Evaluating Refractive and Visual Outcomes with the Alcon Toric-ReSTOR +2.5 and +3.0 models

An investigator initiated clinical trial

1. TITLE PAGE

Protocol Number:	CB-18-001 (Alcon IIT #38562691)
Amendment Number	Version 1.0
IRB / ERC	Salus IRB 2111 West Braker Lane, Suite 400 Austin, Texas 78758
Sponsor Name & Address:	Clayton Blehm, MD Gainesville Eye Associates 2061 Beverly Rd Gainesville, GA 30501 ***(funding only, this is an investigator-initiated study)*** Alcon (a Novartis Company) 6201 South Freeway, Fort Worth, TX 76134-2099, USA
Test Articles:	Alcon Toric-ReSTOR +2.5 and +3.0 models
Investigator:	Clayton Blehm, MD, Gainesville, GA Richard Potvin, MASc, OD, Akron, NY

2 . INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol entitled "Evaluating Refractive and Visual Outcomes with the Alcon Toric-ReSTOR +2.5 and +3.0 models", and understand the use of the study products. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 13 of this protocol.

Signature of Investigator (Date)

Investigator Name (print or type)

Investigator's Title

Name of Facility

Location of Facility (City)

3. GENERAL INFORMATION

Objective	To quantify and provide a normative standard for refractive and visual outcomes in eyes with significant corneal astigmatism undergoing cataract surgery with the Alcon Toric ReSTOR lens. As well as to quantify the postoperative rotational stability of the IOL. The hypothesis is that the addition of toricity will not affect the general performance of the ReSTOR design. As such, it is expected that patients with a ReSTOR toric IOL that achieve a correction of their astigmatism will have visual acuity and visual quality similar to patients implanted with the non-toric ReSTOR models. The Toric ReSTOR lenses (+2.5 and +3.0) will result in a residual refractive cylinder similar to that observed in patients with non-clinically significant astigmatism treated with non-toric ReSTOR lenses. They will also provide excellent distance and near vision in the vast majority of patients; we expect 75% of patients will have 20/25 (0.1 logMAR) or better uncorrected visual acuity at distance and near. The Toric-ReSTOR lens will demonstrate rotational stability that meets or exceeds the recommendations established by the American National Standards Institute.
Test Article(s)	Alcon Toric-ReSTOR +2.5 and +3.0 models
Control Article(s)	None.
Sample size	64 eyes of 32 subjects at 1 clinical site
Study Population	Subjects ≥30 years of age presenting for cataract surgery or refractive lens exchange surgery who are interested in astigmatism reduction and presbyopia correction. Subjects must be eligible for bilateral multifocal toric lens implantation.
Number of sites	One
Study Design	Prospective, non-randomized, single-arm, single center, open-label study.
Masking	None

Variables	Primary: • Residual refractive cylinder Secondary: • Monocular and binocular Uncorrected and Best-corrected distance, intermediate (60cm) and near (40cm) visual acuity • Postoperative orientation changes with the Toric ReSTOR IOL up to 3 months after surgery. • Binocular Uncorrected and Best-corrected defocus curve (3 month visit). • Quality of vision, measured with a subjective questionnaire.
Duration / Follow-up	Preoperative to 3 months postoperative

The study will be registered with clinicaltrials.gov.

The study will be conducted in compliance with the protocol, GCP and applicable regulatory requirements

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5. INTRODUCTION

In the past, patients with significant corneal astigmatism undergoing cataract surgery were given only the option of a monofocal astigmatism-correcting intraocular lens (IOL). Recently, the US FDA has approved intraocular lenses for the correction of astigmatism and presbyopia; these include toric-accommodating, toric-extended depth of focus, and now toric-multifocal (Toric-ReSTOR) IOLs. Patients implanted with non-toric ReSTOR lenses (2.5 and/or 3.0) have exhibited very good vision and high rates of satisfaction with their vision at various distances. Until recently, patients with corneal astigmatism could not take advantage of this option without considering a secondary procedure such as a corneal relaxing incision or refractive surgery. (More than 0.50D of expected postoperative refractive astigmatism has been suggested to materially affect visual quality and satisfaction after multifocal IOL implantation.) The availability of toric versions of the ReSTOR 2.5 and 3.0 lenses now allows for multifocal implantation in eyes with corneal astigmatism.

Postoperative rotational stability is an important consideration with any toric IOL. In general, each degree of misalignment or misorientation of an IOL will decrease the intended astigmatic correction by 3.3%, reducing the resultant image quality. The American National Standards Institute has established an IOL rotation stability standard requiring at least 90% of lenses to exhibit less than 5 degrees of rotation. Recent single-piece IOL studies have shown the AMO toric monofocal platform exhibits less than 5 degrees of rotation in 94.1% of eyes at the 6 month period. Multiple studies reviewing the Alcon toric-monofocal platform reveal similar rotational stability, with 95-96% of lenses showing less than 5 degrees of rotation.

The expectation is that the addition of toricity will not affect the general performance of the ReSTOR design. As such, it is expected that patients with a ReSTOR toric IOL that achieve a correction of their astigmatism will have visual acuity and visual quality similar to patients implanted with the non-toric ReSTOR models.

6. OBJECTIVE(S)

The objective is to provide a normative standard for refractive and visual outcomes in eyes with significant corneal astigmatism undergoing cataract surgery with the Alcon Toric ReSTOR lens.

7. SUBJECTS

7.1. Subject Population

Eligible test subjects will be patients presenting for cataract surgery or refractive lens exchange surgery who are interested in astigmatism reduction and presbyopia correction. Subjects must be eligible for bilateral multifocal toric lens implantation.

A total of 32 subjects at one site will be enrolled. Both eyes of a subject will be enrolled. Subjects must meet the inclusion criteria. Prior to enrollment, subjects will be provided information on the study and asked to sign a patient information and consent form to participate. The patient information and consent form will be approved by an appropriate ethics committee.

7.2. Inclusion Criteria

Subjects are eligible for the study if they meet the following criteria:

Note: Ocular criteria must be met in the eligible eye.

- Bilateral visually-significant cataracts
- Gender: Males and Females.
- Age: 30 or older.
- Willing and able to provide written informed consent for participation in the study.
- Willing and able to comply with scheduled visits and other study procedures.
- have good ocular health, with no pathology that compromises visual acuity (outside of residual refractive error and cataract)
- Regular corneal astigmatism of 1.00D to 2.50D in both eyes
- Potential postoperative acuity of 20/25 or better

7.3. Exclusion Criteria

If any of the following exclusion criteria are applicable to the subject or either eye, the subject should not be enrolled in the study.

- Irregular astigmatism (e.g. keratoconus)
- Corneal pathology (e.g. opacities, EBMD, Fuch’s dystrophy, etc.)
- Monocular status (e.g. amblyopia)
- Previous radial keratotomy, corneal refractive surgery or other corneal surgery (e.g. corneal transplant, DSAEK, lamellar keratoplasty)
- Previous anterior or posterior chamber surgery (e.g., vitrectomy, laser iridotomy)
- Moderate-to-advanced glaucoma
- Strabismus
- Use of arcuate incisions for astigmatism management at the time of surgery
- Diabetic retinopathy
- Macular pathology (e.g. ARMD, ERM, etc.)
- History of retinal detachment

- Subjects who have an acute or chronic disease or illness that would confound the results of this investigation (*e.g.*, immunocompromised, connective tissue disease, clinically significant atopic disease, diabetes, and any other such disease or illness), that are known to affect postoperative visual acuity.
- Participation in (or current participation) any investigational drug or device trial within the previous 30 days prior to the start date of this trial.

The principal investigator reserves the right to declare a patient ineligible or non-evaluable based on medical evidence that indicates they are unsuitable for the trial.

Pregnancy has a known effect on the stability of refractions and visual acuity. As such, subjects who become pregnant during the study will not be discontinued but their data may be excluded from analyses of effectiveness.

7.4 Exclusion Criteria during surgery

If any of the following exclusion criteria are applicable to the study eye, the subject should not continue in the study.

- If there are complications related to completion of the surgery.
- Other procedure, such as pupil stretch, expanders, iris hooks during surgery.

Note: Any subject in which surgery has been aborted for either eye should immediately be discontinued from the study and an exit form completed for that subject. These subjects will be followed up as per the clinic standard of care, monitored for safety, and their data will be excluded from the study efficacy analysis (obtained from FDA database Research Results Feb, 05, 2009). All adverse events will be appropriately documented and reported.

Participants who are considered to be a vulnerable subject population will not be enrolled into the study. Vulnerable populations include, but are not limited to, the following:

- Prisoners
- Nursing home residents /institutionalized individuals
- Mentally disabled /cognitively impaired individuals
- Sponsor employees and their family members
- Site employees and their family members that are directly and indirectly involved with the study
- Economically and/or educationally disadvantaged individuals
- Comatose individuals / traumatized individuals
- Adults who do not read and/or write
- Patients with deafness or severe hearing disability

- Terminally ill individuals / individuals with life-threatening conditions

8. STUDY DESIGN

8.1. Study Design

This study is a prospective, single center, open clinical trial to evaluate visual acuity at distance, intermediate and near as well as rotational stability of the Toric-ReSTOR IOL for 3 months after cataract surgery. Patients will be bilaterally implanted, with the Toric ReSTOR +2.5D model implanted in the dominant eye and the Toric ReSTOR +3.0D model implanted in the non-dominant eye. Patients will self-select for multifocal implantation. Toric IOL calculations will be completed with the Alcon Toric calculator, including the Barrett adjustment for posterior corneal astigmatism. The default surgically-induced astigmatism (0.1D) will be used for all calculations. Results from this study will be compared to outcomes data in the literature for the non-toric ReSTOR IOLs. Quality of vision will be measured using a validated, Rasch-scored questionnaire and compared to data available in the literature for non-toric ReSTOR lenses.

Subjects will be assessed pre-operatively and at 1 day, 1 week, 1 month and 3 months post-operatively.

Clinical evaluations will include measurement of visual acuity, manifest refraction, orientation of the toric ReSTOR IOL, defocus curve and quality of vision assessment.

The primary outcome measure will be the residual refractive cylinder.

Secondary outcome measures are as follows:

- Monocular and binocular Uncorrected and Best-corrected distance, intermediate (60cm) and near (40cm) visual acuity

- Postoperative orientation changes with the Toric ReSTOR IOL up to 3 months after surgery.

- Binocular Uncorrected and Best-corrected defocus curve (3 month visit).

- Quality of vision, measured with a subjective questionnaire.

8.2. Methods Used to Minimize Bias

As a single-arm study there is no expected bias. Patient selection will be based on the patient's interest and the surgeon's opinion as to whether they are a suitable candidate for multifocal toric lens implantation.

The measurement of visual acuity will be conducted in a systematic fashion to minimize bias. Individuals conducting visual acuity measures will be instructed to perform the

same testing in the same fashion for all subjects, with the same level of encouragement to subjects. Questions regarding quality of vision will be asked in a similar manner to all patients.

9. STUDY PROCEDURE

9.1. Informed Consent / Subject enrollment

No subject will be enrolled into the study who does not meet the inclusion/exclusion criteria and does not sign the current approved informed consent document. Informed consent will be obtained prior to collecting any data for the study. The original signed documents will be maintained by the investigator as a permanent part of the subject's medical records. A signed copy will be provided to the subject.

Subjects will each receive a discount on their surgery ($2,000 down to $900) as well as $300 if they attend the 3-month visit.

9.2. Surgery Procedures

Following a full diagnostic examination (history, visual acuity, refraction, slit-lamp exam, fundus exam, topography, biometry, OCT of macula), patients who meet criteria can be admitted to the study. Preoperative photographs at the Verion will be taken for blood vessel axis alignment indicators. The patient will be brought the operating room where standard phacoemulsification and IOL implantation will be performed. At the end of the procedure, a microscope photograph will be taken to document the orientation of the IOL.

9.3. Visits and Examinations

Subjects will participate in six study visits. Visits will include an uptake visit, two operative visits (one for each eye), and 6 postoperative visits (Visit numbers 3, 3A, 4, 4A, 5 and 6 below). The visit schedule, complete with window and associated CRF forms, are displayed in Table 9.3-1. Details of each study visit, including testing to be conducted, are provided below.

Table 9.3-1. Visit Schedule

Visit Number	Visit Name	Visit Window	CRF Number
1	Preoperative	-30 to 0 days from surgery	1
2, 2A	Operative (unilateral)	0 from surgery	2, 2A
3, 3A	1 Day Postoperative	1-2 days postoperative	3, 3A
4, 4A	1 Week Postoperative	7 (±2) days postoperative	4, 4A
5	1 Month Postoperative	30 (±7) days postoperative	5
6	3 Months Postoperative	90 (±15) days postoperative	6

All data collection will be completed through provided Case Report Forms (CRFs). All site personnel involved in the study will be trained in regard to conducting study-specific procedures. Case report forms will be identified by the subject number assigned at the time of randomization. No protected health information (PHI) will be included on any CRF. Subject identities will be removed at the initial visit so that there will be no further need to protect or destroy the information.

9.3.1. Preoperative

The subject will complete an information and consent document. Inclusion and exclusion criteria will be applied to determine qualification for the study.

A medical history will be taken and exams will include the tests described below:

- manifest refraction,
- visual acuity,
- Preoperative photographs at the Verion will be taken for blood vessel axis alignment indicators

In addition, all site-specific, routine preoperative measures will be performed.

Measurements will be made as described in section 9.4 below.

The preoperative visit is expected to take about 30-45 minutes.

9.3.2. Operative (Surgery)

The patient will be brought the operating room where standard phacoemulsification and IOL implantation will be performed. At the end of the procedure, a microscope photograph will be taken to document the orientation of the IOL.

Surgical findings will be recorded and any adverse events/serious adverse events (AEs/ SAEs) occurring during surgery will be noted at this visit. Any other problems during surgery and comments regarding surgery will be documented.

Any subject whose surgery is not completed successfully will be documented. These subjects will be monitored for safety but clinical performance data may be excluded from the analysis.

All study subjects will be placed on an appropriate antibiotic (Vigamox) and steroid (Durezol) drop QID for one week. A non-steroidal anti-inflammatory (Ilevro) drop will also be applied once a day for the first two weeks.

For the following three weeks, the steroid (Durezol) drop will be continued on a tapered dose.

9.3.3. Postoperative 1 Day

All routine postoperative measures will be taken. In addition, the subject will undergo VA testing in accordance with the specifications below (Section 9.4). Intraocular pressure will also be measured. Adverse events will be monitored.

This visit is expected to take around 30 minutes to complete.

9.3.4 Postoperative 1 Week

All routine postoperative measures will be taken. In addition, the subject will undergo VA testing in accordance with the specifications below (Section 9.4). Intraocular pressure (IOP) will also be measured. Adverse events will be monitored.

9.3.5. Postoperative 1 Month

All routine postoperative measures will be taken. In addition, the subject will undergo manifest refraction, IOP measurement, VA testing and dilated Verion photographs to document the postoperative orientation of the IOL. Adverse events will be monitored.

9.3.6. Postoperative 3 Months

All routine postoperative measures will be taken. In addition, the subject will undergo manifest refraction, IOP measurement, VA testing and dilated Verion photographs to document the postoperative orientation of the IOL. The patient's quality of vision will be measured using a validated, Rasch-scored questionnaire. A defocus curve in accordance with the specifications below (Section 9.4) will also be obtained at this visit. Adverse events will be monitored. An exit form will be completed.

9.3.8. Exit Procedures

In the event of premature exit from the study, all study related examinations should be completed where possible. The Exit CRF should be completed, noting that the subject did not complete the study and the reason for premature study exit. If no premature exit from the study occurs, the Exit CRF should be completed at the end of Visit 6 (Postoperative 3 Months).

9.4. Study Methods and Measurements

All routine testing and basic eye examinations should be carried out at each study visit. Abnormalities should be recorded in the CRF "Comment" section. Specific study examination procedures are outlined below.

9.4.1. Manifest Refraction

Perform a manifest refraction with a high contrast logMAR chart under photopic lighting conditions (>85 cd/m^2). Document refraction results with sphere, cylinder and axis readings. If uncorrected visual acuity is not improved by manifest refraction, use zero for sphere and cylinder and draw a line through the blank for the axis.

Note: Each subject should be manually refracted to his/her best correction by an ophthalmologist, optometrist, or a skilled technician using a phoropter or trial lenses.

9.4.2. Visual Acuity (VA)

To obtain logMAR VA, ask subjects to begin reading the chart at a row where all letters are easily distinguishable. Have subjects continue to read rows with smaller letters and encourage subjects to guess at all letters in a line if at least one correct response was given on the previous row. Request subjects read rows until no letters on a row are read correctly or until all letters on a row are too indistinguishable to even be guessed.

Perform uncorrected and best-distance corrected visual acuity testing monocular and binocularly.

Distance VA

Measure distance visual acuity using the 100% contrast ETDRS chart under photopic lighting at a distance of 4-6 m.

Intermediate VA

Have the subject hold a Logarithmic ETDRS Visual Acuity Chart, "Chart 2", at 60cm, using the 60cm cord held at the outer canthus as a reference. Record and score the subject's visual acuity.

Near VA

Conduct near testing with a Logarithmic ETDRS Visual Acuity Chart, "Chart 1" at 40 cm, using the 40cm cord held at the outer canthus as a reference. Visual acuity determined with the chart will be recorded and scored.

9.4.4. Quality of vision questionnaire

Have the subject complete the Q of V (Quality of Vision) questionnaire. Scoring will be through the aggregate spreadsheet provided.

Note: Avoid interpreting survey questions for subjects. That is, avoid re-phrasing questions if a subject asks, "What does this mean?"

9.4.5. Binocular Defocus Curve

With and without the manifest distance refraction in place in a phoropter, and in photopic conditions, perform binocular defocus curve testing. An over-correction starting at +1.0D is placed in the phoropter and binocular VA is recorded. The correction is then reduce by 0.5D (i.e. +0.5 over-correction) and retested. An over-correction of -4.0D is then placed in the phoropter and removed in 0.5D increments, testing VA at each step. The procedure ends with VA testing with a 0.0D over-correction (best-corrected distance refraction). Testing may be conducted using proprietary computer software designed to simplify the procedure and to record results. LogMAR visual acuity will be recorded for each defocus step.

9.5. Unscheduled Visits

Unscheduled exams may be conducted at the discretion of the Investigator with all relevant information from the exam recorded in the source documents and on the Unscheduled Visit pages within the CRF booklet.

9.6. Discontinued Subjects

Discontinued subjects are those who do not have an exit visit or who come into the office to be exited prior to the scheduled final study visit. Subjects may be discontinued from the study at any time if, in the opinion of the investigator, their continued participation in the study poses a risk to their health. The reasons for discontinuation include:

a. Adverse event;
b. Lost to follow-up;
c. Subject decision unrelated to an adverse event;
d. Protocol violation;
e. Treatment failure;
f. Other.

To ensure the safety of all subjects who discontinue prior to Visit 6, investigators should assess each subject and, if necessary, advise them of any therapies and/or medical procedures that might be needed to maintain their health. Any changes in medical health and/or use of concomitant medications should also be captured.

10. ANALYSIS PLAN

10.1. Analysis Data Sets

All subjects who are enrolled in the study will be evaluated for safety. Efficacy analyses will be performed based on data from those eyes where uncomplicated Verion-LenSx guided arcuate incisions were completed.

10.2. Statistical Methodology

All data will be collected by the site and entered into a spreadsheet. Subjects will be assigned an ID number. Data analysis will be performed without patient identification. Statistical analysis will be performed using standard descriptive statistics and other tests as deemed appropriate based on the characteristics of the data to be analyzed. All statistical tests will be two-sided and interpreted at a 5% significance level.

10.3. General Statistical Considerations

The statistical analyses will be performed using Statistica, version 12 or higher. Any statistical tests of hypotheses will employ a level of significance of alpha=0.05.

11. SAMPLE SIZE JUSTIFICATION

Data in the literature suggests that the ReSTOR non-toric IOLs (+3.0D and +2.5D) implanted in a group of eligible eyes showed a residual refractive cylinder of 0.40D ± 0.32D. (Gundersen KG, Potvin R. Comparison of visual outcomes and subjective visual quality after bilateral implantation of a diffractive trifocal intraocular lens and blended implantation of apodized diffractive bifocal intraocular lenses. Clin Ophthalmol. 2016 May 10;10:805-11). We are looking for the toric IOLs to be non-inferior. We powered the study using that mean and SD, a power of 0.9, an alpha of 0.05, and a 0.25D non-inferiority margin. The mean residual refractive cylinders will be compared using a t-test between the two groups, with the mean and SD from the literature (blended bifocal group) and the mean and SD from the current study. The required sample size is 29 subjects. Allowing for 10% dropout we will plan to enroll 32 subjects.

12. CONFIDENTIALITY/PUBLICATION OF THE STUDY

The existence of this Study is confidential and should not be discussed with persons outside of the Study. Results will be submitted for publication and presentation at national and/or international meetings. A manuscript will be submitted to peer-review journals for publication but there is no guarantee of acceptance.

All study data will be collected on appropriate Case Report Forms (CRFs). No protected health information will be included on the forms. CRFs will be retained in the patient's file for a minimum period of 3 years. Collected information will only be used for purposes of this study and no information will be sold to third parties. The following people will have access to your study records:

- Study Doctor and staff involved with the study
- Study Monitor or Auditor
- Sponsor Company or Research Institution
- Review boards or accrediting agencies

- Other State or Federal Regulatory Agencies

The de-identified data may be shared with other researchers for future analysis.

13. QUALITY COMPLAINTS AND ADVERSE EVENTS

All subjects will be monitored for adverse events over the course of the study. A place to record any adverse event is included on each case report form.

13.1. General Information

An Adverse Event (AE) is any untoward medical occurrence in a subject who is administered. a study treatment regardless of whether or not the event has a causal relationship with the treatment. An AE, therefore, can be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study treatment, whether or not related to the treatment. In clinical studies, an AE can include an untoward medical occurrence occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

13.2. Monitoring for Adverse Events

At each visit, after the subject has had the opportunity to spontaneously mention any problems, the Investigator should inquire about AEs by asking if the patient has any problems.

13.3. Procedures for Recording and Reporting AEs and SAEs

Subsequent to signing an informed consent form, all untoward medical occurrences that occur during the course of the study must be documented on an Adverse Event Form (AEF). A separate AEF must be filled out for each event. When possible, signs and symptoms indicating a common underlying pathology should be documented as one comprehensive event. For each recorded event, the AE documentation must include the onset date, outcome, resolution date (if event is resolved), intensity (ie, severity), any action with study treatment taken as a result of the event, and an assessment of the adverse event's relationship to the study treatment.

Nonserious Adverse Events

A nonserious AE is defined as any untoward change in a subject's medical health that does not meet serious criteria noted below (eg, is not life-threatening, does not require hospitalization, does not prolong a current hospitalization, is not disabling, etc.). All adverse events must be reported regardless of whether or not they are related to the study treatment.

For nonserious adverse events, an AEF containing all available information will be collected on a routine basis and submitted to the Medical Monitor at the close of the study.

Serious Adverse Events

A serious adverse event (SAE) is defined as any adverse experience that meets any of the following criteria:

- Results in death.
- Is life-threatening.
  NOTE: Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, ie, it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  NOTE: In general, hospitalization signifies that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
  NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (eg, sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.
  All available information on a serious adverse event(s) and any other associated AE, if applicable, must be forwarded to the study coordinator for forwarding to the Medical Monitor immediately (ie, within one working day of the Investigator's or site's knowledge of the event) as follows:
  - In studies utilizing EDC (electronic data capture), all available information for the SAE and any associated AE(s) must be entered immediately into the EDC system.
  - Additional information for any applicable event is to be reported as soon as it becomes available.

In addition to the reporting of serious adverse events to the study Medical Monitor, the SAE must be reported to the IRB / IEC according to their requirements.

The investigator must document all adverse device events (serious and nonserious but related) and all serious adverse events (related and unrelated) on the Adverse Device

Effect and Serious Adverse Event Form. Any device quality complaints will also be documented.

- **Both the Quality Complaint Form and the Adverse Device Effect and Serious Adverse Event Form must be faxed immediately to the study coordinator at 1-716-442-5110 or emailed to rick@scienceinvision.com.**
- **Additional relevant information is to be reported as soon as it becomes available.**

Study coordinator contact information is provided below.

Table 13.3.-1:
Contact Information for ReSTOR Toric lens Study

Study Staff	Business Phone	Business Fax	Home Phone
Name and number here			

Further, depending upon the nature of the adverse event (serious or nonserious) or quality complaint being reported, the study sponsor may request copies of applicable portions of the subject's medical records. The investigator must also report all adverse events and quality complaints according to the relevant IRB requirements.

12.3.1 Intensity and Causality Assessments

For every adverse event and quality complaint, the investigator must assess the causality as Related or Not Related to the medical device under investigation. An assessment of causality will also be performed by the Medical Monitor utilizing the same definitions, as shown below:

Causality

Related — An adverse event or quality complaint classified as related may be either definitely related or possibly related where a direct cause and effect relationship with the medical device has not been demonstrated, but there is a reasonable possibility that the adverse event or quality complaint was caused by the medical device.

Not Related — An adverse event or quality complaint classified as not related may either be definitely unrelated or simply unlikely to be related (i.e., there are other more likely causes for the adverse event or quality complaint).

Where appropriate, the investigator must assess the intensity (severity) of the adverse event as mild, moderate, or severe based on medical judgment with consideration of any subjective symptom(s), as defined below:

Intensity (Severity)

Mild	An adverse event is mild if the subject is aware of but can easily tolerate the sign or symptom.
Moderate	An adverse event is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities.
Severe	An adverse event is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

The investigator must document any action taken (i.e., medication, intervention, or treatment plan) and outcome of the adverse event or quality complaint when applicable.

13.4. Follow-Up of Adverse Events and Quality Complaints

The investigator is responsible for adequate and safe medical care of subjects during the study and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the study. Any additional data from these follow-up procedures must be documented and available to the study coordinator who, with the Medical Monitor, will determine when the data need to be documented on the CRFs.

13.5. Safety Analyses

The type, severity, duration and frequency of reported ocular adverse events will be tabulated. Adverse events will also be summarized for events that were considered treatment-related.

14. GCP, ICH and ETHICAL CONSIDERATIONS

This study will be conducted in compliance with Good Clinical Practices (GCPs), including International Harmonization (ICH) Guidelines, and in general, consistent with the 1996 version of the Declaration of Helsinki. In addition, all applicable local, state and federal requirements will be adhered to.

This study is to be conducted in accordance with Institutional Review Board regulations. The investigator will obtain appropriate IRB/ethics committee approval prior to initiating the study.

The study will be registered with clinicaltrials.gov.

15. STANDARD EVALUATION PROCEDURES

Table 15.1. Proposed Visits and Study Assessments

(visits are by patient, with both eyes tested)

Activity	Pre-operative	Operative	Postoperative			
	Visit 1	Visit 2, 2A	Visit 3, 3A	Visit 4, 4A	Visit 5	Visit 6
			1 Day	1 Week	1 Month	3 Month
Informed Consent	X					
Demographics	X					
General Information: Medical History	X					
Surgery		X				
Manifest Refraction	X				X	X
Uncorrected Distance VA (monocular and binocular)			X	X	X	X
Corrected Distance VA (monocular and binocular)	X				X	X
Uncorrected Intermediate and Near VA (monocular and binocular)					X	X
Distance-corrected Intermediate and Near VA (monocular and binocular)					X	X
Intraocular pressure			X	X	X	X
Verion photograph	X	X			X	X
Quality of vision questionnaire						X
Binocular Defocus curve (uncorrected and corrected)						X
Monitor for Adverse Events		X	X	X	X	X
Complete Exit Form[1]						X

[1] Complete Exit Form upon termination of subject participation, or at Visit 6, whichever occurs first.

16. CONFIDENTIALITY

No protected health information (PHI), including the patient's name and date of birth, will be collected; to ensure this, no PHI information is permitted to be entered on any of the Case Report Forms (CRFs). Subjects will only be identified by subject IDs and identities will be removed at the initial visit so that there is no further need to protect or destroy the information. Collected information will only be used for purposes of this study and no information will be sold to third parties. The non-PHI information collected may be used for future research, though there is currently no plan to do so.

17. FINANCIAL AND INSURANCE INFORMATION/STUDY RELATED INJURIES

Every effort to prevent study-related injury will be taken by the Study Doctor and staff. In the event a patient is injured as a direct result of the study while following the Study Doctor's instructions and the study requirements, the patient will be instructed to contact his or her doctor immediately. The Study Doctor is to treat the injured subject as needed for those injuries caused directly by this research study. In the event of injury or illness caused by or occurring during a subject's participation in this research study, all charges for medical care provided to the subject will be billed to his or her insurance company. The Study Doctor or Sponsor does not offer to cover the medical care costs for injuries or illnesses that are not caused directly by the research study. The Sponsor does not offer to provide any other compensation, unless specifically agreed to elsewhere in this document. This information will be provided to each study subject before the start of the study in the consent form.

18. STUDY ENDPOINT CRITERIA

18.1. Patient Completion of Study

If a study patient has completed the final visit (Visit 6) of the study, he/she is considered to have completed the study.

18.2. Patient Discontinuation

Each study patient may voluntarily discontinue the study at any time they choose. Study patients who cannot complete the study for administrative reasons (e.g., non-compliance, failure to meet visit schedule, etc.) will be discontinued from the study. Study patients discontinued during the enrollment phase (prior to surgery) of the study will be replaced.

18.3. Patient Termination

A study patient will be terminated if the study patient develops any severe adverse event that may be related to the study. A study patient will receive appropriate treatment at the discretion of the investigator. Notification of termination will be clearly documented. These study patients are considered to have completed the study and will not be replaced.

18.4. Study Termination

The investigator with appropriate notification may terminate the study. If, after clinical observations, the investigator feels that it may be unwise to continue the study, he may stop the study.

18.5. Study Completion

The study will be complete when all enrolled patients have completed Visit 5 or have been terminated from the study.

19. SUMMARY OF RISKS AND BENEFITS

19.1. Summary of risks

The femtosecond laser system to be used in this study is approved for corneal incisions, either full thickness or partial thickness, at the time of cataract surgery. The current study involves creating partial thickness arcuate incisions at a time after cataract surgery.
The most common side effects of arcuate incisions include:

- Irregular astigmatism
- Regression, where the effects of the incision(s) are lower over time

19.2. Summary of benefits

For patients undergoing cataract surgery, they may be offered the option to have a femtosecond laser system create arcuate incisions on the cornea, with the goal of reducing corneal astigmatism (and, by extension, postoperative refractive astigmatism) at the time of surgery.
It is likely that corneal incisions made with a femtosecond laser system will reduce corneal astigmatism, even when applied after successful cataract surgery.
The potential benefit related to the current study is that this procedure could be offered to patients who have had cataract surgery in the past and who have residual refractive astigmatism with a minimal spherical equivalent refraction after surgery.