HRP-591 - Protocol for Human Subject Research

Protocol Title:

Femtosecond Laser Assisted Keratotomies for the Management of Corneal Astigmatism

Principal Investigator:

Name: Seth Pantanelli
Department: Ophthalmology
Telephone: 289897
E-mail Address: spantanelli@pennstatehealth.psu.edu

Version Date:

1/05/2021

Clinicaltrials.gov Registration #:

Not applicable

Important Instructions for Using This Protocol Template:

1. Add this completed protocol template to your study in CATS IRB (http://irb.psu.edu) on the "Basic Information" page, item 7.
2. This template is provided to help investigators prepare a protocol that includes the necessary information needed by the IRB to determine whether a study meets all applicable criteria for approval.
3. **Type your protocol responses below the gray instructional boxes of guidance language. If the section or item is not applicable, indicate not applicable.**
4. **For research being conducted at Penn State Hershey or by Penn State Hershey researchers only, delete the instructional boxes from the final version of the protocol prior to upload to CATS IRB (http://irb.psu.edu). For all other research, do not delete the instructional boxes from the final version of the protocol.**
5. When making revisions to this protocol as requested by the IRB, please follow the instructions outlined in the Study Submission Guide available in the Help Center in CATS IRB (http://irb.psu.edu) for using track changes.

If you need help…	
University Park and other campuses: Office for Research Protections Human Research Protection Program The 330 Building, Suite 205 University Park, PA 16802-7014 Phone: 814-865-1775 Fax: 814-863-8699 Email: irb-orp@psu.edu	**College of Medicine and Hershey Medical Center:** Human Subjects Protection Office 90 Hope Drive, Mail Code A115, P.O. Box 855 Hershey, PA 17033 (Physical Office Location: Academic Support Building Room 1140) Phone: 717-531-5687 Fax number: 717-531-3937 Email: irb-hspo@psu.edu

Table of Contents

1.0 Objectives

1.1 Study Objectives

1. To determine the degree of surgically induced astigmatism of femtosecond laser clear corneal incisions
2. To determine the post-operative mean reduction in keratometric astigmatism and uncorrected distance visual acuities in patients undergoing femtosecond laser-assisted cataract surgery with astigmatic keratotomy (AK)
3. To determine the role of corneal biomechanics (hysteresis) on AK calculations.
4. To develop a nomogram that may be utilized in determining location and arc length of AKs for femtosecond laser-assisted cataract surgery with astigmatic keratotomy

1.2 Primary Study Endpoints

The primary outcome measures are as follows (collected at post-operative month one):

- Uncorrected visual acuity
- Post-operative corneal curvature measurements and astigmatism as assessed using optical biometer
- Post-operative auto-refraction

1.3 Secondary Study Endpoints

The secondary outcome measures are as follows (collected at post-operative month one):

- Mean change in astigmatism in eyes with 'with the rule' (WTR) astigmatism
- Mean change in astigmatism in eyes with 'against the rule' (ATR) astigmatism
- Complications related to placement of femtosecond laser AKs

2.0 Background

2.1 Scientific Background and Gaps

1.1. Nearly 20% of people undergoing cataract surgery have significant corneal astigmatism (1.5 D or greater). Patients increasingly expect spectacle independence after cataract surgery, which requires correction of this astigmatism. Femtosecond laser astigmatic keratotomies (AKs) can be used to treat corneal astigmatism, but there are no nomograms developed to guide surgeons on the parameters (i.e. depth and arc length) to use to correct specific amounts of astigmatism. Instead, surgeons must rely on old nomograms that were developed for manual incisions and adapt them for use with the laser.

A well-validated nomogram exists for determining location and arc length of limbal relaxing incisions (LRI), another type of refractive procedure used to treat astigmatism.[1] This calculator specifically states that it is "intended to support the use of LRIs only, it is not intended for the calculation of femtosecond laser incisions.[1]"

If we could accurately determine the effect femtosecond laser performed AKs have on corneal astigmatism at the time of cataract surgery, a nomogram to be used specifically with the laser could be reverse engineered.

2.2 Previous Data

One previous prospective study has been published evaluating the effectiveness of femtosecond laser corneal relaxing incisions in reducing corneal astigmatism during cataract surgery.[2] This study also proposed a preliminary nomogram based on the 51 eyes that were included in the study.[2] While this study is a landmark paper in proposing a nomogram for AKs, the authors conclude that further study is required to refine and validate the nomogram. In addition, the role of corneal biomechanics, such as corneal hysteresis is not factored into their nomogram. Another study demonstrated that corneal biomechanical parameters are independent predictors of the efficacy of femtosecond laser AKs.[3]

2.3 Study Rationale

The purpose of this study is to build upon the existing literature to create a nomogram based on a large number of eyes that may be utilized to accurately predict location and arc length of AKs to minimize post-operative astigmatism. This nomogram will incorporate corneal biomechanics, including corneal hysteresis.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

- Age: ≥18 years of age
- Sex: male or female
- Patients who are planned to undergo femtosecond laser-assisted cataract surgery with astigmatic keratotomy at the Schein Ernst Mishra Eye clinic within the next 60 days of their cataract consultation visit. Subjects with planned single or bilateral cataract eye surgeries are eligible. Planned opposite eye surgery must be within 2-4 weeks of first cataract surgery.
- Fluent in written and spoken English

3.2 Exclusion Criteria

- Patients with corneal dystrophies, including anterior basement membrane dystrophy, keratoconus, and Fuch's endothelial corneal dystrophy.
- Age < 18 years
- Pregnant women
- Cognitive impairment
- Prisoners

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Subjects may withdrawal from the study if they no longer wish to participate in the study.

Subjects may withdrawal from the study if they no longer plan to undergo femtosecond laser-assisted cataract surgery with astigmatic keratotomy. There are no anticipated safety reasons for which a subject would need to withdrawal from the study. There is no disease progression that would require a subject to withdrawal from the study.

3.3.2 Follow-up for withdrawn subjects

Subjects may withdrawal from the study at any point up to their post-operative one-month exam. Data will be collected for the number and the reason for withdrawal of subjects (eg. withdrawal of consent). A patient disposition flow diagram will be constructed. Subjects that withdrawal from investigational treatment will be treated as any other patient who is undergoing cataract surgery outside of the study.

4.0 Recruitment Methods

4.1 Identification of subjects

Participants will be identified by Dr. Brett Ernst during a scheduled patient clinic visit to review the medically planned femtosecond laser-assisted cataract surgery with astigmatic keratotomy standard of care cataract surgery consent.

4.2 Recruitment process

All eligible patients will be offered the opportunity to participate in the research study. The Dr. Ernst will explain the research study to potential subjects at their pre-surgery clinic visit.

4.3 Recruitment materials

None

4.4 Eligibility/screening of subjects

Not applicable

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

Informed consent is a process. Consent will take place in the ophthalmology clinic when a patient would be regularly consented to undergo cataract surgery (within 60 days of surgery date). As the patient presents for surgery, the consent will be reviewed once again and any additional questions will be addressed to confirm they still want to participate in the study.

5.1.1.2 Coercion or Undue Influence during Consent

Subjects will be informed that participation is voluntary and that their decision will not affect their care. Physician investigators will discuss the study with the patients and answer all questions.

5.1.2 Waiver or alteration of the informed consent requirement

A waiver of consent is requested to review medical record information to determine preliminary eligibility to participate in the research.

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

The consent process will be documented in writing with the long form of consent documentation:

- The current IRB approved consent form will be obtained.
- We will verify that we are using the most current IRB-approved version of the study specific consent form and that the consent form is in language understandable to the subject.
- A copy of the consent form will be provided to the subject. Whenever possible the consent form will be provided to the subject in advance of the consent discussion.

5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

Not applicable

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

Not applicable

5.3.2 Cognitively Impaired Adults

5.3.2.1 Capability of Providing Consent

Not applicable

5.3.2.2 Adults Unable To Consent

Not applicable

5.3.2.3 Assent of Adults Unable to Consent

Not applicable

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission

Not applicable

5.3.3.2 Assent of subjects who are not yet adults

Not applicable

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Study information will be destroyed after the research has ended and all institutional/regulatory requirements for data retention have been met.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Information must be obtained from the subject's electronic medical record during recruitment to determine eligibility and, in some cases, to confirm information discussed with the subject in regards to their medical history.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

The waiver is requested only for recruitment to determine subject eligibility to ensure that no medical conditions that fall into the exclusion criteria are present and would thus preclude enrollment. This waiver will minimize the enrollment of subjects' who may ultimately fail to meet the study inclusion/exclusion criteria.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

This is a prospective cohort study of patients who are undergoing femtosecond laser-assisted cataract surgery with astigmatic keratotomy. Patients will be selected to participate in the study based on inclusion/exclusion criteria.

It should be noted that this is an observational, not interventional study. The parameters to be chosen for the femtosecond AKs will be determined using best practices (surgeon's choice using algorithms created for manual LRIs but adapted for use with the laser). Whether a patient is enrolled in the study or not will not influence the architecture or plan for the femtosecond AKs. The purpose of the study is to carefully examine the effects of these femto AK on corneal astigmatism in a retrospective fashion (after the 1 month post-operative visit) so that a nomogram can be developed using regression analysis. As such, the only 'intervention' patients enrolled in the study will receive that un-enrolled patients will not is measurement of corneal hysteresis and corneal biometry at their 1 month post-operative visit.

7.2 Study Procedures

7.2.1 Visit 1 or Day 1 or Pre-test, etc. (format accordingly)

Pre-operative visit: Inclusion/exclusion criteria will be assessed. Consent will be obtained from eligible subjects who wish to participate in the study. Demographic and baseline characteristics will be recorded. Pre-operative biometry, refraction, and corneal hysteresis data will be collected.

7.2.2 Visit 2

Day of surgery: Data from the femtosecond laser will be collected, including the various laser parameters that are used to make the astigmatic keratotomies and clear corneal incisions.

7.2.3 Visit 3

Day of surgery for contralateral eye: Data from the femtosecond laser will be collected, including the various laser parameters that are used to make the astigmatic keratotomies and clear corneal incisions.

7.2.4 Visit 4 or post-operative month #1 visit (1 month after 2nd operative procedure)

Post-operative month 1 visit: One-month post-operative IOL master, autorefraction, manifest refraction, and uncorrected visual acuity will be collected.

7.3 Duration of Participation

The individual subject will participate in the study from the time consent is obtained at their pre-operative visit, through their femtosecond laser-assisted cataract surgery with astigmatic keratotomy on both eyes, and until their one-month post-operative visit.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

300

8.2 Sample size determination

Eyes may have with-the-rule, against-the-rule, and oblique astigmatism. Corneas with varying forms of astigmatism will respond differently to the AKs; thus it is necessary to have a sufficient number of eyes to produce results for all forms of astigmatism. Approximately 50% of eyes have against-the-rule astigmatism, 30% with-the-rule, and 20% oblique. 20% of 300 eyes = 60, which was felt to be the minimum number to produce meaningful results for this group.

8.3 Statistical methods

Eyes that do not obtain a final best-corrected visual acuity of 20/40 or better will be excluded from the final data analysis. Mean change in keratometric astigmatism will be determined by subtracting preoperative astigmatism from postoperative mean astigmatism. Vector analysis and double-angle plot will be used to analyze aggregate astigmatism. We will require assistance from a statistician.

A sub-group analysis will likely include patients that had prior refractive surgery (i.e. LASIK).

9.0 Confidentiality, Privacy and Data Management

See the Research Data Plan Review Form

10.0 Data and Safety Monitoring Plan

Not applicable

11.0 Risks

Risk of loss of confidentiality

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

None

12.2 Potential Benefits to Others

Accurate correction of astigmatism in patients undergoing femtosecond laser-assisted cataract surgery with astigmatic keratotomy is vital for patients to achieve spectacle independence. While there is a universal LRI calculator readily available to the refractive cataract surgeon, a similar calculator does not exist for AKs. A validated calculator to determine AK parameters would potentially allow for more patients undergoing femtosecond laser-assisted cataract surgery with astigmatic keratotomy to achieve spectacle independence.

13.0 Sharing Results with Subjects

Not applicable

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Subjects will receive a thirty dollar gift card for participating in the study.

15.0 Economic Burden to Subjects

15.1 Costs

The subjects will not be responsible for any research-related costs (data collection from standard of care procedures and the one month follow-up research visit) for participating in the research.

15.2 Compensation for research-related injury

Not Applicable: no greater than minimal risk (loss of confidentiality) research.

16.0 Resources Available

16.1 Facilities and locations

Patients will be recruited from Schein Ernst Mishra Eye (10 Capital Drive Harrisburg PA 17110 or 717 Market St., Ste. 112 Lemoyne, PA 17043). All cataract surgeries for the study will be performed at Capital Surgery and Laser Center (10 Capital Drive, Suite 200 Harrisburg, PA, 17110).

16.2 Feasibility of recruiting the required number of subjects

The study team has access to approximately 10-20 potential subjects per week. At a minimum, 25% of subjects (4-5 per week) would need to be recruited in a one year period to reach the required number of participants for the desired study power.

16.3 PI Time devoted to conducting the research

The PI has 20% academic time and will be contributing half of this to research activities, for a total percentage effort of 10%.

16.4 Availability of medical or psychological resources

Not applicable

16.5 Process for informing Study Team

Team members will meet with the PI periodically during the course of the study to ensure proper training on study protocol and duties.

17.0 Other Approvals

17.1 Other Approvals from External Entities

Not applicable

17.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Clinical Research Center (CRC) Advisory Committee – All campuses – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of HRP-903 - Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

18.0 Multi-Site Research

Not applicable

19.0 Adverse Event Reporting

19.1 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

20.0 Study Monitoring, Auditing and Inspecting

20.1 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

21.0 Future Undetermined Research: Data and Specimen Banking

Not applicable

22.0 References

[1]LRIcalculator.com. Abbott Laboratories Inc. Abbott Park, Illinois, USA. Accessed from http://www.lricalculator.com. Accessed August 13, 2017.

[2]Wang L, Zhang S, Zhang Z, Koch DD, Jia Y, et al. Femtosecond laser penetrating corneal relaxing incisions combined with cataract surgery. *J Cataract Refract Surg.* 2016;42:995-1002.

[3]Day AC, Stevens JD. Predictors of femtosecond laser intrastromal astigmatic keratotomy efficacy for astigmatism management in cataract surgery. *J Cataract Refract Surg*. 2016;42:251-7.

Yang J, Wang X, Zhang H, Pang Y, Wei R. Clinical evaluation of surgery-induced astigmatism in cataract surgery using 2.2 mm of 1.8 mm clear corneal micro-incisions. *Int J Ophthalmol*. 2017;10(1):68-71.

Chan TCY, Cheng GPM, Wang Z, Tham CCY, Woo VCP, Jhanji V. Vector analysis of corneal astigmatism after combined femtosecond-assisted phacoemulsification and arcuate keratotomy. *Am J Ophthalmol*. 2015;160(2):250-255.