisted the study coordinators with looking at the database and contacting sites with outstanding issues.

Tuesday, September 2, 2003—Make follow-up phone calls to study coordinators whom still had outstanding queries in their eCRFs. Scan through all eCRFs with Kym to see

what queries were opened and where, while closing queries that had been answered. Send follow-up e-mails about queries

Wednesday, September 3, 2003—Finalized timeline data that I had accumulated for the EDC study with Marla, data manager, to ensure the dates were accurate. Finalized the construction of the EDC timeline, with the exception of a few dates that can not be attained until after the database lock, and submitted it to Judy for review. Received Judy's comments on my brainstorm for presenting the data and revised my approach to a few per her suggestions. Continued proofreading the thesis material I had typed thus far.

Thursday, September 4, 2003—Continued generating my graphs and charts from the study coordinators' surveys and submitted them to Judy for review. Updated the October 8th Committee Meeting in an e-mail to all members to change the times from 10:00 a.m-11:30 a.m. to 10:30 a.m.-noon due to room scheduling conflicts. Completed last week's journal entries.

Friday, September 5, 2003—Completed this week's journal entries for Judy to sign and typed the journal entries in the thesis draft up to this point. E-mailed Brad Wooldridge, Regulatory Affairs, to confirm our 10 o'clock interview. Interviewed Brad for a perspective of EDC's impact on Alcon's business practices and on his job responsibilities. Began writing results and discussion section of the thesis.

Tuesday, September 9, 2003—Continued writing results and discussion section. Modified timeline for electronic-based process and went to Mary-Lou, data coordinator, to see how to find timeline metrics for C-01-86, the traditional-based study.

Wednesday, September 10, 2003—Modified timeline for the revised data management process and changed the results and discussion section of the thesis to include the

descriptions of the different processes in the background section. Listen to Brad Wooldridge in regulatory affairs interview and made some notes.

Thursday, September, 11, 2003—Get on CIMS to find C-01-86 query metrics by seeing what CRF pages had modifications and for what site and patient so that I can manually look through the CRS's files to follow the audit trail. Finished making changes to the thesis and gave it to Judy for review. Made a spreadsheet for C-01-86 query metrics and talked with Judy about more metrics for C-02-42. Judy e-mailed Phase Forward requesting a listing of query dates after the last closeout visit.

Monday, September, 15, 2003—Scheduled interview with John Peeler, Senior CRS for EDC pilot. Continued listening and transcribing interviews with Brad and Fred. Made changes to some of the graphs and began a spreadsheet for the sponsor's clinical team process preference so that I can generate a pie chart.

Wednesday, September 17, 2003—Received comments from onsite advisors, Judy and Terri, about my thesis content and structure. Continued working on the results and discussion section. Manually search through the C-01-86 files to find the query metrics for the traditional process by looking at the time/date stamps on each modified CRF working copy and added query metrics for the traditional CDM process timeline. Made changes to the revised timeline.

Thursday, September 18, 2003—Wrote my findings about how EDC was accepted by study coordinators and finalized the changes to the traditional and revised timelines to date. Created more pie charts to show 1-Do study coordinators recommend Alcon and other companies to use EDC? 2-Prior to study start, how did study coordinators feel EDC

would impact their duties? 3-Did EDC reduce the amount of time the study coordinator spent recording data for the study?

Friday, September 19, 2003—Incorporated the suggested changes to the thesis from onsite advisors and changed the thesis format to include a methodology section. Wrote the methodology and my findings about how the sponsor's goals were/were not met with EDC. Submitted the results and discussion section up-to-date along with the methodology to Judy for review.

Thursday, September 25, 2003—Get the packet submitted to Judy so that I may add more. Continued typing the results and discussion section and created more pie charts. Read through the guidelines for preparing the thesis and made changes to the timelines. Contacted Darell, senior manager of CDM and Biostatistics, to get the CDM budgets for 01-86 and 03-02 also received a spreadsheet from Marla with C-02-42's up-to-date expenses. Contacted Ovation pipettes and Sonomed about how to calibrate the digital pipettes and pachymeter. Typed up the calibration instructions for Judy.

Friday, September 26, 2003—Received an e-mail from Phase Forward (Dennis) about finding the number of queries from the last closeout visit to the date of database lock. Typed up a potential table of contents, numbered illustrations and charts, and compiled a packet of the thesis with illustrations, table of contents, etc. for submission to Judy for review.

Monday, September 29, 2003—Continued writing journal entries for the previous week and typed up internship experiences to date. Check out a few theses from UNTHSC and set up an appointment to meet with Dr.Roque on Wednesday, October 1st. Discussed

formatting options with Judy for the thesis and ordered dividers for the committee meeting binders.

Tuesday, September 30, 2003—Continued typing the results section of the thesis and began the discussion section. Spoke with Marla about query metrics for the EDC trial.

Wednesday, October 1, 2003—Compiled a thesis draft to bring to Dr. Rudick to review and met with Dr.Roque to go over thesis formatting and organization. Re-numbered the charts and figures and re-typed the thesis' table of contents. Completed typing the results section.

Thursday, October 2, 2003—Attended the weekly teleconference with the clinical team and Phase Forward to: 1-request custom reports for study metrics 2-discuss dates for 'Lessons Learned' 3-discuss new developments with the trial. Continued typing the discussion section.

Friday, October 3, 2003—Organized the drafts of the thesis in binders with the appendices and table for all the committee members to review prior to the meeting. Began working on PowerPoint presentation for committee meeting and set up an individual meeting with Dr. Atiles for October 14th.

Monday, October 6, 2003—Continued working on PowerPoint presentation for committee meeting and made some revisions in the wording of the thesis.

Tuesday, October 7, 2003—Completed slide presentation for committee meeting and e-mailed the slides to Darell and Terri for review. Mailed Dr. Atiles his copy of the thesis and the 'Intent to Defend' form for his signature.

Wednesday, October 8, 2003—Met with advisory committee to present my thesis material to date and received suggestions for revising my presentation as well as the

thesis. Re-evaluated all the data and began making changes per the committee's suggestions

Thursday, October 9, 2003—Typed new evaluation of each piece of data and continued making changes to the thesis. Generated another graph related to the drug development timelines for an added in-depth evaluation.

Friday, October 10, 2003—Continued making revisions to the thesis material.

Monday, October 13, 2003—Completed making the changes in the thesis manuscript and began revising the presentation. Received modifications to the original thesis draft from Terri and began making the changes. Rescheduled tomorrow's meeting with Dr. Atiles for Thursday, October 16th when all the changes and presentation should be done.

Tuesday, October 14, 2003—Completed the revisions to the PowerPoint presentation. Submitted the new slides to Judy for review.

Wednesday, October 15, 2003—Inventoried supplies for the dry eye studies (i.e. pipettes, pachymeters, pipette tips, etc.). Renumbered the table of contents for the thesis and typed the internship experiences up-to-date. Scheduled meeting with Judy, Terri, Darell, and Marla to present findings on EDC for October 27th at 8:30 a.m. Went to UNTHSC and filed 'Intent to Defend' form.

Thursday, October 16, 2003—Reviewed slides with Judy and began making corrections to the presentation. Met with Dr. Atiles at MedTrials to go over thesis manuscript.

Friday, October 17, 2003—Complete the revisions suggested for the PowerPoint slides. Submitted a hard copy and an electronic copy of the slides to Judy for review and e-mailed the remaining committee members the slide presentation for them to review also. Alphabetized the literature citations and re-numbered the references in the thesis. Spoke

with Dr. Rudick to ask if the internship experiences section could be an appendix and she said yes it could. Removed the internship experiences section from the thesis and made it an appendix.

Monday, October 20, 2003—Revised the table of content pages and made revisions to the thesis manuscript. Re-organized and re-numbered the charts, graphs, and illustrations based on the new table of contents. Received suggestions for revisions to the slide presentation.

Tuesday, October 21, 2003—Made the necessary revisions to the slide presentation. Proofread the thesis manuscript. Begin compiling final drafts for committee members.

Wednesday, October 22, 2003—Mailed final draft of the thesis to Dr. Atiles for review and gave onsite advisors their final copy also. Practiced presenting slides and spoke with a department head from Consumer Products and Retina about the availability of a contract position. Printed transparencies of slide presentation as a back up for tomorrow's practice presentation with Judy.

Thursday, October 23, 2003—Practiced with Judy giving the EDC presentation and made revisions based on comments from the practice session. Wrote up notes for slide presentation. Finished compiling the necessary drafts of the thesis for Dr. Simecka and Dr. Roque.

Friday, October 24, 2003—Practice presenting for EDC presentation on Monday. Brought the final drafts of the theses to Drs. Roque and Simecka to begin reviewing prior to the thesis defense.

Monday, October 27, 2003—Gave EDC presentation to Darell who is the Senior Director of Data Management and Biostatistics, Marla who is a Data Manager, and Judy, my

onsite advisor. Reviewed the thesis formatting (i.e. margins) to ensure that it met the school's requirements.

Tuesday, October 28, 2003—Made revisions to the slide presentation based on yesterday's presentation to data management. Submitted final packet of slides to Terri for review by the 'clinical roundtable committee.' Made minor changes to the thesis manuscript's disclaimer.

Wednesday, October 29, 2003—Worked on thesis organization.

Thursday, October 30, 2003—Worked on thesis organization.

Friday, October 31, 2003—Worked on thesis organization.

APPENDIX B

STUDY COORDINATOR SURVEY

Survey for Protocol A: Dry Eye Protocol

This survey will help to capture your perceptions on this study. Please answer all the questions to the best of your ability.

I. Demographic Data

1. Please mark your sex.
   - ☐ Female
   - ☐ Male

2. How many years of clinical research experience do you have?
   - ☐ Less than a year
   - ☐ 1-3 years
   - ☐ 3-6 years
   - ☐ 6 or more years

3. What area do you work in?
   - ☐ Rheumatology
   - ☐ Ophthalmology
   - ☐ Other:_____

4. Do you have an additional role within this office outside of this study?
   - ☐ Yes (go to next question)
   - ☐ No (skip to question 6)

5. What additional role do you hold within this office?(check all that apply)
   - ☐ Nurse
   - ☐ Receptionist/ Secretary
   - ☐ Business/ Office Manager
   - ☐ Office/ Lab Technician
   - ☐ Other:_____

6. Overall, how much is a computer used for this job?
   - ☐ Minimally
   - ☐ Moderately
   - ☐ Excessively

7. How computer savvy would you rate yourself?
   - ☐ Little
   - ☐ Somewhat
   - ☐ A lot
   - ☐ Not at all

II. Experience/ Familiarity with EDC

1. Prior to this study were you familiar with what EDC was?
   - ☐ Yes
   - ☐ No

2. What benefits did you expect from EDC?(check all that apply)
   - ☐ Reduce amount of coordinator involvement
   - ☐ Cleaner data
   - ☐ Fewer queries
   - ☐ Fewer follow-up questions from sponsor
   - ☐ Reduce time of sponsors on-site
   - ☐ Other:_____

3. Have you used EDC previously in the conduct of another study?
   - ☐ Yes
   - ☐ No (skip to section III)

4. How often have you used EDC before?
   - ☐ Once
   - ☐ Twice
   - ☐ Three or more times

5. Relating to the previous study in which EDC was used, how would you rate the overall experience?
   - ☐ Great, I could hardly wait to use EDC again and did not want to use paper CRFs again.
   - ☐ Somewhat good, I liked it, but needed more experience with EDC to confirm my preference of it vs. traditional data collecting on paper CRFs.
   - ☐ Okay, It was not what I envisioned, but I would not be opposed to using EDC again.
   - ☐ Terrible, I hoped I'd never have to use EDC again.

III. Current Perceptions of EDC in relation to this study

1. Prior to study start, how did you feel EDC would impact your duties on this study?

   ☐ Make my duties easier and more timely

   ☐ Make my duties more complex and slow me down

   ☐ Would not impact my duties in any way

2. The following questions ask about specifics of EDC's impact on various aspects of this trial (please circle your responses based on the numbered scale):

		1-Definitely	2-Somewhat	3-Not at All
i.	Overall, EDC decreased the # of CRF queries	1	2	3
ii.	Overall, EDC made the conduct of this trial more timely	1	2	3
iii.	EDC reduced follow-up questions from sponsor	1	2	3
iv.	EDC reduced my follow-up questions	1	2	3
v.	EDC reduced the monitors' time on-site	1	2	3
vi.	EDC reduced the amount of time I spent recording data for this study	1	2	3
vii.	EDC made my data more accurate	1	2	3
vii.	Phase Forward was helpful answering questions related to the system	1	2	3
viii.	Alcon was helpful answering questions related to the system	1	2	3

2. As of now, I will do another trial using EDC with Alcon's current system.

   ☐ Yes

   ☐ No (go to next question)

3. If modifications were done to Alcon's current EDC system, I would do another EDC trial.

   ☐ Yes

   ☐ No (if not, please provide a reason)

   _____

   _____

   _____

IV. Future Promise of EDC

1. How long do you anticipate it will take for the industry to totally adopt EDC as a way of routinely conducting clinical research studies?

   ☐ 1-5 years

   ☐ 5-10 years

   ☐ >10 years

   ☐ Never

2. Would you recommend Alcon and other companies to use EDC in the conduct of studies?
   - ☐ Yes
   - ☐ No

3. What area of EDC, in your opinion, needs the most improvement?
   - ☐ Software Design
   - ☐ Training/ Technical Support
   - ☐ Data Entry
   - ☐ Data Transmission
   - ☐ Needs No Improvements

4. What area of EDC, in your opinion, needs the least improvement?
   - ☐ Software Design
   - ☐ Training/ Technical Support
   - ☐ Data Entry
   - ☐ Data Transmission
   - ☐ Needs No Improvements

5. How do you believe that EDC will impact the following areas once it has been around a while and been perfected?

	1-positively	2-negatively
i. Communication with Sponsor	1	2
ii. Ease of Job	1	2
iii. Overall Efficiency of the Trial	1	2

Please provide any additional comments and/or recommendations pertaining to the EDC system associated with this trial:

_____

_____

_____

_____

_____

Thank you for taking time to complete this survey. Your comments will provide valuable insight to future applications of this system to clinical conduct.

APPENDIX C

INTERVIEW QUESTIONS

- Briefly describe my logic of each system and how I reference them.
- Give interviewee the flowcharts to review.

Questions for Clinical Team Members

1. What is the primary responsibility of your job?

2. What are your duties within the conduct of a trial in relation to your job responsibilities?

Okay, now let's talk more specifically about the process of Case Report Form entry, validation, and review. We will begin with the old system of CRF processing which includes using working CRF photocopies and I-review for query generation.

3. In relationship to your duties, what are the advantages, i.e. things you like, about the old system of data management, which uses the working copies of CRFs and I-review for query generation?

4. On the other hand, what are the disadvantages, with respect to your duties, about the old system of data management, which uses the working CRFs and I-review for query generation?

Okay, let's switch gears and focus on the new CDM process which incorporates electronic edit checks (SEND, COR, and MANUAL) on automatic DCFs.

5. What are the advantages, i.e. things you like, about the new system of data management using electronic edit checks and automatic DCFs for data queries?

6. What are the disadvantages, i.e. things you do not like, about the new system of data management using DCFs for data queries?

7. In comparison with the recent new way of data management, which uses data clarification forms and automatic edit checks, are there any significant changes in the application of your duties? Have any of your duties been eliminated or added to? How?

Now, we must move into the unknown. Let's talk about the pilot trial run here at Alcon with Electronic Data Capture on electronic CRFs.

8. Have you ever worked with an electronic study either here or somewhere else?

9. In relationship to your duties, what are some of the advantages you perceive about the EDC system with electronic CRFs?

10. What are some of the disadvantages you have experienced with the EDC system of data management with electronic CRFs?

11. Have any of your duties been eliminated or added to by this new pilot EDC system? How?

12. Do you prefer working with ClinTrials or electronic CRFs, aside from the fact that EDC is a new process for Alcon?

13. What recommendations for your job role would you make for future applications of EDC based on this experience?

14. Once the process has been perfected, how do you project that EDC will impact Alcon's business practices if adopted as a new way of doing things?

APPENDIX D

ACRONYMS

LIST OF ACRONYMS

AE	Adverse Event
AEF	Adverse Event Form
CDM	Clinical Data Management
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
CIMS	Clinical Information Management System
COR	Correction Needed
CQAU	Clinical Quality Assurance Unit
CRA	Clinical Research Associate
CRF	Case Report Form
CRS	Clinical Research Scientist
CSR	Clinical Study Report
CV	Curriculum Vitae
DIA	Drug Information Association
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HE	Health Economics
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
IT	Information Technology
KCS	Keratoconjuctivitis Sicca
MM	Medical Monitors
MSDS	Material Safety Data Sheet
NCR	Non-Carbon Reporting (Paper)
NDA	New Drug Application
PC	Personal Computer
PDA	Personal Data Assistants
pCRF	Paper Case Report Form
PI	Principal Investigator
PIT	Process Improvement Team
PS	Product Safety
R&D	Research and Development
SAS	Statistical Analytical System
SOP	Standard Operating Procedures

REFERENCES

1. Alcon Laboratories, Inc., "Alcon Clinical Roundtable Meeting: 21 CFR Part 11," November 19, 2002.

2. Alcon Laboratories, Inc., "All Clinical Meeting: Clinical Data Management Definitions," July 25, 2003.

3. Alcon Laboratories, Inc., "PROC-0001994: Clinical Monitors," Alcon Standard Operating Procedures, version 3.0.

4. Alcon Laboratories, Inc., "PROC-0002003: Case Report Forms," Alcon Standard Operating Procedures, version 3.0.

5. Alcon Laboratories, Inc., "PROC-0002008: Initiating Clinical Studies," Alcon Standard Operating Procedures, version 2.0.

6. Alcon Laboratories, Inc., "PROC-0002016: Monitoring," Alcon Standard Operating Procedures, version 3.0.

7. Alcon Laboratories, Inc., "PROC-0002017: CRF Correction," Alcon Standard Operating Procedures, version 2.0.

8. Alcon Laboratories, Inc., "PROC-0002023: Clinical Data Validation," Alcon Standard Operating Procedures, version 1.0.

9. Alcon Laboratories, Inc., "PROC-0002680: Database Close & Lock," Alcon Standard Operating Procedures, version 2.0.

10. Alcon Laboratories, Inc., "PROC-0003163: Data Handling," Alcon Standard Operating Procedures, version 2.0.

11. Alcon Laboratories, Inc., "PROC-0003165: CRF Design," Alcon Standard Operating Procedures, version 2.0.

12. Alcon Laboratories, Inc., "PROC-0003178: Database Design," Alcon Standard Operating Procedures, version 2.0.

13. Alcon Research, Ltd., "Clinical Research: Level I: Roles and Responsibilities," June 2003 version.

14. Bleicher, P., "E-trials: Faster, better and cost effective," *Current Drug Discovery*, September 2002: 35-39.

15. Bohaychuck, W., Ball, G., Lawrence, G., and Sotirov, K., "Data Integrity Needs Upgrading," *Applied Clinical Trials*, January 1999.

16. Bunn, Graham, "Scaling up EDC," *Applied Clinical Trials*, August 2002 Supplement, 11 (8): 12-14.

17. Clinical Data Processing/ Biostatistics, "Data Entry Guidelines," Alcon Training Session (May 2003)

18. Dimenas, E., Johansson, D., Palmblad, M., and Wrangstadh, M., "Clinical Operations Online (COOL)—A worldwide web-based approach to running clinical trials: Results from two international multicenter gastrointestinal trials," *Drug Information Journal*, 35 (3): 754-753 (2001).

19. Food Drug and Administration, United States Code of Federal Regulations: Title 21—Food and Drugs, April 2002.

20. Haskell, Thomas, "What You Should Expect from a User-Friendly EDC Solution," *European Pharmaceutical Contractor*, Spring 2002: 98-100.

21. Intrasphere Technologies, Inc., "Implementing Electronic Data Capture to Achieve Maximum Value," www.jussim.com/pdf/implementingedc.pdf.

22. Jacobson, Anne, "A Historical Review of Electronic Data Capture," *EDC In Depth*, Issue No. 1.1 (2002).

23. Keating, Mary-Lou, "Clinical Data Processing," Alcon Training Session (2003).

24. MacGarvey, A., "An E-Clinical Solution," *Current Drug Discovery*, October 2002: 33-35.

25. Medtrials, Inc., "Aligning the Art and Science of Clinical Research," © 1999-2002.

26. Mousley Consulting, Inc. and EDC Management, "Moving from Paper to Electronic Case Report Forms (eCRFs)—The Electronic Data Capture," www.edcmanagement.com/presentations/kirk_1/edcpres1_files.

27. Nell, M. and Bleicher, P., "Keeping online in-line: Web data management in clinical trials," *Good Clinical Practice Journal*, 7 (1): 8-10 (2000).

28. Pellegrino, Tim, "Supporting EDC in a Clinical Trial Environment," *Applied Clinical Trials*, August 2002 Supplement, 11 (8): 16-19.