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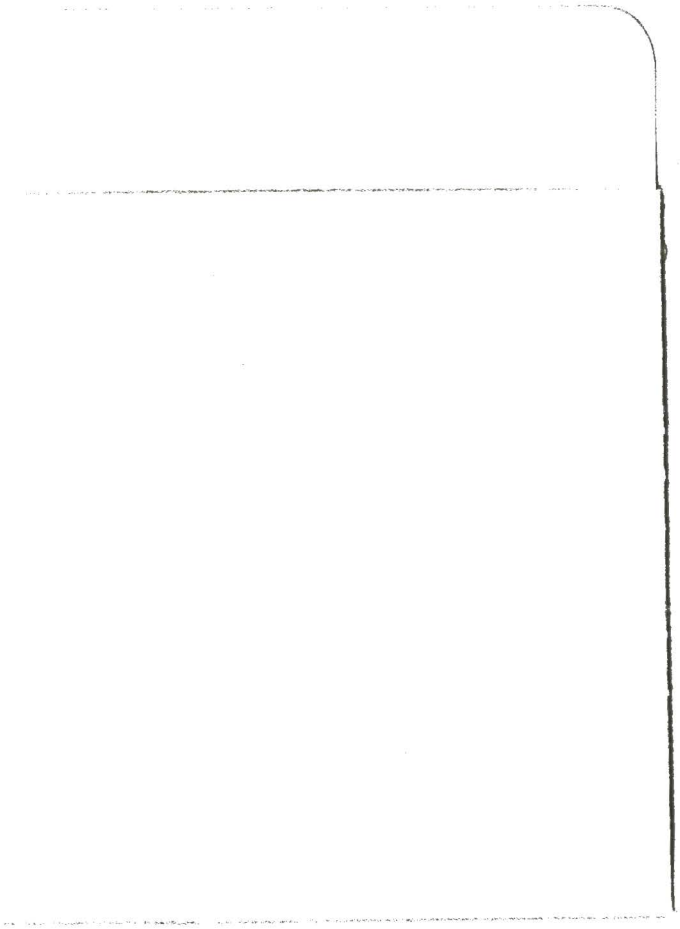

ERGONOMIC EFFICIENCY FIELD EVALUATION OF THE C-03-35 INTRAOCULAR LENS DELIVERY SYSTEM

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THESIS

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MASTER OF SCIENCE

By

Michal Kajtoch, B.S.

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INTRODUCTION

Cataract is a degenerative disease in which the eye's lens gradually becomes clouded leading to vision loss. The most common type of cataract is associated with the aging process, and it is also the leading cause of blindness in the world. It is not known exactly what causes cataracts, however, smoking, diabetes, excessive exposure to sunlight, or even iris color may play a role.[1-2] In the early stages of cataract, only a small part of the lens may become clouded, which may not cause a significant problem for the patient. The physician may choose to treat early stage cataracts with a non-surgical approach that may reduce vision problems by way of more powerful eyeglasses and stronger lighting. However, over time when the disease clouds enough of the lens making vision dull and blurry, surgery will be necessary. A surgeon can successfully treat cataracts by removing the clouded natural lens and replacing it with an artificial intraocular lens.[3] (Figure 1)

Cataract surgery, which today is safe and effective, starts with the surgeon making a small incision on the side of the cornea or sclera through which a phacoemulsification instrument is inserted that breaks up the cloudy center of the lens using ultrasound waves. The lens is then extracted from the eye by suction leaving the capsular bag that normally holds the lens intact. The artificial intraocular lens is then placed inside the capsular bag through the same small incision. It is important that the phacoemulsification incision is not significantly increased during the delivery and placement of the intraocular lens,

because the incision may induce astigmatism in a previously spherical eye. A smaller incision size will produce a lesser postoperative astigmatism, resulting in a more stable visual acuity.[4-7] Other benefits of reduced incision size include self-sealing (no stitch) closures, reduced recovery time, and decreased use of postoperative drug therapy.[8, 3] Today, due to these benefits, most surgeons use foldable intraocular lenses that can be positioned through the small phacoemulsification incision. Most foldable intraocular lens incisions are about 3.2-3.8 mm.[9]

Intraocular lens

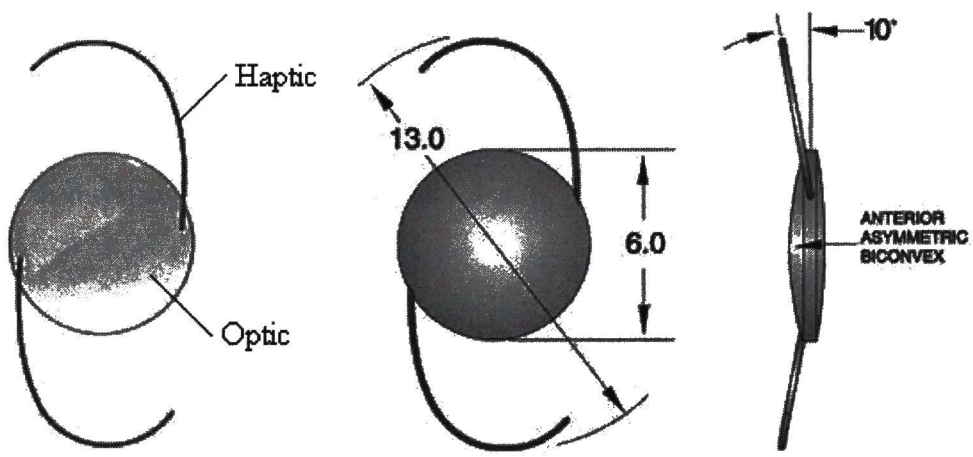

Figure 1: Diagram of an intraocular lens used for implantation following the removal of a cataractous lens.

BACKGROUND

There are three common materials utilized for the development of intraocular lenses. These materials include polymethylmethacrylate (PMMA), silicone, and acrylic. PMMA is a hard plastic used in the manufacture of rigid (non-foldable) intraocular lenses. This material was used to shape the first intraocular lens by Sir Harold Ridley, MD in 1949.[10] Silicone and acrylic have flexible physical properties that may be employed in the development of foldable intraocular lenses. The foldable intraocular lenses have an important advantage over PMMA rigid lenses, since the final incision size of cataract surgery is governed mainly by the enlargement of the phacoemulsification incision that is required to insert the intraocular lens. Today, phacoemulsification can be performed through an incision as small as 1.4 mm,[11] which is significantly smaller than the diameter length of 5.0 – 7.0 mm of the average intraocular optic. Rigid PMMA intraocular lenses typically require a considerably larger surgical incision than foldable intraocular lenses. Due to the benefits to the patient's final visual acuity and recovery resulting from the smaller incision size, surgeons often opt to implant flexible foldable intraocular lenses.

The design of an ideal foldable intraocular lens requires the lens to unfold in a safe and controlled manner. It is important for the foldable intraocular lens to unfold slowly once inserted, since violent unfolding may damage the capsular bag. When compared to a lens made of silicone material, an acrylic lens has the ability to unfold

more slowly, thus providing the surgeon with increased control of lens implantation.[12] The acrylic material also exhibits a refractive index in excess of 1.55, resulting in a thinner optic that further decreases the risk of injury to the patient such as iris chafing or formation of a posterior synechiae.[12]

There are various methods of inserting the foldable intraocular lens through the incision. One common method requires the surgeon to use forceps to fold and implant the intraocular lens. Although a skilled surgeon may not find this task challenging, it does leave room for error. While folding the intraocular lens, the surgeon must take precautions not to scratch the optic or damage the haptics (Figure 1). This, however, is difficult to ensure since damage to the delicate intraocular lens usually isn't apparent until after implantation is complete. Alcon Laboratories offers the ACRYPAK® folder (Figure 2), which is a device used to safely fold ACRYSOF® acrylic foldable intraocular lenses.[13] Once folded using the device, the surgeon can grasp the intraocular lens with forceps and deliver the lens into the capsular bag. (Figure 3)

ACRYPAK® Folder[13]

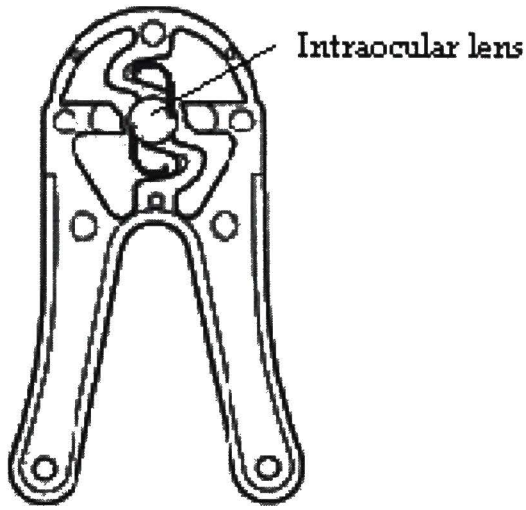

Figure 2: Diagram of an Alcon ACRYPAK® folder used to safely fold ACRYSOF® acrylic foldable intraocular lenses.

Resulting fold using the ACRYPAK® Folder[13]

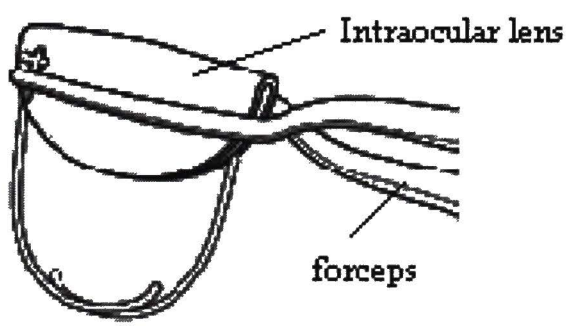

Figure 3: Once folded using the ACRYPAK® folder, the intraocular lens is grasped with forceps ready for implantation.

Another method for intraocular lens implantation is the use of an injector delivery system. A delivery system is capable of folding and inserting the intraocular lens in a predictable and reliable fashion, which helps to decrease the risk of damage that may occur to the intraocular lens as well as reducing surgery time. The use of an injector delivery system to insert the intraocular lens also provides a lesser change in wound diameter than a forceps inserted lens. [14] Due to the simplicity and ease of use associated with a delivery system, this method is often preferred over the forceps technique. Many delivery systems require the surgeon to place the intraocular lens in a special cartridge, which is then inserted into the delivery system. After cartridge loading, the surgeon can advance the intraocular lens through the delivery system in a predictable manner. The folded intraocular lens is subsequently released through the tip of the delivery system into the capsular bag.

MONARCH® II is the injector delivery system currently offered by Alcon Laboratories (Figure 4). It consists of a reusable titanium hand piece plus a disposable cartridge, which requires loading with an Alcon ACRYSOF® intraocular lens. [15] Loading the cartridge is accomplished using forceps to insert the non-folded ACRYSOF® intraocular lens into a cartridge (Figure 5), after which the intraocular lens-containing cartridge is inserted into the reusable titanium hand piece. The surgeon can then advance the lens through the cartridge by turning a knob built into the hand piece. This method offers the surgeon control not found with the forceps technique, because the lens-containing cartridge is introduced into the wound more easily than forceps. [16] It also allows the surgeon to deliver the intraocular lens through the tip of the cartridge in a

predictable manner, folded in an optimal fashion ensuring the final cataract incision is similar to the size of the cartridge tip opening.

MONARCH® II Delivery System[13]

Figure 4: MONARCH® II Delivery System is the predecessor of the C-03-35 Delivery System.

MONARCH® II Cartridge Loading[13]

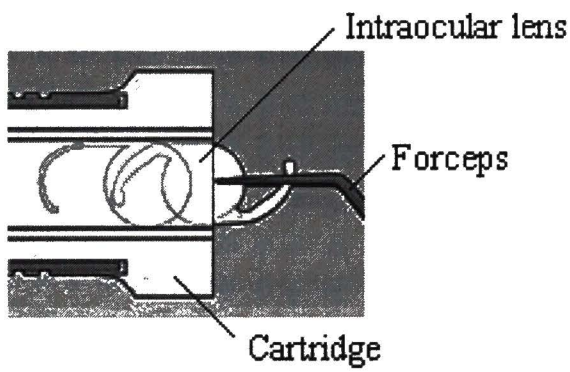

Figure 5: MONARCH® II Delivery System requires the use of forceps to load an intraocular lens into a cartridge.

Monarch II Delivery System is not the only intraocular delivery system currently on the market. Many ophthalmic pharmaceutical companies offer foldable intraocular

lenses with unique injector delivery systems and forceps used for implantation purposes. The general design of each injector delivery system is relatively similar with modifications in the design to fit each company's unique intraocular lens. However, the objective of each delivery system is the same – to deliver the intraocular lens into the capsular bag. For example, Advanced Medical Optics (AMO) offers acrylic and silicone foldable intraocular lenses, which are implanted into the AMO Unfolder system using a cartridge. [17] The Unfolder system has been used for silicone intraocular lens implantations with good results. [18-19] Another company offering silicone and acrylic foldable intraocular lenses is the Staar Surgical Company. [20] The Microstaar injectors are used in conjuction with Staar cartridges to insert foldable intraocular lenses through an incision of 3.0 mm or less. [21-22] Bausch & Lomb is a company also competing in the field of cataract surgery. Bausch & Lomb offers syringe type injector delivery systems such as the Passport II and the M-port injectors. [23] The Bausch & Lomb injectors are used with silicone intraocular lenses, which can be inserted through an incision of 3.0 to 3.3 mm. [23]

It is important to note that even though the basic design and certainly the goal of each injector intraocular delivery system is similar, each ophthalmic pharmaceutical company strives to offer the surgeon a unique delivery system. Since the final incision size utilized in the implantation of the intraocular lens is relatively similar for each delivery system, many companies also consider the ergonomic performance of the delivery system. For example, some companies offer syringe-like injector systems that allow surgeons to insert the intraocular lens using just one hand. Other companies offer an injector delivery in a style that permits the surgeon to use two hands, allowing for

more control with the ability to steady the injector while performing the procedure. Each delivery system design caters to a surgeon's individualized technique and style, therefore, some companies even offer both types of design.

Although an injector delivery system may likely decrease the chance of intraocular lens damage during cataract surgery, [24-25] a chance for error still exists related to the surgeon's degree of ability to correctly insert the intraocular lens into the cartridge without scratching or causing damage to the lens. Ophthalmic pharmaceutical companies address this issue by developing next generation intraocular lens delivery systems with built in lens-containing cartridges. Alcon Laboratories is currently conducting clinical trials to validate the ergonomic efficiency of such a delivery system. It is also noteworthy that no company has yet marketed this type of delivery system, and it is very likely Alcon will be the first. My internship experience at Alcon Laboratories gave me the opportunity to play a significant role in the Protocol, Case Report Form, and Informed Consent Document design of Alcon's next generation intraocular lens injector delivery system referred to in this thesis paper as the C-03-35 Delivery System.

REGULATORY STRATEGY

In order to obtain approval required to market a device, a company must successfully provide proof to the Federal Food and Drug Administration (FDA) ensuring the proposed investigational device is safe and effective. This process is often lengthy, requiring the pharmaceutical company to gather sufficient data in order to file a comprehensive Premarket Approval (PMA) application, which the FDA is required to review before permitting the marketing of the investigational device. The FDA's regulations provide 180 days for the review of the PMA; however, due to the copious amounts of data involved, the process usually takes much longer. Nevertheless, the agency has made strides to try and shorten the amount of time it takes to deliver a device to market.

The FDA provides several regulations and guidance documents that help streamline the process by reducing the review time of certain devices. The "Real-Time" review program for PMA supplements is one of the guidelines released. This program allows the FDA to abbreviate the review process to one formal meeting thus allowing companies to deliver new devices to market sooner. In order to qualify for the "Real-Time" review program, the FDA considers only devices that meet the following requirements:

- Sterilization changes to another known method
- Minor design changes

- Minor labeling changes
- Supplements which contain requests similar to other previously approved supplements

Note: List obtained from the FDA "Real-Time" PMA guidance document[26]

Alcon Laboratories has taken advantage of the new guidelines in order to secure market approval for the C-03-35 Delivery System. This delivery system meets the criteria for the "Real-Time" review program, since the design is similar to the MONARCH® II Delivery System with only minor design modifications. The MONARCH® II is the predecessor of the C-03-35 Delivery System; however, the intended use of both products is identical. Both devices are used to deliver a FDA approved ACRYSOF® single piece soft acrylic intraocular lens into the capsular bag following cataract extraction.

With regard to "Real-Time" review program regulatory requirements, one of the key differences between the two devices is that the C-03-35 Delivery System also acts as a lens case storing the intraocular lens. Thus, Alcon needed to present evidence to the FDA establishing that this minor design change does not impact the safety and effectiveness of the device. In order to do so, the company conducted a number of assessments that met FDA's requirement standards including biocompatibility testing, optical testing, mechanical testing and dimensional tolerances, sterility testing, labeling, shelf life and shipping testing.[26] This information was then presented to the agency during the "Real-Time" review of the PMA supplement. Following the data presentation and scientific discussion, the FDA was required to provide an action letter within five

days of the meeting, which is significantly quicker than the standard 180 days. Alcon was successful at demonstrating the safety and efficacy of the C-03-35 Delivery System during the "Real-Time" review meeting, and thus was granted PMA. This, in turn, was valuable since the medical device market is extremely competitive, therefore, gaining expedited approval of the C-03-35 Delivery System may possibly translate into considerably larger profits.

OUTLINE OF THE POST-MARKET STUDY OF THE C-03-35 DELIVERY SYSTEM

Objective:

The purpose of this post-market clinical investigation is to validate the ergonomic efficiency of the C-03-35 Intraocular Delivery System following cataract removal by phacoemulsification. The C-03-35 Delivery System is a newly approved device developed by Alcon Laboratories, Inc, which allows the delivery of the ACRYSOF® Model SA60AS soft acrylic intraocular lens in a sterile, single-use and disposable unit that combines the hand piece plus the ACRYSOF® intraocular lens-contained cartridge in an integrated system. (Figure 6) This system is somewhat different from the predecessor MONARCH® II Delivery System, which requires the surgeon to correctly insert the ACRYSOF® intraocular lens into a cartridge and then assemble the cartridge into a reusable hand piece. The C-03-35 Delivery System eliminates these steps; therefore, it should decrease the risk of damage that may occur to the optic or the haptic (Figure 1) as well as reducing surgery time.

The C-03-35 Delivery System[27]

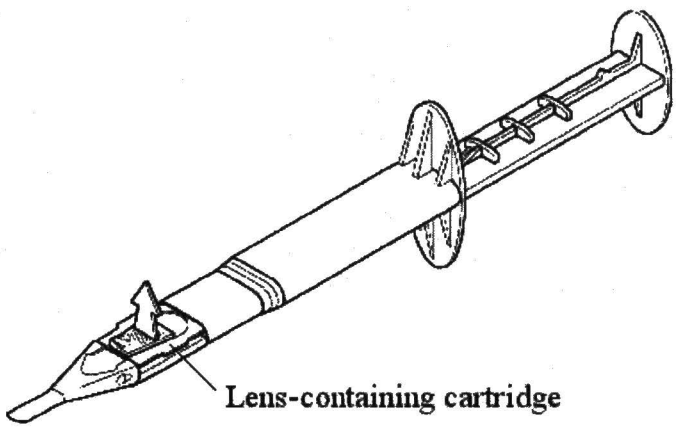

Figure 6: The C-03-35 Delivery System is preloaded with an intraocular lens.

Materials and Methods:

This study is an open label ergonomic assessment of the C-03-35 Delivery System that will be completed after the operative visit (performed on one eye only) of 120 patients by up to twelve investigators. The investigators will enroll patients requiring cataract extraction with intraocular lens implantation into the study that meet predetermined inclusion/exclusion criteria:

Inclusion Criteria

- In good general and ocular health, and have an age-related cataract in the intended operative eye
- Willing and able to complete all required postoperative visits
- Able to comprehend and sign a statement of informed consent
- Adults of either sex or any race

- Expected to achieve postoperative visual acuity of 20/40 or better

Exclusion Criteria Before Surgery

- Clinically severe corneal dystrophy (e.g., Fuch's dystrophy)
- Extremely shallow anterior chamber, not due to swollen cataract
- Microphthalmos
- Nonfunctioning (Visual Acuity worse than Hand Motion)/Absent fellow eye
- Previous corneal transplant
- Subject currently participating in an investigational drug or device study that might confound the results of this investigation

Note: Inclusion/Exclusion criteria obtained from the C-03-35 Delivery System Protocol[28]

If a subject successfully meets the inclusion/exclusion criteria required for this study, the principal investigator may formally enroll the patient by initiating the process of informed consent. Informed consent is a step strictly enforced by the FDA in order to ensure that the rights and welfare of the subject are protected. The investigator has the responsibility to make certain the patient is properly informed before initiating any investigational procedure and is kept up to date concerning any changes relevant to the patient's willingness to continue enrollment in the study. In addition, the patient must sign an informed consent document containing all the required elements defined in Title 21: Part 50 of the Code of Federal Regulations. The required informed consent document used to enroll patients into the post-market study of the C-03-35 Delivery System is included in Appendix A. Furthermore, the study must be conducted in accordance to the ethical principles set forth by the Declaration of Helsinki (Appendix B).[29] Once enrolled

in the study, the subject must also meet the following inclusion/exclusion criteria at the time of surgery in order to continue in the study:

Exclusion Criteria Noted During Surgery (Prior to C-03-35 Delivery System Use)

- Anterior chamber bleeding (significant)
- Capsular rupture
- Corneal endothelial touch
- Iris damage
- Capsulorhexis tear
- Zonular dehiscence

Exclusion Criteria Noted During Surgery (During C-03-35 Delivery System Use)

- Wound tear requiring a suture
- Anterior chamber bleeding (significant)
- Corneal endothelial touch
- Iris damage
- Capsular rupture
- Capsulorhexis tear
- Zonular dehiscence
- Trauma from aborted implantation

Note: Inclusion/Exclusion criteria obtained from the C-03-35 Delivery System Protocol[28]

The subjects enrolled in the study will undergo phacoemulsification cataract removal with intraocular lens implantation using the C-03-35 Delivery System, which is designed to fold and subsequently deliver the ACRYSOF® Model SA60AS lens into

position enabling the physician to place the lens in the capsular bag. In most cases, the C-03-35 Delivery System will allow the positioning of the intraocular lens correctly within the capsular bag with both haptics in place; however, in some situations the surgeon may choose to guide the trailing haptic of the lens inside the capsular bag using a positioning instrument.

Data Collection and Analysis:

Upon concluding the surgical procedure, the investigator will complete a series of Case Report Forms consisting of questions assessing the ergonomic efficiency of the C-03-35 Delivery System. The Case Report Forms will comprise of questions regarding the optic and haptic damage during the intraocular loading and delivery, incision characteristics, haptic placement, ease of use, as well as any adverse events that might have occurred. In addition, the investigator will complete an Exit Case Report Form once the patient concludes the study, is discontinued from the study, or if the patient fails to attend the follow-up visits. The required C-03-35 Case Report Form examination schedule is included in Appendix C.

The information obtained from the Case Report Forms will then be entered into a clinical database. The safety information will be analyzed by the Biostatistics Department by comparing the safety data obtained from the field evaluation to the Federal Food and Drug Administration's standards called the FDA Grid of Historical Controls. The FDA Historical Grid provides pharmaceutical companies with performance guidelines by which the investigational test article is measured. In the case of intraocular lenses, the FDA Historical Grid provides standards for overall visual acuity

(% ≥ 20/40), best-case visual acuity (% ≥ 20/40), and adverse events. Only adverse events will be compared to the FDA Historical Grid and analyzed for this field evaluation. The visual acuity parameters of the intraocular lens will not be analyzed in this study, since the C-03-35 Delivery System uses a FDA approved ACRYSOF® Model SA60AS lens with established performance. In addition, the ergonomic efficiency questions such as ease of use will be summarized into a table. Although not currently on the protocol of the study, this information may also be further compared against the MONARCH® II Delivery System analysis results, since safety as well as ergonomic efficiency data were also collected during that study. [30] The FDA Grid of Historical Controls is included in Appendix D.

DISCUSSION

Even the most meticulously planned clinical investigations run into unforeseen tribulations. This is often the case, because a clinical investigation involves the input and cooperation of many different departments and individuals. This is also the reason why a successful Clinical Research Associate (CRA) working on a clinical trial must have an excellent ability to adapt to an ever-changing study. My internship experience at Alcon Laboratories gave me the opportunity to have a significant role in the Protocol, Case Report Form, and Informed Consent Document design of Alcon's C-03-35 Delivery System. In preparing this thesis, I was expecting to include some of the preliminary results from the delivery system field evaluation, since the enrollment for this study was originally planned to start in October 2003. Unfortunately, the project start date has been moved back to a date subsequent to the conclusion of my internship practicum. Although inconvenient to my thesis, moving project datelines are a common reality in the pharmaceutical world.

Major Requirements for Running a Clinical Device Trial:

A pharmaceutical company will occasionally obtain information from basic research to generate ideas for a new device. If the device shows promise, the company will often decide to conduct a clinical trial involving human subjects to validate the safety and effectiveness of the new investigational product. Conducting FDA-approved clinical trials is the means by which pharmaceutical companies collect data necessary to obtain

marketing permission from the FDA. It is necessary to obtain FDA approval before marketing a device, since "it is the function of the FDA to see that the food we eat is safe and wholesome, the cosmetics we use will not cause harm, the medicines and medical devices we use are safe and effective, and that the radiation-emitting products such as microwave ovens will not do us harm."[26] In order to perform these duties, the FDA employs inspectors that have the power necessary to enforce the Federal Food, Drug, and Cosmetic Act or any other laws enforced by the FDA.[26] If a company is found in violation of one of the laws, the agency has the power to deny approval or recall the product from the market. In addition, the FDA has the power to punish offenders by legal sanctions, steep fines, or even criminal penalties including prison sentences.

In order to begin a clinical investigation, a company must file with the FDA an Investigational Device Exemption (IDE). (Note: An IDE is only required for "significant risk" devices)[26] Thirty days after the submission of the IDE, if the FDA does not officially object in writing, the company is allowed to study the investigational device in human subjects. However, in order to submit an IDE application, the pharmaceutical company must:

- Select qualified investigators
- Develop an investigational plan (protocol) so as to give the investigator guidelines to conduct the clinical study
- Ensure proper monitoring of the investigation
- Ensure IRB review and approval are obtained

- Ensure to promptly inform any reviewing IRB and FDA of significant new information regarding the clinical study

Note: General Responsibilities of Sponsors obtained from Title 21: Part 812.40 of the Code of Federal Regulations. [26]

Each general requirement is further subdivided in the Code of Federal Regulations giving guidance on conducting the clinical trial using Good Clinical Practices (GCP). The federal law defining Good Clinical Practices cumulatively serves to ensure that "the rights, safety, and well-being of trial subjects are protected and that the clinical trial data are credible." [26] These guidelines are strict, thus the device development process from conception to market approval can take several years to complete.

Thirty days after the submission of an IDE, the application is considered approved unless otherwise notified by the FDA. Therefore, thirty days following IDE submission, the pharmaceutical company can lawfully start enrolling (via informed consent) subjects to collect safety and effectiveness data required for the submission of the Premarket Approval (PMA) application. The clinical trial must be conducted in accordance to the guidelines defined in the clinical study protocol by qualified investigators. In addition, the sponsoring pharmaceutical company is responsible for monitoring the clinical trial site to ensure all guidelines and regulations are obeyed.

Following the conclusion of a successful clinical trial, the FDA reviews the Premarket Approval (PMA) application. This application contains all the scientific

information the company gathered including the safety and efficacy data regarding the investigational new device.

Some of the scientific information required for the PMA application includes providing proof that the device was manufactured under Good Manufacturing Practices (GMP) at a site that meets FDA's quality control inspections. The company must provide a complete description of the methods used in manufacturing, packaging, and storage of the device, as well as all the controls used in the study of the investigational device. It is also important to provide detailed specifications of the physical description of the device, and the intended use of the device. In addition, the FDA requires that the labeling of the device be included in the PMA application, allowing the FDA to inspect all the claims made by the company, especially of safety and effectiveness. Specifics concerning all the scientific information required by the PMA submission is provided by the FDA in the form of guidance documents. [31-34]

The FDA is required to review this information prior the approval of the PMA. The regulations of the FDA provide 180 days for the review of the PMA; however, due to the copious amounts of data involved, the process usually takes much longer. Once approved, the pharmaceutical company may distribute the new device for sale.

My Role in the Clinical Trial:

The FDA has released guidance documents that allow pharmaceutical companies to streamline the review process for certain medical devices. Alcon Laboratories was able to utilize the "Real-Time" review program guidance document in order to secure the Premarket Approval (PMA) of the C-03-35 Delivery System. The PMA obtained allows

Alcon to legally market and distribute the delivery system. Nevertheless, Alcon management decided to conduct a post-market clinical investigation to validate the ergonomic efficiency of this delivery system. In addition, it was decided by Alcon management to conduct the study as a typical clinical investigation; therefore, the study must meet all the FDA requirements including the development of an investigational plan (protocol).

I spent a substantial part of my internship composing the C-03-35 protocol. The information contained in this clinical protocol spells out precisely the manner by which the field evaluation will be conducted. It is written similar to a traditional research paper with all the major sections, in addition to elements unique to clinical protocols such as Obligations of Investigators, Elements of Informed Consent, and The Declaration of Helsinki. It was necessary that the protocol be written in accordance to Alcon Standard Operating Procedures (SOPs); therefore, a few of the sections contained in the document are similar to all Alcon clinical protocols. Regrettably, I was unable to include the C-03-35 Delivery System protocol in this thesis due to the proprietary information included in the document.

Steps Required to Complete the Project:

With the completion of the clinical protocol, the stage is set to begin the clinical investigation to validate the ergonomic efficiency of the C-03-35 Delivery System. Before enrolling patients into the study, the investigator must contact an Institutional Review Board (IRB). The function of the IRB is to ensure that the rights and welfare of the human subjects involved in biomedical research are protected. It is also the

responsibility of the IRB to review and approve the clinical protocol and the informed consent document. Once the investigator obtains IRB approval of the research, the study will start.

All the ergonomic efficiency and safety data will be captured on Case Report Forms (CRFs). Throughout the study, Clinical Research Associates (CRAs) will monitor the clinical investigation sites in order to ensure all the data captured on the CRFs is correct. Following the conclusion of the study, the Biostatistics department will analyze the data submitted. The final results of the study will be summarized in a Clinical Study Report (CSR). The CSR contains all the clinical safety and effectiveness data captured in a study, and it is written as a collective effort between all the departments involved in a clinical study.

Additional Responsibilities

In addition to my work with the C-03-35 Delivery System, I was also able to participate in various other aspects of the CRA profession. As soon as I arrived at Alcon, I had the opportunity to attend the mandatory three-week Clinical Science Training held in June, where I attended classes designed to introduce me to Alcon's Standard Operating Procedures (SOPs).

One of my recurring responsibilities at Alcon was to perform in-house monitoring of C-01-63 Case Report Forms. By conducting this type of monitoring, I was required to flag omissions and erroneous data. These flags along with all the Case Report Form information were then verified at the clinical investigation site against the source documentation in order to confirm that it was accurately represented. A major goal of the

clinical investigation site monitoring trip was to ensure that the subject's rights and welfare were protected by making certain the subject met all inclusion/exclusion criteria and signed the proper Informed Consent Document. I had the opportunity to travel to a few of the clinical investigation sites, where I was able to learn many of the aspects of monitoring a site, including case report form review and investigational test article accountability. While at the clinical site, I was required to make certain the study was conducted in compliance with the clinical protocol, Alcon Standard Operating Procedures (SOPs), along with all the required regulations.

Due to the innate nature of the profession, I was also required to perform a range of additional tasks that involved the use of various skills. It was essential for me to be proficient with different computer applications in order to compose presentations, enrollment logs, graphs and charts. Each week was different, and I never fully knew what I was going to work on next. I absolutely enjoyed this type of challenge. It gave me a chance to work on different types of projects showcasing a variety of skills while keeping the work novel and interesting.

DESCRIPTION OF THE INTERNSHIP EXPERIENCE

Note: A list of acronym descriptions is contained in Appendix E

June 9, 2003

- Attended Clinical Science Training Sessions on:
  - Legal Basics
  - Archives and Tour
  - Test Article Label Basics
  - Diseases and Alcon Products

June 10, 2003

- Attended Clinical Science Training Sessions on:
  - IRB / IEC Basics
  - Clinical Protocol / Amendments Basics and OEM Basics
  - CIB Basics
  - R&D Systems, Organization & Program / Project Development
- Attended a "Clinical Roundtable" meeting on FDA-483

June 11, 2003

- Attended Clinical Science Training Sessions on:
  - Financial Grants Basics
  - Financial Disclosure Basics
  - Clinical Investigator Basics

- Introduction to Alcon Clinical Research
- Overview of Clinical Data Processing
- Initiating Studies Basics

June 12, 2003

- Attended Clinical Science Training Sessions on:
  - Clinical Monitors Basics
  - Study Management Planning
  - Product Complaints Basics
  - Protocol Registration System
- Met with Dr. Kendra Hileman to discuss the content of the Research Proposal.
- Checked Integrated Review queries against Case Report Forms

June 13, 2003

- Attended Clinical Science Training Sessions on:
  - Adverse Event
  - Concur Expense Reporting System
  - Final Clinical Data
- Read articles relevant to Research Proposal

June 16, 2003

- Attended Clinical Science Training Sessions on:
  - CIMS Training
  - Financial Systems Basics
  - EZ Web Training

- CRF Basics

- Read C-01-63 Clinical Protocol

June 17, 2003

- Attended Clinical Science Training Sessions on:
  - Introduction to Clinical Research Level I (8:30 – 5:00)

June 18, 2003

- Attended Clinical Science Training Sessions on:
  - Introduction to Clinical Research Level I (8:30 – 5:00)

June 19, 2003

- Attended Clinical Science Training Sessions on:
  - Test Article Shipment / Return Basics
  - Study Files Basics
  - Report Completion Basics
  - Clinical Forms Basics
- Met with Blake Harris to discuss Research Proposal
- Worked on Research Proposal

June 20, 2003

- Attended Clinical Science Training Sessions on:
  - Introduction to Quality Management Systems
  - Marketing
  - International Clinical Development
- Initiated Oracle and VMS Aries accounts on my computer

- Worked on Research Proposal

June 23, 2003

- Met with Dr. Kendra Hileman to discuss my Research Proposal
- Attended Clinical Science Training Sessions on:
  - Site Audits Basics
  - Introduction to Clinical Quality Assurance Unit
- Worked on Research Proposal
- Worked on Protocol AS-6466

June 24, 2003

- Attended a meeting on AS-6466 (Discussed the study design as well as my Research Proposal) with Blake Harris, Kyle Brown, and Dr. Kendra Hileman.
- Attended Clinical Science Training Sessions on:
  - Introduction to Biostatistics
  - Introduction to US Regulatory Submissions
  - Introduction to Global Regulatory Requirements
- Worked on Research Proposal

June 25, 2003

- Attended Clinical Science Training Sessions on:
  - Investigational Device Manufacturing / Pilot Line Tour
  - Monitoring Basics
  - Requesting Test Articles Basics
  - Investigator IND

- Met with Kristi Rushin to discuss protocol C-01-63
- Reviewed the In-house Case Report Forms for mistakes and omissions.
- Worked on Research Proposal

June 26, 2003

- Attended Clinical Science Training Sessions on:
  - JDE Clinical Supplies Inventory System
  - Traveling
  - Labeling / Global Graphics
  - Eye Clinic – had a chance to inspect a slit–lamp and other optometrist instruments
- Worked on Research Proposal

June 27, 2003

- Attended Clinical Science Training Sessions on:
  - Introduction to Clinical Applications
  - Introduction to Clinical Supplies Manufacture and Distribution
- Met with Dr. Bens to discuss Research Proposal
- Worked on Research Proposal
- Read Clinical Protocol C-01-63

June 30, 2003

- Read Clinical Protocol C-01-63
- Worked on In-house monitoring of C-01-63 Case Report Forms for Kristi Rushin
- Made adjustments to Research Proposal based on suggestions from Dr. Annita Bens

July 1, 2003

- Rewrote the C-00-26 protocol in order to reflect the AS-6466 protocol. I tried to keep as much of the original narrative as possible; however, in many cases I was forced to make significant revisions (also used sentences from my Research Proposal.) The protocol modifications will need to be checked by Blake Harris in order to make sure the study design remains accurately depicted.

July 2, 2003

- Provided proof of Hepatitis B vaccinations to Alcon Nurse
- Continued work on AS-6466 protocol

July 3, 2003

- Continued work on AS-6466 protocol
- In-house monitored C-01-63 Case Report Forms for Kristi Rushin

July 7, 2003

- Worked on AS-6466 protocol, which now has a formal clinical number assigned to it: C-03-35

July 8, 2003

- Worked on protocol C-03-35
- Received more product information from Kyle Brown, which I included in the protocol

July 9, 2003

- Finished work on protocol C-03-35, which I gave to Blake Harris for review

- Updated study binder documents (C-01-63 for Kristi Rushin) by checking the imaged archived clinical study records (using EZ Web) and ensuring all study binder documents are present

July 10, 2003

- Worked on protocol C-03-35 Case Report Form design with Danny Day

July 11, 2003

- Worked on arranging a group training session, and assembled SOP Training Packets for five individuals
- Completed the required SOP training:
  - Emergency Evacuation
  - Tornado Emergency
  - Waste Minimization
  - Control of Non-critical Electrical Consumption
- The training was accomplished by reading the specified SOP guidelines and filling out an Individual Training Record
- Updated study binder documents (C-01-63 for Kristi Rushin) by checking the imaged archived clinical study records (using EZ Web) and ensuring all study binder documents are present

July 14, 2003

- Attended various management meetings with Dr. Kendra Hileman
- Attended a research seminar on LASIK surgery

July 15, 2003

- Attended various management meetings with Dr. Kendra Hileman
- Read the International Standard (ISO WD 11979-7 Clinical Investigation of Monofocal Intraocular Lens for Correction of Aphakia) Draft Guidelines

July 16, 2003

- Attended various management meetings with Dr. Kendra Hileman

July 17, 2003

- Created "Visit Date Out of Range" summary report charts for a power point presentation
- Composed a Request for Manufacture of Clinical Supplies memo
- Read the Initiating Clinical Studies SOP

July 18, 2003

- Reviewed Audit Reports of European Investigators
- Attended various management meetings with Dr. Kendra Hileman including an enrollment meeting
- Started work on C-01-19 enrollment charts

July 21, 2003

- Attended a meeting on C-03-35, which is the study relevant to my thesis. The meeting pertained to Development's progress on the project and did not involve the Clinical side. Nevertheless, it was interesting to hear how much work is involved with a project before it reaches Clinical.
- Started work on C-01-19 Enrollment chart

July 22, 2003

- Worked on C-01-19 Enrollment chart
- Reviewed Draft Case Report Forms for C-03-35
- Updated C-01-63 Enrollment Log

July 23, 2003

- Attended an Ethics Training Session
- Updated C-01-63 Enrollment Log

July 24, 2003

- Updated C-01-63 Enrollment Log
- Began literature search work for my thesis
- Met with Dr. Patricia Gwirtz to turn in my Research Proposal

July 25, 2003

- Attended the "All Clinical Meeting," topics:
  - Clinical Data Management Update
  - CDM Clinical Experiences
  - DIA Trip Reports
- Updated C-01-63 Enrollment Log
- Reviewed C-01-63 Monitoring Reports to prepare for Albuquerque, NM monitoring trip

July 28, 2003

- Participated in a C-01-63 Albuquerque, NM monitoring trip. This was an outstanding opportunity for me to learn all the different requirements of site monitoring, as well

as get hands-on training. Kristi Rushin was excellent at explaining the process in detail and answering my numerous questions. I spent the entire day monitoring Case Report Forms.

July 29, 2003

- Continued site monitoring. Spent most of the day monitoring Study Binders

July 30, 2003

- Worked on C-03-35 protocol revisions

July 31, 2003

- Attended a Unit 96 Mandatory Clinical Research Meeting on recent SOP changes
- Met with Kristi Rushin to learn how to perform Quality Monitoring
- Worked on C-01-63 (Investigator 2435) Study Binder making sure all documents are present (scanned) in EZ Web

August 1, 2003

- Worked on C-01-63 (Investigator 2435) Study Binder making sure all documents are present (scanned) in EZ Web
- Worked on C-03-35 protocol revisions

August 4, 2003

- Worked on C-03-35 protocol revisions
- Worked on In-house monitoring of C-01-63 Case Report Forms for Wayne Donahue

August 5, 2003

- Worked on In-house monitoring of C-01-63 Case Report Forms for Wayne Donahue
- Worked on quality monitoring of C-01-63 (Investigator 1434) for Kristi Rushin

August 6, 2003

- Attended the Fort Worth Surgical Quarterly Review (All IOL Meeting)
- Worked on quality monitoring of C-01-63 (Investigator 1434) for Kristi Rushin
- Continued literature search for thesis

August 7, 2003

- Worked on In-house monitoring of C-01-63 Case Report Forms for Shannon Spock
- Reviewed Case Report Form revision 2 of C-03-35

August 8, 2003

- Worked on In-house monitoring of C-01-63 Case Report Forms for Shannon Spock
- Worked on In-house monitoring of C-01-63 Case Report Forms for Wayne Donahue

August 11, 2003

- Participated in a C-01-63 Nacogdoches, TX monitoring trip. Monitored Case Report Forms and Study Binder. Dr. Lehmann allowed me to observe a few of the cataract surgeries he performed that morning. While performing the surgeries, he also took the time to explain the procedure to me in detail. I was able to witness the last implantation of the C-01-63 investigational lens.

August 12, 2003

- Continued monitoring the Study Binder. Conducted lens accountability by verifying the lens distribution log and inventory. All lenses were accounted for and the remaining investigational lenses were brought back to Alcon.

August 13, 2003

- Worked on In-house monitoring of C-01-63 Case Report Forms for Kristi Rushin

- Continued literature search for thesis

August 14, 2003

- Went to Alcon library to watch training videos
- Worked on In-house monitoring of C-01-63 Case Report Forms for Shannon Spock
- Worked on In-house monitoring of C-01-63 Case Report Forms for Wayne Donahue

August 15, 2003

- Worked on In-house monitoring of C-01-63 Case Report Forms for Wayne Donahue
- Continued literature search for thesis

August 18, 2003

- Worked on In-house monitoring of C-01-63 Case Report Forms for Wayne Donahue
- Worked on literature search for thesis

August 19, 2003

- Attended Dr. Cagle's All Employee Meeting
- Composed a C-03-35 Memo for Blake Harris
- Made C-03-35 protocol packets and delivered to management
- Reviewed C-03-35 Case Report Forms (draft version 3)

August 20, 2003

- Worked on C-03-35 Pre-Study Visit Power Point Presentation

August 21, 2003

- Worked on C-03-35 Pre-Study Visit Power Point Presentation
- Worked on Clinical Intraocular Lens Group 2003 Travel Summary

August 22, 2003

- Worked on Clinical Intraocular Lens Group 2003 Travel Summary

August 25, 2003

- Worked on Clinical Intraocular Lens Group 2003 Travel Summary

August 26, 2003

- Worked on Clinical Intraocular Lens Group 2003 Travel Summary
- Made changes to Protocol C-03-35
- Completed Internship Evaluations
- Worked on In-house monitoring of C-01-63 Case Report Forms for Kristi Rushin

August 27, 2003

- Worked on In-house monitoring of C-01-63 Case Report Forms for Kristi Rushin
- Filled out validation sheets for Shannon Spock

August 28, 2003

- Made changes to Protocol C-03-35
- Checked Protocol C-03-35 against SOP requirements
- Worked on In-house monitoring of C-01-63 Case Report Forms for Kristi Rushin

August 29, 2003

- Worked on In-house monitoring of C-01-63 Case Report Forms for Kristi Rushin
- Worked on literature search for thesis

September 1, 2003

- Holiday

September 2, 2003

- Worked on In-house monitoring of C-01-63 Case Report Forms for Kristi Rushin
- Worked on C-03-35 protocol additions
- Designed the C-03-35 Informed Consent Document

September 3, 2003

- Worked on thesis

September 4, 2003

- Worked on thesis
- Made revisions to C-03-35 Case Report Forms and Informed Consent Document
- Magali Hall and I met Dr. Annita Bens and Dr. Victoria Rudick for lunch
- Worked on literature search for Tonya Jones

September 5, 2003

- Read the C-01-63 Night Driving Simulator Study Report
- Obtained Obligations of Investigators, Declaration of Helsinki, Elements of Informed Consent, and Manual of Definitions documents from Document Processing for protocol C-03-35

September 8, 2003

- Worked on C-01-63 Night Driving Simulator Power Point Presentation for Tonya Jones

September 9, 2003

- Worked on C-01-63 Night Driving Simulator Power Point Presentation for Tonya Jones

- Attended the GSA lunch seminar presented by Dr. Annita Bens

September 10, 2003

- Worked on C-01-63 Night Driving Simulator Power Point Presentation for Tonya Jones

September 11, 2003

- Finished C-01-63 Night Driving Simulator Power Point Presentation for Tonya Jones
- Worked on thesis

September 12, 2003

- Designed graphs for C-01-63 Night Driving Simulator Power Point Presentation for Tonya Jones
- Worked on In-house monitoring of C-01-63 Case Report Forms for Kristi Rushin

September 15, 2003

- Worked on In-house monitoring of C-01-63 Case Report Forms for Kristi Rushin

September 16, 2003

- Made changes to C-03-35 Case Report Forms
- Worked on thesis

September 17, 2003

- Worked on thesis

September 18, 2003

- Worked on thesis
- Worked on In-house monitoring of C-01-63 Case Report Forms for Wayne Donahue

September 19, 2003

- Worked on visual acuity literature search for Blake Harris

September 22, 2003

- Worked on visual acuity literature search for Blake Harris

September 23, 2003

- Worked on thesis
- Worked on In-house monitoring of C-01-63 Case Report Forms for Wayne Donahue

September 24, 2003

- Worked on thesis
- Worked on In-house monitoring of C-01-63 Case Report Forms for Wayne Donahue

September 25, 2003

- Worked on thesis

September 26, 2003

- Attended Mandatory Unit 96 SOP meeting
- Worked on In-house monitoring of C-01-63 Case Report Forms for Kristi Rushin

September 29, 2003

- Worked on thesis
- Worked on IRB documentation required for initiation of the C-03-35 clinical study for Randy Russell

September 30, 2003

- Worked on thesis

October 1, 2003

- Worked on thesis
- Worked on In-house monitoring of C-01-63 Case Report Forms for Kristi Rushin

October 2, 2003

- Worked on thesis
- Worked on IRB documentation required for initiation of the C-03-35 clinical study for Randy Russell
- Worked on In-house monitoring of C-01-63 Case Report Forms for Kristi Rushin

October 3, 2003

- Worked on thesis
- Worked on In-house monitoring of C-01-63 Case Report Forms for Kristi Rushin

October 6, 2003

- Worked on In-house monitoring of C-01-63 Case Report Forms for Kristi Rushin

October 7, 2003

- Worked on thesis
- Worked on accommodative intraocular lens literature search for Dr. Kendra Hileman

October 8, 2003

- Attended ATLAS Training Classes:

  Anatomy of the Eye and Ear – Basic

  - learn the parts of the eye and ear and how they function
  - learn how Alcon's products are used to prevent and cure disease

  Anatomy of the Eye – Advanced

- learn more detail about the parts of the eye
- learn about major eye diseases and how they are treated

October 9, 2003

- Worked on accommodative intraocular lens literature search for Dr. Kendra Hileman

October 10, 2003

- Met with Tim Adkins to discuss the "Real-Time" PMA Supplement process implemented for C-03-35
- Worked on accommodative intraocular lens literature search for Dr. Kendra Hileman

October 13, 2003

- Worked on thesis
- Worked on In-house monitoring of C-01-63 Case Report Forms for Kristi Rushin

October 14, 2003

- Worked on thesis

October 15, 2003

- Attended the Fort Worth Surgical Quarterly Review meeting
- Worked on In-house monitoring of C-01-63 Case Report Forms for Kristi Rushin

October 16, 2003

- Worked on In-house monitoring of C-01-63 Case Report Forms for Kristi Rushin

October 17, 2003

- Worked on thesis

October 20, 2003

- Met Dr. Annita Bens to discuss the first draft of my thesis

- Worked on thesis

October 21, 2003

- Participated in a C-01-63 New Orleans, LA monitoring trip. I spent the day monitoring Case Report Forms.

October 22, 2003

- Participated in a C-01-63 New Orleans, LA monitoring trip. I spent the day monitoring Case Report Forms.

October 23, 2003

- Participated in a C-01-63 New Orleans, LA monitoring trip. I spent most of the day monitoring Case Report Forms. In addition, I was able to go over a few of the corrections with the study coordinator.

October 24, 2003

- Worked on thesis

October 27, 2003

- Worked on thesis

October 28, 2003

- Worked on Thesis Defense Presentation

October 29, 2003

- Worked on Thesis Defense Presentation

October 30, 2003

- Worked on Thesis Defense Presentation

October 31, 2003

- Worked on Thesis Defense Presentation

APPENDIX A

Informed Consent for C-03-35 Delivery System Subjects

INFORMED CONSENT FOR C-03-35 DELIVERY SYSTEM SUBJECTS

STUDY SPONSOR:	**Alcon Research, Ltd.**
CITY AND STATE:	**Fort Worth, TX**
NUMBER AND NAME OF STUDY:	**C-03-35; Post-Market Study of the C-03-35 Delivery System**
STUDY DOCTOR:	
ADDRESS OF STUDY SITE:	
TELEPHONE NUMBERS, DAYTIME & AFTER HOURS:	

INTRODUCTION & PURPOSE

You have been asked to participate in a research study sponsored by a major intraocular lens manufacturing company. The information contained in this consent form will help you understand the possible risks and benefits involved in your study participation. Also, your rights and responsibilities as a volunteer study patient will be outlined.

To participate in this research study, you have been advised of and agree to the following:

- Your doctor believes you to be in good general and good eye health.
- You are an adult with an age related cataract.
- Certain conditions may arise during surgery that would prevent the use of the study device. In such a case, an alternative device will be used and your participation in the study will be terminated.

PURPOSE/DURATION

You have been asked to take part, as a voluntary participant, in this study to confirm how well the C-03-35 Delivery System performs. The C-03-35 Delivery System is a FDA-approved device used to fold and implant the intraocular lens that will be placed in your eye during cataract surgery. The study will also require postoperative observation of your eye.

Up to one hundred and twenty (120) patients will participate in this research study at up to twelve (12) locations in the United States. You will be in this study for as long as required to perform a routine cataract operation and for up to one hundred and eighty (180) days after your surgery.

After your surgery, you will be asked to return for postoperative visits during each of the time periods listed below:

- Visit 1 (1-2 days after surgery)
- Visit 2 (7-10 days after surgery)
- Visit 3 (21-40 days after surgery)
- Visit 4 (120-180 days after surgery)

PROCEDURES

With the exception of the device used to fold and insert the lens, you will undergo a typical cataract extraction procedure. In addition, you will undergo some additional postoperative visits.

The testing required at the time of the postoperative visits follow below:

Visual Acuity - A procedure to learn how well you can see up close and far away

Slit Lamp - Examination of the front of your eye under magnification

Direct/Indirect Ophthalmoscopy - Examination of the back of your eye under magnification

Tonometry - Measurement of the pressure inside your eye

RISKS OR DISCOMFORTS

There are no anticipated risks or discomforts associated with participation in this study beyond those associated with routine cataract surgery. Surgery risks include reactions to medications and vision changes. There is a small chance that vision could actually be made worse by the surgical procedure – especially as the result of bleeding, infection, detachment of the retina, glaucoma or clouding of the cornea. These risks are rare and may be outweighed by the potential quality of life benefits provided through vision restoration.

While every effort will be made to perform all necessary tests in a timely manner, it is possible that your eye examinations (Visits 1, 2, 3, and 4) may last slightly longer than usual.

NEW FINDINGS

You will be informed of any significant findings that may relate to your willingness to continue in the study.

BENEFITS

The C-03-35 Delivery System is designed to make lens folding and implantation easier and more consistent. This may reduce the likelihood of damage to the intraocular lens surface. In addition, your participation in this research study may benefit others. The postoperative examinations you undergo may provide useful information, but this cannot be guaranteed.

COST/PAYMENT

You and your insurance company will be responsible for the routine costs of the cataract surgery and any repeat surgeries. Participation in this study will result in no extra costs to you.

LEGAL RIGHTS

You do not waive any of your legal rights by signing this informed consent.

ALTERNATIVE TREATMENTS

Participation in this study does not involve the use of any investigational (not approved by the FDA) device. The C-03-35 Delivery System only functions to fold and implant the intraocular lens.

Alternative treatments include not participating in this study and having the intraocular lens implanted by other means.

You understand that the following alternative treatments are also available if you decide not to have cataract surgery:

Cataract Spectacles

Cataract spectacles required to correct vision following cataract removal (with no IOL replacement) are thicker and heavier than conventional eyeglasses. These spectacles increase the apparent size of objects about 25%. Clear vision is obtained only through the central part of the spectacles. The patient must learn to turn his/her head to see clearly on either side.

Contact Lens

A hard or soft contact lens increases the apparent size of objects about 8%. Handling of a contact lens is difficult for some individuals. Most lenses must be inserted and removed daily and not everyone can tolerate them. Some soft contact lenses may be worn for an extended period of time without removal. For near tasks, eyeglasses (not cataract spectacles) may be required in addition to contact lenses.

You have been given the opportunity to discuss your participation in this study and these alternative treatments with your doctor

CONFIDENTIALITY

You understand that the information gathered will be treated as confidential. Your study results will be kept by your doctor and by the device manufacturer. While maintaining strict confidentiality, the study information and your medical record may be reviewed by the U.S. Food and Drug Administration (FDA) and/or appropriate regulatory authorities, the device manufacturer and the Institutional Review Board (IRB).
Results of this study may be reported to the FDA and/or other regulatory agencies and may also be used in scientific publications or presentations, but your identity will remain confidential.

You give permission to your doctor and others working with him to photograph or to televise your surgery for teaching purposes and for medical data concerning your operation and future treatment to be used in clinical testing.

VOLUNTARY PARTICIPATION / WITHDRAWAL

You acknowledge that participation in this post-market study is voluntary. You will be informed of any significant new findings that may relate to your willingness to continue in the study. You have the right to withdraw from the post-market study at any time. Should you choose to withdraw from the study for any reason, you should contact your doctor immediately.

Refusal to participate in this study will not result in any penalties or loss of benefits or affect your future routine medical care.

If you wish to leave the study, please call the study doctor at the phone number listed on page one.

Your part in this study may be stopped at any time without you being asked. The following people can stop your participation.

- the study doctor
- the Institutional Review Board (IRB)
- the United States Food and Drug Administration (FDA)
- the medical device company.

IN CASE OF RESEARCH RELATED INJURY

In case of a study related injury, you should contact the study doctor immediately for medical care. If an unforeseen physical injury should occur, appropriate medical care as determined by the study doctor will be provided, but you will not be offered reimbursement for the costs of such care and no financial payment will be offered by the study doctor, the associated hospital or the lens manufacturer.

WHOM TO CONTACT

If you have any study related problems or any research related injuries, you can reach the study doctor at the number listed on the first page of this informed consent document. You may contact the study doctor or staff:

- for answers to questions about this research study
- to report a research related injury or
- for information about study procedures

This consent form and study have been approved by the Institutional Review Board (IRB). The IRB is a group of scientific and non-scientific people who review and approve or disapprove research involving people by following the Food and Drug Administration (FDA) rules. This group is also required by FDA to do periodic reviews of ongoing research studies. Questions about your rights as a volunteer may be addressed to:

Chairman, IRB
Address
City, State ZIP

or you can call ###-###-####.

CONSENT

In giving your permission for use of the C-03-35 Delivery System during your cataract surgery, you are stating that you have read this informed consent (or it has been read to you) and have discussed the study with your doctor to your satisfaction. You acknowledge that participation in this study requires four postoperative follow-up visits for a period of up to 180 days. You understand the description of the study and freely volunteer to participate.

You reserve the right to withdraw from the study at any time. You understand if you withdraw from the study, your future routine medical care will not be affected.

You indicate by your signature that you wish to have a cataract operation with the use of the C-03-35 Delivery System to implant a FDA approved ACRYSOF Intraocular Lens.

You will receive a copy of this consent form after you sign below.

Patient's Name:_____(PLEASE PRINT)

Patient's
Signature:_____Date:_____

Name of Person
Explaining Consent:_____(PLEASE PRINT)

Signature of Person
Explaining Consent:_____ Date:_____

Consent for Cataract Operation
On behalf of a Visually Disabled Person

_____ is unable to sign an informed consent because he/she is disabled. As the legal representative of the patient, my signature below confirms the following:

1. I have read and understand the informed consent for participation in this study.
2. I have read the informed consent to the patient.
3. I understand that the use of the C-03-35 Delivery System has been approved by the U.S. Food and Drug Administration.
4. The patient will be followed for a period of up to 180 days.
5. The information gathered will be treated as confidential with the exception that it may be reviewed by the U.S. Food and Drug Administration and/or other appropriate regulatory authorities, the IRB, and the lens manufacturer.

Representative's Name (Printed):_____

Representative's
Signature:_____Date:_____

Relationship to Patient:_____

Patient's Name (Printed):_____

Name of Person
Explaining Consent (Printed):_____

Signature of Person
Explaining Consent:_____ Date:_____

APPENDIX B

Declaration of Helsinki

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving

consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically

competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given

informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

APPENDIX C

C-03-35 Study Plan

C-03-35 Study Plan

STUDY ACTIVITY	FORM 00 Surgery day	FORM 1 days 1-2	FORM 2 days 7-10	FORM 3 days 21-40	FORM 4 days 120-180
MEASUREMENTS:					
Best Spectacle Corrected VA		X	X	X	X
Correction Method		X			
Manifest Refraction			X	X	X
Tonometry		X	X	X	X
Pre-insertion Incision Size	X				
Post-insertion Incision Size	X				
STATUS:					
C-03-35 Lot No.	X				
Clinical Observations		X	X	X	X
Ease of Lens Advancement	X				
Exclusion Criteria Prior to Use	X				
Haptic Damage	X				
Incision Site	X				
IOL Observations		X	X	X	X
Keratome Size	X				
Optic Damage	X				
Overall Performance	X				
Subjective Posterior Capsule Opacification				X	X
Posterior Capsulotomy				X	X
Surgical Problems During Device Use	X				
Surgical Reintervention		X	X	X	X
Tilt and Decentration		X	X	X	X
Adverse Events		X	X	X	X

APPENDIX D

FDA Grid of Historical Controls

Overall Visual Acuity (% ≥ 20/40)

Age	Posterior Chamber		Anterior Chamber – by Surgical Intent							
			Primary		Back-up		Secondary		All A/C Subjects	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
<60	230/235	97.9	94/102	92.2	13/16	81.3	59/65	90.8	166/183	90.7
60-69	968/1012	95.7	192/223	86.1	19/23	82/6	105/123	85.4	316/369	85.6
70-79	1793/1920	93.4	312/391	79.8	29/50	58.0	153/207	73.9	494/648	76.2
≥80	901/1042	86.5	165/233	70.8	15/30	50.0	70/101	69.3	250/364	68.7
Total*	3893/4210	92.5	763/949	80.4	76/119	63.9	387/496	78.0	1226/1564	78.4

Best Case Visual Acuity (% ≥ 20/40)

Age	Posterior Chamber		Anterior Chamber – by Surgical Intent							
			Primary		Back-up		Secondary		All A/C Subjects	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
<60	203/206	98.5	81/83	97.6	12/13	92.3	47/50	94.0	140/146	95.9
60-69	793/822	96.5	150/169	88.8	12/13	92.3	76/78	97.4	238/260	91.5
70-79	1338/1372	97.5	234/264	88.6	17/25	68.0	92/106	86.8	343/395	86.8
≥80	601/634	94.8	107/119	89.9	9/15	60.0	37/42	88.1	153/176	86.9
Total*	2936/3035	96.7	572/635	90.1	50/66	75.8	252/276	91.3	874/977	89.5

- The "Total" rates represent the rates associated with the distribution of subjects in the four age subgroups found in the historical control data. For a clinical study with different age distributions of subjects, the age-adjusted "Total" control rate should be calculated from the weighted average of the age subgroup rates in study.

Adverse Events

	Posterior Chamber		Anterior Chamber – by Surgical Intent							
			Primary		Back-up		Secondary		Total (A/C)	
#Cohort**	4219		952		119		496		1567	
# Core	5906		***		***		***		2197	
	n	%	n	%	n	%	n	%	n	%
Cumulative Hyphema	91	2.2	41	4.3	5	4.2	17	6.9	63	4.0
Cumulative Macular Edema	124	3.0	95	10.0	24	20.2	34	1.2	153	9.8
Cumulative Retinal Detachment	11	0.3	11	1.2	2	1.7	6	0.6	19	1.2
Cumulative Pupillary Block	5	0.1	19	2.0	3	2.5	3	1.2	25	1.6
Cumulative Lens Dislocation	5	0.1	10	1.1	5	4.2	6	0.4	21	1.3
Cumulative Endophthalmitis	4	0.1	2	0.2	0	0.0	2	0.2	4	0.3
Cumulative Hypopyon	16	0.3	***		***		***		4	0.2
Cumulative Surgical Reintervention	46	0.8	***		***		***		58	2.6
Persistent Macular Edema	19	0.5	36	3.8	11	9.2	16	0.2	63	4.0
Persistent Corneal Edema	11	0.3	5	0.5	2	1.7	11	2.2	18	1.1
Persistent Iritis	11	0.3	9	0.9	4	3.4	11	1.8	24	1.5
Persistent Raised IOP Requiring Treatment	17	0.4	20	2.1	10	8.4	9	0.6	39	2.5

** All adverse event rates except for cumulative hypopyon and cumulative surgical reintervention were derived from the cohort subjects.
Hypopyon and surgical reintervention data were derived from all core subjects.

*** It was not possible to determine cumulative hypopyon and cumulative surgical reintervention rates by surgical intent for anterior chamber IOLs.

APPENDIX E

List of Acronym Descriptions

AMO – Advanced Medical Optics

CDM – Clinical Data Management

CFR – Code of Federal Regulations

CIB – Clinical Investigator's Brochure

CIMS – Clinical Information Management System

CRA – Clinical Research Associate

CRF – Case Report Form

CSR – Clinical Study Report

FDA – Federal Food and Drug Administration

GCP – Good Clinical Practice

GMP – Good Manufacturing Practice

GSA – Graduate Student Association

IDE – Investigational Device Exemption

IEC – Independent Ethics Committee

IND – Investigational New Drug Application

IOL – Intraocular Lens

IRB – Institutional Review Board

ISO – International Organization for Standardization

PMA – Premarket Approval

R&D – Research and Development

SOP – Standard Operating Procedures

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