

Epithelium-On Corneal Collagen Crosslinking for Keratoconus

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CONFIDENTIAL

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1.0 BACKGROUND

This study is being conducted to evaluate the safety and efficacy of epithelium-on corneal collagen crosslinking using the KXL System with riboflavin Photrexa (riboflavin 5'-phosphate ophthalmic solution) 0.146% for treatment of progressive keratoconus (KC).

Keratoconus (KC) is a biomechanical disorder of the cornea which causes the cornea to progressively distort, causing loss of its optical properties. Because of the visual aberrations caused by this progressive distortion and out-bowing of the cornea in KC, patients usually require rigid or complex curvature contact lenses to "cover-up" the optical irregularities to achieve functional vision; spectacle correction most frequently does not result in acceptable vision and function. Given the distortion of the cornea, contact lens fitting may not be possible in many patients. Furthermore, keratoconus tends to progress over the second to 5th decades of life and can lead to progressive intolerance of contact lenses and, ultimately, necessitate corneal transplantation. Together, keratoconus and post-refractive corneal ectasia are the second most frequent indication for corneal transplantation, accounting for about 15% of the corneal transplant performed in the United States.¹

Any modality, such as corneal collagen cross-linking, that can delay or prevent corneal transplantation in patients with these conditions is of great benefit. Investigations of CXL have shown the procedure not only to decrease keratoconus progression, but also to decrease the steepness of the cone and improve uncorrected and best corrected visual acuity in some cases.

Standard epithelium-off crosslinking treatment regimen is as follows

1. Pretreatment with riboflavin 0.146% in 20% dextran T500 solution. 1 drop is administered every 2 minutes for 30 minutes after the corneal epithelium has been removed.
2. If the cornea after drop administration is ≥ 400 microns thick, UV administration (step 3) is begun. If the cornea is <400 microns thick, then hypotonic riboflavin is administered until the cornea swells to 400 microns or greater
3. UV light (365 nm) is then administered at an irradiance of $3\text{mW}/\text{cm}^2$ for 30 minutes. During this time, riboflavin/dextran is administered every 2 minutes to maintain proper riboflavin concentration in the corneal stroma.

Epithelium-on crosslinking, in which the epithelium is not removed, has been proposed to offer a number of advantages over traditional crosslinking including an increased safety profile by reducing the risk for infection as no epithelial removal will be performed, faster visual recovery and improved patient comfort in the early postoperative healing period since re-epithelization is not required.

¹ Eye Bank Association of America Statistical Report. 2006

1.1 Rationale

Two riboflavin preparations, Photrexa® Viscous (riboflavin 5'-phosphate 0.146% in 20% dextran ophthalmic solution) and Photrexa® (hypotonic riboflavin 5'-phosphate 0.146% ophthalmic solution) are currently FDA approved for use with the KXL® System for corneal collagen crosslinking (CXL) for the treatment of progressive keratoconus and corneal ectasia following refractive surgery in the United States. The first preparation containing riboflavin in a dextran solution tends to draw water out of the cornea and keep it thinner. The second preparation contains riboflavin in a hypotonic (low salt) solution without dextran, which may tend to keep the cornea more swollen.

In the currently FDA approved CXL procedure, the first step involving removal of the corneal epithelium allows adequate penetration of the riboflavin, a large macromolecule that otherwise is unable to penetrate an intact epithelium. With the addition of certain topical drugs such as benzalkonium chloride (BAK) or ethylenediaminetetraacetic acid (EDTA), an increase in the epithelial permeability to hydrophilic molecules like riboflavin is observed. In addition, removal of the dextran in the riboflavin solution seems to facilitate penetration through the epithelium. A number of reports of the effectiveness of this procedure have been published.^{2,3}

This current study proposes to evaluate the safety and efficacy of epithelium-on crosslinking using Photrexa.

The potential benefits of the proposed treatment regimens compared with the standard CXL with epithelial debridement are:

1. Less potential risk of infection because the epithelium is not removed .
2. Faster visual recovery including return to contact lens wear sooner.
3. Improved patient comfort in early postoperative period during where re-epithelialization is not required.
4. Use of hypotonic riboflavin may afford better maintenance of corneal thickness and allow treatment of more severe disease where corneal thickness may preclude treatment.
5. Maintenance of the epithelium may decrease corneal stromal haze postoperatively.

1.2 Prior Experience

United States Phase 3 Clinical Studies

The safety and efficacy of the corneal collagen cross-linking procedure were evaluated in 3 randomized, parallel-group, open-label, sham-controlled trials; patients were followed

² Pinelli R, Mometto C. Corneal epithelium: Should it stay or should it go? Ophthalmology times Europe, April 2007, pages 18-19. Available at <http://www.oteurope.com/ophthalmologytimeseuropa/Cornea/Corneal-epithelium-should-it-stay-or-should-it-go/ArticleStandard/Article/detail/415196>

³ Chan CCK, Sharma M, Boxer Wachler BS. Effect of inferior-segment Intacs with and without Cx-R on keratoconus. J Cataract Refract Surg. 2007;33:75-80.

for up to 12 months. In each study, only one eye of each patient was designated as the study eye. Study eyes were randomized to receive one of the two study treatments (CXL or sham) at the baseline visit and were followed up at Day 1, Week 1, and Months 1, 3, 6, and 12. At Month 3 or later, sham study eyes and non-study eyes had the option of receiving CXL treatment, and were followed-up for 12 months from the time of receiving CXL treatment. Each CXL treated eye received a single course of CXL treatment only. Overall, 512 eyes (293 keratoconus, 219 corneal ectasia) in 364 patients received CXL treatment.

In each study, the maximum corneal curvature (Kmax) was assessed at baseline, Months 1, 3, and 12. The CXL-treated eyes showed increasing improvement in Kmax from Month 3 through Month 12. Progressive keratoconus patients had an average Kmax reduction of 1.4 diopters in Study 1 and 1.7 diopters in Study 2 at Month 12 in the CXL treated eyes while the sham eyes had an average increase of 0.5 diopter in Study 1 and 0.6 diopter in Study 2 at Month 12; the difference (95% CI) between the CXL and sham groups in the mean change from baseline Kmax were -1.9 (-3.4, -0.3) diopters in Study 1 and -2.3 (-3.5, -1.0) diopters in Study 2.

The most common ocular adverse reactions in any CXL-treated eye were corneal opacity (haze), punctate keratitis, corneal striae, corneal epithelium defect, eye pain, reduced visual acuity, and blurred vision. These events are expected sequelae following epithelial corneal debridement and occurred at a higher incidence than observed in control patients, who did not undergo debridement or exposure to UVA light. The majority of adverse events reported resolved during the first month, while events such as corneal epithelium defect, corneal striae, punctate keratitis, photophobia, dry eye and eye pain, and decreased visual acuity took up to 6 months to resolve and corneal opacity or haze took up to 12 months to resolve. In 1-2% of patients, corneal epithelium defect, corneal edema, corneal opacity and corneal scar continued to be observed at 12 months.

Epithelium-on Corneal Collagen Crosslinking

Modifications to the standard CXL technique have been undertaken by a number of investigators with varying results. Addition of preoperative anesthetic drops containing BAK serves to loosen the epithelial cell tight junctions and appears to result in crosslinking without the delayed wound epithelial healing effects and immediate postoperative period discomfort.⁸

A prospective clinical trial evaluating an approach comparable to the method proposed in this study has been conducted in the United States. Epithelium-on CXL was performed in eyes with keratoconus using proparacaine with BAK 0.01% to facilitate riboflavin absorption and riboflavin 0.10% without dextran. Eyes were randomized to receive ultraviolet-A treatment (365 nm, 3 mW/cm²) with concurrent administration of riboflavin randomized to every 1 minute or every 2 minutes for 30 minutes. Patients were followed for 6 months. Thirty eyes of 25 patients were treated. The mean maximum K value flattened by 0.9 diopter (D) (baseline 58.7 D; 6 months 57.8 D). The maximum K worsened by 2.0 D or more in 1 patient. The mean CDVA improved by 0.83 Snellen

lines. One patient lost 2 lines of CDVA. There were no differences in the UDVA, CDVA, or keratometry outcomes between the 1-minute instillation subgroup and the 2-minute instillation subgroup.⁴

2.0 PRODUCT DESCRIPTION

The test articles to be used in this study are approved in the US by the FDA for the treatment of keratoconus and corneal ectasia following refractive surgery, and are marketed by Avedro (Waltham, MA).

2.1 KXL[®] System

The KXL System is an electronic medical device which delivers ultraviolet light (365 nm wavelength) in a circular pattern onto the cornea after riboflavin phosphates ophthalmic solution (Photrexa Viscous and/or Photrexa) has been applied. Irradiating the riboflavin phosphates ophthalmic solution creates singlet oxygen, which forms intermolecular bonds in corneal collagen. UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system. The Optics Head houses the UVA irradiation mechanism. The LED emits continuous UVA radiation at a wavelength of 365 nm at an intensity of 3 mW/cm². A fixed aperture mounted in the UVA irradiation beam path is used to produce a circular area of irradiation at the treatment plane with a diameter of 9.5 mm. Alignment lasers are used to aid the user in focusing the beam on the patient's cornea. Fine alignment of the UV beam through observation of the alignment lasers is controlled by the user through a wireless remote.

The KXL is a portable system with an articulating arm to allow movement of the system for alignment of the UV beam to the patient's cornea. An internal battery powers the system; the battery is recharged by a system internal charger from any standard AC outlet. The treatment parameters (Riboflavin Induction Period, Total UV Energy and UV Power) are confirmed through the user interface touch screen computer. The KXL System is used in conjunction with Photrexa Viscous and Photrexa and an RFID activation card.

⁴ Lesniak SP, Hersh PS. Transepithelial corneal collagen crosslinking for keratoconus: six-month results. J Cataract Refract Surg. 2014 Dec;40(12):1971-9.

The KXL System specifications are as follows:

Specification	Description
Electrical	Battery Powered: 12V 35 Ah SLA Line voltages 100 – 240 volts AC Current: 2A – 1A Single Phase RMS, 50/60 Hz Remote 2x AAA batteries
User accessible Fuses	250 V~ T2AH
Energy Delivery	UV Radiation 3 mW/cm ² ±10% 365 nm
UVA LED Light Source	UV Radiation 365 nm
External Interfaces	USB 2.0
Physical Dimensions	No larger than 60 x 60 x 150 cm ³ (Length x Width x Height)
Weight (crated system)	NW 45 Kg GW 120 Kg
System Battery Life (normal operating conditions)	16 hours
Remote Battery Life (normal operating conditions)	18 hours
Environmental Operating Conditions	The system operates under the following atmospheric conditions (no condensation).
Ambient temperature	+10 to +40 °C
Relative humidity	30% to 75%, non-condensing
Atmospheric pressure	700 to 1060 mbar
Transport and Storage Conditions	The instrument withstands the following transport and storage conditions without damage or performance deterioration.
Ambient temperature	-15 to +70 °C
Relative humidity	10% to 100% non-condensing
Atmospheric pressure	500 to 1060 mbar

2.2 PHOTREXA[®] (riboflavin 5'-phosphate ophthalmic solution):

The drug product, Photrexa (riboflavin 5'-phosphate ophthalmic solution) 0.146%, is a yellow sterile buffered solution containing 1.46 mg/mL riboflavin 5'-phosphate. The pH of the solution is approximately 7.1 and the osmolality is 157-177 mOsm/kg. Each 1 mL of solution contains 1.53 mg of riboflavin 5'-phosphate sodium (equivalent to 1.20 mg [0.12%] riboflavin). Riboflavin 5'-phosphate sodium USP is a mixture of the sodium

salts of riboflavin, riboflavin monophosphates, and riboflavin diphosphates. The inactive ingredients are dibasic sodium phosphate, monobasic sodium phosphate, sodium chloride, and water for injection. The chemical formula for riboflavin 5'-phosphate sodium (Vitamin B2) is $C_{17}H_{20}N_4NaO_9P$ with a molecular mass of 478.33 g/mol.

How Supplied/Storage and Handling

Photrexa is provided by the manufacturer in bulk packs of 10 (ten), single-use foil pouches. Each foil pouch contains a 3 mL glass syringe of Photrexa contained within a Tyvek pouch. The entire bulk pack should be stored at 15°-25°C (59°-77°F) and care should be taken to minimize exposure of the syringe to light once removed from its protective packaging. Discard syringe after use.

3.0 OBJECTIVES

The primary objective of this study is to evaluate the safety and efficacy of epithelium-on corneal collagen crosslinking performed with riboflavin 0.146% solution (Photrexa) and the KXL system for reducing corneal curvature.

4.0 SAFETY AND EFFICACY ENDPOINTS

The primary efficacy parameter is the change from baseline over time in maximum keratometry (Kmax). Additional analyses for efficacy will include uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA).

Safety assessments will include a tabulation of adverse events, loss of visual acuity >3 lines, slit lamp examination of the cornea and lens, and contact lens tolerance for contact lens wearers.

5.0 STUDY DESIGN

Subjects with a diagnosis of progressive keratoconus will be evaluated for suitability as a candidate for CXL. Subjects that are candidates for CXL will be asked to participate in this study and will undergo the required screening procedures to determine study eligibility. Informed consent will be obtained from each subject before performance of any required study procedures that are not part of the investigator's routine examination.

All subjects will be evaluated at screening/baseline, Day 0 (treatment day), and 1 day, 1 week, and 1, 3, 6 and 12 after treatment. Pentacam measurements and measurements of best spectacle-corrected visual acuity will be obtained at baseline and at appropriate times after the epithelium-on CXL procedure. Safety monitoring throughout the study will include observations at appropriate times for adverse events, clinically significant findings on ophthalmic examination, and slit lamp examination.

6.0 SUBJECT POPULATION

Approximately 100 eyes will be enrolled to provide at least 89 evaluable eyes at 12 Months post-procedure.

6.1 Inclusion Criteria

Subjects who have at least one eye (the study eye) that meet all of the following criteria will be considered candidates for this study:

1. 14 to 40 years of age
2. Having a diagnosis of keratoconus
3. Signed written informed consent
4. Willingness and ability to comply with schedule for follow-up visits

6.2 Exclusion Criteria

All subjects meeting any of the following criteria will be excluded from this study:

1. Previous ocular condition (other than refractive error) in the eye(s) to be treated that may predispose the eye for future complications, for example:
 - a. History of corneal disease (e.g., herpes simplex, herpes zoster keratitis, recurrent erosion syndrome, corneal melt, corneal dystrophy, etc.)
 - b. Clinically significant corneal scarring in the CXL treatment zone
2. Pregnancy (including plan to become pregnant) or lactation during the course of the study
3. Corneal pachymetry < 350 microns at the thinnest point measured by Pentacam in the eye to be treated
4. Patients with nystagmus or any other condition that would prevent a steady gaze during the CXL treatment or other diagnostic tests.
5. Patients with a current condition that, in the investigator's opinion, would not be a good candidate for the study.

7.0 SCREENING FOR CXL ELIGIBILITY

7.1 Pre-operative Evaluation (Day -45 to Day 0)

Potential CXL candidates will undergo a complete eye examination to determine their eligibility for study participation. Subjects will sign a consent form before any clinical protocol procedures or tests specific to the study protocol are performed. The screening visit could be combined with part of the routine office visit. If the patient agrees to participate in the study, then any tests that are done on the initial evaluation as part of the normal testing for that exam prior to entering the study may be used as the initial screening tests for the study. The data from that visit may be used as your screening visit so that they do not need to repeat the same tests.

A complete ocular history, medical history and medication history will be obtained. The complete eye examination and ocular history will include:

- History of contact lens wear
- UCVA (distance)

- BSCVA (distance)
- Pentacam measurements
- Slit lamp examination of the cornea, anterior chamber and lens

7.2 CONTACT LENS DISCONTINUATION

Contact lens wearers should discontinue contact lenses for at least 1 week prior to the preoperative eye examination. Contact lens wearers must exhibit a stable refraction at two exams that are at least 7 days apart. A stable refraction is first determined as one in which the manifest refraction measurement taken at the first visit does not differ by more than 0.75 diopters MRSE from the respective measurement taken at the second exam. If the difference is greater than 0.75 diopters MRSE, the subject should either: (1) be declared a screening failure; or, (2) additional visits should be completed until stability ($\leq 0.75D$ MRSE difference) is attained. All exam dates for these visits should be at least 7 days apart. If the patient has been out of contacts for greater than one month, then that patient will not be considered a contact lens wearer and will not need to have a stable refraction on two consecutive visits.

8.0 STUDY PROCEDURES

8.1 CXL Procedure

The subject will lie on a surgical table or chair with the head supported in a head rest. The bed will be adjusted so the subject can lie flat or recline comfortably for the duration of the procedure without moving.

Proparacaine with BAK 0.01% (or similar topical ocular anesthetic) is instilled at a rate of 1 drop every 20 seconds for one minute. The corneal surface is prepped with a Weck-Cel sponge, and a lid speculum will be placed between the lids of the eye to be treated. Then, Photrexa riboflavin will be administered at a rate of 1-2 drops every 2 minutes for 30 minutes, along with continued application of topical anesthetic every 2 minutes for 10 minutes. The investigator may use discretion as to whether more anesthetic is needed. Adequate riboflavin saturation at slit lamp will be confirmed (i.e., uniform green/yellow hue throughout the entire corneal depth) before proceeding. If saturation is not appropriate, riboflavin application will continue until adequate saturation is achieved.

When riboflavin uptake into the corneal stroma has been confirmed, pachymetry will be performed to record corneal thickness. The eye will then be aligned under the KXL System using the laser cross-hairs of the UVA device. Administration of Photrexa riboflavin will continue at a rate of 1 drop every 2 minutes concurrently with UV light (with continuing administration of topical anesthetic every 5 minutes) for 30 minutes. At the end of 30 minutes, the UV light source will automatically switch to the off position. Selected treatment information and procedure details, including the topical anesthetic, riboflavin administration, irradiance settings, and duration of irradiation exposure will be documented.

8.2 POST-OPERATIVE CARE

Prescriptions for postoperative medications and written postoperative instructions will be given to each subject and reviewed prior to discharge per the site's standard of care for management of corneal cross-linking. All postoperative eye drop usage will be recorded in the subject's chart. Other prescription or nonprescription medications may be taken as needed throughout the study.

8.3 Follow-Up Visits (1 Day, 1 Week, 1, 3, 6, and 12 Months)

All subjects will be seen at 1 day, 1 week, 1, 3, 6, 12 months after CXL. The week 1 visit should be between 5 and 9 days. The one month visit should be between 1 week before and 1 week after the one month date. The three month visit should be between 2 weeks before and 2 weeks after the three month visit. The six month visit should be between 2 weeks before and 2 weeks after the six month visit. The twelve month visit should be between 1 month before and 1 month after the twelfth month visit. If a subject has both eyes involved in the study, and coordinating office visits becomes a burden to the patient due to the two eyes not being in synch, it will be up to the investigator's discretion to allow study visits outside of the above schedule.

The following will be performed at each visit unless noted otherwise:

- UCVA distance
- Slit lamp examination of the cornea, anterior chamber and lens
- Documentation of interim medical, medication, and ocular histories.

The following tests will be additionally performed at the 1, 3, 6 and 12 Month visits:

- BSCVA distance
- Pentacam measurements

Reasonable effort will be made by telephone and mail to contact subjects who miss a scheduled follow-up visit.

8.4 Safety Monitoring

Ophthalmic safety will be evaluated by slit lamp examination of the operated eye, measurements of refraction, and measurement of visual acuity. In the case of an adverse event, these tests may be repeated before the next scheduled visit at the investigator's discretion. Any ocular adverse events will be recorded in the medical record/case report form.

8.5 Early Withdrawal from Study

Subjects will be advised that they are free to withdraw from the study at any time. Subjects experiencing adverse safety events will be followed until the reaction has resolved. Appropriate supportive and/or definitive therapy will be administered as required. The investigator may discontinue a subject if a serious adverse event occurs and it is in the subject's best interest not to continue in the study or if the subject moves and the subject cannot complete the remainder of the follow-up visits. When a subject withdraws early from the study, a final examination will be performed at the time of withdrawal if possible.

8.6 Study Duration

The study duration for each subject is a total of approximately 12 months.

9.0 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

Tabulation of summary statistics, graphical presentations, and statistical analyses will be performed. All subjects who are enrolled and treated in this study will be included in the safety analysis. All two sided testing and confidence intervals will use a significance level of 5%.

9.1 Sample Size

The primary efficacy analysis for the treatment of keratoconus is to determine whether the mean decrease in Kmax from baseline to 12 months is at least 0.75 D.

Based on paired T statistics, assuming a population standard deviation of 2.5 D, a two-sided threshold probability of rejecting the null hypothesis (alpha) of 0.05, and 80% power to detect a difference from baseline of 0.75D, a sample size of 89 evaluable eyes is needed.

The primary efficacy analysis will follow an intent-to-treat (ITT). The ITT population consists of any study eye enrolled in the study (defined as having the study drug instilled). The ITT population will be used for all safety and efficacy evaluations.

9.2 Primary Efficacy Criteria

The change in maximum keratometry (Kmax) from baseline will be evaluated at 12 months. Data will be summarized using descriptive statistics, and a one-group t-test comparing the mean change from baseline value to the target value of 0.75 D will be performed.

9.3 Additional Analyses

Change in BSCVA and UCVA compared to the baseline examination will be evaluated at 12 months postoperatively. Data will be summarized using descriptive statistics. As a secondary analysis of this endpoint, a repeated measures analysis of variance will be conducted to assess the profile of the treatment across time at 1 month and again at 3, and 6 months following the CXL procedure.

9.4 Adverse Events

All adverse events will be tabulated and summarized.

9.5 Key Safety Parameters

For each time point, the following key safety parameters will be estimated for the entire cohort.

1. Percentage of eyes that had a loss of 2 or more lines in BSCVA
2. Percentage of eyes that had a greater than 2D increase in Kmax

9.6 Dropouts/Lost-to-Follow-up

Patients may drop out at any time during the study. All treated patients/eyes will be included in the safety analysis.

10.0 ETHICAL AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with ICH Good Clinical Practice.

10.1 Informed Consent

Each subject will provide written informed consent for participation in this study prior to the treatment under investigation (see Appendix B for elements of an informed consent).

The study will be explained to the prospective subject by the investigator or his designee. The nature of the experimental product/technique will be explained together with potential hazards of the surgical procedure, including any possible adverse reactions. The subject will be informed that he/she is free to terminate participation in the study for any reason without affecting his/her care or relationship with the Investigator or Institution. Each subject will be given the opportunity to ask questions before signing the informed consent. The financial responsibilities of the subject will be discussed. All subjects will also be required to sign a Health Insurance Portability and Accountability Act (HIPAA) form. One copy of the signed consent form will be retained in the medical record and one will be provided to the subject

10.2 Institutional Review Board

This protocol and the informed consent form will be approved initially and reviewed annually by an Institutional Review Board (IRB) constituted according to FDA regulations.

The IRB that will review and oversee this study is:

Western Institutional Review Board
1019 39th Avenue SE Suite 120
Puyallup, WA 98374-2115

Phone: 360-252-2500

Email: clientservices@wirb.com

Progress reports will be submitted at the completion of the study or at least once yearly, whichever comes first, to the IRB. Serious adverse events will be reported to the IRB in accordance with the IRB's requirements.

10.3 Adverse Event Reporting

Adverse events that are observed by the investigator or reported by the subject will be recorded on the study source documents. For all adverse events, a description of the event, date first observed, any action taken, resolution will be recorded. The Investigator must also assess the adverse event for seriousness criteria and relationship to the test article(s).

- Possibly, Probably, or Definitely Related Expected AE – Report to IRB on annual basis
- Possibly, Probably, or Definitely Related Expected **Serious** AE – Report to IRB on annual basis
- Possibly, Probably, or Definitely Related **Unexpected** AE – Report to IRB within 30 days of event
- Possibly, Probably, or Definitely Related **Unanticipated** (Device) Problem – Report to IRB within 7 days of event
- Possibly, Probably, or Definitely Related **Unexpected Serious** AE – Report to IRB within 7 days of event

10.4 Study Records/Source Documents

Adequate records will be maintained for the study including subject medical and surgical records, test reports, work sheets, nursing notes, signed informed consent forms, drug and device use records, adverse experience reports and information regarding subject discontinuation and reasons for discontinuation. All original source documentation will remain at the investigative site. Study data that are stored at the investigator site in any electronic medical records system, including measurements that are obtained electronically (e.g., Pentacam), will be printed and retained in the study files.

10.5 Deviation from the Protocol

The investigator will notify the IRB of any protocol deviation to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event any later than 5 working days after the emergency occurred. All other deviations, revisions and/or amendments to the protocol that affect subject treatment, study outcome, or subject safety will be submitted in writing to the IRB per IRB requirements. The investigator will maintain a record of all protocol deviations showing the dates of, and the reason for, each protocol deviation.

APPENDIX A: CFR 50.25 - ELEMENTS OF INFORMED CONSENT

BASIC ELEMENTS OF INFORMED CONSENT: In seeking informed consent, the following information shall be provided to each subject.

1. A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
2. A description of any reasonably foreseeable risks or discomforts to the subject.
3. A description of any benefits to the subject or to others which may reasonably be expected from the research.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the U.S. Food and Drug Administration may inspect records.
6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
7. An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury.
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.