COLLABORATIVE LONGITUDINAL EVALUATION OF KERATOCONUS

(CLEK) STUDY

OPERATIONS MANUAL
# CLEK Study Operations Manual

## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Chapter 1 Background</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 CLEK Study Synopsis</td>
<td>1-1</td>
</tr>
<tr>
<td>1.1.1 CLEK Study Organization</td>
<td>1-1</td>
</tr>
<tr>
<td>1.1.2 Eligibility</td>
<td>1-3</td>
</tr>
<tr>
<td>1.1.3 CLEK Participating Clinic Structure</td>
<td>1-4</td>
</tr>
<tr>
<td>1.1.4 Fluorescein Photography</td>
<td>1-5</td>
</tr>
<tr>
<td>1.1.5 Visual Acuity Measurement</td>
<td>1-5</td>
</tr>
<tr>
<td>1.1.6 Keratometry</td>
<td>1-6</td>
</tr>
<tr>
<td>1.1.7 Slit Lamp Biomicroscopy</td>
<td>1-6</td>
</tr>
<tr>
<td>1.1.8 Corneal Photography</td>
<td>1-6</td>
</tr>
<tr>
<td>1.1.9 Quality of Life</td>
<td>1-6</td>
</tr>
<tr>
<td>1.2 Specific Aims of the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study</td>
<td>1-7</td>
</tr>
<tr>
<td>1.2.1 General Description of the Course of Keratoconus</td>
<td>1-8</td>
</tr>
<tr>
<td>1.2.2 Factors Related to Vision in Keratoconus</td>
<td>1-8</td>
</tr>
<tr>
<td>1.2.3 Factors Related to Disease Progression (Corneal Curvature) in Keratoconus</td>
<td>1-8</td>
</tr>
<tr>
<td>1.2.4 Factors Related to Corneal Scarring</td>
<td>1-8</td>
</tr>
<tr>
<td>1.3 Specific Aims beyond Year 08</td>
<td>1-9</td>
</tr>
<tr>
<td>1.4 Diagnosis of Keratoconus</td>
<td>1-9</td>
</tr>
<tr>
<td>1.5 Course of Keratoconus</td>
<td>1-9</td>
</tr>
<tr>
<td>1.6 Surgical Intervention</td>
<td>1-12</td>
</tr>
<tr>
<td>1.7 Treatment with Contact Lenses</td>
<td>1-14</td>
</tr>
<tr>
<td>1.7.1 Fitting Methods: Flat Lenses vs. Steep Lenses in Keratoconus</td>
<td>1-15</td>
</tr>
<tr>
<td>1.8 Tissue Changes in Keratoconus</td>
<td>1-15</td>
</tr>
<tr>
<td>1.9 References</td>
<td>1-16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter 2 Study Design, Timetable and Rationale</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 CLEK Study Summary</td>
<td>2-1</td>
</tr>
<tr>
<td>2.1.1 CLEK Study Timetable</td>
<td>2-1</td>
</tr>
<tr>
<td>2.1.2 CLEK Study Calendar</td>
<td>2-2</td>
</tr>
<tr>
<td>2.2 Specific Aims</td>
<td>2-3</td>
</tr>
<tr>
<td>2.2.1 Specific Aim A. General Description of the Course of Keratoconus</td>
<td>2-2</td>
</tr>
<tr>
<td>2.2.2 Specific Aim B. Factors Related to Vision in Keratoconus</td>
<td>2-2</td>
</tr>
<tr>
<td>2.2.3 Specific Aim C. Factors Related to Disease Progression (Corneal Curvature) in Keratoconus</td>
<td>2-3</td>
</tr>
<tr>
<td>2.2.4 Specific Aim D. Factors Related to Corneal Scarring</td>
<td>2-3</td>
</tr>
<tr>
<td>2.2.5 Specific Aims through Year 12</td>
<td>2-4</td>
</tr>
<tr>
<td>2.3 Rationale for Observational Study</td>
<td>2-4</td>
</tr>
<tr>
<td>2.4 Patient Eligibility</td>
<td>2-5</td>
</tr>
</tbody>
</table>
# 2.4 Inclusion Criteria
- **2.4.1 Inclusion Criteria** ............................................. 2-5
- **2.4.2 Exclusion Criteria** ........................................... 2-6
- **2.4.3 Rationale for Inclusion and Exclusion Criteria** ........... 2-6
  - **2.4.3a Age** ..................................................... 2-6
  - **2.4.3b Corneal Irregularity** .................................. 2-6
  - **2.4.3c Vogt’s Striae, Fleischer’s Ring, or Characteristic Corneal Scarring** 2-7
  - **2.4.3d Contact Lenses Are Not an Entry Criterion** ............. 2-7
  - **2.4.3e Other Criteria** ......................................... 2-7
  - **2.4.3f Representativeness of the CLEK Study Sample** ........ 2-8
- **2.5 CLEK Study Measures** ........................................... 2-8
  - **2.5.1 Visual Acuity** ............................................ 2-8
  - **2.5.2 Corneal Curvature** ...................................... 2-9
  - **2.5.3 Corneal Scarring** ....................................... 2-10
  - **2.5.4 Biomicroscopic Signs** ................................... 2-10
  - **2.5.5 Quality of Life** ......................................... 2-11
  - **2.5.6 First Definite Apical Clearance Lens** .................... 2-11
  - **2.5.7 Surgical Intervention** ................................... 2-12
  - **2.5.8 Other Measures** ......................................... 2-12
- **2.6 Issues of Recruitment and Retention** .......................... 2-12
- **2.7 Routine Ophthalmic Care and Emergencies** .................. 2-13
- **2.8 Sample Size Requirement and Rationale** ...................... 2-13
- **2.9 Analysis of Data** ............................................... 2-16
  - **2.9.1 General Considerations** ................................ 2-16
  - **2.9.2 Cross-sectional Regression Analyses** .................... 2-16
  - **2.9.3 Longitudinal Regression Analyses With Paired Continuous Outcomes** 2-17
  - **2.9.4 Longitudinal Regression Analyses With Paired Dichotomous Outcomes** 2-17
  - **2.9.5 Analyses Keyed to Specific Aims** ........................ 2-17
    - **2.9.5a Specific Aim A** ..................................... 2-17
    - **2.9.5b Specific Aim B** ..................................... 2-18
    - **2.9.5c Specific Aim C** ..................................... 2-19
    - **2.9.5d Specific Aim D** ..................................... 2-19
- **2.10 Human Subjects Considerations** ............................ 2-19
- **2.11 References** .................................................. 2-21

## Chapter 3 Entry and Enrollment
- **3.1 Screening for Eligibility** ..................................... 3-1
- **3.2 Implementation of Eligibility Criteria** ...................... 3-1
- **3.3 Inclusion Criteria** ........................................... 3-1
- **3.4 Exclusion Criteria** ........................................... 3-2
- **3.5 Assignment of Patient Identification Numbers** ............ 3-2
- **3.6 Procedure for Informed Consent** ............................ 3-3
- **3.7 Study Entry Date** ............................................. 3-3
- **3.8 Follow-up Beyond Year 08** .................................. 3-3
## Chapter 4 Patient Education, Informed Consent, and Patient Recruitment

4.1 Patient Education and Informed Consent ........................................... 4-1  
4.2 Patient Education ................................................................. 4-1  
4.3 Special Consent Procedures for Minors ........................................ 4-2  
4.4 Costs and Reimbursements to Patients ....................................... 4-3  
4.5 Recruitment Publicity .......................................................... 4-3  
4.6 Informing Other Clinics of Successful Recruitment Strategies .......... 4-4  
4.7 Sample Informed Consent Form ............................................... 4-5  

## Chapter 5 Scheduling and Guidelines for Emergency Care

5.1 Introduction ............................................................................. 5-1  
5.2 Eligibility ............................................................................... 5-1  
5.3 Scheduling ............................................................................ 5-3  
5.4 Baseline Examination .............................................................. 5-3  
5.5 Annual (Follow-up) Visits ....................................................... 5-4  
5.6 Repeat Visits .......................................................................... 5-4  
5.7 Non-CLEK Study Eye Care ...................................................... 5-4  
5.8 General Forms Procedures ...................................................... 5-4  
5.9 Retention of Patients .............................................................. 5-5  
5.10 Missed Visits ......................................................................... 5-7  

## Chapter 6 Vision Assessment

6.1 Measurement of Visual Acuity .................................................... 6-1  
   6.1.1 Introduction ....................................................................... 6-1  
   6.1.2 Calibration of Chart Lighting ............................................. 6-2  
   6.1.3 Visual Acuity Technique .................................................... 6-3  
6.2 Measurement of Refractive Error .............................................. 6-5  
6.3 Alternative Refraction Technique ............................................. 6-6  
6.4 Measurement of Over-Refraction ............................................. 6-7  

## Chapter 7 Slit Lamp Examination, Fundus Examination, and Tonometry

7.1 Slit Lamp Examination ............................................................ 7-1  
7.2 Slit Lamp Examination Procedure .......................................... 7-1  
7.3 Corneal Scarring .................................................................... 7-2  
7.4 Corneal Staining .................................................................... 7-3  
7.5 Funduscopy ........................................................................... 7-3  
   7.5.1 Direct Ophthalmoscopy or Biomicroscopy with Condensing or Hruby Lens .................................................. 7-4  
   7.5.2 Binocular Indirect Ophthalmoscopy ................................... 7-4  
7.6 Tonometry ............................................................................. 7-4  
   7.6.1 Technique ........................................................................ 7-4  
   7.6.2 Alternative Tonometry Technique .................................... 7-5
# Chapter 8 Corneal Curvature and Topography

8.1 Introduction .................................................................................................................. 8-1  
8.2 Keratometry .................................................................................................................. 8-1  
  8.2.1 Eyepiece Focusing .................................................................................................... 8-1  
  8.2.2 Calibration ............................................................................................................... 8-2  
  8.2.3 Keratometry Measurement Procedure ................................................................... 8-2  
  8.2.4 Extending the Keratometer’s Range ....................................................................... 8-3  
8.3 Videokeratography ........................................................................................................ 8-7  
8.4 TMS-1 ............................................................................................................................ 8-7  
  8.4.1 TMS-1 Calibration Verification ................................................................................ 8-7  
  8.4.2 TMS-1 Topography Protocol ................................................................................. 8-8  
  8.4.3 Central Processing of TMS Topographic Data ......................................................... 8-10  
8.5 EyeSys ............................................................................................................................ 8-10  
  8.5.1 System 2000 Hardware and Software Version 3.x Protocol & Calibration ............ 8-11  
  8.5.2 Model 2 Hardware Calibration ................................................................................ 8-14  
  8.5.3 Model 2 hardware and software version 3.x protocol ............................................. 8-15  
  8.5.4 Model 2 hardware and software version 2.11 protocol .......................................... 8-17  
8.6 Visioptic EH-270 Topography ....................................................................................... 8-19  
  8.6.1 Visioptic EH-270 Calibration Verification ............................................................... 8-19  
  8.6.2 Visioptic EH-270 Protocol ...................................................................................... 8-21  
8.7 Humphrey Mastervue .................................................................................................... 8-21  
  8.7.1 Calibration verification ............................................................................................. 8-22  
  8.7.2 Humphrey Mastervue Patient Confidentiality ....................................................... 8-22  
  8.7.3 Humphrey Mastervue Protocol ............................................................................. 8-23  
  8.7.4 Humphrey Mastervue Data Storage ..................................................................... 8-24  
  8.7.5 Processing of Mastervue Data ................................................................................ 8-25  

# Chapter 9 First Definite Apical Clearance Lens Determination and Assessment of Habitual Contact Lenses

9.1 Introduction .................................................................................................................... 9-1  
9.3 Verification of the CLEK Study Trial Contact Lens Set .............................................. 9-5  
9.4 Protocol for Habitual Contact Lens Fit Assessment .................................................... 9-6  
9.5 Lens Verification Protocol ......................................................................................... 9-6  
9.6 Summary ...................................................................................................................... 9-6  

# Chapter 10 Photodocumentation of Fluorescein Pattern

10.1 Introduction .................................................................................................................. 10-1  
10.2 Fluorescein Photography Technique .......................................................................... 10-1  
10.3 Film Utilization for CLEK Photography ..................................................................... 10-3  

# Chapter 11 Photodocumentation of Corneal Scarring

11.1 Introduction .................................................................................................................. 11-1  
11.2 Cornea Photography Schedule ................................................................................. 11-1
11.3 Technique ................................................................. 11-1
11.4 Handling of Film after Photography ................................. 11-4
11.5 Film Utilization for CLEK Photography .............................. 11-4

Chapter 12 Certification Procedures
12.1 Introduction ............................................................ 12-1
12.2 Certification for Visual Acuity Measurement ....................... 12-3
12.3 Certification for Refraction ........................................... 12-3
12.4 Certification for Keratometry ......................................... 12-4
12.5 Certification for Corneal Topography (Video-keratography) .... 12-5
12.6 Certification for Slit Lamp Biomicroscopy ........................... 12-5
12.7 Certification for First Definite Apical Clearance Fitting Protocol 12-6
12.8 Certification for Corneal Photography ................................ 12-7
12.9 Certification for Study Coordination ................................ 12-8
12.10 Certification for Contact Lens Verification ........................ 12-8
12.11 Recertification for Year 12 Annual Visit ............................ 12-9

Chapter 13 Chairman’s Office and Participating Clinic Operations
13.1 Chairman’s Office Functions .......................................... 13-1
   13.1.1 Per-Patient Payment to Participating Clinics .................. 13-1
   13.1.2 Per-Patient Payment to Patients ................................. 13-1
13.2 CLEK Study Newsletters .............................................. 13-2
13.3 Introduction to Participating Clinic Operations ..................... 13-2
13.4 Eligibility .................................................................... 13-3
13.5 Baseline Visit .............................................................. 13-3
13.6 Annual Visits ............................................................... 13-4
13.7 Repeat Visits ............................................................... 13-5
13.8 Completion of the Patient-Completed Forms and the Medical History Portion of the CLEK Examination Form ......................... 13-5

Chapter 14 CLEK Photography Reading Center (CPRC) Procedures
14.1 Organization of the CLEK Photography Reading Center ............. 14-1
14.2 Photography Schedules for Participating Clinics .................... 14-2
14.3 CLEK Photography Reading Center Procedures ..................... 14-3
14.4 Repeat Photography ...................................................... 14-3
14.5 Certification of CLEK Photography Reading Center Personnel .... 14-4
   14.5.1 Certification of Photograph Readers ............................. 14-4
   14.5.2 Certification of CPRC Coordinator ............................... 14-5
14.6 Summary of CLEK Photography Reading Center Procedures ........ 14-5
Chapter 15 Coordinating Center
15.1 Introduction ......................................................... 15-1
15.2 Protocol Development Phase ................................. 15-2
15.3 Recruitment and Follow-up Phase ............................. 15-2
   15.3.1 Activities .................................................. 15-2
   15.3.2 Quality Assurance ....................................... 15-3
   15.3.3 Reports Prepared by the Coordinating Center .......... 15-4
15.4 Analysis of Baseline Data ........................................ 15-5
15.5 Patient Closeout Phase .......................................... 15-6
15.6 Termination Phase ................................................. 15-6
15.7 Form Design ....................................................... 15-6
15.8 Records Flow Within the Coordinating Center ............ 15-7
15.9 Data Management ................................................ 15-8
15.10 Dataset Backup ................................................... 15-9
   15.9.1 Data Security ............................................. 15-9
15.11 Electronic Mail .................................................. 15-9
15.12 References ....................................................... 15-10

Chapter 16 Study Organization and Policy Matters
16.1 Introduction ....................................................... 16-1
   16.1.1 CLEK Clinics ............................................. 16-1
   16.1.2 Coordinating Center ...................................... 16-1
   16.1.3 CLEK Photography Reading Center ................... 16-2
   16.1.4 CLEK Topography Reading Center ...................... 16-2
   16.1.5 CLEK Executive Committee and the Study Chairman 16-2
   16.1.6 National Eye Institute Program Office ............... 16-2
16.2 Study Administration ............................................ 16-3
16.3 Executive Committee ............................................ 16-3
   16.3.1 Executive Committee Membership ..................... 16-3
   16.3.2 Executive Committee Functions ....................... 16-4
16.4 Data Monitoring and Oversight Committee ................. 16-4
   16.4.1 Data Monitoring and Oversight Committee Membership 16-5
   16.4.2 Data Monitoring and Oversight Committee Functions 16-5
16.5 Patient Consent .................................................. 16-6
16.6 Patient Costs ..................................................... 16-6
16.7 Publicity .......................................................... 16-7
16.8 Editorial Policy ................................................... 16-7
   16.8.1 Publication of Study Design, Methods, and Findings 16-7
   16.8.2 Presentations ............................................. 16-9
   16.8.3 Publications from Ancillary Studies .................. 16-9
   16.8.4 Publications Concerning Methodology ............... 16-10
16.9 Ancillary Studies ............................................... 16-10
   16.9.1 Introduction ............................................. 16-10
   16.9.2 Definition of an Ancillary Study ..................... 16-10
16.9.3 Rationale for Approval Requirement ............................................. 16-11
16.9.4 Preparation of Approval Request for Ancillary Study .................. 16-11
16.9.5 Procedures for Obtaining Ancillary Study Approval .................... 16-12
16.9.6 Funding of Ancillary Studies ...................................................... 16-12
16.9.7 Publication of Ancillary Study Results ....................................... 16-12
16.9.8 Progress Reports ....................................................................... 16-12
16.10 Access to Study Information ......................................................... 16-13
  16.10.1 Study Documents ................................................................. 16-13
  16.10.2 CLEK Study Data ................................................................. 16-13
1.1 CLEK Study Synopsis

The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study is a multi-center, observational study designed to describe the course of this chronic ocular disease and to describe the associations among its visual and physiological manifestations. One thousand keratoconus patients are enrolled at 16 Participating Clinics over the course of 10 months. Patients will be examined annually for at least three years. Examinations include visual acuity, patient-reported visual quality of life, manifest refraction, keratometry, photodocumentation of the cornea to identify central corneal scarring, photodocumentation of the flattest contact lens from the CLEK Study trial set to achieve apical clearance, and slit lamp biomicroscopy. In rigid contact lens wearers, the fluorescein pattern of the patient’s habitual contact lenses is photodocumented.

The CLEK Study characterizes keratoconus over the course of the disease both by initially enrolling patients at various disease stages and by following these patients for at least three years. The goal is to characterize the disease across its course and to identify risk factors and protective factors that determine the severity and progression of the disease.

1.1.1 CLEK Study Organization

Figure 1-1. CLEK Study Organization.
The organization of the CLEK Study is outlined below (Figure 1-1) and discussed in greater detail in Chapter 16 of this Operations Manual.

The CLEK Study Chairman is:
- Karla Zadnik, OD PhD, The Ohio State University College of Optometry.

The CLEK Executive Committee is comprised of:
- Joseph T. Barr, OD MS, The Ohio State University, College of Optometry;
- Timothy B. Edrington, OD MS, Southern California College of Optometry;
- Donald F. Everett, MA, National Eye Institute, National Institutes of Health;
- Mae O. Gordon, PhD, Washington University, Department of Ophthalmology and Visual Sciences and the Division of Biostatistics;
- Timothy T. McMahon, University of Illinois at Chicago, Department of Ophthalmology and Visual Sciences; and
- Karla Zadnik, OD PhD, The Ohio State University College of Optometry.

The Coordinating Center is at Washington University, Department of Ophthalmology and Visual Sciences and the Division of Biostatistics, under the direction of Dr. Mae Gordon.

The CLEK Photography Reading Center to evaluate photographs of contact lenses and the presence of corneal scarring is at The Ohio State University, College of Optometry, under the direction of Dr. Joseph T. Barr.

The CLEK Topography Reading Center to evaluate videokeratography images and evaluate corneal topographic data is at the University of Illinois at Chicago, Department of Ophthalmology and Visual Sciences, under the direction of Dr. Timothy T. McMahon.

The CLEK Participating Clinics are:
- University of Alabama, Birmingham School of Optometry, under the direction of William J. Benjamin, OD, PhD
- University of California at Berkeley, School of Optometry, under the direction of Nina E. Friedman, OD MS in collaboration with Kaiser Permanente, Oakland, CA, and Dennis C. Burger, OD
- University Hospitals of Cleveland, University Ophthalmologists, Inc., Cleveland, OH, under the direction of Loretta Szczotka, OD
- Gundersen Lutheran, LaCrosse, WI, under the direction of John Sterling, OD
- University of Illinois at Chicago, Department of Ophthalmology, Chicago, IL, under the direction of Timothy T. McMahon, OD
- Indiana University School of Optometry, under the direction of Gerald E. Lowther, OD PhD in collaboration with the Indianapolis Eye Care Center.
1.1.2 Eligibility

All keratoconus patients presenting to a Participating Clinic are screened for potential CLEK Study eligibility. Efforts to recruit eligible patients encompass the surrounding optometric and ophthalmologic communities. Preliminary screening for eligibility may be conducted by the referring doctor, but final eligibility is determined by the CLEK Participating Clinic.

Eligible patients are enrolled in the 16 CLEK Study Participating Clinics in various eye care settings across the country. Each Participating Clinic is expected to enroll 80 patients over an eleven-month period for a total of 1,000 keratoconus patients enrolled in the study. This satisfies sample size requirements based on the criteria described in Section 2.8 of this Operations Manual.

All patients are to be followed annually for at least three years for a total of at least four CLEK Study Visits. Patients requiring corneal surgery for keratoconus during the Study are seen for one additional Presurgical Visit within one month prior to their date of surgery. If the corneal surgery is scheduled within 3 months after a routine Baseline or Annual visit, then the routine visit also serves as the Presurgical Visit. They then continue their annual follow-up schedule according to the CLEK Study protocol.

Eligibility is a patient-based, rather than an eye-based determination.

Inclusion Criteria
If all of the following conditions are satisfied, the patient is eligible for the study:

- Age: At least 12 years old
- Irregular corneal surface in either eye determined by distortion of keratometric mires, of the retinoscopic reflex, or of the red reflex.
- Either Vogt’s striae in the deep stroma or Fleischer’s ring of at least 2 mm of arc or corneal scarring characteristic of keratoconus in either eye.
- Able to complete at least 3 years of follow-up.

Exclusion Criteria

If a patient has the following s/he is excluded from the CLEK Study:

- Bilateral corneal transplants
- Non-keratoconic ocular disease in both eyes: cataract, intraocular lens implant, macular disease, optic nerve disease other than glaucoma (eg, optic neuritis, optic atrophy)

1.1.3 CLEK Participating Clinic Structure

Each CLEK Participating Clinic is reimbursed in the Study on a “capitated” basis. Reimbursement for any given visit is contingent on the Coordinating Center’s and the CLEK Photography Reading Center’s reports of quality data from that visit. Clinics are reimbursed on a graduated scale: $100 for the patient’s first visit, $125 for the second visit, and $150 each for the third and fourth visits. Extra visits as mandated by the Coordinating Center (Repeat Visits for reproducibility purposes) or when a patient requires a Presurgical Visit are reimbursed at the rate of $150 each.

CLEK Study patients are directly reimbursed $20 from the Chairman’s Office for their expenses for each CLEK Study Visit.

Each Participating Clinic has at least two people trained and CLEK Study-certified to perform each of the key CLEK Study tasks. Each Participating Clinic may assign these tasks to a Clinician, a Technician and/or a Photographer (Table 1-1). All Participating Clinic staff must participate in the centralized CLEK Study training and certification meeting prior to patient enrollment. Site visits are performed by members of the Executive Committee and the Coordinating Center for quality assurance in the first year of the Study and every other year thereafter and on an as-needed basis (eg, if a Participating Clinic is generating consistently poor data or poor quality photographs, if there are extensive personnel changes at a Participating Clinic, or if a new Participating Clinic joins the CLEK Study).
Table 1-1. CLEK Study Key Tasks Requiring Study Certification.

<table>
<thead>
<tr>
<th>Task</th>
<th>Who Can Be Certified to Perform Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity (high and low contrast Bailey-Lovie visual acuity)</td>
<td>Clinician, Technician*</td>
</tr>
<tr>
<td>Refraction</td>
<td>Clinician, Technician*</td>
</tr>
<tr>
<td>Slit lamp examination</td>
<td>Clinician</td>
</tr>
<tr>
<td>Contact lens fit assessment, First Definite Apical Clearance Lens</td>
<td>Clinician</td>
</tr>
<tr>
<td>Corneal photography</td>
<td>Clinician, Photographer</td>
</tr>
<tr>
<td>Fluorescein photography</td>
<td>Clinician, Photographer</td>
</tr>
<tr>
<td>Keratometry (all Clinics) and topography</td>
<td>Clinician, Technician*, Photographer*</td>
</tr>
<tr>
<td>Study Coordination</td>
<td>Clinician, Technician, Photographer</td>
</tr>
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*A Technician is permitted to perform these measurements on CLEK Study patients if appropriately trained and Study-certified and if it is legal in that Clinic’s state for a Technician to perform these measurements.

Note: CLEK Study personnel can utilize a “Recorder” to transcribe Study data as long as the Recorder is certified in at least one key task of the CLEK Study.

1.1.4 Fluorescein Photography

Fluorescein photography is performed as follows:

- On CLEK Study patients who wear rigid contact lenses to document the fluorescein pattern of the patient’s habitual contact lenses.

- On all CLEK Study patients, to document the flattest lens from the CLEK Study trial lens set that shows apical clearance (the First Definite Apical Clearance Lens) and the CLEK Study trial lens with base curve 0.2 mm flatter than the First Definite Apical Clearance Lens.

Fluorescein photography film is sent to the CPRC for processing and grading. Standardized grading of these photographs by the CLEK Photography Reading Center provides information on corneal curvature and disease progression and on how contact lenses are fitted on CLEK Study patients.

1.1.5 Visual Acuity Measurement

Visual acuity is measured by the Clinician or the Technician. The procedure for measuring visual acuity was originally developed for the Early Treatment of Diabetic Retinopathy Study (ETDRS) using Bailey-Lovie high contrast visual acuity charts. The following visual acuity measurements are conducted at each CLEK Study Visit: (1) High and low contrast Bailey-Lovie visual acuity with habitual correction, for each eye
separately and both eyes together; (2) High and low contrast Bailey-Lovie visual acuity with best correction (for rigid contact lens wearers (including Softperm and piggyback wearers): contact lenses with optimal over-refraction, for non-rigid contact lens wearers: a CLEK Study Trial Lens Set contact lens with base curve equal to steep “K” plus optimal over-refraction), for each eye separately; and (3) High contrast Bailey-Lovie visual acuity with manifest refraction, for each eye separately.

1.1.6 Keratometry

Central keratometric readings are determined at each CLEK Study Visit. In addition, at all Participating Clinics with TMS devices, corneal topographic video images are obtained at each Study Visit, stored on diskette, and shipped to the Chairman’s Office for storage and future analysis. At Clinics without TMS devices, videokeratographic data are collected and stored on-site at the Clinic.

1.1.7 Slit Lamp Biomicroscopy

A thorough slit lamp biomicroscopic examination is performed at each CLEK Study Visit. Corneal findings, including Vogt’s striae, Fleischer’s ring, corneal scarring, and corneal staining are carefully recorded.

1.1.8 Corneal Photography

Corneal photography is performed at each CLEK Study Visit. The corneal photography protocol is performed following pupillary dilation and includes two photographs in oblique, diffuse illumination and four parallelepiped photographs of the apical cornea. The film is sent to the CPRC for processing. Photographs are read by the CLEK Photography Reading Center. The results of the readings are sent to the Coordinating Center.

1.1.9 Quality of Life

Our pilot studies demonstrate the importance of measuring quality of life in the CLEK Study. Results from the Medical Outcomes Study Short Form (SF-36) are available for 29 of the 30 keratoconus patients who were randomized in the CLEK pilot study comparing two contact lens fitting strategies. Despite the fact that all respondents rated their general health as “Good,” “Very Good,” or “Excellent,” and despite the fact that they reported almost no impairment in the performance of physical role functions, 69% of the patients reported experiencing “bodily pain” in the past four weeks (31% very mild, 14% mild, 24% moderate), and 34% reported that this pain interfered with their normal work (22% a little bit, 7% moderately, 4% quite a bit). This finding is striking given the fact that these patients appear “healthy” and functional in almost every other respect. The measurement of quality of life in this sample will provide
information on role limitations that cannot be inferred from other clinical measures.

Several instruments for measuring quality of life were considered, including the Sickness Impact Profile and the Index of Well-Being, in addition to the Medical Outcomes Study Short Form (MOS SF-36). Furthermore, specific depression scales like the Beck Depression Scale and the Community Epidemiological Study Depression Scale (CES-D) were considered because of the widely held belief that keratoconus patients are at higher risk of depression and anxiety. (Mannis et al., 1987; Swartz et al., 1990; Besançon et al., 1980). We selected the MOS SF-36 and decided against the inclusion of an instrument specific to depression. There are several reasons for these two decisions. (1) Keratoconus is a chronic disease that does not severely compromise health status, although keratoconus might result in impaired social and physical role functioning. Results from the CLEK pilot study suggest that instruments that focus only on activities of daily living that reflect physical functioning are insensitive to the role impairment associated with keratoconus. The results from the CLEK pilot study demonstrate the utility of assessing “role functioning” independently from “activities of daily living.” (2) The instrument needs to be sensitive to small degrees of impairment since large degrees of impairment are likely to be rare. (3) The instrument needs to measure several dimensions of well-being. We considered using the CES-Depression scale in addition to the SF-36; however, results using the CES-Depression scale that were administered at the same time as the SF-36 in the CLEK pilot study showed absolutely no trend for increased risk of depression in the total score for the CES-D or in the mental health and emotional role functioning scale of the SF-36. Thus, the measurement of emotional functioning does not justify a separate instrument like the CES-D. (4) We desire a scale that could be self-administered without compromising reliability. (5) We desire an instrument with strong psychometric properties including good factor structure, high internal consistency reliability, high test-retest reliability, and good external validity. For these reasons, the Medical Outcomes Short Form with 36 items (SF-36) was selected.

In addition to the SF-36 scale, the vision specific scale will be administered. Vision specific scales developed by the following investigators were reviewed: (1) Haase and Bryant (1973); (2) Bernth-Peterson (1981); (3) Javitt et al. (1993); (4) Mangione et al. (1992); (5) Sloane et al. (1992). The Javitt Visual Function Questionnaire (Javitt, 1993) was selected because the format of questions resembles the SF-36, which reduces response errors, and because it has high test-retest reliability.

The National Eye Institute Visual Function Questionnaire is administered beginning in the first year of follow-up in the CLEK Study (Mangione et al., 1998).

1.2 Specific Aims of the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study

This multi-center observational study, the Collaborative Longitudinal Evaluation
of Keratoconus (CLEK) Study, characterizes keratoconus patients cross-sectionally at various stages of the disease and follows them for at least three years to assess changes in the disease over time. The goal is to characterize the disease across its course and to identify risk factors and protective factors that determine the severity and progression of the disease.

1.2.1 General Description of the Course of Keratoconus

The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study will describe the distribution and rate of change in best corrected high and low contrast visual acuity, corneal curvature, the proportion of patients developing incident corneal scarring, and the proportion of patients progressing to surgical intervention.

1.2.2 Factors Related to Vision in Keratoconus

The CLEK Study will characterize the association between best corrected visual acuity and visual quality of life and each of several pre-defined covariates. Best corrected and habitual visual acuity will be measured using high and low contrast Bailey-Lovie charts. Visual quality of life will be measured using the SF-36 and Javitt Visual Function Questionnaire and the NEI VFQ. The covariates of interest are corneal curvature, corneal irregularity, corneal scarring, the patient’s age, whether the patient wears spectacles or contact lenses, the type of contact lens worn, and the first definite apical clearance contact lens base curve. We will determine what measure of visual acuity—high or low contrast with best correction, habitual correction, or manifest refraction—best predicts visual quality of life.

1.2.3 Factors Related to Disease Progression (Corneal Curvature) in Keratoconus

The CLEK Study will characterize the relationship between corneal curvature, as measured by keratometry, and each of several pre-defined covariates. The covariates of interest are corneal irregularity, corneal scarring, the patient’s age, whether the patient wears spectacles or contact lenses, and the type of contact lens worn. (Although contact lenses will influence our measurement of these variables, it has been previously established that it would be unethical to conduct an observational study of keratoconus that would prohibit the use of rigid contact lenses in optical management of the disease.)

1.2.4 Factors Related to Corneal Scarring

The CLEK Study will describe the relationship between corneal scarring, as determined by a standardized photography and reading method, and each of several pre-defined covariates. The covariates of interest are corneal curvature, the patient’s
age, high and low contrast best corrected and habitual visual acuity, whether the patient wears spectacles or contact lenses, the type of contact lens worn, and the first definite apical clearance contact lens base curve.

It is expected that the results of these four sets of evaluations, and the relationship between those results will lead to a better understanding of the clinical course of keratoconus and will provide the framework for new approaches to the management of keratoconus.

1.3 Diagnosis of Keratoconus

Keratoconus is a progressive disease characterized by steepening and distortion of the cornea, thinning of the apical cornea, scarring, and treatment-related sequelae, such as abrasions from contact lenses and surgical complications. Although various geometries of keratoconus have been described (Caroline et al., 1978; Perry et al., 1980) it is not usually possible to identify these types in the early stages of the disease, except keratoglobus, which is actually a separate disease (Krachmer et al., 1984). The diagnosis of early keratoconus depends primarily on assessment of the corneal topography (Krachmer et al., 1984). An irregular, scissoring motion can be detected by viewing the retinoscopic reflex (Swann and Waldron, 1986). Inferior corneal steepening (Edmund, 1987b; Zabala and Archila, 1988) and irregular mires are observed with the keratometer. Devices which more accurately depict corneal topography, such as a hand-held Placido disc, photokeratoscope, or videokeratography system show inferior corneal steepening as well as irregular astigmatism. Documented increases in keratometric curvature of the cornea over time are valuable in diagnosing early keratoconus (Krachmer et al., 1984). Lack of agreement between corneal toricity and refractive astigmatism is also a sign of early keratoconus, especially when accompanied by documented irregular astigmatism.

There are several characteristic biomicroscopic signs which increase as the disease progresses (Krachmer et al., 1984). These include an inferiorly displaced, thinned protrusion of the cornea, visually evident corneal thinning over the apex, Vogt’s (1919) striae at the level of Descemet’s membrane, superficial scars at the level of Bowman’s membrane, and Fleischer’s ring (of iron) at the base of the cone, either full or partial. Vogt’s striae and Fleischer’s ring are considered pathognomonic for keratoconus. The CLEK Study protocol requires a patient to have at least one of these two classic biomicroscopic findings or corneal scarring in at least one eye in order to be eligible for the study. This stringent eligibility criterion confirms the diagnosis of keratoconus and excludes alternative conditions such as irregular corneal surface without these signs (Rabinowitz et al., 1990), pellucid marginal degeneration, and keratoglobus.

1.4 Course of Keratoconus
Previous large-scale studies of keratoconus have focused on describing the disease’s incidence and prevalence, (Kennedy et al., 1986) attempting to distinguish disease etiologies (Macsai et al., 1990; Swann and Waldron, 1986), or on trends in the clinical management of keratoconus (Smiddy et al., 1988; Lass et al., 1990; Fowler et al., 1988; Belin et al., 1988). Few have characterized the course of the disease and its associated factors in large samples of keratoconus patients (Eggink et al., 1988). All previous studies have relied on retrospective evaluations of keratoconus patients’ records.

The studies outlined in Table 1-2 below represent the largest samples of keratoconus patients assembled to date, but they suffer from the following limitations:

- These studies have not reported on the prevalence of the biomicroscopic slit lamp signs associated with keratoconus, including scarring, in anything but small samples (Kennedy et al., 1986; Swann and Waldron, 1986).
- None of the biomicroscopic signs of keratoconus has been evaluated prospectively in a sample of keratoconus patients.
- None of the previous studies has characterized the interactions of corneal curvature, biomicroscopic findings, and vision in keratoconus.
- Although non-acuity visual function has been described in small samples of keratoconus patients (Carney, 1982a; Carney, 1982b; Mannis et al., 1986; Zadnik et al., 1987; Zadnik et al., 1984), none of the large-scale studies in Table 1-2 have characterized vision and visual function beyond retrospective Snellen measurements as recorded by the examining clinician.
- No surveys of visual quality of life in keratoconus have been performed, although clinical, anecdotal reports of keratoconus patients’ dissatisfaction with their vision are common.
- No data exist comparing keratoconus patients’ visual symptoms with their clinically measured visual performance.
- Attempts to stage and/or classify keratoconus have been based on the severity of corneal distortion (Mandell, 1988), on the corneal thickness profile (Mandell and Polse, 1969), and on cone “type” or shape (Perry, et al., 1980). None of these systems use criteria that are measurable in a standardized fashion.
Table 1-2. Summary of large-scale studies of the characteristics of keratoconus.

<table>
<thead>
<tr>
<th>Study</th>
<th>Source of patients</th>
<th># of eyes/pts</th>
<th>% unilateral cases</th>
<th>% female</th>
<th>% w/ Vogt’s striae</th>
<th>% w/ Fleischer’s ring</th>
<th>% with scarring</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kennedy et al., 1986</td>
<td>Mayo Clinic</td>
<td>102/64</td>
<td>20</td>
<td>45</td>
<td>6</td>
<td>2</td>
<td>??</td>
<td>Incidence and prevalence, no increased mortality</td>
</tr>
<tr>
<td>Macsai et al., 1990</td>
<td>Cornea specialty practice</td>
<td>398/199</td>
<td>0</td>
<td>44</td>
<td>??*</td>
<td>??*</td>
<td>??*</td>
<td>If cls first, then kcn pt is older, has central cone, and flatter cornea</td>
</tr>
<tr>
<td>Eggink et al., 1988</td>
<td>Academic and non-academic clinical centers</td>
<td>?/874</td>
<td>8</td>
<td>45</td>
<td>??</td>
<td>??</td>
<td>??</td>
<td>6% wore contact lenses before kcn diagnosis</td>
</tr>
<tr>
<td>Lass et al., 1990</td>
<td>Three corneal specialty practices</td>
<td>834/417</td>
<td>3.5</td>
<td>45</td>
<td>??**</td>
<td>??**</td>
<td>??**</td>
<td>74% of patients fitted with cls; 21% underwent corneal surgery</td>
</tr>
<tr>
<td>Swann and Waldron, 1986</td>
<td>Private optometry practice</td>
<td>87/57</td>
<td>9</td>
<td>56</td>
<td>46</td>
<td>25</td>
<td>2</td>
<td>Association of kcn with atopy, obesity; low IOP; retinoscopic scissoring, inferior steepening</td>
</tr>
</tbody>
</table>

*Data are only available on 106 eyes of 53 patients who wore contact lenses before they were diagnosed with keratoconus. In this group, 92.5% of eyes had either Vogt’s striae, a Fleischer’s ring, or anterior stromal scarring.

**In this multicenter, retrospective study, the authors did not analyze these data due to a “lack of ... a consistent description for each eye regarding ... apical scarring, presence or absence of Fleischer’s ring, [and] Vogt’s striae.”

None of the studies cited in Table 1-2 have identified the key risk factors and protective factors that predict whether and how keratoconus progresses. We expect that utilizing factors that commonly define keratoconus clinically (best corrected high contrast visual acuity, corneal curvature, corneal scarring, and mode of optical correction), as well as less commonly described variables that may better characterize the patient’s symptoms (best corrected and habitual low contrast visual acuity and visual quality of life) will enable us to identify these key risk and protective factors in both the cross-sectional and longitudinal phases of the study.

1.5 Surgical Intervention

Keratoconus patients are generally treated with contact lenses by optometrists in
the early stages of the disease. These optometrists often work in association with ophthalmology centers or refer regularly to ophthalmologists for necessary medical therapy including surgery. Surgery is required by only about 10% - 20% of keratoconus patients (Kennedy et al., 1986; Smiddy et al., 1988), and 11% of penetrating keratoplasties performed in the United States are for keratoconus (Eye Bank Association of America statistics, 1992).

Most keratoconus patients require the primary mode of successful management: rigid contact lenses. Several recent retrospective studies have demonstrated good success following the refitting of contact lenses in patients who were being considered as possible surgical candidates due to presumed intolerance of contact lenses (Smiddy et al., 1988; Kastl et al., 1987; Belin et al., 1988; Fowler et al., 1988; Dana et al., 1990). Most practitioners avoid surgery in the early stages of keratoconus because of the risks of surgical complications, corneal graft rejection, or post-surgical corneal distortion, and because contact lens fitting in keratoconus has a high success rate (Kastl et al., 1987). Surgery—in the form of penetrating keratoplasty or epikeratoplasty—is required when contact lenses can no longer be tolerated due to either discomfort or poor vision associated with scarring (Sharif and Casey, 1991).

Epikeratoplasty is a procedure where an on-lay graft of lyophilized lamellar tissue is sewn to Bowman’s membrane of the keratoconic cornea. The ideal epikeratoplasty candidate has no corneal scarring and is contact lens intolerant but can achieve 20/40 visual acuity with a contact lens in place (Lembach et al., 1989; Dietze and Durrie, 1988). This procedure has significant advantages in that it is not an intraocular procedure and does not require donor tissue that might be immunologically rejected. This procedure represents a recent advancement in the surgical management of keratoconus, and its early success has been reported from several centers (Dietze and Durrie, 1988; Kaufman and Werblin, 1982; McDonald et al., 1983; McDonald et al., 1986; McDonald et al., 1987; Lass et al., 1987). The long term follow-up data for this procedure, however, are demonstrating that many of these patients with a successful surgical result still require the use of contact lenses to maximize visual improvement (Lembach et al., 1989). The role of epikeratoplasty compared to penetrating keratoplasty has not been clearly identified at this time (McDonald et al., 1987; Steinert and Wagoner, 1988). There is a growing opinion that rapid identification of those patients with changing keratometric readings and marked disease progression may benefit from earlier surgery with epikeratoplasty before a penetrating keratoplasty is necessary. There is some suggestion that the use of moist-pack nonlyophilized tissue may improve the rehabilitation and quality of vision achieved in these patients.

Although the rate of success with penetrating keratoplasty is higher for keratoconus than for most other indications for corneal grafts (Steinert and Wagoner, 1988; Sharif and Casey, 1991), significant risks and costs are associated with keratoplasty. Immunological rejection episodes, sometimes irreversible, are reported to
occur at a rate of 8 to 39% (Keates and Falkenstein, 1972; Chandler and Kaufman, 1974; Sayegh et al., 1988; Sharif and Casey, 1991). Recent evidence has shown endothelial cell loss five years after corneal transplant (Bourne et al., 1994). Less frequent, but vision-threatening complications include wound dehiscence, endophthalmitis, iris injury, synechia formation, glaucoma, cataract formation, and operative suprachoroidal hemorrhage (Brown and Tragakis, 1971; Binder et al., 1975; Sharif and Casey, 1991). Because of these significant risks and the protracted recovery rate, keratoplasty is one of the last steps considered in the management of keratoconus.

Contact lens intolerance and/or poor vision are the primary indications for surgery (Dana et al., 1990), whether epikeratoplasty or penetrating keratoplasty. However, several studies have demonstrated that a substantial proportion of patients (68%) with moderate to advanced keratoconus (corneal curvature of 50 to 60 D) who were referred because of poor vision or contact lens intolerance can be successfully fit with contact lenses. Smiddy et al. (1988) report that 87% of 115 consecutive keratoconus patients could be fit with contact lenses. Forty-four percent of eyes that eventually had keratoplasties needed three or fewer contact lens changes over a 5 year period prior to surgery. Sixty percent of 88 postoperative eyes needed contact lenses for best vision. Keratoplasty was delayed or avoided by using contact lenses in 69% of the selected patients of Smiddy et al. (1988) followed for an average of 5 years and in 95% of 64 patients of Kastl et al. (1987) followed for up to 20 years. Moreover, Belin et al. (1988) have noted that 47 of 61 eyes of 33 patients with keratoconus that had been previously diagnosed as contact lens intolerant could be successfully fitted. Smiddy et al. (1988) conclude that while “successful [contact lens] wear requires significant commitment on the part of the patients and contact lens fitter, ... those undergoing keratoplasty require at least a similar degree of care and commitment.” Moreover, although the costs of numerous follow-up visits and a large number of contact lens fittings over a long period of time are not negligible, they compare favorably with the costs of even an uncomplicated surgical procedure. Furthermore, potential surgical complications can be avoided altogether.

Those patients who go on to penetrating keratoplasty spend almost a year engaged in the surgery and tedious attendant follow-up care, typically sacrificing functional vision for a period of 3-12 months, depending on the course of the postoperative period. Even optically clear grafts still have refractive problems, such as high or irregular astigmatism or anisometropia, and corneal transplantation does not guarantee the keratoconus patient freedom from contact lens wear. After keratoplasty, many patients continue to need to wear contact lenses for best vision (Genvert et al., 1985; Mannis et al., 1986; Zadnik, 1988).

1.6 Treatment With Contact Lenses

Prior to the availability of modern contact lenses, keratoconus could not be
optically corrected. Spectacles cannot adequately correct the irregular astigmatism present in keratoconus, so before contact lenses, surgery was the only recourse. After diagnosing keratoconus and establishing a need for improved vision beyond that which can be achieved with spectacles, rigid contact lenses are the method of choice for optimizing vision and managing the irregular astigmatism (corneal distortion) associated with keratoconus (Mandell, 1988). The ultimate objective is to provide the best vision, comfort and wearing time possible while minimizing any adverse effect on corneal physiology from the contact lens.

Scleral contact lenses were used a century ago to treat corneal distortion and keratoconus and were made of glass and later of a plastic, polymethylmethacrylate (PMMA) (Gould, 1970). From approximately 1950 through the mid-1970s, PMMA contact lenses provided the most common management of keratoconus and the fitting methods used today were developed (Hall, 1963; Voss and Liberatore, 1962; Soper and Jarrett, 1972). More recently, soft contact lenses have been used in the earliest stage of the disease (Koliopoulos and Tragakis, 1981; Lundh, 1978).

Because of the inability of soft contact lenses to correct significant amounts of irregular astigmatism, gas permeable rigid corneal lenses are required for mild, moderate, and advanced keratoconus (Raber, 1986; Rosenthal, 1986; Belin et al., 1988; Gasset and Lobo, 1975; Mackie, 1977; Buxton, 1978; Mobilia and Foster, 1979; Raber, 1983; Maguen et al., 1983; Cohen and Parlato, 1986). These lenses may be fitted flat (touching the center or apex of the cornea) or steep (not touching, or clearing the corneal apex).

The piggyback approach, a rigid lens fitted over an underlying soft lens (Baldone, 1984) is currently only used in very complicated, advanced stages of the disease due to excessive corneal edema and inconvenience of lens care systems.

While contact lenses provide improved vision, they also have the potential to damage the cornea. Scarring of the central cornea may occur in keratoconus without contact lens wear (Krachmer et al., 1984), but it is possible that contact lenses can hasten axial scarring (Korb et al., 1982). Whether by causing hypoxia, entrapment of biodebris and tears, or physical trauma, the contact lens may induce deep central corneal abrasions. Due to the loss of epithelial layers, disruption of the anterior limiting membrane and Bowman’s membrane, and disruption of the regular anterior stroma collagen structure (Pataa et al., 1970), the central cornea may become scarred—and thus the vision reduced—secondary to contact lens wear in keratoconus.

1.6.1 Fitting Methods: Flat Lenses vs. Steep Lenses in Keratoconus

The major techniques for fitting rigid lenses in keratoconus (as described by Korb et al., 1982) are:
1. Flat, with primary lens support on the apex of the cornea (Hall, 1963), where the central optic zone of the lens actually touches or “bears on” the central corneal epithelium.

2. Steep, with lens support and bearing directed off the apex and onto the paracentral cornea, with clearance (vaulting) of the apex of the cornea (Voss and Liberatore, 1962); and

3. Divided support, or “three-point touch,” with lens support and bearing shared between the corneal apex and the paracentral cornea.

Most optometrists continue to use central corneal touch fitting since it is easier and appears to provide better vision, comfort, and wearing time. We have shown in a prospective survey of almost 1,600 keratoconus patients that 75% of the patients wearing rigid contact lenses are fitted with apical touch (Edrington et al., 1991). In addition, it has been argued (Kemmetmuller, 1962) that flat lenses delay the need for surgery by physically keeping the shape of the conus relatively flat. In contrast, it has been argued that the flat fitting method, which the majority of practitioners use today, may actually increase the risk of corneal compromise in the form of scarring.

However, only one prospective randomized clinical trial has compared central corneal touch fitting to central corneal clearance fitting in keratoconus (Korb et al., 1982), and the results are inconclusive as to whether contact lenses influence the disease course directly.

1.7 Tissue Changes in Keratoconus

Keratoconus corneas are structurally and biochemically different from normal corneas. The distribution of stromal fibers is uneven. The results of a number of investigations appear to indicate that there is an increase in intercellular substance and a decrease of total collagen accompanied by an increase of structural glycoproteins (Robert et al., 1970; Critchfield et al, 1988; Yue et al, 1984). However, others argue that correction for age negates these observations (Zimmermann et al., 1988). Teng (1963) demonstrated early changes in keratoconus in the basal epithelium indicating enzymes may be released from fragile basal epithelial cells which may cause fragmentation, fibrillation and liquefaction of the anterior stroma with invasion of fibroblasts and resultant scarring. Fibrin and fibrinogen are decreased in the epithelial basement membrane in keratoconus (Millin et al, 1986). In scarred areas of keratoconus corneas, collagen type III predominates (Maumenee, 1978; Newsome et al, 1981). Some studies have found high amounts of lysinonorleucine in keratoconus corneas indicating abnormal collagen cross linking (Cannon and Foster, 1978), while others have not.
corroborated this finding (Critchfield et al., 1988). Increased collagenase activity in excised keratoconus corneas has been observed (Rehany et al., 1982). Corneas from keratoconus patients contain less protein per mg of dry weight than normals. Reduced protein content may indicate increased nonproteinaceous materials. A high amount of polyanions including glycosaminoglycans are observed (Yue et al., 1988a). Plasma membranes of keratoconus patient stromal cells may contained elevated amounts of glycoconjugates. Glycoconjugates may be influential on cell differentiation and migration by mediating differences between wounded (or migrating) and nonwounded corneal epithelial cells. Keratoconus corneas contain reduced levels of a2-macroglobulin, a proteinase inhibitor (Sawaguchi et al., 1994). Although there is no certainty that these variations are associated with the pathogenesis of keratoconus, these variations are of great interest (Yue et al., 1988b).

Central anterior corneal epithelial staining formations (trauma) are typical in keratoconus (Dangel et al., 1984). Central corneal sensitivity is reduced in keratoconus, especially in those keratoconus patients wearing contact lenses and is correlated with disease severity in the contact lens-wearing subgroup (Zabala and Archila, 1988; Millodot and Owens, 1983). It is possible that some keratoconus patients are destined to scar rapidly. For example, two groups of keratoconus patients have been identified based on stromal collagen content. Group I has collagen similar to normal controls, and Group II has reduced collagen content (Yue et al., 1984). Unfortunately, to date, this analysis cannot be performed in vivo.

1.8 History of the CLEK Study

- **June 1988**: CLEK Study concept initiated at the first Clinical Trials Workshop, sponsored by the AOA Council on Research and the American Academy of Optometry Research Committee.
- **December 1988**: Initial meeting, involving all members of the Executive Committee. Pilot studies initiated.
- **February 1989**: Meeting with Richard Mowery, PhD, National Eye Institute staff.
- **April 1989**: Screening study initiated.
- **May 1989**: Major meeting in conjunction with the ARVO conference in Sarasota, Florida. Representatives of potential clinical centers invited. Consensus that the Study Group had indeed developed a high level of collaboration around a common purpose, decision to proceed with additional pilot studies even as the Planning Grant proposal was being prepared.
- **August 1989**: Planning grant submitted to National Eye Institute.
- **March 1990**: NEI Planning grant funded (R21 EY08652-01). Weekly conference calls initiated between Drs. Barr (Ohio State University), Edrington (Southern California College of Optometry), Gordon (Washington University), and Zadnik (UC Berkeley).
- **March-April 1990**: Pilot randomization begun at SCCO by Timothy Edrington, to
test fitting protocol. Initial scarring photography protocol tested by Joseph Barr. Initial scarring grading meeting at ARVO.

- **July-August 1990**: Photography grading meeting at UC Berkeley School of Optometry.
- **Spring 1990**: Pilot randomization initiated at Southern California College of Optometry and UC Davis Department of Ophthalmology.
- **Summer 1990**: Pilot randomization begun at Bethesda Eye Institute, St. Louis (Larry Davis, OD), University of Illinois-Chicago, Department of Ophthalmology (Timothy McMahon, OD), State University of New York College of Optometry (David Libassi, OD), and Ohio State University College of Optometry (Joseph Barr, OD MS).
- **December 9, 1990**: First meeting of Screening Clinics and Pilot Randomization Clinics, American Academy of Optometry, Nashville, TN.
- **April-May 1991**: First Clinic applications in from Bethesda Eye Institute, University of Illinois-Chicago, Department of Ophthalmology, OSU, SCCO, SUNY, and UC Berkeley/Davis. Meeting in Sarasota.
- **June 1992**: CLEK Study proposals submitted to the National Eye Institute.
- **March 1993**: Revised CLEK Study core grant proposals resubmitted to the National Eye Institute with new administrative structure and modifications in design.
- **September 1993**: Review by the National Eye Institute’s Vision Research Review Committee and comments from National Advisory Eye Council urge restructuring to an observational study.
- **March 1994**: Revised Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study core grant proposals resubmitted to the National Eye Institute as a multi-center, observational study.
- **December 1994**: Full Investigators Group Meeting, San Diego
- **September 1994**: CLEK Study funded by the National Eye Institute.
- **March 1995**: First CLEK Data Monitoring and Oversight Committee (DMOC) meeting
- **April 1995**: CLEK Study Training Meeting, The Ohio State University College of Optometry
- **May 31, 1995**: CLEK Study patient enrollment begins.
- **October 1995**: CLEK DMOC meeting
- **December 1995**: Full Investigators Group meeting, New Orleans

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Zadnik K: Post-surgical contact lens alternatives. International Contact Lens Clinician
2.1 CLEK Study Summary

Keratoconus is a visually disabling thinning disorder of the central cornea that results in irregular astigmatism, progressive corneal distortion, and corneal scarring (Krachmer et al., 1984). The astigmatism and distortion are usually treated with rigid contact lenses. When severe scarring occurs, or when the visual distortion is beyond optical correction, in 10 to 20% of patients, the cornea is repaired or replaced by surgery (Kennedy et al., 1986).

The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study is a multi-center, observational study designed to describe the course of this chronic ocular disease and to determine the associations among its visual and physiological manifestations. One thousand keratoconus patients are enrolled at 16 Participating Clinics over the course of ten months. Each is examined at baseline and annually for at least three years. Examinations include visual acuity, manifest refraction, patient-reported quality of life, keratometry, photodocumentation of the cornea to identify central corneal scarring, and slit lamp biomicroscopy. In rigid contact lens wearers, the fluorescein pattern of the patient’s lenses is documented. The flattest CLEK Study trial lens that demonstrates an apical clearance fluorescein pattern is photodocumented in all patients.

The CLEK Study characterizes keratoconus over the course of the disease both by initially enrolling patients at various diseases stages and by following all those patients for three years. The goal is to characterize the disease across its course and to identify risk factors and protective factors that determine the severity and progression of the disease.

2.1.1 CLEK Study Timetable

Each Clinic is expected to enroll at least 80 patients in a 10-month period, and patients are followed annually for nine years for a total of eight visits. Participating Clinics are reimbursed by the Study Chairman’s office for each CLEK Study patient visit ($300 for each visit). Patients are reimbursed $20 for each Study Visit. Participating Clinics and their referring doctors continue to administer all routine eye care, contact lens care, and surgical care to CLEK Study patients on their usual fee-for-service basis.
2.1.2 CLEK Study Calendar

<table>
<thead>
<tr>
<th>Month</th>
<th>Event</th>
<th>Who’s Primarily Involved</th>
</tr>
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<tbody>
<tr>
<td>October 1994 to May 1995</td>
<td>Startup, central training meeting</td>
<td>Chairman, CLEK Photography Reading Center (CPRC), Coordinating Center, Participating Clinics</td>
</tr>
<tr>
<td>June 1995 to April 1996</td>
<td>Enrollment</td>
<td>Participating Clinics, Coordinating Center</td>
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<tr>
<td>October 1995</td>
<td>Enrollment review</td>
<td>Data Monitoring and OVER Committee</td>
</tr>
<tr>
<td>June 1996 to June 1997</td>
<td>1-year follow-up</td>
<td>Participating Clinics, Coordinating Center</td>
</tr>
<tr>
<td>June 1997 to June 1998</td>
<td>2-year follow-up</td>
<td>Participating Clinics, Coordinating Center</td>
</tr>
<tr>
<td>June 1998</td>
<td>Interim status or progress review</td>
<td>Data Monitoring and OVER Committee</td>
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<tr>
<td>June 1998 to June 1999</td>
<td>3-year follow-up vs. more enrollment</td>
<td>Participating Clinics, Coordinating Center</td>
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<tr>
<td>June 1999 to July 2004</td>
<td>4-8 year follow-up</td>
<td>Chairman, CLEK Photography Reading Center (CPRC), Coordinating Center, CLEK Topography Reading Center, Participating Clinics</td>
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<tr>
<td>July 2004-September 2004</td>
<td>Data analysis, manuscript writing</td>
<td>Chairman, Coordinating C CPRC, CTRC, Writing Committees</td>
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2.2 Specific Aims

2.2.1 Specific Aim A. General Description of the Course of Keratoconus

The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study will describe the distribution and rate of change in best corrected high and low contrast visual acuity, corneal curvature, the proportion of patients developing incident corneal scarring, and the proportion of patients progressing to surgical intervention.

2.2.2 Specific Aim B. Factors Related to Vision in Keratoconus

The CLEK Study will characterize the association between best corrected visual
acuity and visual quality of life and each of several pre-defined covariates. Best corrected and habitual visual acuity will be measured using high and low contrast Bailey-Lovie charts. Visual quality of life will be measured using the SF-36 and Javitt Visual Function Questionnaire. The covariates of interest are corneal curvature, corneal irregularity, corneal scarring, the patient’s age, whether the patient wears spectacles or contact lenses, the type of contact lens worn, and the first definite apical clearance contact lens base curve. We will seek to determine what measure of visual acuity—high or low contrast with best correction, habitual correction, or manifest refraction and with either eye, the better eye, or both eyes—best predicts visual quality of life.

2.2.3 Specific Aim C. Factors Related to Disease Progression (Corneal Curvature) in Keratoconus

The CLEK Study will characterize the relationship between corneal curvature, as measured by keratometry, and each of several pre-defined covariates. The covariates of interest are corneal irregularity, corneal scarring, the patient’s age, whether the patient wears spectacles or contact lenses, and the type of contact lens worn.

2.2.4 Specific Aim D. Factors Related to Corneal Scarring

The CLEK Study will determine the relationship between corneal scarring, measured by a standardized photography and reading method, and each of several pre-defined covariates. The covariates of interest are corneal curvature, the patient’s age, high and low contrast best corrected and habitual visual acuity, whether the patient wears spectacles or contact lenses, the type of contact lens worn, and the first definite apical clearance contact lens base curve.

It is expected that the results of these four sets of evaluations, and the relationship between those results will lead to a better understanding of the clinical course of keratoconus and will provide the framework for new approaches to the management of keratoconus.

2.3 Rationale for Observational Study

The CLEK Study Executive Committee has considered the recommendations of the National Eye Institute’s Vision Research Review Committee and has concurred that a clinical trial of contact lens fitting methods in keratoconus is premature, primarily because of the many things that are unknown about keratoconus. Data required for assumptions key to the planning and design of the clinical trial are absent, eg, the proportion of patients exhibiting visual acuity loss of clinically important magnitude, the proportion of keratoconus patients who experience contact lens intolerance, and the incidence of corneal scarring. These data are required to provide a sound basis for estimating proposed clinical trial outcome measures such as visual acuity loss, decrease in contact lens wearing time, and the occurrence of corneal scarring. Unfortunately, these variables have not been systematically studied in this population. An
observational study addresses these deficiencies in our understanding of keratoconus and its course.

Following the second study section review of the clinical trial and based on the reviewers’ recommendations, the CLEK Executive Committee conducted a survey in fall 1993 of all CLEK Study investigators involved in the pilot screening study. The 32 respondents (29 optometrists, 10 of whom are practicing or have practiced in ophthalmologic settings, and 3 ophthalmologists/cornea specialists) classified 10 areas of potential study in keratoconus as to their importance. Disease progression, etiology, and corneal scarring were considered very important to study by 81%, 72%, and 63% of the respondents respectively. Other high-ranking areas were corneal topography, the best method for fitting contact lenses, and visual acuity. The survey results and a subsequent series of conference calls to discuss these issues with the original clinical trial clinic investigators led the CLEK Executive Committee to the conclusion that there are important unanswered questions in keratoconus that should be studied before attempting to conduct a clinical trial of optical management methods, namely to fully describe keratoconus in the areas of its effect on vision, its progression, and its accompanying corneal changes.

The need for such an observational study is underscored by recommendations from the VRRC’s two summary statements and by the recommendation of the National Advisory Eye Council in September 1993 on a previous proposal for a randomized clinical trial in keratoconus patients. The initial summary statement, from the October/November 1992 review, emphasized disease progression, stating, “Most of all, [the reviewers] felt that disease progression should be the primary focus.” Further, they identified specific parameters that should be evaluated to describe progression in keratoconus, namely, “in lens-wearing keratoconus patients, changes in visual acuity ... and lens fit are good clinical indicators of progression of keratoconus.... Given the expense of this study [the previously proposed randomized clinical trial], it seems a shame that the more important question of disease progression will not be evaluated.” These same reviewers identified a strength of the study, a randomized clinical trial, as “the development of a patient base for longitudinal studies in this population.”

The second summary statement, from June 1993, called for “pilot data supporting the validity of the principal hypothesis [of the clinical trial] ... and by estimates of the sensitivity of the proposed primary variables [visual acuity loss and contact lens wearing time decrease] in the target population.” They observe that “the natural history and progression of [keratoconus] is very poorly documented. This is particularly true in patients who are not wearing contact lenses, since rather few patients go through a complete evolution of the disease process in the absence of contact lens intervention.” A more detailed request for pilot data noted, “No data was provided from trial studies of the likelihood of participants losing two lines of vision or failing to wear their contact lenses for at least ten hours a day.”

Further, in September 1993 the Council Action sheet from the National Advisory
Eye Council stated,

Council believes that relatively little is known about the natural progression of keratoconus and that focusing on an observational study looking at the general experience of individuals with this disorder is perhaps of greater scientific merit than that of the proposed clinical trial. A study designed to obtain information on progression may provide the most valuable information on keratoconus. The investigators are likely to be able to retain many scientific aspects of the current application and incorporate these into a more general observational study. Council recognizes the outstanding team of investigators and the well developed manual of operations.

2.4 Patient Eligibility

2.4.1 Inclusion Criteria

If all of the following conditions are satisfied, the patient is eligible for the study:

• Age: At least 12 years old
• Irregular corneal surface in either eye determined by distortion of keratometric mires, of the retinoscopic reflex, or of the red reflex.
• Either Vogt’s striae in the deep stroma or Fleischer’s ring of at least 2 mm of arc or corneal scarring characteristic of keratoconus in either eye.
• Able to complete at least 3 years of follow-up.

2.4.2 Exclusion Criteria

If a patient has the following s/he is excluded from the CLEK Study:

• Bilateral corneal transplants
• Non-keratoconic ocular disease in both eyes: cataract, intraocular lens implant, macular disease, optic nerve disease other than glaucoma (eg, optic neuritis, optic atrophy)

2.4.3 Rationale for Inclusion and Exclusion Criteria

2.4.3a Age

To be eligible a patient must be at least 12 years old.

The age of onset of keratoconus is typically cited as the second or third decade of life (Krachmer, 1984). It is rare to see the disease in children under the age of 10 years.

2.4.3b Corneal Irregularity
To be eligible, the presence of corneal irregularity must be confirmed by abnormal retinoscopic or ophthalmoscopic reflex or irregular keratometric mires in either eye of an eligible patient. The inclusion criterion of corneal irregularity in either eye of an eligible patient helps define keratoconus as determined by clinical examination. Preliminary studies by Maguire and Bourne (1989) indicate a high degree of sensitivity in the detection of very early keratoconus by the identification of subtle inferior corneal steepening with computerized corneal topography systems. However, the reliability of these instruments has not been systematically evaluated in either normal or keratoconic corneas (National Advisory Eye Council, 1994), hence the decision to classify corneal irregularity for study entry purposes by other methods.

While computerized corneal topography systems may provide a high degree of sensitivity in the detection of very early keratoconus, the lack of validity and reliability studies for normal and keratoconic corneas, as well as the limited availability and high cost of the equipment, limit the use of computerized corneal topography. Also, the influence of contact lens wear on corneal topography is marked; potentially eligible study patients could not be asked to discontinue contact lens wear—even for a few days—to determine study eligibility. Participating Clinics may choose to screen potential subjects by corneal topography (shape), but eligibility as to corneal surface irregularity must be determined by an abnormal retinoscopic reflex, by an irregular ophthalmoscopic red reflex, or by irregular keratometric mires.

Quantitative keratometry to confirm the keratoconus diagnosis is not an inclusion or exclusion criterion. Kennedy et al. (1986) documented variability in keratometric corneal curvatures (ranging from 40 to 56 DK) at the time of diagnosis. Central corneal curvature in keratoconus is unreliable because the cornea is irregular and the keratometer is designed for regular spheres or toric surfaces. Central corneal curvature can also be in the range of normal in obvious keratoconus because the thinned area of the cornea is often displaced inferiorly (Mandell, 1988). Keratoconus classification schemes for disease severity based on keratometry have been proposed (Buxton, 1978), but they are of limited usefulness because central corneal curvature varies markedly and is not well correlated with disease severity by other indicators.

**2.4.3c Vogt’s Striae, Fleischer’s Ring, or Characteristic Corneal Scarring**

The presence of Vogt’s striae and/or a Fleischer’s ring of at least 2 mm arc and/or apical corneal scarring in the presence of corneal irregularity is considered pathognomonic for keratoconus. The CLEK Study requires patients to have at least one of these classic slit lamp biomicroscopic findings in at least one eye in order to be eligible for the study. Because Vogt’s striae, Fleischer’s ring, and/or the corneal scarring characteristic of keratoconus are objective, observable signs of keratoconus, they represent stringent entry criteria which confirm the diagnosis of keratoconus and exclude other disorders producing corneal thinning and/or irregularity (e.g., corneal warpage, pellucid marginal degeneration, keratoglobus, etc.).
The Executive Committee considered whether the presence of Vogt’s striae or a Fleischer’s ring or characteristic corneal scarring should be required in each eligible eye or in one eye. Keratoconus is bilateral 95% of the time (Krachmer et al., 1984). Because keratoconus can progress at different rates in each eye of a patient, Vogt’s striae or a Fleischer’s ring or corneal scarring may be present only in the more advanced eye. The probability that the corneal irregularity in an eye with a fellow eye showing Vogt’s striae or a Fleischer’s ring or corneal scarring does not represent keratoconus is very low. Also, such eyes typify the mild to moderate stages of the disease. Therefore, the eligibility criteria require either Vogt’s striae or a Fleischer’s ring or corneal scarring characteristic of keratoconus in at least one eye.

2.4.3d Contact Lenses Are Not an Entry Criterion

Because contact lenses are an integral part of the standard care in keratoconus, it is reasonable to enter current wearers of contact lenses as well as non-wearers.

2.4.3e Other Criteria

An entry criterion that was considered but rejected was evidence of an apical touch fluorescein pattern with a rigid contact lens whose base curve was equal to the flatter keratometric reading. Although this is an accepted clinical technique for early diagnosis of keratoconus, the reliability and validity of this procedure has not been evaluated. It would be prohibitively time-consuming to perform such an evaluation on all potentially eligible subjects.

Another entry criterion that was suggested but rejected was the requirement of progressive change in the manifest refraction with time. This potential entry criterion would unnecessarily delay entry into the CLEK Study until some arbitrary increase in myopia and/or astigmatism was documented. Reliable manifest refractions are difficult to perform in keratoconus, so actual progression in the degree of myopia or astigmatism would be difficult to discern from the expected variability in subjective refraction.

2.4.3f Representativeness of the CLEK Study Sample

The specific aim of the CLEK Study is to describe the course of patients with the diagnosis of keratoconus. No claim is made that patients identified with the diagnosis are representative of the undiagnosed keratoconus population or that the patients enrolled in the CLEK Study are representative of all diagnosed keratoconus patients. However, patients are typically first diagnosed with keratoconus by optometrists and typically receive eye care follow-up from optometrists prior to referral to ophthalmologists. Because the patients participating in the CLEK Study are recruited primarily from optometric clinics who receive referrals from community optometrists and ophthalmologists, the CLEK Study sample is “community” based. The alternative would have been to enroll patients from hundreds of smaller optometric and ophthalmologic practices which would be more costly and more time-consuming.
2.5 CLEK Study Measures

2.5.1 Visual Acuity

Visual acuity is an important measure for the following reasons:

(1) It is widely acknowledged as a good clinical indicator of disease severity in keratoconus.

(2) It relates directly to the keratoconus patient’s satisfaction with his or her mode of visual correction and frustration with the disease.

(3) The clinically accepted criteria for penetrating keratoplasty in the 10% to 20% of keratoconus patients requiring surgery is insufficient visual acuity and/or intolerance to contact lenses that prevents the performance of the patient’s everyday tasks.

(4) Measurement methods for visual acuity are straightforward and reliable.

Visual acuity is measured in three ways: (1) High and low contrast Bailey-Lovie visual acuity with habitual correction, each eye separately and both eyes together; (2) High and low contrast Bailey-Lovie (Bailey and Lovie, 1976) visual acuity with best correction (rigid contact lenses (including Softperm and piggyback systems) with optimal over-refraction for rigid contact lens wearers or steep “K” contact lens (from the CLEK Study Trial Lens Set) with over-refraction for non-rigid contact lens wearers), each eye separately; and (3) High contrast Bailey-Lovie visual acuity with manifest refraction, each eye separately.

The Bailey-Lovie chart is very similar to the visual acuity chart used in the Early Treatment of Diabetic Retinopathy Study (Ferris et al., 1982). The high and low contrast Bailey-Lovie charts are reversible wall charts. The chart is mounted at a distance of 4 meters from the patient. (If the largest letters cannot be read at 4m, the chart can be moved to 1 m.) The required chart luminance is 70 to 110 cd/m². The same method for prompting the patient as used in the ETDRS (Chapter 6 of this Operations Manual) is employed to assure standardization of testing conditions, and a total number score (letters correct) is recorded.

The CLEK Study visual acuity stopping rule requires that the patient reads letters across an entire row on the Bailey-Lovie chart. When 3 or more letters in a given row are read incorrectly, the visual acuity testing stops at the end of that row.

Best corrected visual acuity provides a measure of the eye’s optimal level of performance and provides information comparing the current standard of care in optical management with the best achievable correction, including how much vision is lost by the inadequacy of current modes of correction to manage the corneal distortion and scarring exhibited in keratoconus. Habitual visual acuity provides an estimate of the vision that the patient experiences in the real world and may provide the best association with the visual quality of life estimates. This information also enables us to
assess the adequacy of current standards of optical management in the CLEK Study patient sample. Because keratoconus patients often request back-up eyeglasses, the information from the manifest refraction supplies information on the visual acuity that can be achieved with this mode of correction. The CLEK Study will also determine the stability of the resultant prescription and will provide the ophthalmic community with guidelines for prescribing spectacles for keratoconus patients.

2.5.2 Corneal Curvature

Corneal curvature and changes in corneal curvature (central keratometry) are monitored for disease progression. Although videokeratography has been repeatedly recommended to the CLEK Executive Committee for characterizing disease severity and progression, we selected keratometry over corneal topography for the following reasons.

It has been demonstrated that current videokeratoscopy systems can measure spherical surfaces with at least ±0.37 D accuracy (Hannush, et al., 1989; Koch, et al., 1992). The normal corneal surface can be measured with repeatability of ±0.37 D to ±0.50 D (Zadnik, et al., 1992; Williams, et al., 1991). However, the instrumentation lacks normative standards and reproducibility standards for the measurement of abnormal corneas (National Advisory Eye Council, 1994; Antalis, et al., 1993), such as keratoconic corneas. Mandell and Shie (1993) have documented a videokeratographic value of 57.79 D for a keratoconus patient’s decentered corneal apex in primary gaze. Upon changing the patient’s fixation to center the keratoconic corneal apex, the value was 76.70 D. This example illustrates the limitations of the currently available software with regard to evaluating irregular corneal surfaces (Mandell and Shie, 1993).

Nonetheless, videokeratography will be a required measure for all CLEK Participating Clinics. CLEK Clinics will collect videokeratography data with Tomey’s Topographic Modeling System if they have one, or with whatever videokeratography system they do have if not a TMS, for future analysis and possible ancillary studies. Data from Clinics with TMS devices are sent to the Chairman’s Office for storage and future analysis. Data from Clinics with non-TMS devices are stored at the Clinics.

2.5.3 Corneal Scarring

Corneal scarring is a direct measure of corneal compromise. Scarring will be observed clinically, documented photographically, and evaluated in a masked fashion by the CLEK Photography Reading Center.

Corneal scarring is measured in two ways: (1) by an on-site Clinician and (2) by independent, masked reading of corneal photographs.

Apical corneal scarring is directly related to many of the parameters that determine contact lens success in keratoconus. Scarring of the corneal apex contributes
to visual acuity loss (Yackels, 1991; Burger, 1990). Elevated corneal scars and associated abrasions can prohibit the comfortable, long-term wear of rigid contact lenses (Moodaley, 1991; Rosenthal, 1993). Corneal scars that either limit visual acuity or decrease contact lens comfort can provide the rationale for surgical intervention (Sharif and Casey, 1991).

The CLEK Photography Reading Center performs an independent, masked, standardized assessment of the presence or absence of corneal scarring at every CLEK Study Visit. It also maintains hard copy documentation that can be reviewed and re-evaluated when needed. In addition, photodocumentation of corneal scarring permits monitoring of CLEK Study personnel to ensure that the protocol is being adhered to in a standardized fashion. In the absence of photographic documentation, it would be difficult to determine whether differences between Clinics in the rate of scarring observed could be attributable to subtle shifts or differences in the criteria used by Clinicians to assess scarring or to true differences in scarring rates.

### 2.5.4 Biomicroscopic Signs

Vogt’s striae and Fleischer’s ring have been poorly documented in keratoconus (Lass et al., 1990). The significance of these pathognomonic signs of the disease in terms of disease staging or disease prognosis has never been determined. Although the presence of one of these signs and/or corneal scarring in at least one eye is a CLEK Study entry criterion, many eyes will not have one or more of these signs and will enable us to evaluate their importance longitudinally.

Corneal staining may be an indicator of compromised corneal epithelium integrity in keratoconus, especially in contact lens wearers (Maguen, 1983; Korb, 1982). Many eyes in this study will show some degree of corneal staining, and the type and the severity of corneal staining is assessed by the Clinician with slit lamp biomicroscopy at each CLEK Study Visit. The Executive Committee felt that independent, photographic assessment of corneal staining would not have been feasible. Indeed, corneal fluorescein photography of CLEK pilot study patients revealed much variability of photograph quality.

### 2.5.5 Quality of Life

We selected the MOS SF-36 and decided against the inclusion of an instrument specific to depression. There are several reasons for these two decisions. (1) Keratoconus is a chronic disease that does not severely compromise health status, although keratoconus might result in impaired social and physical role functioning. Results from the CLEK pilot study suggest that instruments that focus only on activities of daily living that reflect physical functioning are insensitive to the role of the visual impairment associated with keratoconus. The results from the CLEK pilot study demonstrate the utility of assessing “role functioning” independently from “activities of daily living.” (2) The instrument needs to be sensitive to small degrees of impairment
since large degrees of impairment are likely to be rare. (3) The instrument needs to measure several dimensions of well-being. We considered using the CES-Depression scale in addition to the SF-36; however, results using the CES-Depression scale that were administered at the same time as the SF-36 in the CLEK pilot study showed absolutely no trend for increased risk of depression in the total score for the CES-D or in the mental health and emotional role functioning scale of the SF-36. Thus, the measurement of emotional functioning does not justify a separate instrument like the CES-D. (4) We desire a scale that could be self-administered without compromising reliability. (5) We desire an instrument with strong psychometric properties including good factor structure, high internal consistency reliability, high test-retest reliability, and good external validity. For these reasons, the Medical Outcomes Short Form with 36 items (SF-36) was selected.

In addition to the SF-36 scale, a vision specific scale will be administered. The Javitt Visual Function Questionnaire (Javitt et al., 1993) was selected because the format of questions resembles the SF-36, which reduces response errors, and because it has high test-retest reliability. The National Eye Institute Visual Function Questionnaire is administered beginning in the first year of follow-up in the CLEK Study (Mangione et al., 1998).

2.5.6 **First Definite Apical Clearance Lens**

At each CLEK Study Visit, the Clinician applies a series of CLEK Study trial lenses, beginning with the lens with base curve equal to the steep keratometric reading, until the first definite apical clearance fluorescein pattern is observed. This fluorescein pattern is photographed, as is the lens that is 0.2 mm flatter than the first definite apical clearance lens. This measurement provides an estimate of how flat or steep the patient’s current lenses are and better defines the current standard of contact lens care in the CLEK Study sample.

Thus, the CLEK Photography Reading Center provides an independent, masked, standardized assessment of the habitual contact lens fit, the First Definite Apical Clearance Lens, and the 0.2 mm flatter lens throughout the course of the study. In doing so, the CLEK Photography Reading Center provides photodocumentation of the standard of contact lens care of keratoconus patients in the CLEK Study sample and an estimate of the degree of flatness (or steepness) of the habitual contact lens as compared to the first definite apical clearance lens. Additionally, the First Definite Apical Clearance Lens provides an estimate of the progression of the steepness of the apex of the cornea during the Study.

2.5.7 **Surgical Intervention**

Corneal surgery is indicated in 10-20% of all cases of keratoconus (Kennedy et al., 1986; Smiddy et al., 1988). The need for surgery has high clinical relevance, definable
costs and known risks, and evaluation of keratoconus patients as they undergo penetrating keratoplasty in terms of their visual function is important. Both the corneal surgeon and the keratoconus patient apply subjective criteria in making the surgery decision. Patients seen annually who have undergone penetrating keratoplasty in the previous year will contribute to our body of knowledge about postoperative results.
2.5.8 Other Measures

Other measures are outlined on the CLEK Study Forms. A case history is taken by the Clinician that includes family history, systemic and ocular disease history, contact lens wearing time, and contact lens comfort. Additional procedures included as part of routine, annual ophthalmic care are a dilated fundus exam and applanation tonometry. See Chapter 7 of this Operations Manual for detailed information on these techniques.

No additional tests or measures can be made on CLEK Study patients without prior approval by the Executive Committee and/or the Data Monitoring and Oversight Committee. Similarly, CLEK Study patients cannot be enrolled in other eye studies after enrollment in CLEK without prior approval of the Executive Committee and the DMOC.

2.6 Issues of Recruitment and Retention

Each Clinic is responsible for recruitment of patients. Recruitment depends on referral patterns within the community, on other doctors’ willingness to refer patients, and on the type of CLEK Study marketing appropriate for the community. CLEK Study meetings are an important forum for sharing successful recruitment and retention strategies.

Although the CLEK Executive Committee believes that keratoconus patients are likely to be interested in participating in the study, patients are reimbursed a nominal amount for each visit to offset such expenses as transportation, parking, and child care. This reimbursement is processed by the Chairman’s Office, thereby facilitating a centralized, annual CLEK Study patient address update.

Health maintenance organizations (HMOs) are expected to be an excellent source of potential enrollees for the Study. In fact, one of the HMOs participating in the screening study screened the largest number of potential subjects. However, HMOs are not likely to refer patients to the Study if additional costs are incurred. Each Clinic contacts local HMOs and makes appropriate arrangements.

2.7 Routine Ophthalmic Care and Emergencies

Each CLEK Study patient receives all his or her routine, non-Study related care from his or her Participating Clinic and/or referring doctor. Usual and customary fees for these services and ophthalmic materials will apply and are unaffected by CLEK Study participation.

In the event that an enrolled CLEK Study patient goes on to corneal surgery, an extra study examination is conducted within one month before surgery. The patient is scheduled according to his original date of enrollment for postsurgical CLEK Study
examinations. If the surgery occurs within 3 months after a routine CLEK Study visit, this routine visit serves as the Presurgical Visit, too.

Note: If the procedure is included in the CLEK Examination Form, that procedure is defined as Study-related care. If the procedure is not included in the CLEK Examination Form, or the procedures are performed at a necessary visit other than the CLEK Annual Visit, that represents non-Study related care.

Usual and customary requirements for care of any conditions detected at a CLEK Study Visit apply. Any conditions requiring immediate attention and management (e.g., a corneal abrasion or a retinal detachment) should be brought to the attention of the referring doctor, if appropriate, and should be referred for care appropriately.

2.8 Sample Size Requirement and Rationale

The sample size of 1,000 for the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study was selected for several reasons:

Specific Aim A is the description of the distribution and rate of change in best corrected visual acuity, corneal curvature, and central corneal scarring. The distribution of visual acuity, corneal curvature, and central corneal scarring at baseline and changes in their values over time will be described using 95% confidence intervals. The determination of sample size for Specific Aim A, which is descriptive in nature, was evaluated by considering the width of the 95% confidence interval for each of these variables of interest.

Data from the CLEK Recruitment Survey were used to estimate variances in visual acuity, corneal curvature, and proportion of patients affected with corneal scarring. A total of 1,012 patients from the Recruitment Survey would be eligible for the CLEK Study, given the six key eligibility criteria: age, unilateral corneal irregularity, unilateral presence of Vogt’s striae, Fleischer’s ring, or corneal scarring, and transplant status. These data form the basis for our sample size estimates for visual acuity, corneal curvature, and corneal scarring. The distribution of visual acuity (computing the mean and variance in visual acuity; Snellen values were converted to Bailey-Lovie logmar values), mean and standard deviation for keratometry, and the proportion of patients with corneal scarring are given in the following tables (2-1 through 2-3):

| Table 2-1. Percent of patients with visual acuity worse than 20/40 by age decade. |
|--------------------------------------|-----------------|-----------------|-----------------|
| Age by decade (years) | n | One eye worse (n/%) | Both eyes worse (n/%) |
| < 30 | 322 | 74/23% | 22/7% |
| 30-39 | 346 | 97/28% | 28/8% |
| 40-49 | 245 | 80/34% | 29/12% |
| > 50 | 99 | 40/41% | 21/21% |
Table 2-2. Mean (SD) keratometric reading by age decade.

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<th>Age by decade (years)</th>
<th>Mean keratometric reading</th>
<th>SD</th>
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<td>&lt; 30</td>
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<td>40-49</td>
<td>50.4</td>
<td>6.1</td>
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<td>&gt; 50</td>
<td>50.4</td>
<td>5.5</td>
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</table>

Table 2-3. Percent of patients with corneal scarring by age decade.

<table>
<thead>
<tr>
<th>Age by decade (years)</th>
<th>Neither eye (n/%)</th>
<th>One eye (n/%)</th>
<th>Both eyes (n/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>192/62%</td>
<td>74/24%</td>
<td>42/14%</td>
</tr>
<tr>
<td>30-39</td>
<td>158/52%</td>
<td>98/32%</td>
<td>47/16%</td>
</tr>
<tr>
<td>40-49</td>
<td>89/41%</td>
<td>70/31%</td>
<td>57/26%</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>31/36%</td>
<td>37/42%</td>
<td>19/22%</td>
</tr>
</tbody>
</table>

For Specific Aim A, the width of the 95% confidence interval for continuous variables such as Bailey-Lovie logmar score or mean keratometry expressed in terms of standard deviation units are given in Table 13 below for total sample sizes of 250, 500, and 1000. The width of the 95% confidence interval for visual acuity (Bailey-Lovie logmar score) or keratometry for a sample of 1000 would be 0.13 SD units wide. However, in most instances, estimates for variables using the entire sample are neither interesting nor interpretable. It is important to provide adequate power for subgroups of interest defined by risk factors with prevalences of 25% or greater. A sample of 1000 would provide an adequately narrow 95% confidence interval of 0.25 SD for subgroups of 250. For example, if the variable of interest was corneal curvature, the 95% confidence interval for a subgroup of 250 patients would be approximately 0.25 SD units wide.

Table 2-4. 95% confidence intervals expressed as standard deviation units.

<table>
<thead>
<tr>
<th>Total sample size</th>
<th>SD units</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>0.25</td>
</tr>
<tr>
<td>500</td>
<td>0.18</td>
</tr>
<tr>
<td>750</td>
<td>0.14</td>
</tr>
<tr>
<td>1000</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Similarly, for estimates of proportions, eg, the proportion of patients with central corneal scarring, the 95% confidence intervals are as follows for sample sizes of 250, 500, and 1000. The sample size of 1000 again provides adequate 95% confidence intervals for subgroups of about 250.

Table 2-5. 95% confidence intervals for proportions.

<table>
<thead>
<tr>
<th>Total sample size</th>
<th>.05</th>
<th>.10</th>
<th>.15</th>
<th>.20</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>.023 - .077</td>
<td>.063 - .137</td>
<td>.106 - .194</td>
<td>.150 - .250</td>
</tr>
<tr>
<td>500</td>
<td>.031 - .069</td>
<td>.074 - .126</td>
<td>.119 - .181</td>
<td>.165 - .235</td>
</tr>
<tr>
<td>750</td>
<td>.034 - .066</td>
<td>.079 - .122</td>
<td>.124 - .176</td>
<td>.171 - .229</td>
</tr>
<tr>
<td>1000</td>
<td>.037 - .064</td>
<td>.081 - .119</td>
<td>.128 - .172</td>
<td>.175 - .225</td>
</tr>
</tbody>
</table>

Tables 2-1 through 2-3 report the proportion of patients with risk factors of interest, and we propose a sample size of 1000 in the face of uncertainty about event
rates. In Specific Aims B, C, and D, we propose to evaluate risk factors that contribute to worsening visual acuity, increasing corneal curvature, and increasing central corneal scarring respectively. Projecting rates of progression from the above data or projecting incidence of corneal scarring requires great caution, because it is clear that a high degree of migration into and out of this patient sample occurs. The low number of patients older than 50 years suggests a marked out migration, for example. A sample size of 1000 will provide reasonable power for detecting risk factors with odds ratios of 2.00 or greater for events of relatively low occurrence, such as central corneal scarring, that have high clinical relevance and functional significance.

Table 2-6. Power for detecting an odds ratio of ≥2.00 for various sample sizes.

<table>
<thead>
<tr>
<th>Total sample size</th>
<th>% with risk factor</th>
<th>P1= 0.10 P2= 0.18</th>
<th>P1= 0.15 P2= 0.26</th>
<th>P1= 0.20 P2= 0.33</th>
<th>P1= 0.25 P2= 0.40</th>
</tr>
</thead>
<tbody>
<tr>
<td>600</td>
<td>15%</td>
<td>.530</td>
<td>.671</td>
<td>.737</td>
<td>.805</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>.626</td>
<td>.768</td>
<td>.828</td>
<td>.884</td>
</tr>
<tr>
<td></td>
<td>25%</td>
<td>.695</td>
<td>.830</td>
<td>.882</td>
<td>.928</td>
</tr>
<tr>
<td>800</td>
<td>15%</td>
<td>.652</td>
<td>.792</td>
<td>.850</td>
<td>.902</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>.750</td>
<td>.875</td>
<td>.919</td>
<td>.954</td>
</tr>
<tr>
<td></td>
<td>25%</td>
<td>.814</td>
<td>.920</td>
<td>.953</td>
<td>.977</td>
</tr>
<tr>
<td>1000</td>
<td>15%</td>
<td>.748</td>
<td>.873</td>
<td>.918</td>
<td>.953</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>.838</td>
<td>.935</td>
<td>.963</td>
<td>.983</td>
</tr>
<tr>
<td></td>
<td>25%</td>
<td>.890</td>
<td>.964</td>
<td>.982</td>
<td>.993</td>
</tr>
</tbody>
</table>

P1 is the probability of the event in the group without the risk factor.
P2 is the probability of the event in the group with the risk factor.
w=odds ratio
P2=wP1/(wP1+Q1) (Fleiss, 1981)

2.9 Analysis of Data

2.9.1 General Considerations

As embodied in Specific Aim A, the primary goal of the CLEK Study is to provide a comprehensive description of both baseline and longitudinal data from patients with keratoconus. Two fundamental features of our analytic plans for the remaining Aims are: (1) the implementation of procedures that account for the inherent pairing of the data and (2) for longitudinal data, utilizing models that permit missing data. We will employ longitudinal models that do not require that measurement times be the same across patients. For both dichotomous and continuous outcomes, traditional repeated measures designs cannot be appropriately applied when data are missing or when patients have different evaluation schedules. Moreover, a fundamental assumption of both linear and logistic regression, whether applied cross-sectionally or longitudinally, is the independence of the error terms. In the CLEK Study, the unit of observation will be the eye. However, the association between the characteristics of two eyes in the same individual is likely to be stronger than the association between the characteristics of two eyes of different individuals (Ederer, 1971). That is, the independence assumptions of ordinary linear and logistic regression are almost certain to be violated when applied to these data.
To address the above problems, our analysis of data which addresses Aims B-D will employ four analytic strategies that are specifically designed to analyze the data on an eye-specific basis while formally accounting for the correlation between two eyes in the same individual. These analytic methods are as follows.

2.9.2 Cross-sectional Regression Analyses

Investigators may not independently analyze or present CLEK Study data collected at their CLEK Participating Clinic without specific prior approval from the Executive Committee.

Cross-sectional regression analyses (of baseline data) with paired outcomes will be performed using the procedures described by Rosner (1984). Rosner describes regression approaches that generalize both linear and logistic regression analyses so as to account for the intraclass correlation coefficient between eyes of the same patient. The linear generalization requires normally distributed outcome measures. Both the linear and the logistic generalizations permit eye-specific and patient-specific covariates. Both models can also be applied when data are available on only one eye of some patients. The CLEK Coordinating Center has copies of software, written by Professor Rosner and his staff, which will implement these methods.

2.9.3 Longitudinal Regression Analyses with Paired Continuous Outcomes

Longitudinal regression analyses with paired continuous outcomes will be performed using the random-effects models described by Laird and Ware (1982). The Laird and Ware approach fits a linear regression model to each subject and assumes that both error terms and regression coefficients are normally distributed in these lines. It then uses the EM algorithm to combine the individual lines and generate empirical Bayes, maximum likelihood, and restricted maximum likelihood estimates of model parameters. Because lines are generated for individuals, the model is more general than repeated measures analysis of variance in that it has no requirements about common measurement times between subjects and can deal easily with missing data. The Laird and Ware model can handle the correlated outcome measures that will be characteristic of CLEK Study data and is appropriate for continuous, dichotomous, and time-dependent covariates. The CLEK Coordinating Center has substantial experience implementing this model using both PROC MIXED in SAS (SAS Institute, 1992) and the original software (Stram, 1986). PROC MIXED will be employed in analyzing CLEK Study data.

2.9.4 Longitudinal Regression Analyses with Paired Dichotomous Outcomes

Longitudinal regression analyses with paired dichotomous outcomes will be performed using the generalized linear models of Liang and Zeger (1986). The Liang and Zeger model eliminates the normality assumptions of the Laird and Ware model.
and can be applied under very general assumptions which do not require the specification of the distribution of the repeated measures. It permits missing data, the absence of between-subject comparability of measurement times, time-dependent as well as continuous and dichotomous covariates, and correlated outcome measures. The CLEK Coordinating Center has experience in implementing the Liang and Zeger model using a SAS macro prepared by Karim and Zeger (1988).

2.9.5 Analyses Keyed to Specific Aims

2.9.5a Specific Aim A

The purpose of this Aim is largely descriptive in that the primary goals are to provide estimates of visual acuity, corneal curvature, whether keratoconus patients wear spectacles or contact lenses and the type of contact lens, the percent of patients with central corneal scarring and other biomicroscopic signs of keratoconus, and the percent of patients who require corneal surgery. We will also describe the rate at which the latter two dichotomous measures develop in patients who do not exhibit them at baseline. (Finally, with a particular focus on those patients who develop central corneal scarring and those patients who go to surgery during the study, we will quantify the before/after changes in Bailey-Lovie high and low contrast visual acuity.) Ninety-five percent confidence bounds will be placed around all parameters estimated for this Specific Aim. Because Specific Aims B through D are focused on a detailed analysis of these parameters with an emphasis on accounting for the correlation between two eyes of the same patient, the descriptive Aim will simplify both the methodology and the description of results by focusing on a single eye. Specifically, baseline estimates will be generated with an eye of each subject chosen randomly. The rate of development of the dichotomous parameters will be described separately using: (1) the randomly selected eye when the condition is not present at baseline in either eye or (2) the fellow eye when the condition is present at baseline in one eye. With the development of each dichotomous condition between baseline and the final study measurement treated as a yes/no variable, chi square tests will compare the rate of development of each condition in patients who had the condition in neither eye at baseline versus patients who had the condition in one eye at baseline. Using this same dichotomy defined by the number of eyes (0 or 1) in which a condition is present at baseline, the rate of change in best corrected high and low contrast visual acuity from baseline to final measurement will be described and compared in the two groups. Thus, we will compute the mean change in high and low contrast visual acuity in one randomly selected eye of patients with no central corneal scarring at baseline and in the fellow eye of subjects with central corneal scarring in only one eye at baseline. Confidence bounds will be placed around those changes. Before/after differences in high and low contrast visual acuity will be statistically compared using analysis of covariance with final visual acuity as the dependent variable and with baseline visual acuity and whether central corneal scarring was present in one eye as compared to no eyes at baseline as independent variables.

2.9.5b Specific Aim B
The purpose of this aim is to evaluate factors associated with and affecting best corrected, habitual, and manifest high and low contrast visual acuity and visual quality of life. Cross-sectional analyses will be performed on baseline data approximately one year after patient recruitment begins (month 18 of the study). These analyses will use the Rosner model (Rosner, 1984) to evaluate the association between best corrected, habitual, and manifest high and low contrast visual acuity and visual quality of life and several covariates. The pre-defined, eye-specific covariates are corneal curvature, and central corneal scarring. Patient-specific covariates include age, whether the patient is wearing spectacles or contact lenses, and the type of contact lenses worn. The Laird and Ware model (Laird, 1982) will provide longitudinal information about changes in visual acuity and visual quality of life and about the impact of the defined covariates on those changes. Since intervening surgery may be an important factor, this variable will be added to the longitudinal analysis as an eye-specific, time-dependent covariate. On the basis of the pilot survey study, we anticipate that Bailey-Lovie visual acuity data are likely to have a skewed distribution whose logarithm is closer to being normally distributed, all analyses involving this variable will, pending an evaluation of the distribution of the data, probably be performed after logarithmic transformation. To simplify the reporting of correlation coefficients, one eye of each subject will be selected randomly (unless it has had pre-study surgery, in which case the fellow eye will be used), and Pearson correlation coefficients between best corrected, manifest, and habitual baseline high and low contrast visual acuity and visual quality of life will be computed.

2.9.5c Specific Aim C

The purpose of this aim is to evaluate factors associated with and affecting corneal curvature. Because mean corneal curvature is a continuous variable, and because our evaluation of this variable is focused on the same issues as is the case for visual acuity, the analytic methods to be applied to this variable are nearly identical to those that will be applied to visual acuity. The only exception may be in the appropriateness of using data transformations in implementing the Rosner (1984) and the Laird and Ware (1982) models. For this reason, we refer the reader to the section discussing the analysis of data in Specific Aim B.

2.9.5d Specific Aim D

The purpose of this aim is to evaluate factors associated with an affecting central corneal scarring. The concerns in these analyses are analogous to the concerns which motivated the analytic strategies in Specific Aims B and C. Because central corneal scarring is a dichotomous outcome, the longitudinal analysis of this variable will employ a Liang and Zeger (1986) model rather than the Laird and Ware (1982) approach used above. Aside from this, all analytic considerations in this aim have already been discussed.
2.10 Human Subjects Considerations

The CLEK Study is limited to keratoconus patients who have corneal irregularity and slit lamp signs of keratoconus. There are no limitations based on gender, ethnic group, race, or religious affiliation.

Because the inclusion criterion for age includes minors older than age 12 years, special procedures are outlined in Chapter 4 of this Operations Manual for obtaining informed consent from minors who are eligible for the CLEK Study. All procedures to be performed and eye drops to be used in the CLEK Study are considered standard clinical practice. Great care is taken to explain the effects of the drops and testing procedures to both minors eligible for the Study and their parents. Particular benefit may accrue to minors enrolled in the Study since there is a tendency for keratoconus patients diagnosed in the second decade of life to progress faster.

The research data consist of written records, corneal photographs, and fluorescein pattern photographs. All materials are kept in locked file cabinets and are available only to the investigators and coordinators at the various Clinics, the CLEK Photography Reading Center, the Coordinating Center, and the Data Monitoring and Oversight Committee. No material will be published or released with a patient’s name, medical record number, social security number, or other identifier. Data at the Clinic retain patient identifiers. With the patient’s permission, the Chairman’s Office will maintain a patient name and address list for reimbursement and mailing purposes, but the list will not be linked to CLEK Study patient ID numbers.

After determining that a Study candidate has satisfied the eligibility requirements, the Clinician discusses participation in the CLEK Study with the Study candidate. Each Study candidate signs an Informed Consent Form or Decline to Participate Form after a discussion of keratoconus and the study. A detailed explanation of the informed consent procedure is in Chapter 4, “Patient Education, Informed Consent, and Patient Recruitment.” The individual retains a copy of the signed consent form, and the original signed form is retained at the Clinic. In order to protect patient confidentiality, the signed consent form is not sent to the Coordinating Center. The signed consent form is a very important legal document and is subject to audit at site visits.

The patient’s name, social security number, and address are supplied to the Study Chairman’s office in order to process patient reimbursement, but they are not be attached to the patient’s Study identification number to preserve confidentiality. Reimbursement forms are supplied to each Clinic. Patients will complete them and mail them to Dr. Zadnik in an addressed, stamped envelope so that check disbursement will be processed.

The data and the progress of the Study are monitored on an ongoing basis by the Coordinating Center and annually by the Data Monitoring and Oversight Committee.
In addition, the Data Monitoring and Oversight Committee determines whether recruitment is sufficient and/or whether to approve changes to the Study protocols for reasons of patient safety or study scientific integrity.

There are no risks to participating in this observational study beyond those incurred in routine clinical care of keratoconus. The potential benefits of this study to the individual patient are that he or she will receive regular eye exams and that he or she may directly benefit from information about the progression of keratoconus. Thus, the risk-benefit ratio has been judged to be favorable.

2.11 References

Korb DR, Finnemore VM, and Herman JP. Apical changes and scarring in keratoconus as related to contact lens fitting techniques. Journal of the American Optometric


Chapter 3
Entry and Enrollment

3.1 Screening for Eligibility

Screening for CLEK Study eligibility is conducted on any patient who carries the working diagnosis of keratoconus or in whom keratoconus is a possible diagnosis.

An Eligibility Form is completed by the Clinician on any keratoconus patient evaluated for CLEK Study eligibility at any visit to a Participating Clinic. Referring doctors can complete a draft Eligibility Form to evaluate a patient, but the Participating Clinic must complete its own Eligibility Form for submission to the Coordinating Center. This will track non-eligible patients and eligible patients who decline to participate in the CLEK Study. The Eligibility Form is forwarded to the Coordinating Center.

3.2 Implementation of Eligibility Criteria

Any patient carrying a working diagnosis of keratoconus is a CLEK Study candidate. Given the relative simplicity of a preliminary screening for the entry and exclusion criteria, patients can be quickly evaluated to determine whether it is worth the Study candidate’s and the Clinic’s time to schedule the Baseline Visit. The Clinician should complete the Eligibility Form on any patient carrying the working diagnosis of keratoconus and should forward a copy of the form—whether the patient turns out to be eligible or not—to the Coordinating Center. If the patient appears eligible upon completion of the Eligibility Form, the Clinician explains the CLEK Study to the patient, requests that the patient sign an informed consent form, and schedules the patient for his or her Baseline Visit once the patient has provided informed consent.

CLEK Participating Clinic personnel are informed at the beginning of the Study and at annual CLEK Study Group meetings that enrollment of an ineligible patient is a serious protocol error. The Participating Clinics will be reminded of the ramifications of enrolling a patient who is later deemed ineligible. Corrective action will be taken against Clinics who repeatedly enroll ineligible patients.

3.3 Inclusion Criteria

If all of the following conditions are satisfied, the patient is eligible for the CLEK Study:

- Age: At least 12 years old
- Irregular corneal surface in either eye as determined by distortion of keratometric mires, of the retinoscopic reflex, or of the red reflex.
• **Either** Vogt’s striae in the deep stroma or Fleischer’s ring of at least 2 mm arc or corneal scarring characteristic of keratoconus **in either eye**.
• Able to complete at least 3 years of follow-up.

### 3.4 Exclusion Criteria

If **either** of the following conditions is present, a patient is not eligible:

• Bilateral corneal transplants
• Non-keratoconic ocular disease **in both eyes**: cataract, intraocular lens implant, macular disease, optic nerve disease other than glaucoma (eg, optic neuritis, optic atrophy)

### 3.5 Assignment of Patient Identification Numbers

Any candidate appearing for the Baseline Visit is entered into the patient log and assigned a patient identification number by the Participating Clinic. Once an ID number is assigned to a patient, it stays with that patient and is not reassigned to another patient. The patient identification number is constructed in the following manner. The first and second digits of the patient ID are the Participating Clinic’s identification code. The third, fourth, fifth, sixth, and seventh digits indicate the sequential number from the patient log from 00001 to 99999. The eighth and ninth digits are two letters selected from the patient’s name according to a system chosen by the Participating Clinic (eg, using first or last initial, or any other method) that is used consistently. The Coordinating Center is not informed as to how the two letters are selected.

**Example:** Patient ID# = C1-00023-JS

**Clinic ID:** **Digit 1-2** (C1) is Clinic ID.
One alphabetic and one numeric code number assigned by the Coordinating Center to designate the Clinic

eg, Clinic Identification Code is C1

**Patient ID:** **Digit 3-4-5-6-7** (00023)
Five numbers indicating the sequential order of patients who complete any part of the Baseline Visit.

These digits are assigned to the CLEK forms distributed by the Coordinating Center.

**Digit 8-9** (JS)
Clinic C1 always uses the patient’s initials.
For the patient John Smith at C1, the code is “JS”

The patient identification number (Digits 3-4-5-6-7-8-9) stays with the patient for the duration of the Study. If the patient is followed later by another CLEK Clinic, he/she retains the original identification number. Again, the patient’s unique identification (3-9) stays with the patient.

3.6 Procedure for Informed Consent

After patient education and informed consent is completed, the Study candidate is requested to sign an Informed Consent Form. A detailed explanation of the informed consent procedure is in Chapter 4, “Patient Recruitment, Education and Informed Consent.” The individual keeps a copy of the consent form, and the original signed form is kept by the Clinic. In order to protect patient confidentiality, the signed consent forms are never sent to the Coordinating Center. If signed forms are accidentally sent to the Coordinating Center, they are returned.

3.7 Study Entry Date

The date of the Baseline Visit serves as the official date that the patient is entered into the CLEK Study. The Coordinating Center generates the follow-up schedule for each participant from the date of the Baseline Visit.
Chapter 4
Patient Education, Informed Consent, and Patient Recruitment

4.1 Patient Education and Informed Consent

The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study requires that written consent be obtained from each patient prior to enrollment in the study. The patient is asked to sign the Clinic’s own institution-approved consent form only after eligibility has been established and after patient education has been completed. The signed informed consent is kept by the Participating Clinic in locked patient files located in the individual CLEK Clinic. The Data Monitoring and Oversight Committee and the CLEK Study Executive Committee review consent forms periodically to assure adherence to CLEK Study standards.

Each Clinic Principal Investigator is responsible for obtaining approval of his or her Clinic’s consent form and approval for conducting the CLEK Study from the local institutional review board. (See sample at the end of this chapter.) A copy of each Clinic’s approved consent form and documentation of approval must be submitted to the Study Chairman before patients can be enrolled in the CLEK Study. Each Participating Clinic will receive an annual reminder that its Human Subjects approval is due to be renewed two months before the annual expiration date.

All patients in the CLEK Study should understand the purpose of the study, the need for his or her commitment to long-term follow-up, and costs and reimbursements. All of the patient education and informed consent activities require the participation of the Clinician. The time required for these activities should not be underestimated.

In the event that a CLEK patient needs to be seen at a Participating Clinic other than the one he or she originally enrolled at, the patient will need to sign an informed consent form at the Clinic at which he or she is to be seen.

4.2 Patient Education

Once the Clinician has examined the patient, completed the Eligibility Form, and determined the patient’s eligibility, the following procedures must be followed:

• Keratoconus is explained to the patient and to his or her family, if necessary.

• Each patient reads the informed consent form. The form is then explained, and time is allowed for the patient to ask questions.

• The CLEK Study, the need for long-term follow-up, and costs and reimbursements are explained.
• The patient is given the opportunity to view the CLEK Study Recruitment Video. This presentation is designed to give the patient an overview of the Study and provide him or her with the perspective that this is a national study.

• The patient should not be subjected to any pressure; if the patient would like to consider the Study and return at a later time, that is quite acceptable.

• All the patient’s questions must be answered. If an answer is not known, the Clinician should admit frankly that it is not known and follow-up should be promised. The Participating Clinician calls Dr. Zadnik, CLEK Study Chairman at (510) 643-0568, to obtain the answer and then responds to the patient.

• The CLEK Study’s status as a large, national, multi-center program is emphasized. No analytical results will be available for months to years. Each patient should be reminded of the importance of his or her individual efforts.

• After the patient signs the informed consent form, the form is copied, and the patient receives the copy. The original informed consent form is filed at the Participating Clinic.

4.3 Special Consent Procedures for Minors

Because the inclusion criterion for age includes minors ages 12 years and over, special procedures are outlined here for obtaining informed consent from minors’ guardians who are eligible for the CLEK Study. The minor must provide signed assent. All procedures to be performed and eye drops to be used in the CLEK Study are within the realm of ordinary clinical contact lens practice. Great care must be taken to explain the effects of the drops and testing procedures to both minors eligible for the Study and their parents. Particular benefit may accrue to minors enrolled in the Study since there is a tendency for keratoconus patients diagnosed in the second decade of life to progress faster.

Each CLEK Participating Clinic will meet its individual Institutional Review Board’s requirements on informed consent for minors.

4.4 Costs and Reimbursements to Patients

Keratoconus patients enrolled in the CLEK Study are not charged for Study-related examinations and tests and receive $20 reimbursement per Study visit. All other routine eye care, including contact lens services and materials and surgical care, is the responsibility of the patient, his or her doctor, and his or her insurance provider. If the procedure is part of the CLEK Study protocol (ie, contained on the CLEK Examination
Form), it is part of the Study-related care at that visit. If the procedure is not on the CLEK Examination Form or if it is a non-CLEK Study Visit, it constitutes non-Study related care.

4.5 Recruitment Publicity

Keratoconus patients who are regular patients of the CLEK Clinic are the best candidates for the CLEK Study. Each Clinician should inform the other clinicians at his or her site of the need to inform him or her of any keratoconus patient or keratoconus suspect examined in the Clinic so that they may be screened for potential inclusion in the study. This is best done by presentations to all clinicians and by written memorandum to all clinicians and clinic staff. Initially this should be done in writing weekly for one month and then monthly for the remaining 9 months of the enrollment period.

Other methods of patient recruitment include:

- Announcements of the CLEK Study at local, state, and national research and continuing education meetings. A slide presentation will be provided to each Clinic Principal and Co-Investigator for use in such presentations.

- Letters to colleagues requesting that they refer keratoconus patients to the Participating Clinic. These letters should be sent to every eye care practitioner in the Clinic’s area. Clinic Principal Investigators will be supplied with “CLEK Affiliate Doctors’ Certificates” to use in conjunction with their referring doctors. Referring doctors will receive CLEK Study patient newsletters.

- Review of medical records of keratoconus patients and recalling these patients for screening for possible inclusion in the CLEK Study. This should be done by telephone calls (two, if necessary), then with at least two recall letters, and finally another telephone call.

- Instructing Participating Clinic keratoconus patients and other Clinic patients about the CLEK Study with the CLEK patient brochure or by letter.

Recruitment materials will be provided by the CLEK Executive Committee to the CLEK Participating Clinics. Use of other materials will require approval by the CLEK Executive Committee prior to their use.

4.6 Informing Other Clinics of Successful Recruitment Strategies

Each Participating Clinician will give a brief report of his or her Clinic’s recruitment strategies and his or her degree of success with those strategies at each
CLEK Study annual Study Group meeting. Additionally, there will be a monthly CLEK Study newsletter, “CLEK on Deck,” generated by the CLEK Study Chairman, that will serve as a forum for more frequent dissemination of successful recruitment campaigns and techniques.
4.7 Sample Informed Consent Form

A generic Informed Consent Form for use by the CLEK Clinics to obtain their institution’s Human Subjects approval follows.
Sample CLEK Study Consent Form

1. STUDY TITLE: Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study

2. PERFORMANCE SITE: ________________________________

3. INVESTIGATOR: ___________________ PHONE: ____________

4. PURPOSE OF THE STUDY

This is a multi-center research study to observe how keratoconus progresses and to identify any associations between vision and corneal changes that occur with this disorder. The Study is sponsored by the National Eye Institute, a division of the National Institutes of Health. Approximately 1,000 people are expected to enter the study nationwide.

5. STUDY PARTICIPANT INCLUSION CRITERIA

Persons may enter the Study if they are at least 12 years old, have a clinical diagnosis of keratoconus (as determined by an optometrist or ophthalmologist), and are able to complete at least 3 years of follow-up.

6. STUDY PARTICIPANT EXCLUSION CRITERIA

Persons are excluded from the study if they have had corneal transplants in both eyes, have significant cataracts, have certain disorders of the retina or optic nerve, or have had cataract surgery.

7. DESCRIPTION OF THE STUDY

Consecutive patients with keratoconus who satisfy the inclusion and exclusion criteria will be asked to participate in this study. Study participants will have an eye examination when they enter the study and yearly for eight years. Some Study participants will be asked to return for an additional eye examination two to six weeks after entering the Study. The eye examination includes testing of vision, checking the eyeglass prescription, measuring the curvature of the cornea, fitting contact lenses (for diagnostic purposes only), measuring the pressure in the eye, examining the front of the eye, and examining the back of the eye, which requires the pupil to be dilated. Photographs of the front of the eye will be done at each visit. Routine eye care will be done by the Study participant’s optometrist or ophthalmologist.

8. BENEFITS TO STUDY PARTICIPANTS

The benefit to Study participants is that they will receive at least four complete eye examinations using the most modern equipment and techniques. Although there is no guarantee, the results of the Study may benefit Study participants with regard to future management of keratoconus.
9. RISKS TO STUDY PARTICIPANTS

The risks to Study participants is the same as for any other patient with keratoconus: corneal swelling, corneal abrasion, corneal scarring, corneal thinning, corneal vascularization, decrease in contact lens comfort and wearing time, reduction in visual acuity, redness, and infection of the eye. There may be discomfort and tearing the Study participants during the fitting of contact lenses. Vision, especially near vision, will usually be blurred for several hours after the pupils have been dilated.

10. ALTERNATIVES TO PARTICIPATION IN THE STUDY

The alternative to participation in the Study is to not participate in the Study, and to have routine eye care by an optometrist and/or ophthalmologist.

11. STUDY PARTICIPANT REMOVAL

Study participants are strongly encouraged to return for scheduled eye examinations. Participants who do not return for scheduled eye examinations may be removed from the Study.

12. STUDY PARTICIPANT’S RIGHT TO REFUSE TO PARTICIPATE OR WITHDRAW

Study participants may refuse to participate or withdraw from the Study at anytime without jeopardizing, in any way, their medical treatment at this institution in the present or future. Should significant new findings develop during the course of the research that may relate to the Study participant’s willingness to continue participation, that information will be provided to the Study participant.

13. STUDY PARTICIPANT’S RIGHT TO PRIVACY

The results of the Study may be published, but the privacy of Study participants will be protected and they will not be identified in any way. All data from the Study will be maintained in confidentiality in two locations: (1) each Study participant’s medical record, and (2) a separate record of visits and photographs in which each Study participant is identified by a number code. All data files will be maintained and pooled data analyzed at a central Coordinating Center at Washington University in St. Louis, Missouri. At no time will the Coordinating Center know the identity of Study participants, since all information kept there will be by number code only. Study participants are asked to provide their name and address to the Study Chairman in order to receive reimbursement for Study visits and to receive Study newsletters. The Study Chairman will not be able to link the names of Study participants with their number code or Study data.

14. RELEASE OF INFORMATION

The medical records related to the Study are available to the National Eye Institute.
15. FINANCIAL INFORMATION

Participation in this Study will not result in any charges. All Study examinations and photography will be paid for by the Study. Study participants will receive $20 for each Study visit as reimbursement for transportation, child care, and other personal costs related to Study visits.

Regular eye care, including contact lens and/or surgical care, is not paid for by the Study, and is the responsibility of the Study participant and/or his/her insurance company. The costs of Study related and unforeseen complications must be met by the Study participant.

***********************************************************************
You have been given full opportunity to ask any questions you may have, and all your questions have been answered to your satisfaction. You have also been given the opportunity to consult with any person or persons outside ________ Clinic to obtain their opinions and recommendations.

You have carefully read and fully understand the above statements and hereby consent thereto.

You will be given a signed and dated copy of this form to keep.

Your signature, below, will indicate that you have decided to volunteer as a research subject and that you have read and understand the information provided above, and the bill of rights.

_________________________  Signature of Participant or Legal Representative

_________________________  Signature of Parent if Participant is < 18 Years Old

_________________________  Signature of Investigator
Chapter 5
Scheduling of Patient’s Visits, Tests, and Measures

5.1 Introduction

This chapter discusses: scheduling and timing of examinations, tests, and measures.

Table 5-1 illustrates the time windows for each visit. Forms needed for each type of CLEK Study Visit are listed in Table 5-2. All of the examinations, tests, and measures listed in Table 5-3 are conducted at each CLEK Study Visit.

5.2 Eligibility

The Clinician completes an Eligibility Form for ALL patients who are keratoconus suspects or previously diagnosed as having keratoconus.

If the patient is eligible, the Clinician explains the CLEK Study to the patient and requests informed consent or has the patient return after considering informed consent (Chapter 4, “Patient Education, Informed Consent, and Patient Recruitment”).

Table 5-1. Timing for visit scheduling.

<table>
<thead>
<tr>
<th>VISIT</th>
<th>TARGET DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>As soon as eligibility is determined and informed consent is obtained.</td>
</tr>
<tr>
<td>Annual Visit 1</td>
<td>12 months from Baseline date ± 1 month</td>
</tr>
<tr>
<td>Annual Visit 2</td>
<td>24 months from Baseline date ± 1 month</td>
</tr>
<tr>
<td>Annual Visit 3</td>
<td>36 months from Baseline date ± 1 month</td>
</tr>
<tr>
<td>Annual Visit 4</td>
<td>48 months from Baseline date ± 1 month</td>
</tr>
<tr>
<td>Annual Visit 5</td>
<td>60 months from Baseline date ± 1 month</td>
</tr>
<tr>
<td>Annual Visit 6</td>
<td>72 months from Baseline date ± 1 month</td>
</tr>
<tr>
<td>Annual Visit 7</td>
<td>84 months from Baseline date ± 1 month</td>
</tr>
<tr>
<td>Annual Visit 8</td>
<td>96 months from Baseline date ± 1 month</td>
</tr>
<tr>
<td>Repeat Visit</td>
<td>Within one month of a Baseline visit as instructed by the Coordinating Center</td>
</tr>
</tbody>
</table>

Note: The target dates are a goal. However, it is very important that enrolled CLEK Study patients be followed no matter what. Thus, longer intervals between visits are preferable to missed visits.
Table 5-2. Forms used at CLEK Study Visits.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Patient-Completed Forms</th>
<th>Investigator-Completed Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient Background</td>
<td>Patient History</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quality of Life</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eligibility</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Examination</td>
</tr>
<tr>
<td>Baseline</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Repeat</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Year 1</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Year 2</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Year 3</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Year 4</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Year 5</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Year 6</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Year 7</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Year 8</td>
<td>-</td>
<td>X</td>
</tr>
</tbody>
</table>

Table 5-3 Examinations, tests and measures.

<table>
<thead>
<tr>
<th>VISIT</th>
<th>TESTS AND MEASURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Quality of life</td>
</tr>
<tr>
<td>Annual Visits 1-8</td>
<td>History</td>
</tr>
<tr>
<td>Presurgical Visit</td>
<td>Visual acuity</td>
</tr>
<tr>
<td>Repeat Visit</td>
<td>In rigid contact lens wearers: current contact lens evaluation</td>
</tr>
<tr>
<td></td>
<td>Manifest refraction</td>
</tr>
<tr>
<td></td>
<td>Keratometry/corneal topography</td>
</tr>
<tr>
<td></td>
<td>Slit lamp examination</td>
</tr>
<tr>
<td></td>
<td>Corneal photography</td>
</tr>
<tr>
<td></td>
<td>Fluorescein photography of first apical clearance lens and trial lens 0.2 mm flatter than that</td>
</tr>
</tbody>
</table>

5.3 Scheduling

All scheduling of visits is performed by the Participating Clinic. Each visit after the Baseline Visit is scheduled one month ahead. The Clinic Coordinator telephones the patient to remind him/her of his/her appointment day and time one week before the appointment and then again one day before the appointment.

5.4 Baseline Examination

After evaluating eligibility and obtaining informed consent, the patient is requested to complete the Patient Background Form, the Quality of Life Form, and the Patient History Form. The Clinician and other Clinic personnel (as certified per Chapter 12 of this Operations Manual) complete the Examination Form.
Corneal and fluorescein photography are performed according to the protocols outlined in Chapters 10 and 11 of this Operations Manual, and the exposed film is mailed within 24 hours of exposure to:

CLEK Photography Reading Center  
c/o Dr. Joseph Barr  
The Ohio State University College of Optometry  
338 West Tenth Avenue  
Columbus, Ohio 43210  
(614) 292-9511  
FAX (614) 688-3285

Mailers are provided by the CLEK Photography Reading Center.

In all Clinics with TMS devices, corneal topography is performed, and floppy disks with stored video files are sent to:

CLEK Study Chairman’s Office  
c/o Dr. Karla Zadnik  
The Ohio State University  
College of Optometry  
338 West Tenth Avenue  
Columbus, OH 43210-1240  
(614) 292-6603  
Fax (614) 292-4705

In all Clinics without TMS devices, videokeratographic raw data are collected and stored on-site at the Participating Clinic.

5.5 Annual (Follow-up) Visits

Annual Visits are scheduled using the Baseline Visit date as the reference point, according to the schedule provided by the Coordinating Center. Three Annual Visits are scheduled at the end of year 1, year 2, and year 3, for a total of at least four measurement sessions per patient. The protocol for Annual Visits is identical to that for the Baseline Visit.

5.6 Repeat Visits

Ten patients per Participating Clinic are selected randomly by the Coordinating Center for repeat visits to evaluate the reproducibility of CLEK Study measurement techniques and protocols. Participating Clinics are notified by the Coordinating Center immediately following a patient’s Baseline Visit that the patient should return within 2
to 6 weeks for a Repeat Visit. Notification begins after the Clinic has enrolled its first 8 patients. The same protocol as the Baseline Visit’s protocol is followed for the Repeat Visit.

In the event a patient declines to return for a Repeat visit, the patient’s Repeat Visit forms are discarded, and the Coordinating Center is notified. The Coordinating Center then selects another patient for that Repeat Visit and notifies the Clinic.

The CLEK personnel performing Study measures at the Repeat Visit should not have access to the initial Baseline Visit data during the Repeat visit.

5.7 Non-CLEK Study Eye Care

All non-CLEK Study eye care, whether for keratoconus, related conditions, or non-related conditions will be the responsibility of the patient and his or her doctor. Usual and customary fees, reimbursement schedules, and insurance plans apply.

In the event a CLEK Study patient would ask to transfer his or her routine care to the CLEK Participating Clinic, the CLEK Principal Investigator should explain how this creates a potential conflict of interest. The patient can be given a list of alternate doctors that the CLEK Principal Investigator would recommend.

5.8 General Forms Procedures

The Clinic Coordinator reviews all forms for completeness prior to the patient’s departure and sees that the original forms are mailed to the Coordinating Center, preferably on the same workday but no more than 24 hours after the patient’s visit. A copy of all forms is retained in the Participating Clinic’s CLEK Study files for back-up purposes.

5.9 Retention of Patients

Birthday cards should be sent within one week of each patient’s birthday, and seasonal greeting cards should be sent to all patients as appropriate.

Patients should be telephoned 2-4 weeks in advance to schedule or confirm an appointment. A postcard should be sent one week in advance of the appointment. Patients should be telephoned one day before an appointment to confirm or to reschedule (if necessary).

If a patient misses an appointment, he or she should be telephoned the next day to reschedule the missed appointment. If telephone contact is not made with the patient
that day, a postcard should be sent immediately advising the patient to call and reschedule.

At the six-month point between visits, each patient should be telephoned to update the information on the CLEK Subject Tracking Form and to see how the patient is doing. This establishes an additional time of contact other than the Annual Visit.

A periodic review of the appointment book for the CLEK Study should be conducted. Special attention should be paid to no-shows, cancellations, and reschedules (both on the part of the patient and CLEK personnel) to determine if a pattern emerges that can be addressed.

Late Visit Forms are faxed to the Clinic two weeks after a patient’s Annual Visit anniversary date if the Coordinating Center does not have evidence that the patient has been seen. Late Visit Forms are completed by Clinic personnel and faxed to the Chairman’s Office.

Missed Visit Forms are faxed to the Chairman’s Office by the Coordinating Center six months after the Annual Visit anniversary date if the Coordinating Center does not have evidence that the patient has been seen. The Chairman’s Office transmits them via fax to the Clinics. They are completed and faxed back to the Coordinating Center.

Please get the patient in for an appointment whenever he or she is available, even if an appointment time outside the target or six-month windows is scheduled. A seen patient is not a lost-to-follow-up patient.

An internet search should be conducted by the clinic if access is available. If the patient is still considered “unable to locate,” the patient’s name and all available locator information should be forwarded to Jodi M. Malone, RN at the Chairman’s Office (malone.6@osu.edu) for a more thorough search. For patients who have missed at least their last two visits, Ms. Malone will conduct a search of the National Death Registry, too.

The Clinic Principal Investigator should call the patient if the patient is a “no-show” at least twice in a row. Also, the Clinic Principal Investigator should call the patient if the patient expresses interest in discontinuing the study.

The Chairman’s Office can call and/or write any patient anytime as the Clinic sees fit. Contact the Study Chairman, Karla Zadnik, OD PhD at zadnik.4@osu.edu to generate that contact.
Each patient receives a CLEK newsletter, *Insight*, annually. The newsletter is produced by the Chairman’s Office.

Patients receive a copy of all CLEK publications, except those reporting quality of life data.
The original forms are mailed to:

CLEK Study Coordinating Center  
c/o Dr. Mae Gordon  
Washington University Medical School  
Department of Ophthalmology & Visual Sciences  
Box 8203 660 S. Euclid Ave.  
St. Louis, MO 63110  
(314) 362-3716  
FAX (314) 747-1325

5.10 Missed Visits

To avoid missed visits, the Clinic Coordinator should make every attempt to see that the patient is scheduled early in the visit window as designated by the Coordinating Center, so that, if necessary, the patient can be rescheduled within the time of the visit window.

If any visit is missed the Clinic reschedules the patient for a visit as soon as possible. If the patient fails to make the appointed visit, the Study Coordinator calls the patient by telephone every one-half day for two days until the patient is rescheduled; if this fails, the Study Coordinator contacts the patient by mail. If the patient still does not respond, the Study Coordinator attempts to contact the patient at least once a week until contact is made.
Chapter 6
Vision Assessment

6.1 Measurement of Visual Acuity

High and low contrast visual acuity are measured by a member of the CLEK Participating Clinic personnel Study-certified for visual acuity. The procedure for measuring visual acuity was originally developed for the Early Treatment of Diabetic Retinopathy Study (ETDRS) using Bailey-Lovie high contrast visual acuity charts.

The Clinician and/or Technician is/are certified by the Chairman’s Office according to procedures outlined in Chapter 12 of this Operations Manual.

6.1.1 Introduction

Bailey-Lovie distance visual acuities are utilized during the course of the CLEK Study. All Bailey-Lovie visual acuity charts are supplied by the Chairman’s Office from the School of Optometry, University of California, Berkeley, CA. The chart is located at 4 meters, and the white background of the chart has a luminance as specified in Section 6.1.2 below.

At each Study Visit, visual acuity is measured in three ways in the following order: (1) High and low contrast Bailey-Lovie visual acuity with habitual correction, for each eye separately and both eyes together; (2) High and low contrast Bailey-Lovie visual acuity with best correction (for rigid contact lens wearers (including Softperm and piggyback wearers): contact lenses with optimal over-refraction, for non-rigid contact lens wearers: a CLEK Study Trial Lens Set contact lens with base curve equal to steep “K” plus optimal over-refraction), for each eye separately; and (3) High contrast Bailey-Lovie visual acuity with manifest refraction, for each eye separately.

Table 6-1 shows the sequence of visual acuity measurements and the chart to be used for each.
Table 6-1. Mandatory Sequence of Visual Acuity Testing for all CLEK Study Visits.

<table>
<thead>
<tr>
<th>Correction</th>
<th>Test</th>
<th>Eye</th>
<th>Chart Used</th>
<th>Type of Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habitual</td>
<td>High contrast</td>
<td>OD</td>
<td>HC-Chart 4</td>
<td>All</td>
</tr>
<tr>
<td>Habitual</td>
<td>High contrast</td>
<td>OS</td>
<td>HC-Chart 5</td>
<td>All</td>
</tr>
<tr>
<td>Habitual</td>
<td>High contrast</td>
<td>OU</td>
<td>HC-Chart 4</td>
<td>All</td>
</tr>
<tr>
<td>Habitual</td>
<td>Low contrast</td>
<td>OD</td>
<td>LC-Chart 7</td>
<td>All</td>
</tr>
<tr>
<td>Habitual</td>
<td>Low contrast</td>
<td>OS</td>
<td>LC-Chart 6</td>
<td>All</td>
</tr>
<tr>
<td>Habitual</td>
<td>Low contrast</td>
<td>OU</td>
<td>LC-Chart 7</td>
<td>All</td>
</tr>
<tr>
<td>Over correction</td>
<td>High contrast</td>
<td>OD</td>
<td>HC-Chart 5</td>
<td>All*</td>
</tr>
<tr>
<td>Over correction</td>
<td>High contrast</td>
<td>OS</td>
<td>HC-Chart 4</td>
<td>All*</td>
</tr>
<tr>
<td>Over correction</td>
<td>Low contrast</td>
<td>OD</td>
<td>LC-Chart 6</td>
<td>All*</td>
</tr>
<tr>
<td>Over correction</td>
<td>Low contrast</td>
<td>OS</td>
<td>LC-Chart 7</td>
<td>All*</td>
</tr>
<tr>
<td>Manifest refraction</td>
<td>High contrast</td>
<td>OD</td>
<td>HC-Chart 4</td>
<td>All</td>
</tr>
<tr>
<td>Manifest refraction</td>
<td>High contrast</td>
<td>OS</td>
<td>HC-Chart 2</td>
<td>All</td>
</tr>
</tbody>
</table>

*Over correction for contact lens-wearing patients is their habitual contact lenses plus sphero-cylindrical over-refraction results. Over correction for spectacle wearers is over the rigid contact lens from the CLEK Study Trial Lens Set with base curve equal to the steep keratometric reading.

6.1.2 Calibration of Chart Lighting

Light meters are provided by the CLEK Chairman’s Office.

The light meter is removed from the pouch. The M button is pressed, and the LCD display illuminates. The only other buttons needed are the horizontal FUNCTION arrows on the right. These move the square cursor along the settings at the top of the screen. The Cursor must be set to the EV icon (as it should be when your meter arrives).

To calibrate, the investigator should be positioned as close as possible to the letter charts without blocking the illumination falling on them. The M button should be pressed, and the two numbers on the bottom left should be inspected (“94” in Figure 6-1).

Figure 6-1. Light meter display.

<table>
<thead>
<tr>
<th>t f</th>
<th>EV</th>
<th>cal</th>
<th>ISO</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>EV</td>
<td>94</td>
<td>t' 125</td>
<td>s</td>
<td></td>
</tr>
</tbody>
</table>

This EV scale is arbitrary (ie, not in candela/m²), but it has been calibrated such that the target range is 96 to 102 EV. Too low and more light is needed. Too high and
less light is needed. This range applies to the whole useful area of the chart (the bottom corners are unimportant). Calibrating using the high contrast charts and testing in the four areas shown in Figure 6-2 is recommended.

**Figure 6-2. Areas for visual acuity chart lighting calibration.**

![Image of a visual acuity chart with letters indicating areas for lighting calibration]

EV numbers should be logged weekly and at each new set-up.

**Important:** The numbers 100 and 125 should always appear on the right of the display when in EV mode. If not, then the settings have been disturbed, most likely from interference with the vertical arrows on the right. These should never be pressed, and doing so will render your readings worthless. In this event, take the battery out of the meter, and wait 15 seconds and re-insert the battery. Then, the horizontal arrows should be set to move the square cursor to the EV setting.

The light meter turns itself off after use.

**6.1.3 Visual Acuity Technique**

For each of the testing conditions listed above in Table 6-1, the following protocol is completed. Start with high contrast visual acuity measurement in the right eye, followed by high contrast visual acuity measurement in the left eye. After high contrast visual acuity is completed, this same protocol is employed using the low contrast Bailey-Lovie charts.

Visual acuity testing begins at 4 meters for both the high and low contrast charts. The distance from the patient’s eye to the visual acuity chart must be exactly 4 meters. The patient may stand or sit for the testing. The Clinician or Technician should ensure that the patient’s head does not move forward or backward during the test so that the patient’s eyes remain at the set test distance.
The testing begins in the right eye with the left eye occluded carefully, and when needed, after refraction and placement of the proper lenses in the trial frame.

Instruct the patient to read each letter on the chart starting in the top left hand corner with the first line, line by line, letter by letter, from left to right.

Advise the patient to read slowly and to keep his or her head as still as possible. The pace should not be faster than about one letter per second, so as to achieve the best identification of each letter. Demonstrate the desired pace by reciting, “A, B, C.” If the patient at any point reads too quickly, s/he should be asked to stop, go back to the beginning of the line, and read more slowly.

S/he is not to go to the next letter until s/he has given a definite response. If the patient reads a number, s/he should be reminded that the chart contains no numbers and the Clinician or Technician should request a letter in lieu of a number.

When the patient says s/he cannot read a letter, s/he should be encouraged and required to guess. A maximum effort should be made to identify each letter. If a patient identifies a letter as one of two letters, s/he should be asked to choose one letter and, if necessary, to guess. You can suggest that the patient fixate eccentrically or turn or shake his or her head in any manner if this improves visual acuity. If the patient employs these maneuvers, care must be taken to ensure that the fellow eye remains covered and that the patient is not leaning forward. There are several reasons for encouraging patients to guess:

1. Patients’ statements that they cannot identify a letter are often unreliable.
2. The procedure helps to maximize patient effort.
3. It helps to assure uniformity of procedure.
4. It may help to prevent patient bias.

The Clinician or Technician uses the CLEK Visual Acuity Form to record the patient’s answers. Score each letter as right or wrong. Letters read correctly are marked with a “slash” through them. Letters read incorrectly are circled. If all the letters on a row are read correctly, draw a horizontal line through all the letters on that line, or slash through each of the 5 letters on that row. Record a perfectly read line by putting a checkmark or the number “5” in the right-hand column. (See example at the end of this chapter.)

If the patient is unable to read all 5 letters correctly on the top line of the chart at 4 m, the testing distance is decreased to 1 meter test and the above protocol is completed in the same manner. If the patient is unable to read any letters on the chart at 1 m, then vision is recorded as “count fingers” or “hand motion.” These designations are not used for recording low contrast acuity.
If the patient is able to read all 5 letters on the first line of the chart at 4 m, the testing continues to the next line with smaller letters. The patient continues reading down the chart to the last letter of each line, until the patient has missed 3 letters on a given line. The incorrect letters can occur at the beginning, middle or end of this line and do not have to be consecutive. Visual acuity testing for an eye stops when the patient has read the last letter of the line with 3 incorrect letters.

The Clinician or Technician tallies the total number of letters read correctly for each visual acuity measurement of each eye on the Visual Acuity Form and records this total in the visual acuity section of the CLEK Study Examination Form.

6.2 Measurement of Refractive Error

The measurement of refractive error for a keratoconus patient is difficult and tends to be highly variable. Reliability of an endpoint manifest refraction is similar to that of an amblyopic patient. Repeatability from visit to visit can be extremely poor. Refractive error and its progression are not primary or secondary outcome measurements in the study.

Retinoscopy without contact lenses is performed at all Study Visits, and the absence or presence of reflex distortion is noted. It also serves as a starting point for the manifest subjective refraction.

A sphero-cylinder manifest subjective refraction is performed at all Study Visits. The endpoint of this refraction is the maximum “plus” sphere which allows the patient to read the threshold visual acuity line.

The procedure to obtain the endpoint subjective refraction follows:

1. Open the projector aperture and project acuity lines from the visual acuity obtained by retinoscopy (at the bottom) to the largest line possible (at the top).

2. Occlude the eye not being tested and reduce room illumination to a moderate level.

3. Starting with the net retinoscopic value, add plus sphere or reduce minus sphere to fog the largest projected Snellen visual acuity line.

4. Unfog in 0.25 diopter steps to the patient’s best visual acuity (BVA). BVA is achieved by reducing fog until no further improvement (that is, greater readability or clarity) of the threshold letters is reported by the patient.
Additional minus may result in no change or a degradation of the clarity of these letters. When unfogging, monitor the patient's visual acuity with each addition of -0.25 diopter until best visual acuity is achieved. This is accomplished by having the patient read the smallest letters possible with each addition of -0.25 diopter.

(5) Place the Jackson Crossed-Cylinder (JCC) in the phoropter for the eye being tested. Isolate a line of letters 2 to 3 lines above threshold. Refine the cylinder axis found in retinoscopy to an endpoint — when the patient reports equality of visual acuity of the two JCC positions with the JCC axes 45 degrees on either side of the endpoint axis.

(6) Following refinement of the cylinder axis, refine the cylinder power. The endpoint for cylinder power refinement is the least minus cylinder for equality of the two JCC positions or 0.25 diopter cylinder less than the reversal power if equality is not obtained. Change the sphere component by 0.25 diopter of opposite sign for each 0.50 diopter cylinder change.

(7) Following cylinder testing, fog the eye by 0.75 diopter sphere and unfog in 0.25 diopter steps to the maximum plus sphere or least minus sphere which allows the patient to read the most letters possible on the threshold visual acuity line. Ask the patient to read the smallest line possible with each addition of -0.25 diopter sphere until the threshold acuity is achieved. If a +0.25 diopter sphere is added to the endpoint sphere, the patient will lose the ability to read some or all of the letters.

(8) Occlude the tested eye, and repeat procedures three through seven on the fellow eye.

(9) The refraction results are transferred to a trial frame for visual acuity testing. For spherical equivalents exceeding ± 5.00 D, a vertex distance for each eye behind the trial frame must be measured with a distometer and recorded.

If the sphere and/or cylinder value needed exceed that in the phoropter, the manifest refraction must be accomplished using a trial frame.

6.3 Alternative Refraction Technique

If the patient’s manifest refraction visual acuity is compromised to an extent where he or she does not respond to small changes in lens power, a determination of what interval of lenses (the Just Noticeable Difference or “JND”) to use should be made.
(1) Table 6-1 shows JND powers based on best corrected visual acuity from retinoscopy.

(2) The values for the JND in Table 6-1 are suggested starting points. If the patient responds quickly and/or easily to the starting JND power, then use the next lower JND power. If the patient does not respond to the JND power, then use the next higher JND power in routine subjective refraction as described above in Section 6.2.

(3) Example:
Retinoscopy –4.00 = –4.00 X 130 20/400
JND power (from Table 6-1) ±2.00 D

Patient responds easily to ±2.00 D choices. Use the next lower JND power ±1.00 D.

(4) The cylinder refraction should be conducted using a hand-held Jackson cross cylinder (JCC) of a magnitude approximately equal to the JND value. If the acuity is between 20/50 and 20/100, use ±0.50 D JCC; if it is between 20/120 and 20/160, use a ±0.75 JCC; and if it is worse than 20/160, use a ±1.00 D JCC. Proceed with the cylinder refraction as you would with a normally sighted patient. If a significant change of cylinder power and/or axis occurs, recheck the sphere. Remember to maintain the equivalent sphere when changing cylinder power.

Note: Occasionally, it is useful for some patients to determine the best axis subjectively by allowing them to manually turn the axis of the cylinder in the phoropter or trial frame. Visual acuities need to be monitored with any changes in lens power to insure better performance and to act as a guide to the proper amount of power for the JND spheres and cylinders.

Table 6-1. Acuity after retinoscopy and power of the just noticeable difference lens for subjective refraction.

<table>
<thead>
<tr>
<th>Visual acuity after retinoscopy</th>
<th>JND power</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/20 to 20/40</td>
<td>±0.25 D</td>
</tr>
<tr>
<td>20/40 to 20/100</td>
<td>±0.50 D</td>
</tr>
<tr>
<td>20/100 to 20/200</td>
<td>±1.00 D</td>
</tr>
<tr>
<td>20/200 to 20/400</td>
<td>±2.00 D</td>
</tr>
<tr>
<td>Worse than 20/400</td>
<td>±3.00 D</td>
</tr>
</tbody>
</table>

6.4 Measurement of Over-Refraction
At each Study Visit a sphero-cylindrical over-refraction is performed on all CLEK Study patients who wear contact lenses. The over-refraction procedure is exactly the same as in Sections 6.2 or 6.3 above. If the over-refraction is plano, it is recorded on the CLEK Examination Form as 00.00. Plano trial lenses (or +0.12 D and –0.12 D) are inserted into the trial frame, and visual acuity is measured according to protocol.

In non-rigid contact lens wearing CLEK Study patients, a sphero-cylindrical over-refraction is also performed (Sections 6.2 and 6.3 above). This sphero-cylindrical over-refraction must be over a contact lens from the CLEK Study Trial Lens Set equal in base curve to the steep keratometric meridian. If a referring corneal surgeon requests that no rigid contact lenses be placed on a grafted eye, that request must be honored. However, it is optimal to perform all required CLEK Study procedures on all eyes of all patients.

For non-rigid contact lens wearers only, keratometry is performed to select the appropriate contact lens (with base curve equal to the steep keratometric reading) for over-refraction and best-corrected visual acuity measurement.

Note: The lens used for the steep keratometry/visual acuity measurement is also the first lens used in the First Definite Apical Clearance Lens protocol (Chapter 9), and its central and peripheral fluorescein patterns can be assessed at the same time.
Chapter 7
Slit Lamp Examination, Fundus Examination, and Tonometry

7.1 Slit Lamp Examination

All corneal slit lamp examinations are performed with the designated CLEK Study slit lamp in each Participating Clinic. These slit lamps are kept covered when not in use. The eyepieces should be checked for cleanliness prior to every examination and cleaned as needed. The slit lamp chin rest and head rest are cleaned with an alcohol swab prior to each examination. The patient is positioned to be comfortable in the chin rest and at the proper height.

Results from the slit lamp examination at each visit are recorded on the CLEK Examination Form as described in Chapter 17 of this Operations Manual.

7.2 Slit Lamp Examination Procedure

The following procedure should be performed on the right eye first and then on the left eye.

(1) Set the slit lamp at 3/4 maximum illumination. Using 10X* magnification and a diffuse, wide open illumination beam, scan the eyelids and lashes for signs of inflammation.

(2) Scan the inferior palpebral and bulbar conjunctiva.

(3) Evert the upper eyelid and scan the superior tarsal conjunctiva at 7-10X* magnification.

(4) Release the upper eyelid and scan the superior, nasal, and temporal bulbar conjunctiva.

(5) At 16X* or greater magnification use a wide open, diffuse beam to observe the entire cornea for signs of opacification.

(6) Observe the limbus at higher magnification using an approximately 3 mm wide parallelepiped (16X*).

(7) Use an approximately 3 mm wide parallelepiped at 16X* or greater magnification to scan the cornea. Set the biomicroscope lamp arm on the patient's temporal side. Scan the inferior half of the cornea from the temporal side to the nasal side. Swing the lamp arm to the nasal side and reverse the
scan, nasal to temporal. Repeat this procedure for the superior half of the cornea. Scan for signs of scarring, Vogt's striae, and/or Fleischer's ring.

(8) Observe the anterior chamber, iris, and crystalline lens.

(9) Place an approximately 2 mm wide parallelepiped at the limbus and observe the cornea with the naked eye outside the microscope using sclerotic scatter for signs of edema or opacification.

(10) Instill fluorescein and using 16X* magnification, a wide open slit beam, a cobalt filter over the light source, and a yellow (Tiffen or equivalent) filter over the slit lamp objectives, observe for staining.

(11) Complete the slit lamp portion of the CLEK Examination Form, including the Scarring and Staining Form for each eye separately.

(12) At the end of the slit lamp examination, dilating drops are instilled. Instill one drop each of 1% tropicamide and 2.5% phenylephrine in each eye. If the patient has an iris clip intraocular lens or occludable anterior chamber angles, dilation is contraindicated. All other patients should be dilated, since the oblique corneal photographs are not readable in the absence of pupillary dilation.

*If using a slit lamp with limited magnifications, use the nearest magnification to the magnification listed.

Note: If certain critical corneal findings (eg, Vogt’s striae or Fleischer’s ring) can only be seen with higher magnification than those specified above, the observations at higher magnifications can be used to satisfy the eligibility criteria.

7.3 Corneal Scarring

Corneal scarring is defined as a permanent corneal opacity which is white with direct illumination and not attributable to corneal edema, corneal staining, or corneal haze. Corneal scarring from keratoconus may be superficial (anterior lamina) and round, linear or stellate-or-it may be deeper (stromal) and stellate, linear or round. For the purposes of the CLEK Study, the density of the scar is graded on a 0 to 4 scale to be more fully defined as the Study progresses.

Corneal scarring has been operationally defined for the CLEK Study based on extensive pilot studies described in detail in the CLEK Photography Reading Center Operations Manual. These pilot studies were conducted by ophthalmologic and optometric corneal experts. The scars of concern are circular, linear, or stellate areas
with loss of transparency in the central cornea. They are usually less dense than either of the corneal light reflexes, overlie Vogt’s striae, and can be either singular or multiple.

The corneal scarring density grading scale is as follows:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Just noticeable</td>
</tr>
<tr>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>Easily noticeable</td>
</tr>
<tr>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>3.0</td>
<td>Dense</td>
</tr>
<tr>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>4.0</td>
<td>Opaque</td>
</tr>
</tbody>
</table>

The density of each scar is recorded on the CLEK Examination Form.

The host-graft interface of a corneal graft does not have to be documented as corneal scarring. However, any other scarring in the donor button of the corneal graft should be recorded on the CLEK Examination Form.

**7.4 Corneal Staining**

For the purposes of the CLEK Study, corneal staining is described during the slit lamp examination based on its shape and its density.

In terms of shape:

- Arc staining is typically caused by the posterior lens surface junctions or lens edge or deposits on the posterior surface.
- Punctate staining is synonymous with stipple staining.
- Foreign body staining is from debris behind the lens and is randomly located. It could also be caused by a chipped, cracked or broken lens.
- Coalesced staining is the coalescence of punctate staining into a patch, eg, coalesced staining from peripheral corneal staining, from “3 and 9 o’clock” staining, or from deposits on the posterior lens surface or from a raised epithelial lesion.
- A full thickness defect is an absence of epithelium in an area, ie, it must show stromal fluorescein absorption.

In terms of density of staining:

- Trace is just noticeable and requires no treatment.
- Mild is easily detected and requires no treatment.
- Moderate is easily visible and requires treatment.
- Severe involves pain and requires treatment.
7.5 **Funduscop y**

Each CLEK Study patient will undergo a dilated fundus examination in order to monitor ocular health. Minimum examination includes the following, to be recorded in the appropriate place on the CLEK Examination Form:
7.5.1 **Direct Ophthalmoscopy or Biomicroscopy with Condensing or Hruby Lens**

(1) Ocular media: Focus progressively back through ocular media, noting the location of any opacities as seen in retroillumination or slit lamp optic section.

(2) Optic nerve head: Grade the vertical cup-to-disk ratio.

(3) Macula: Inspect macular area and fovea.

7.5.2 **Binocular Indirect Ophthalmoscopy**

Use a 28 D or other appropriate condensing lens; recline patient if possible.

(1) Peripheral retina: Perform a 360° scan of the peripheral retina, out to the ora serrata.

(2) Paramacula: Obtain an overall binocular view of posterior pole, including disk, macula, and vascular arcades.

Media opacities or fundus abnormalities requiring attention should be referred back to the referring practitioner. In the unlikely event of an ocular emergency, a reasonable attempt should be made to contact referring doctor for disposition. If the referring doctor cannot be reached then patient should be referred directly for appropriate care.

7.6 **Tonometry**

The intraocular pressure is measured using a Goldmann applanation tonometer. The tonometer is calibrated every month.

7.6.1 **Technique**

The right eye is always tested first.

The single measurement is made as follows:

(1) The examiner adjusts the force on the tonometer dial to an initial setting corresponding to 10 mm Hg. The slit lamp magnification is set at 10X. The light source is positioned at an angle of approximately 45°, and the aperture is maximally opened. A cobalt blue filter is employed.
(2) After instillation of 0.5% proparacaine, a fluorescein paper strip is placed near the lateral canthus in the lower conjunctival sac. Once the lacrimal fluid is sufficiently colored, the paper strip is removed. Alternatively, one drop of premixed fluorescein and anesthetic (Fluress, Barnes Hind) may be instilled. The examiner should use the same technique each time, be it a paper strip or a pre-mixed eyedrop.

(3) The patient and slit lamp are adjusted so that the patient’s head is firmly positioned on the chin rest and against the forehead rest without leaning forward or straining. Tight-fitting neckwear is loosened. The patient is asked to look straight ahead at a distant object or fixation target. If it is necessary to hold the eyelids open, the examiner holds the eyelids against the orbit rim, taking care not to apply any pressure to the globe. The patient is cautioned not to hold his breath.

(4) The examiner looks through the slit lamp and gently brings the tip of the prism into contact with the center of the cornea. The mires are well-focused, centered horizontally, and positioned vertically so that they are of equal circumference above and below the horizontal dividing line. If the mires are narrower than approximately 1/10 their diameter, additional fluorescein is instilled.

(5) The examiner adjusts the measuring drum until the inner borders of the two mires just touch each other or, if pulsation is present, until the mires separate a given distance during systole and overlap the same distance during diastole.

(6) The examiner removes the tip from the cornea and records the reading on the dial, rounded to the next highest integer. If, for example, the measurement indicated is between 16 and 17, 17 is recorded as the measurement.

(7) If corneal astigmatism is greater than 3.0 D, the prism is rotated so that the red line corresponds to the orientation of the longer axis of the elliptical applanated area.

Steps 1-7 above are repeated on the left eye.

7.6.2 Alternative Tonometry Technique

If Goldmann applanation tonometry cannot be performed, another tonometer is used and so noted on the CLEK Examination Form.
Chapter 8
Corneal Curvature and Topography

8.1 Introduction

Corneal curvature and topography are measured primarily by central keratometry according to the protocol that follows. CLEK Participating Clinics who have Tomey Technologies’ TMS videokeratographic devices perform videokeratography according to the protocol outlined below. Clinics without TMS devices that have other videokeratographic devices should store at least one video image from each eye on site at the Participating Clinic. Disks for corneal topography data storage are supplied to these designated Clinics after they have been certified for this procedure. Disks are returned to the Chairman’s Office for storage and future data analysis only from Participating Clinics with TMS devices.

8.2 Keratometry

Keratometry is a long accepted method of measuring central corneal curvature. Although its reliability is well described, its usefulness in measuring keratoconic corneas is unclear. It has been chosen as the primary measure of corneal curvature for the CLEK Study because of the availability of keratometers across Participating Clinics, the ease with which keratometry can be performed, and the inadequacy of more modern devices for assessment of irregular corneas.

8.2.1 Eyepiece Focusing

The keratometer eyepiece is focused prior to each use as follows:

(1) Hold a white card at the front of the instrument housing of the keratometer or use the white occluder if present on the instrument. The purpose of using the white background is to allow greater ease in viewing the black eyepiece reticule (black cross).

(2) The eyepiece is turned all the way counterclockwise into most plus power.

(3) Both eyes are kept open as the Clinician looks into the eyepiece to decrease accommodation. The eyepiece is then slowly rotated clockwise until the black cross first clears.

8.2.2 Calibration

The following protocol is used for calibrating the keratometer on a weekly basis by the Clinician or the Back-up Clinician. Calibration results should be logged in the Clinic.
(1) Attach the steel ball holder (Lensco-meter) to the upright support of the forehead rest, at approximately the canthus mark, if present. Angle the steel ball holder toward the barrel of the instrument so that the steel calibration ball is approximately at the plane that the eye would be during routine keratometry.

(2) Take a reading from each steel ball (40.50 D, 42.50 D, and 44.75 D) in both the vertical and horizontal meridians.

(3) If the keratometer is more than 0.25 D out of calibration, recalibrate the keratometer by adjusting the measuring wheels. This is accomplished by loosening the two set screws and rotating the wheels into the appropriate positions.

8.2.3 Keratometry Measurement Procedure

Keratometry is performed at each CLEK Study Visit as follows:

(1) Ask the patient to place his/her chin in the chin rest and forehead against the headrest.

(2) With the keratometer in the straight ahead position, sight down the outside of the instrument and adjust the instrument vertically until the leveling sight is aligned with the patient’s temporal canthus.

(3) Occlude the eye not being tested. Release the knob for locking the instrument and rotate the instrument until it points directly at the eye to be tested. Instruct the patient to look into the instrument where he/she may see a reflection of his/her own eye.

(4) Adjust the focus of the instrument until the image of the mires is clear.

(5) Make fine vertical and horizontal adjustments necessary to place the reticule cross near the center of the lower right mire image.

(6) Rotate the instrument (to locate the horizontal or near horizontal principal meridian) until the horizontal bars of the two crosses to the left of the focusing mire are aligned. Maintain clarity of the image during this step by continual refinement of the focus.

(7) Turn the horizontal measuring knob (on the left of the instrument) until these two crosses are superimposed.
(8) The orientation of the keratometer drum may have to be changed to align the mires for the vertical meridian. This represents irregular astigmatism, i.e., the two principal meridians are not oriented exactly 90° apart, and they should be recorded as they appear on the keratometer.

(9) Direct your attention to the two horizontal lines above the focusing mire and turn the vertical measuring knob (on the right of the instrument) until these lines are superimposed.

(10) Record the dioptric value of the flatter and steeper curvatures to the nearest 0.12 D, and the meridians of each curvature as indicated on the instrument scale.

(11) Move the vertical and horizontal measuring knobs away from the final measurement, and repeat steps 7-9 on the right eye and record a second set of keratometric readings.

(12) Repeat procedure steps 1 through 10 for the left eye.

8.2.4 Extending the Keratometer’s Range

If the patient’s cornea is steeper than 52.00 D (i.e., off the scale) in either meridian, the range of the keratometer will need to be extended as follows:

(1) Insert the supplied +1.25 D lens to the keratometer target (objective side).

(2) Table 8-1 should be consulted to convert the readings with the +1.25 D lens in place to actual readings.

(3) If the patient’s cornea is off the scale of the keratometer in either meridian with the +1.25 D lens in place, steps 1-2 above should be repeated with the +2.25 D lens in place, consulting Table 8-2 for the conversion of the drum reading to the actual reading.

(4) If the patient’s cornea is off the scale of the keratometer in either meridian with the +2.25 D lens in place, record the keratometric meridian in that meridian as “> 68.30,” inserting the “>” sign just to the left of the keratometry reading boxes on the CLEK Examination Form.
Table 8-1. Extending the range of the keratometer with a +1.25 D lens.

<table>
<thead>
<tr>
<th>Drum reading</th>
<th>Corneal power in diopters</th>
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</thead>
<tbody>
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</table>
Table 8-2. Extending the range of the keratometer with a +2.25 D lens.

<table>
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<th>Drum reading</th>
<th>Corneal power in diopters</th>
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### Chapter 8 Corneal Curvature and Topography

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#### 8.3 Videokeratography

All CLEK Participating Clinics are required to collect videokeratographic data for CLEK Study purposes. Tomey Technologies’ TMS device is the device of choice. Each Participating Clinic will use the TMS (or use the device that Clinic has) to store videokeratographic images from each CLEK Study Visit. Only TMS data are sent to the Chairman’s Office.

#### 8.4 TMS-1

**8.4.1 TMS-1 Calibration Verification**

Calibration of the TMS is performed weekly throughout the course of the CLEK Study. The calibration verification procedure follows:

1. Use a Computed Anatomy 43.00 D steel ball standard.
(2) Choose Option 8 from the Utilities Submenu. The label on the back of the standard housing identifies it as either an A or B Cone standard and gives the power of the standard in diopters. Enter this power, including the decimal. Press the joystick button. Hold the ball standard against the front face of the cone so that the standard housing fits snugly and evenly with the cone edge. Holding the standard in place, check for damage or contamination of the standard surface by watching the image on the live video monitor. The image should be sharp and free from defect.

(3) Take one picture and process it as per the standard procedure.

(4) The ring processing screen will appear with a “43.xx diopter” in the patient name field. The horizontal/vertical alignment error is reported, and the ring information displays the average value of the standard.

(5) If the TMS is properly calibrated, the message “OK, Value=43.xx” is displayed. If the message “No Good” flashes, you should:
   • Make sure the cone is seated properly.
   • Make sure that the cone is properly identified in the set-up routine.
   • Check the standard for scratches or dirt.
   • Take another picture and confirm that the horizontal/vertical alignment error is minimal.

8.4.2 TMS-1 Topography Protocol

The TMS-1 (Tomey Technologies) is used to obtain corneal topography data at all Clinics equipped with a unit. Clinics without a TMS-1 will use whatever videokeratographic device they have. Two diskettes are needed per patient visit, and each is labeled with a stick-on diskette label bearing the patient’s CLEK Study identification number (eg, C1-00099-JS), the date, and the eye (OD or OS).

The Clinician, Technician, or Photographer enters the patient’s complete CLEK ID number (eg, C1-10459-JS), and the eye on the TMS-1’s history screen.

The measurement procedure is as follows:

(1) Position the patient with his/her chin resting comfortably on the chin rest and forehead resting against the forehead rest.

(2) Adjust the chin rest up or down so that the patient’s eyes align with the red mark on the chin rest shaft.

(3) Ask the patient to turn his/her head slightly to the side opposite the eye being examined to get a clear path with the patient’s nose out of the way.
(4) Press the joystick button to turn on the laser rangefinder and the keratoscope lamp. The fixation light will blink and the black-and-white alignment monitor will show a live picture with a cross-hair target.

(5) Ask the patient to try to keep absolutely still and to fixate the blinking light in the center of the rings.

(6) Ask the patient to blink a few times to lubricate the eye and make it more reflective, and then to open both eyes as wide as possible.

(7) If the cone touches the patient’s brow, raise the instrument by raising its table, or lower the patient’s chair. This will tilt the patient’s head back, and his/her forehead will no longer touch the rest.

(8) Using the joystick, move the instrument head left, right, up, or down, until the blinking light is centered on the cross-hair.

(9) Use the joystick to move the instrument head forward or backward until the two laser beams converge on the cross-hair target.

(10) When the blinking fixation light and the laser beams are all centered in crosshair, press the joystick to take the picture.

(11) The “Ready” message on the computer screen shows that the system is ready to take another picture.

(12) Check photograph quality before proceeding. Good patient photographs are well focused, with complete, or nearly complete, exposure of the cornea.

(13) Take four photographs of each eye of each patient.

(14) After four pictures have been taken, access the File Transfer Menu from the System Menu by pressing “f” and then <enter>. The command “cv” is used to copy the right eye’s video files to the floppy disk.

(15) A write protect label is applied to the notch on the diskette.

(16) Steps 1 through 15 of this protocol are repeated for the left eye.
Both diskettes are mailed to the:  
CLEK Topography Reading Center (CTRC)  
c/o Dr. Timothy T. McMahon  
Department of Ophthalmology and Visual Sciences  
University of Illinois at Chicago  
Suite 3.164 (M/C 648)  
1855 W. Taylor St.  
Chicago, IL 60612  
(312) 996-5410  
Fax (312) 996-4908  
timmcm@uic.edu

### 8.4.3 Central Processing of TMS Topographic Data

Once the CTRC has received the two diskettes for the patient (per Study Visit), the CTRC Research Assistant performs the following quality control procedure to assure that the stored data are usable.

1. Verify that the diskette is labeled with the patient’s id#, the date of testing, the Clinic ID # (eg, C1), and the eye (OD or OS).
2. Insert diskette into TMS computer floppy drive.
3. Type `dir a:` to display the files on the diskette. Verify that the exam number on the label corresponds to the files listed in the directory.
4. Diskettes will be stored in customized drawers for this purpose in the CTRC.
5. As batches of TMS diskettes are processed as above at the CTRC, tables showing the patient’s CLEK Study identification number, the eye, and the status of the data (eg, “ok,” data missing, diskette mislabeled, etc.) are faxed to the individual Participating Clinics with TMS devices. Once the Clinic knows that the CTRC has received the data appropriately, the Clinic may delete or store that patient’s TMS data as they choose.

Periodically, all TMS data are backed up at the CTRC on Bernoulli cartridges.

The TMS data received by the CTRC are compared monthly to patients enrolled, according to the Coordinating Center. Clinics are notified of missing TMS data by the CTRC and asked to resubmit those data.

### 8.5 EyeSys
The EyeSys system is an alternative means of collecting videokeratography data for clinics not equipped with a TMS unit. It is currently utilized at the University of Illinois-Chicago, Northeastern Eye Institute, the University of Missouri-St Louis and Southern California College of Optometry. Data are stored at each site.

Various hardware and software configurations are being used by institutions with EyeSys instruments. Hardware may be either System 2000 or EyeSys Model 2 units. Software may vary from Windows ver. 2.11 W to Windows 95 System 2000 version 3.x. Protocols for Participating Clinic configuration variations are listed below. Follow the version appropriate for your institution.

**8.5.1 System 2000 Hardware and Software Version 3.x Protocol and Calibration**
(Northeastern Eye Institute, University of Missouri at St. Louis).

Perform this calibration protocol weekly:

1. From Main Menu, click System Utilities
2. Place calibration object on hole in center of chin rest, and raise the chin rest until you see a small hole in the stem.
3. Click on Calibration Button.
4. Click “Verify Calibration”.
5. Follow the instructions on the screen, and click “Continue”.
6. Align the 55.06 D calibration sphere, and press the acquisition button on the joystick.
7. The calibration “Verification Rings Located” screen should appear. Verify that red and yellow rings alternate.
8. If the rings look OK, click on “ACCEPT”.
9. Observe the color map. The values should be within 0.13 D (± 1 SD) over all points on the surface, if this occurs, then press “Done”, and the system does not need to be calibrated.
10. If the system is not within curvature values, proceed to calibration below:

To calibrate the instrument:
(1) Follow steps 1-3 above.

(2) Click on “Calibration”.

(3) Click “Continue”.

(4) Align the 55.06 D calibration sphere, and press the acquisition button.

(5) The system takes 15 minutes to automatically perform the calibration, no further operator attention is required.

(6) The system should be calibrated at the end of this process.

The examination protocol follows:

Patient confidentiality is maintained as follows: From the main menu select patient examination. If new, enter the patient’s full CLEK ID number into the “Patient Last Name,” “Patient First Name,” and “Patient ID #” fields.

The measurement procedure is as follows:

(1) Insert CLEK Syquest disk (or equivalent).

(2) From main menu select Patient Examination.

(3) Enter Operator’s Initials. Select OD and appropriate exam protocol button. (Note: EyeSys System 2000 has four exam protocol buttons. Select one that will automatically save the Eye Image and Exam Data. For additional information, see “Custom Exam Protocol Setup” below).

(4) Choose patient. (If new, enter the patient’s full CLEK ID number into the patient “Last Name,” “First Name,” and “Patient ID #” fields, and enter CLEK as the group. Once you have chosen the patient you are ready to capture an image.

(5) Position the patient with his or her chin resting comfortably on the chin rest and forehead on the forehead rest.

(6) Ask the patient to fixate the blinking green light inside the central ring using the eye being tested.
(7) Align and focus the instrument by placing the central reflected ring inside the square.

(8) While maintaining centration, focus by centering the green line within the center of the box.

(9) Ask the patient to blink and maintain fixation on the green light upon eye opening (as widely as possible).

(10) Upon eye opening and after verification of centration and focus, press the capture button on the top of the joystick.

(11) Verify position of corneal apex in relation to the small red box. If OK, press accept. If not aligned, press cancel, and repeat exam.

(12) Verify that the processed image has been digitized correctly. If OK, press accept. Edit (delete) points placed on the lid margin and/or limbal rings. DO NOT add points.

(13) Discard pupil placement.

(14) Upon viewing the displayed color map, press Done/Save.

(15) Verify that the data and Image is being saved. (The orange LED light on the Syquest drive is blinking).

(16) Repeat 2-15 once for OD and twice for OS.

(17) Upon completion of four exams, return to “Display Patient Data” from the main menu and verify that four exams (2 OD and 2 OS) have been saved.

(18) Backup database each time that you exit the EyeSys software.

To create a Custom Exam Protocol:

(1) From Main Menu, select “System Utilities”.

(2) Select System Settings.

(3) Select Custom Exam Protocol Design.

(4) Select New Protocol.
(5) Include:
Find or Add the patient.
Save Exam data.
Save eye Image.

(6) Name protocol (ie CLEK study or similar).

(7) From Patient Examination Screen Change one protocol button to the newly created protocol.

Changing patient names in the database (for confidentiality)

(1) Backup directory (insert CLEK Syquest disk, go to system utilities, patient directory file, and backup directory).

(2) Select system utilities.

(3) Select file management.

(4) Select patient information.

(5) Select patient you want to change.

(6) Select Edit Patient (BE CAREFUL!).

(7) In the separate fields for first and last name, the CLEK patient ID number should be entered into the “Last Name”, “First Name”, and “Patient ID #” fields.

(8) Save. (Note: if at any time you notice an error message select cancel or close, record the patient name, and proceed with the next patient. This should be an infrequent occurrence.)

(9) Continue steps 4-8 until all patients have been changed.

(10) Once completed, repeat #1 above to backup the directory.

8.5.2 Model 2 Hardware Calibration

Perform this calibration protocol weekly:

(1) From Main Menu, click System Utilities
(2) Place calibration object on hole in center of chin rest, and raise the chin rest until you see a small hole in the stem.

(3) Click on Calibration Button.

(4) Click “Verify Calibration”.

(5) Follow the instructions on the screen, and click “Continue”.

(6) Align the 55.06 D calibration sphere, and press the acquisition button on the joystick.

(7) The calibration “Verification Rings Located” screen should appear. Verify that red and yellow rings alternate.

(8) If the rings look OK, click on “ACCEPT”.

(9) Observe the color map. The values should be within 0.13 D (± 1 SD) over all points on the surface, if this occurs, then press “Done”, and the system does not need to be calibrated.

(10) If the system is not within curvature values, proceed to calibration below:

To calibrate the instrument:

(1) Follow steps 1-3 above.

(2) Click on “Calibration”.

(3) Click “Continue”.

(4) Align the 55.06 D calibration sphere, and press the acquisition button.

(5) The operator must manually focus each calibration sphere according to the instructions on the screen.

(6) The system should be calibrated at the end of this process.

8.5.3 Model 2 hardware and software version 3.x protocol (University of Illinois at Chicago).
Patient confidentiality is maintained as follows: From the main menu select patient examination. If new, enter the patient’s full CLEK ID number into the “Patient Last Name,” “Patient First Name,” and “Patient ID #” fields.

The measurement procedure is as follows:

(1) Insert CLEK Syquest disk (or equivalent).

(2) From main menu select Patient Examination.

(3) Enter Operator’s Initials. Select OD and appropriate exam protocol button. (Note: EyeSys System 2000 has four exam protocol buttons. Select one that will automatically save the Eye Image and Exam Data. For additional information, see “Custom Exam Protocol Setup” below).

(4) Choose patient. (If new, enter the patient’s full CLEK ID number into the patient “Last Name,” “First Name,” and “Patient ID #” fields, and enter CLEK as the group. Once you have chosen the patient you are ready to capture an image.

(5) Position the patient with his or her chin resting comfortably on the chin rest and forehead on the forehead rest.

(6) Ask the patient to fixate the blinking green light inside the central ring using the eye being tested.

(7) Align and focus the instrument by placing the central reflected ring inside the square.

(8) While maintaining centration and focus, adjust the joystick to bring the cross hairs into the center of the white circles located in the horizontal, peripheral regions of the image.

(9) Ask the patient to blink and maintain fixation on the green light upon eye opening (as widely as possible).

(10) Upon eye opening and after verification of centration and focus, press the enter key on the keyboard.

(11) Verify that processed image has been digitized correctly. If OK, press accept. Edit (delete) points placed on the lid margin and/or limbal rings. DO NOT add points.

(12) Discard pupil placement.
(13) Upon viewing the displayed color map, press Done/Save.

(14) Verify that the data and Image is being saved. (the orange LED light on the Syquest drive is blinking).

(15) Repeat 2-15 once for OD and Twice for OS.

(16) Upon completion of four exams, return to Display Patient Data from the main menu and verify that four exams (2 OD and 2 OS) have been saved.

(17) Backup database each time that you exit the EyeSys software.

To create a Custom Exam Protocol:

(1) From Main Menu, select “System Utilities”.

(2) Select System Settings.

(3) Select Custom Exam Protocol Design.

(4) Select New Protocol.

(5) Include:
Find or Add the patient.
Save Exam data.
Save eye Image.

(6) Name protocol (ie CLEK study or similar).

(7) From Patient Examination Screen Change one protocol button to the newly created protocol.

Changing patient names in the database (for confidentiality)

(1) Backup directory (insert CLEK Syquest disk, go to system utilities, patient directory file, and backup directory).

(2) Select system utilities.

(3) Select file management.

(4) Select patient information.
(5) Select patient you want to change.

(6) Select Edit Patient (BE CAREFUL!).

(7) In the separate fields for first and last name, the CLEK patient ID number should be entered into the “Last Name”, “First Name”, and “Patient ID #” fields.

(8) Save. (Note: if at any time you notice an error message select cancel or close, record the patient name, and proceed with the next patient. This should be an infrequent occurrence.)

(9) Continue steps 4-8 until all patients have been changed.

(10) Once completed, repeat #1 above to backup the directory.

8.5.4 Model 2 hardware and software version 2.11 protocol (Southern California College of Optometry).

Patient confidentiality is maintained as follows: From the main menu select patient examination. If new, enter the patient’s full CLEK ID number into the “Patient Last Name,” “Patient First Name,” and “Patient ID #” fields.

The measurement procedure is as follows:
(1) Insert CLEK Syquest disk (or equivalent).

(2) From the Capture Image Menu select Patient from the menu bar, then choose Capture OD Image.

(3) Position the patient with his or her chin resting comfortably on the chin rest and forehead on the forehead rest.

(4) Ask the patient to fixate the center of the middle ring.

(5) Align and focus the instrument by placing the central reflected ring inside the square.

(6) While maintaining centration and focus, adjust the joystick to bring the cross hairs into the center of the white circles located in the horizontal, peripheral regions of the image.

(7) Ask the patient to blink and maintain fixation at the center of the middle ring upon eye opening as wide as possible.
(8) Upon eye opening and after verification of centration and focus press the left mouse button or space bar on the keyboard or other “Capture” button designated for your instrument.

(9) Verify that processed image has been digitized correctly. If OK, press accept. Edit (delete) points placed on the lid margin and/or limbal rings. DO NOT add points.

(10) Discard pupil placement.

(11) Upon viewing the displayed color map, press Done/Save.

(12) Verify that the data and image are being saved. (The orange LED light on the Syquest drive is blinking.)

(13) Repeat 2-12 once for OD and Twice for OS.

(14) Upon completion of four exams return to Display Patient Data from the main menu and verify that four exams (2 OD and 2 OS) have been saved.

(15) Backup database each time that you exit the EyeSys software.

Changing Patient names in the database (for confidentiality)

(1) Backup directory (insert CLEK Syquest disk, go to system utilities, patient directory file, and backup directory).

(2) Select Patient from the menu bar.

(3) Choose Review System Patient from the patient menu.

(4) Select the patient from the patient directory.

(5) Click on Edit Patient in the patient selection screen. To edit existing information, you can click on the box with the information you want to edit and use the Insert and Delete keys to modify the text.

(6) In the separate fields for first and last name, the CLEK patient ID number should be entered into the “Last Name,” “First Name,” and “Patient ID” fields.

(7) Save. (Note: if at any time you notice an error message select cancel or close, record the patient name, and proceed with the next patient. This should be an infrequent occurrence.)
(8) Continue steps 2-7 until all patients have been changed.

(9) Once completed, repeat #1 above to backup the directory.

8.6 Visioptic EH-270 Topography

Perform quarterly:

8.6.1 Visioptic EH-270 Calibration Verification

(1) Install 22.37 or 22.38 steel ball into holder.

(2) Select “Patient” from main menu, then press enter.

(3) Press F1 to insert a new patient.

(4) Type “FIN” into last name field, then press enter.

(5) Type 22.37 or 22.38 into first name field, then press enter.

(6) Press F10 to save, then press enter.

(7) Confirm that left eye is highlighted, then press enter.

(8) Using the arrow keys, center crosshair in smallest ring of steel ball image.

(9) Use the page up and page down keys to sharply focus the image of the LED.

(10) Press C (center) then F(focus), and repeat until the focus is consistent. Note: Use manual focus for 22.37 or 22.38 steel ball

(11) Press enter to capture the image.

(12) Select analysis, then press enter.

(13) Select “1 DEG DETECTION”, then press enter.

(14) Center the green cross hair inside the smallest ring using the arrow keys, press enter. If there are some green or red dots inside the smallest ring: (1) select “adjust parameter”, then press enter; (2) Select “DETECTION THRESHOLD”, then press page up key to increase detection threshold to 55; (3) Press enter; and (4) repeat step 13 above.
(15) Verify that “SAVE AND CONTINUE” is highlighted, then press enter.

(16) Verify that “horizontal line” plot is displayed with no “spikes” or “waviness”, then press enter.

(17) Verify that the dioptic plot is automatically displayed. Note: The plot should be in tangential mode and standard scale. If sagittal is indicated, press (Alt) + F1 to change to tangential. If standard scale is not indicated, press (~) (tilda key) and select standard scale.

(18) Verify that Ks and Kf are within specification listed in Table 8-3.

(19) Press (Esc) twice.

(20) Repeat steps 1-19 for remaining steel balls. Note: If the steel ball image has bad detection lines, go to “adjust parameter”, then change detection threshold to 8 and radius variance to 0.6 by pressing the page down key.

(21) Is system does not meet specifications, contact your Alcon representative for calibration service.

Table 8-3.

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<thead>
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<tr>
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<td>±1.5D</td>
</tr>
<tr>
<td>85.04</td>
<td>±4.5D</td>
</tr>
</tbody>
</table>
8.6.2 **Visioptic EH-270 Protocol**

(1) From the MAIN MENU, select the PATIENT command, and press ENTER. Press F1 to enter the patient’s last and first name in the appropriate fields. Press F10 to permanently file this information.

(2) With the CURRENT PATIENT correctly identified, position the patient with his or her chin resting comfortably on the chin rest and forehead resting against the forehead rest. Adjust the chin rest up or down so that the patient’s eyes align with the LED markers on the side of the instrument.

(3) From the CURRENT PATIENT INFORMATION screen, highlight the word LEFT on the bottom.

(4) Ask the patient to try and keep still and to fixate the central ring. Ask the patient to blink a few times to lubricate the eye and make it more reflective, and then to open both eyes as wide as possible.

(5) Position the patient’s eye near the center of the screen, and adjust the focus by use of the keyboard controls. The LEFT and RIGHT arrow keys move the optical head horizontally, while the PgUp and PgDn keys move the optical head vertically. The UP and DOWN arrow keys move the optical head in and out to adjust focus.

(6) When the ring images are focused—automatically, if possible, otherwise manually—and the crosshair is close to the center, ask the patient to completely blink. Then ask the patient to open both eyes as widely as possible while fixating the fixation light, and press the ENTER key to capture an image.

(7) Verify image quality before proceeding to take a second image of the left eye. A good image has complete ring data, eyelids are open, and good corneal wettability as evidenced by smooth rings.

(8) Repeat steps 3 through 7 for the left eye.

(9) After all images have been obtained, select UTILITIES from the MAIN MENU. Select COPY IMAGE TO DISKETTE to transfer the images one at a time to a floppy diskette labelled with the patient’s CLEK ID number, eye (OD or OS), and date.

(10) Diskettes are stored on site.

8.7 **Humphrey Mastervue**
The Mastervue unit is an alternative means of collecting videokeratography data for clinics not equipped with a TMS unit. It is currently being utilized at the Nova Southeastern Participating Clinic. Data are stored on site.

8.7.1 Calibration Verification

Calibration of the Mastervue unit is performed weekly throughout the course of data collection for the CLEK Study.

The calibration procedure is as follows:

1. Place the frame of the calibration bar in the two holes located at the base of the chin rest.

2. Select Utilities from the Main Menu.

3. Select Run Calibration from the Utilities Submenu.

4. Position the projection head in front of the 35 D sphere.

5. Select OK.

6. Align the projection head by centering the cross hairs in the smallest ring of the image. Use the joystick to focus the image. Press the button on the joystick to capture the image. If the image capture is within an acceptable value, the word “passed” will be displayed on the screen; if not within an acceptable value, the word “over” or “under” will be displayed along with the actual diopteric value. To continue the calibration procedure, select Yes; to repeat the measurement of the 35 D sphere, select No.

7. Repeat the above procedure for the 42.25 D and 55 D spheres.

8. Final results will be displayed on the screen. Maintain a record documenting weekly calibration. If the machine is improperly calibrated, contact Humphrey Instruments Technical Support for assistance at 800-227-1508. If machine cannot be recalibrated properly prior to patient visit, continue with the examination protocol. Following the examination, complete a Feedback Report documenting the calibration results only if a calibration error occurred. Submit the Feedback Report with patient record and maintain copies in the Clinic patient record and Clinic calibration record.

8.7.2 Humphrey Mastervue Patient Confidentiality

Patient confidentiality is maintained as follows:
(1) Enter a letter identifying the clinic followed by the last two numerical digits of the patient ID in the screen labeled “patient last name”.

(2) Enter the last two letters of the patient ID in the screen labeled “patient first name”.

(3) Record the patient’s complete ID number on an adhesive diskette label with the addition of the eye, the examination type, and the date (month-day-year).

(4) Place the diskette label on the 3-inch floppy diskette.

Example of Mastervue Patient Information Screen: F45 (under Last Name)
Example of Diskette Label: BF106045-ZZ OD 01-01-97

8.7.3 Humphrey Mastervue Protocol

The measurement procedure is as follows:

(1) Clean the head and chin rest with alcohol and allow to air dry.

(2) Position the patient with his/her chin resting comfortably on the chin rest and forehead resting on the forehead rest.

(3) Adjust the chin rest up or down so that the patient’s eye aligns with the blinking red light.

(4) Ask the patient to fixate on the blinking red light in the center of the ring image.

(5) Using the joy stick, move the instrument head left, right, up, or down until the cross hairs are centered in the smallest ring of the live image. Use the joystick to move the instrument head forward or backward until the proper focus is achieved.

(6) Ask the patient to blink and then open the eye as wide as possible.

(7) Press the button on top of the joystick to capture the image.

(8) Instruct the patient to relax outside the instrument while processing the image. The screen will display “Processing” while it processes the captured image and will display “Storing” while it saves the captured image.

(9) When the live image reappears, re-focus and re-align using the joystick.

(10) Press the button on the joystick to capture another image.
(11) Four images may be captured by repeating the above procedure; when an image of sufficient quality is achieved, select “No More”.

(12) Select the best quality image by placing the cursor on the image and “clicking”. A full size view will be displayed. If the enlarged image is of satisfactory quality, select OK.

(13) Proceed to the other eye and repeat.

(14) Repeat the above procedure for a minimum of two pictures for each eye.

8.7.4 Humphrey Mastervue Data Storage

The data storage procedure is as follows:

(1) Images will be processed and saved on the hard drive utilizing the procedure above.

(2) Images should also be saved on 3-inch floppy diskettes by selecting Utilities from the Main Menu.

(3) Select Export/Import from the Utilities Submenu.

(4) Insert floppy diskette.

(5) Select Export from the Export/Import Submenu.

(6) Select the patient by placing the cursor on the patient’s name and “clicking”. After you have selected the patient, the exams will be displayed in the Associated Exams field. Export appropriate examinations by placing cursor on the exam files and “clicking”. Select OK when complete.

(7) Repeat for the other eye.

(8) If available, store an additional copy utilizing the above procedure with a ZIP drive. The floppy diskettes are stored with patient records in the Clinic Coordinator’s office. The ZIP disks are stored in the Clinic Principal Investigator’s Office.

NOTE: The software may have difficulty processing some keratoconic eyes. An error message will be displayed on the screen. The clinician is required to make a minimum of four attempts on each eye before proceeding. This difficulty of obtaining
data should be recorded on a log which is stored with the patient diskettes. A Feedback Report should be completed for the patient visit if data cannot be processed.
8.7.5 Processing of Mastervue Data

Processed data will be stored at the Participating Clinic as described above. The Clinic Principal Investigator will monitor the quality of data and complete Feedback Reports are needed. The CTRC will analyze the examination data.
Chapter 9
Assessment of Habitual Contact Lenses and First Definite Apical Clearance Lens (FDACL) Determination

9.1 Introduction

At each CLEK Study Visit, the Clinician will apply a series of CLEK Study trial lenses, beginning with the lens with base curve equal to the steep keratometric reading, until the first definite apical clearance fluorescein pattern is observed. This lens represents the flattest lens that shows apical clearance—our so-called First Definite Apical Clearance Lens or FDACL. This fluorescein pattern will be photographed, as will the lens that is 0.2 mm flatter than the first apical clearance lens. This measurement provides an estimate of corneal curvature as well as a measure of how flat or steep the patient’s current lenses are and better defines the current standard of rigid contact lens care in the CLEK Study sample.

The First Definite Apical Clearance Lens (FDACL) determination is made on all CLEK Study patients, even those who do not currently wear rigid contact lenses. FDACL is not required on eyes of CLEK Study eligible patients with corneal grafts. The FDACL protocol should be followed on the non-grafted eye of these patients.

It is desirable to obtain data summarizing how the eye care community optically manages its keratoconus patients. The most common method of managing keratoconus is to fit the patient with rigid gas permeable contact lenses. Although many approaches have been advocated in the literature, a standardized fitting method has not been universally utilized. Screening results from a CLEK pilot study indicate that 75% of keratoconus patients are wearing rigid contact lenses fitted flat or with apical touch. Although we know that the majority of keratoconus patients are currently being fitted flat, there are no data indicating the degree of apical touch. Also, there have been various suggestions in reports in the literature as to the potential relationship between certain fitting methods and corneal scarring. Therefore, to properly characterize the habitual contact lens treatment of CLEK Study patients an assessment of the degree of apical touch or apical clearance must be performed.

Data on habitual rigid lenses are obtained for all patients wearing rigid gas permeable contact lenses at the time they are enrolled into the CLEK Study and at each CLEK Study Visit. If the patient is fitted into rigid gas permeable contact lenses during the course of his or her participation in the study, these data are collected at every CLEK Study Visit after they are fitted. Enrolled CLEK Study patients who are not habitual rigid contact lens wearers, eg, spectacle-only or soft contact lens wearers, obviously are not assessed.
9.2 Protocol for Determination of the First Definite Apical Clearance Lens

The CLEK Study Trial Contact Lens Set is described in Table 9-1. To determine the First Definite Apical Clearance Lens for a given patient, the lens from the CLEK Study Trial Set with its base curve equal to the patient’s steeper keratometric reading is applied, and its fluorescein pattern is evaluated. In patients who do not wear rigid contact lenses, one drop of 0.5% proparacaine to provide corneal anesthesia during this procedure may facilitate it and the required fluorescein photography.

If the fluorescein pattern is flat (central touch), then the next steeper trial lens is applied. This procedure is repeated until a definite apical clearance pattern is achieved. Therefore, the endpoint of the trial contact lens procedure is to determine the flattest and first lens in the trial lens set that exhibits a definite apical clearance fluorescein pattern such that the sagittal depth of the base curve chord diameter is greater than the sagittal depth of the cornea for the same chord diameter. The base curve radius of this lens is the base curve radius of the “First Definite Apical Clearance Lens.”

If the fluorescein pattern of the lens with base curve equal to the steep keratometric reading is steep (central clearance), then the next flatter trial lens is applied. When the first definite touch pattern is seen, the next steeper trial lens is applied and photographed.

The clinician can utilize clinical judgment to determine the degree or amount of apical touch or clearance of a given lens in the FDACL series and use greater than 0.1 mm incremental changes to determine the First Definite Apical Clearance Lens. If so, it is imperative that the lens between FDACL and the 0.2 mm flatter than FDACL lens be applied to the patient’s eye, its fluorescein pattern analyzed, and its central and peripheral fitting relationships recorded on the CLEK Examination Form. The central and peripheral fitting relationships of the 0.2 mm flatter than FDACL lens must also be recorded on the Examination Form.

If the steepest lens in the CLEK Trial Contact Lens Set (5.00 mm base curve) still appears flat, that lens should be photographed on the eye according to the protocol below and noted on the Clinic Photographer’s Film Log before faxing it to the CPRC. Likewise, if the flattest lens in the CLEK Trial Lens Set (8.00 mm base curve) appears steep, it should be photographed on the eye according to the protocol below and noted on the Clinic Photographer’s Film Log before faxing it to the CPRC.

If the patient has an elevated apical scar (a so-called proud nebula), the FDACL lens should vault the surrounding cornea, not the elevated area.

The FDACL procedure is not performed on grafted eyes.

Once the First Definite Apical Clearance Lens is determined for each eye:
(1) Take two fluorescein pattern photographs of the First Definite Apical Clearance Lens on the right eye.

(2) Photograph the closed eyelid.

(3) Insert the lens 0.2 mm flatter than the First Definite Apical Clearance Lens on the right eye, allow it to settle on the eye, and then take two fluorescein pattern photographs. Verify that the central and peripheral relationships have been recorded on the Examination Form for the 0.2 mm flatter than FDACL lens.

(4) Photograph the nose in between the fluorescein photographs of the right and left eyes.

(5) Repeat steps 1, 2, and 3 for the left eye.

(6) Label and mail the exposed fluorescein film canister in the envelopes provided to the CLEK Photography Reading Center:

Dr. Joseph T. Barr  
CLEK Photography Reading Center Director  
The Ohio State University  
College of Optometry  
338 West Tenth Avenue  
Columbus, Ohio 43210  
(614) 292-9511  
FAX (614) 688-3285

After photography of the 0.2 mm flatter than FDACL lens, its central and peripheral fluorescein patterns must be evaluated and results recorded on the CLEK Examination Form.

CLEK Study trial lenses must be disinfected with hydrogen peroxide following each use or cleaned with Miraflow and thoroughly rinsed with RGP conditioning solution prior to storage. Trial lenses are stored dry.
### Table 9-1. CLEK Study Trial Contact Lens Set.

<table>
<thead>
<tr>
<th>BASE CURVE (D)</th>
<th>POWER</th>
<th>OAD/OZ</th>
<th>SCr</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.00(42.19)</td>
<td>8.6/6.5</td>
<td>9.00</td>
<td></td>
</tr>
<tr>
<td>7.90(42.72)</td>
<td>8.6/6.5</td>
<td>9.00</td>
<td></td>
</tr>
<tr>
<td>7.80(43.27)</td>
<td>8.6/6.5</td>
<td>9.00</td>
<td></td>
</tr>
<tr>
<td>7.70(43.83)</td>
<td>8.6/6.5</td>
<td>9.00</td>
<td></td>
</tr>
<tr>
<td>7.60(44.41)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>7.50(45.00)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>7.40(45.61)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>7.30(46.23)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>7.20(46.87)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>7.10(47.54)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>7.00(48.21)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>6.90(48.91)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>6.80(49.63)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>6.70(50.37)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>6.60(51.14)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>6.50(51.92)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>6.40(52.73)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>6.30(53.57)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>6.20(54.44)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>6.10(55.33)</td>
<td>8.6/6.5</td>
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<td></td>
</tr>
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<td>6.00(56.25)</td>
<td>8.6/6.5</td>
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<td></td>
</tr>
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<td>5.90(57.20)</td>
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<td></td>
</tr>
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<td>5.80(58.19)</td>
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<td></td>
</tr>
<tr>
<td>5.70(59.21)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>5.60(60.27)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>5.50(61.36)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>5.40(62.50)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>5.30(63.68)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>5.20(64.90)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>5.10(66.18)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>5.00(67.50)</td>
<td>8.6/6.5</td>
<td>8.50</td>
<td></td>
</tr>
</tbody>
</table>

All diagnostic contact lenses are PMMA with a third curve radius of 11.00 mm and a third curve width of 0.2 mm. On base curves from 5.00 to 7.60 mm, the secondary curve radius is 8.50 mm. On base curves from 7.70 through 8.00 mm, the secondary curve radius is 9.00 mm. The lenses are lightly blended and the center thickness is 0.15 mm.
Table 9-2. Tolerances of fabrication for CLEK Study Trial Lens Set

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base curve radius</td>
<td>0.05 mm without distortion or warpage</td>
</tr>
<tr>
<td>Power</td>
<td>0.25 D</td>
</tr>
<tr>
<td>Overall diameter</td>
<td>0.1 mm</td>
</tr>
<tr>
<td>Optic zone diameter</td>
<td>0.1 mm</td>
</tr>
<tr>
<td>Center thickness</td>
<td>0.02 mm</td>
</tr>
<tr>
<td>Surface quality</td>
<td>No surface quality degradation is accept</td>
</tr>
</tbody>
</table>

9.3 Verification of the CLEK Trial Contact Lens Set

It is important that CLEK Study trial lenses be verified throughout the Study to confirm parameter stability. It is also imperative that after every use, each lens is returned to its appropriate storage case. To monitor parameter stability and lens labeling, all trial lens base curves must be verified monthly for base curve radius, warpage, and correct storage. The CLEK Trial Contact Lens Verification Form is used to record these findings at each Participating Clinic. It is completed monthly and stored on-site.

The base curve radius can be verified using a radiuscope, keratometer, or handheld keratometer. Trial lens base curves should not be warped by more than 0.02 mm and should not be more than 0.05 mm from the targeted or labeled value (Table 9-2). If the base curve findings fall outside these targeted parameters, contact the Chairman’s office for a replacement lens.

The following protocol is used for verifying the order and parameter stability of the CLEK Study Trial Lens Set on a monthly basis by Clinic personnel certified for rigid contact lens verification.

1. Use a radiuscope, keratometer, or handheld keratometer to analyze the base curve radius of each lens in the CLEK Study Trial Lens Set every month. The measurement of other lens parameters is not required.

2. Record the base curve radius in millimeters in the column labeled Analyzed Base Curve Radius opposite the target or labeled value on the CLEK Trial Contact Lens Verification Form.

3. Any lens found in the wrong case should be transferred to the appropriate case.

4. Any lens analyzed as at least 0.06 mm different from the target measurement on the lens case should be replaced. Report the lens to be replaced to the Chairman’s Office.
(5) Any lens analyzed as warped by at least 0.03 mm should be replaced. Report the lens to be replaced to the Chairman’s Office.
9.4 Protocol for Habitual Contact Lens Fit Assessment

In rigid contact lens-wearing CLEK Study patients, the Clinician assesses the apical and peripheral fit of the patient’s habitual rigid gas permeable contact lenses. The Clinician enters these data onto the CLEK Examination Form. Fluorescein photographs are taken of the patient’s habitual contact lens fit, according to the Fluorescein Photography protocol detailed in Chapter 10 of this Operations Manual.

9.5 Lens Verification Protocol

Accurate analysis and verification of CLEK Study patients’ habitual contact lens parameters are important.

Table 9-3 lists the Study lens parameters to be verified and the instrumentation to be utilized. Data are recorded on the CLEK Examination Form.

Table 9-3. CLEK Study contact lens verification.

<table>
<thead>
<tr>
<th>Lens Parameter</th>
<th>Verification Instrument</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base curve</td>
<td>Radiuscope, keratometer, handheld keratometer</td>
</tr>
<tr>
<td>Lens power</td>
<td>Lensometer</td>
</tr>
<tr>
<td>Overall diameter</td>
<td>Hand-held 7X reticule</td>
</tr>
<tr>
<td>Optic zone diameter</td>
<td>Hand-held 7X reticule</td>
</tr>
<tr>
<td>Center thickness</td>
<td>Thickness gauge</td>
</tr>
</tbody>
</table>

9.6 Summary

The assessment of CLEK Study patients involving rigid contact lenses can be summarized as follows. Steps 1 and 2 are performed on rigid lens-wearing CLEK Study patients only. Steps 3-7 are performed on all CLEK Study patients.

1. Assess and photodocument the fluorescein patterns of the patient’s habitual rigid gas permeable contact lenses. Enter the assessment of central and peripheral fit on the CLEK Examination Form.

2. Completely analyze the patient’s habitual contact lenses and enter the parameters on the CLEK Examination Form. Parameters to be analyzed are base curve radius, contact lens power, overall diameter, optic zone diameter, and center thickness.

3. Follow the protocol in Section 9.2 of this Operations Manual to determine the First Definite Apical Clearance Lens.

4. Enter the labeled base curve radii of each diagnostic lens applied and record the apical relationship and peripheral clearance in the spaces provided on the CLEK Examination Form.
(5) Photodocument the fluorescein patterns for the First Definite Apical Clearance Lens and the trial lens 0.2 mm flatter than the First Definite Apical Clearance Lens.

(6) Enter the labeled base curve radii of the First Definite Apical Clearance Lens and the lens 0.2 mm flatter than FDACL in the boxes provided on the CLEK Examination Form.

(7) Label and mail the exposed film of the fluorescein photographs to the CLEK Photography Reading Center within 24 hours:

Dr. Joseph T. Barr  
CLEK Photography Reading Center Director  
The Ohio State University  
College of Optometry  
338 West Tenth Avenue  
Columbus, Ohio 43210  
(614) 292-9511  
FAX (614) 688-3285
Coordinating Center to Add Trial Lens Verification Log
Chapter 10
Photodocumentation of Fluorescein Pattern

10.1 Introduction

Fluorescein photography allows for objective verification of the habitual rigid contact lens fit for rigid contact lens wearing patients enrolled in the CLEK Study. At least one person at each Participating Clinic is trained and certified to perform fluorescein photography. Fluorescein photography is performed at all Study Visits and when directed by the CLEK Photography Reading Center or the Coordinating Center for rephotography as per the CLEK Photography Reading Center Operations Manual.

10.2 Fluorescein Photography Technique

The CLEK Photography Reading Center Coordinator provides, as needed, rolls of Kodak Ektachrome 100 ASA film to each CLEK Participating Clinic. It is advised that the film be placed in a cool, dry location.

The Clinic Photographer loads the film into the camera, and the Photographer turns on the Nikon FS-2 slit lamp and the Nikon FS-2 flash power source (or other photographic system used for certification).

The Clinic Photographer adheres to the following fluorescein photography protocol:

(1) Clean the slit lamp biomicroscope chin and head rests.

(2) Verify that the flash intensity is set at 5.

(3) Verify that the beam splitter is in.

(4) Verify that the magnification is set at 16X.

(5) Verify the background illuminator is off.

(6) Verify that the aperture is wide open.

(7) Verify that the cobalt filter is in place.

(8) Place the Wratten 12 or Tiffen 2 yellow filter in front of the slit lamp’s objective lenses.

(9) Assure the patient’s comfort and position in the slit lamp camera.
(10) Set the light tower angle at 30 degrees temporal, moving the illumination angle slightly to eliminate light reflexes.

(11) Set the light intensity to a tolerable level for the patient. Lowering the light intensity may be particularly helpful with extremely photophobic patients.

(12) Instill sodium fluorescein as follows:

- Wet the fluorescein strip with ReNu Multi-Purpose Disinfecting Solution.
- Apply a small amount of fluorescein by just touching the tip of the wetted fluorescein strip to the superior bulbar conjunctiva.
- Wait 30 to 60 seconds after fluorescein application to take the photograph.

(13) Photograph the fluorescein pattern as follows:

- Photograph fluorescein pattern less than 5 seconds after a blink, but not immediately following the blink.
- Take two photographs for each lens.
- Photograph the eyelid between FDACL and the lens 0.2 mm flatter than FDACL.
- Photograph the nose between the right eye and left eye photographs.
- It is important to photograph the fluorescein pattern when the lens is centered over the cone apex.

Each Clinic has an abbreviated version of this protocol in laminated form for display.

After the patient photographs have been taken, the Clinic Photographer labels the metal film canister with labels provided by the CPRC. Each label has a space for the type of visit, the site ID number, the patient’s ID number, the photographer’s certification initials, and the date the photographs were taken. A sample page of labels can be found at the end of this Chapter.

10.3 Film Utilization for CLEK Photography
36-exposure and 24-exposure canisters of Ektachrome 100 film for each patient are sent to each CLEK Participating Clinic by the CLEK Photography Reading Center. The film should be stored in a cool, dark, dry place.

The film canister (the Ektachrome metal canister, not the plastic container) should be labeled with the type of visit, the site ID number, the patient ID number, the date of photography, and the photographer certification number.

The 36-exposure roll is for fit/fluorescein pattern of the habitual rigid lens fit and for corneal parallelepiped photographs according to the protocol in Chapter 11 of this Operations Manual.

The 24-exposure roll is for the corneal oblique photographs, the First Definite Apical Clearance Lens photographs, and the lens 0.2 mm flatter than the First Definite Apical Clearance Lens photographs.

Note: If the patient blinks during photography and more photographs will be needed to complete the left eye’s corneal photography (ie, the 36-exposure roll has been used up before all the photographs have been taken), the beginning of the 24-exposure roll should be used. The First Definite Apical Clearance Lens photograph series then follows the oblique corneal photographs on the 24-exposure roll.

After removing the film from the camera, it is placed in a preaddressed, postage paid mailer provided by the CPRC. The Photographer or Study Coordinator completes the Clinic Photographer’s Film Log, which is faxed to the CPRC at (614) 688-3285. Any exceptions to the photography protocol (eg, no habitual fluorescein photographs because the patient does not wear contact lenses, no FDACL because one eye is grafted, etc.) are noted on the Clinic Photographer’s Film Log before faxing. The film in the mailer is mailed to the CPRC the same or the next working day.
Chairman’s Office to Add Fluorescein Photography Technique/Nikon FS-2

Chairman’s Office to Add Fluorescein Photography Technique/Nikon FS-3
Chapter 11
Photodocumentation of Corneal Scarring

11.1 Introduction

Corneal scarring is an important clinical outcome measure of the CLEK Study, and its assessment is a very important component of the Study. The cornea photography protocol must be followed precisely. At least one person is trained and certified at each CLEK Clinic to perform cornea photography.

11.2 Cornea Photography Schedule

Corneal photography is performed on each patient at each Study Visit and as requested by the CLEK Photography Reading Center and the Coordinating Center for rephotography (according to the CLEK Photography Reading Center Operations Manual).

11.3 Technique

Film is labeled as described in Section 10.2 of this CLEK Operations Manual.

The Clinic Photographer adheres to the following protocol to perform cornea photography (A copy of the protocol should be placed next to the Nikon FS-2 or other photo slit lamp used for certification photography.):

(1) Clean slit lamp head and chin rest.

(2) Focus the eyepieces, especially the right eyepiece reticle.

(3) Instill 1 drop OU of 1.0% tropicamide and 1 drop 2.5% phenylephrine.

(4) PARALLELEPIPED PHOTOGRAPHS:
   • NO filter or background illuminator in place
   • Maximum slit lamp intensity (may be lowered later to assure patient comfort while maintaining adequate intensity for good focusing).
   • Set flash intensity to 3.
   • Set beam size at 1 mm and at maximum height
   • Set background illuminator on medium.
   • Set microscope straight ahead and light tower to 45 degrees temporal
   • Set magnification to 30X.
   • Use right eyepiece to focus.
   • Assure patient comfort and position in slit lamp.
• Instruct patient to look at Cornea Photographer’s right earlobe.
• Place the right edge of the parallelepiped (Pp) in the center of the pupil.
• Center the eye in the field of view vertically
• Focus carefully on the tear film.
• Instruct the patient to open wide and take 2 photographs.
• Notice where the left edge of the first parallelepiped is, and place the right edge of the second parallelepiped at this point (Pp2 is 1 mm left of the Pp1).
• Tell the patient to close his or her eyes. Expose one frame.
• Take 2 photographs. NOTE: Sometimes on this photo, the corneal reflex (Purkinje image 1) is on top of the second parallelepiped; if this occurs, have the patient fixate slightly to the left (nasal) so that this tear reflection moves just to the left of the location of Pp2.
• Move the light tower to 45 degrees nasal to the microscope.
• Place the left edge of Pp3 in the center of the pupil and position the eye in the center of the field of view vertically
• Focus on the tear film and instruct the patient to open his or her eyes wide.
• Take 2 photographs of Pp3.
• Tell the patient to close his or her eyes. Expose one frame.
• Move the slit lamp 1 mm nasal and take 2 photos of Pp4.
• Photograph the bridge of the nose.
• Proceed to the left eye and follow the above procedure with the patient fixating the Cornea Photographer’s left earlobe.

4) OBLIQUE PHOTOGRAPHS (Obl T and Obl N).
• After full dilation of pupil, open the slit beam to full horizontal and vertical dimensions. (Note: topical corneal anesthetic can be instilled before the mydriatic drops, but it is not required.)
• Put the neutral density filter in place and move the background illuminator intensity to off.
• Change the flash intensity to 5 and the magnification to 25X.
• Place the light tower 50 degrees temporal.
• Position the patient for comfort.
• Focus on the central tear film and ask the patient to fixate the Cornea Photographer’s right earlobe and to open his or her eyes wide.
• Take 2 photographs.
• Move the light tower to 30 degrees nasal.
• Take 2 photographs.
• Photograph the bridge of the nose.
• Move to the left eye.
• Repeat the steps above for left eye with patient fixating the Cornea Photographer’s left earlobe.
NOTE: If patient blinks during any of the above photographs, retake that specific photograph. If you need extra film, use the 24-exposure roll used for the corneal oblique and First Definite Apical Clearance Lens photographs.
11.4 Handling of Film After Photography

The CLEK Clinic Cornea Photographer removes the film from the camera.

The same or the next working day, the CLEK Clinic mails the film to the CLEK Photography Reading Center Coordinator in the preaddressed, postage paid mailers provided by the CPRC:

Dr. Joseph T. Barr  
CLEK Photography Reading Center Director  
The Ohio State University  
College of Optometry  
338 West Tenth Avenue  
Columbus, Ohio 43210  
(614) 292-9511  
FAX (614) 688-3285

11.5 Film Utilization for CLEK Photography

36-exposure and 24-exposure canisters of Ektachrome 100 film will be sent to each CLEK Participating Clinic by the CLEK Photography Reading Center. The film should be stored in a cool, dark place.

The film canister (the Ektachrome metal canister, not the plastic container) should be labeled with labels provided by the CPRC. Each label will have a space for the type of visit code, the site ID number, the patient’s ID number, the photographer’s certification number and the date the photographs were taken.

The 36-exposure roll is for fit/fluorescein pattern of the habitual rigid lens fit and for corneal parallelepiped photographs according to the protocol in Chapter 11 of this Operations Manual.

The 24-exposure roll is for the corneal oblique photographs, the First Definite Apical Clearance Lens photograph, and the lens 0.2 mm flatter than the First Definite Apical Clearance Lens photographs.

Note: If the patient blinks during photography and more photographs will be needed to complete the left eye’s corneal photography (ie, the 36-exposure roll has been used up before all the photographs have been taken), the beginning of the 24-exposure roll should be used. The First Definite Apical Clearance Lens photograph series then follows the corneal oblique photographs on the 24-exposure roll.
Chairman’s Office to Add Sample Page of Film Labels

Chairman’s Office to Add Clinic Photographer’s Film Log

Chairman’s Office to Add Cornea Photography Technique/Nikon FS-2

Chairman’s Office to Add Cornea Photography Technique/Nikon FS-3
Chapter 12
Certification Procedures

12.1 Introduction

The purpose of certification requirements in the CLEK Study is to assure that procedures are being performed in accordance with the CLEK Study protocol in each Clinic. Certification is supervised by the Executive Committee and its designates.

The Executive Committee oversees certification, issues certification documents and reports any deviation from protocol to the Executive Committee.

Prior to enrolling any CLEK Study patients or collecting any CLEK Study data, each Clinic must have at least two individuals certified to perform each of the tasks listed below. The CLEK Executive Committee encourages both individuals to participate actively in examining CLEK Study patients, and in order to be re-certified each year, each individual must process at least 10 CLEK Study patients in a calendar year.

The key CLEK Study tasks requiring certification are:

- Visual acuity
- Refraction
- Keratometry
- Videokeratography
- Slit lamp evaluation
- Corneal photography
- First definite apical clearance lens (FDACL), contact lens fit assessment, and fluorescein photography
- Study coordination
- Contact lens verification

CLEK Photography Reading Center certification procedures are described in Chapter 14.

In order to maximize stability of CLEK Participating Clinic personnel and to enhance data quality, trainees at Participating Clinics (eg, optometry students, optometry and ophthalmology residents, optometry and ophthalmology fellows) cannot be certified as CLEK Participating Clinic personnel. Exceptions must be approved by the Study Chairman.
Each CLEK Study certified task has two levels of certification (granted by members of the Executive Committee or people they designate):

- Full certification for a given task is granted upon satisfactory completion of a written examination on that task and demonstration of the specific procedures associated with that task as detailed below. Full certification is usually granted following the initial training meeting but will sometimes be accomplished at annual Study Group meetings or at site visits. Throughout the Study, full certification is maintained by performing the specific task on at least 10 CLEK Study patients in a calendar year.

- Probationary certification is granted in the event of unsatisfactory performance. Full certification must be restored within a reasonable period of time, or termination from the Study should be considered.

All CLEK Study personnel are required to: (1) read the CLEK Operations Manual and (2) demonstrate their ability to perform their appointed tasks by completion of a written examination and demonstration of proper Study procedures.

A centralized training and certification meeting was held at The Ohio State University College of Optometry April 8-9, 1995, prior to patient enrollment. Each Participating Clinic will send at least two people to be certified in each of the key CLEK Study tasks:

- Visual acuity
- Refraction
- Keratometry
- Videokeratography
- Slit lamp evaluation
- Corneal photography
- First definite apical clearance lens (FDACL), contact lens fit assessment, and fluorescein photography
- Study coordination
- Contact lens verification

In the event someone joins a CLEK Participating Clinic after the April 1994 training meeting, he or she will be certified for the appropriate key tasks as follows:

(1) Complete a written test
(2) Complete a telephone interview with the examiner who certifies that task.
If a new person needs to be certified after Study startup, the CLEK Participating Clinic Principal Investigator should call the Study Chairman for certification materials and instructions.

Each person certified in at least one of the key tasks listed above is assigned his or her certification initials (eg, KSZ) by the Chairman’s Office. These certification initials are entered on all CLEK Forms as indicated.

12.2 Certification for Visual Acuity Measurement

Visual acuity is one of the most important measures of the CLEK Study. Each Clinic must have at least two people certified for visual acuity measurement in order to enroll and follow CLEK Study patients. This person can be either a Clinician or a Technician.

The certification requirements for visual acuity are:

- To attend a CLEK Study training session concerning CLEK Study design and methods, visual acuity measurement, and forms completion and data inspection;

- To read the CLEK Operations Manual, particularly Chapter 6, “Vision Assessment;”

- To review CLEK Study data collection forms, particularly the CLEK Examination Form;

- To set up a visual acuity testing room following the procedures in Chapter 6;

- To complete a written examination on visual acuity measurement; and

- To complete an in-person or telephone visual acuity training session.

After satisfactory completion of all requirements, verification of certification is issued and forwarded by the Chairman’s Office to the Coordinating Center and the Executive Committee. To keep certification current, the certified task must be performed satisfactorily on at least 10 Study patients in a calendar year.

Annual recertification may be granted at an annual Full Investigators Group meeting.

12.3 Certification for Refraction
Each Clinic must have at least two people certified for refraction in order to enroll and follow CLEK Study patients. This person can be either a Clinician or a Technician. In order for a Technician to be CLEK-certified in refraction, it must be legal in that Technician’s Participating Clinic’s state for technicians to perform refractions.

The certification requirements for refraction are:

• To attend a CLEK Study training session concerning CLEK Study design and methods, refraction, and forms completion and data inspection;

• To read the CLEK Operations Manual, particularly Chapter 6, “Vision Assessment;”

• To review CLEK Study data collection forms, particularly the CLEK Examination Form;

• To complete a written examination on refraction; and

• To complete an in-person or telephone refraction training session.

After satisfactory completion of all requirements, verification of certification is issued and forwarded by the Chairman’s Office to the Coordinating Center and the Executive Committee. To keep certification current, the certified task must be performed satisfactorily on at least 10 Study patients in a calendar year.

Annual recertification may be granted at an annual Full Investigators Group meeting.

12.4 Certification for Keratometry

Each Clinic must have at least two people certified for keratometry. Certification requirements for keratometry are:

• To attend the CLEK Study training session concerning the design of the CLEK Study and the methods for corneal curvature assessment and documentation;

• To read the CLEK Operations Manual, especially Chapter 8, “Corneal Curvature and Topography” (as well as Chapters 2 and 3), and to learn the documentation of corneal curvature using the CLEK Examination Form;

• To review CLEK Study data collection forms, especially the CLEK Examination Form;
• To complete a written examination on keratometry; and

• To complete an in-person or telephone keratometry training session.

After satisfactory completion of all requirements, verification of certification is issued and forwarded by the Chairman’s Office to the Coordinating Center and the Executive Committee to be used on all CLEK Study forms completed. To keep certification current, this certified task must be performed on at least 10 Study patients in a calendar year.

Probationary certification is granted in the event of unsatisfactory performance. Full certification must be restored within a reasonable period of time, or termination from the Study should be considered.

Annual recertification may be granted at an annual Full Investigators Group meeting.

12.5 Certification for Videokeratography

Each CLEK Participating Clinic must have at least two people certified for corneal topography measurement. Certification requirements for videokeratography are:

• To attend a CLEK Study training session concerning the design of the CLEK Study and the methods for corneal curvature assessment and documentation;

• To read the CLEK Operations Manual, especially Chapter 8, “Corneal Curvature and Topography” (as well as Chapters 2 and 3), and to learn video-keratography measurement and disk storage techniques;

• To complete a written examination on videokeratography; and

• To complete an in-person or telephone topography training session.

After satisfactory completion of all requirements, verification of certification is issued and forwarded by the Chairman’s Office to the Coordinating Center and the Executive Committee. To keep certification current, the certified task must be performed satisfactorily on at least 10 Study patients in a calendar year.

Probationary certification is granted in the event of unsatisfactory performance. Full certification must be restored within a reasonable period of time, or termination from the Study should be considered.
Annual recertification may be granted at an annual Full Investigators Group meeting.

12.6 Certification for Slit Lamp Biomicroscopy

Each Clinic must have two CLEK Study-certified people for slit lamp biomicroscopic examination. Certification requirements for the slit lamp examination protocol are:

- To attend a CLEK Study training session concerning the design of the CLEK Study and the methods for corneal assessment and documentation;

- To read the CLEK Operations Manual, especially Chapter 7, “Corneal Slit Lamp Examination” (as well as Chapters 2 and 3), and to learn the documentation of corneal scarring and staining on the CLEK Examination Form;

- To review CLEK Study data collection forms, especially the CLEK Examination Form;

- To complete a written examination on slit lamp biomicroscopy; and

- To complete an in-person or telephone training session.

After satisfactory completion of all requirements, verification of certification is issued and forwarded by the Chairman’s Office to the Coordinating Center and the Executive Committee. To keep certification current, the certified task must be performed satisfactorily on at least 10 Study patients in a calendar year.

Probationary certification is granted in the event of unsatisfactory performance. Full certification must be restored within a reasonable period of time, or termination from the Study should be considered.

Annual recertification may be granted at an annual First Investigators Group meeting.

12.7 Certification for Fluorescein Protocol

Each CLEK Participating Clinic must have at least two people certified for the fluorescein protocol, including FDACL, contact lens fit assessment, and fluorescein photography. Certification requirements for the fluorescein protocols are:
• To attend the CLEK Study training session concerning CLEK Study design and methods for First Definite Apical Clearance Lens fitting protocol, fluorescein pattern interpretation, and fluorescein photography;

• To read the CLEK Operations Manual, particularly Chapter 9, “Assessment of Habitual Contact Lenses and First Definite Apical Clearance Lens Determination” and Chapter 10, “Photodocumentation of Fluorescein Pattern;”

• To review CLEK Study data collections forms, particularly pages 15-16 of the CLEK Examination Form;

• To complete a written examination on the fluorescein protocols; and

• To demonstrate photodocumentation of fluorescein patterns by submitting two series of readable slides of the First Definite Apical Clearance Lens series on two keratoconus patients to the CLEK Photography Reading Center.

After satisfactory completion of all requirements, verification of certification is issued and forwarded by the Chairman’s Office to the Coordinating Center and the Executive Committee. To keep certification current, the task must be satisfactorily completed on at least 10 Study patients in a calendar year.

Probationary certification is granted in the event of unsatisfactory performance. Full certification must be restored within a reasonable period of time, or termination from the Study should be considered.

Annual recertification is granted by maintaining a 95% readable slide and 95% grade 2 or higher slide quality as graded by the CLEK Photography Reading Center.

12.8 Certification for Corneal Photography

Each Clinic must have at least two people certified in corneal photography. Certification requirements for corneal photography are:

• To attend the CLEK Study training session concerning the design of the CLEK Study and the methods for corneal photography and documentation;

• To read the CLEK Operations Manual, especially Chapter 10, “Photodocumentation of Corneal Scarring” (as well as Chapters 2, 3, and 7);

• To complete a written examination on corneal photography; and
Following the directions of the Director of the CLEK Photography Reading Center: to photograph two keratoconus patients with at least two scarred eyes between them and send the exposed film to the CLEK Photography Reading Center.

After satisfactory completion of all requirements, verification of certification is issued and forwarded by the Chairman’s Office to the Coordinating Center and the Executive Committee. To keep certification current, the task must be satisfactorily completed on at least 10 Study patients in a calendar year.

Probationary certification is granted in the event of unsatisfactory performance. Full certification must be restored within a reasonable period of time, or termination from the Study should be considered.

Annual recertification is granted by maintaining a 95% readable slide and 95% grade 2 or higher slide quality as graded by the CLEK Cornea Photography Reading Center.

12.9 Certification for Study Coordination

The training of the personnel who serve as the CLEK Participating Clinic Coordinators is conducted prior to start-up. Certification will be granted upon the successful completion of certification at the time of the centralized training meeting. Full certification may be withdrawn or down-graded to probationary certification if performance is not satisfactory; otherwise, certification is current for one year. Certification must be renewed by telephone annually.

The Study Coordinator’s role is critical to the smooth day-to-day operation of the Clinic, but because of the patient flow requirements of this observational study, the clinic coordination tasks will be assigned to a less-than-full-time person. The training program will emphasize skills in patient management, data quality control, and organizational ability. Similarly, the certification procedure will evaluate some of the following skills: 1) simulated data with problems to evaluate data editing expertise, and 2) hypothetical patient problems to evaluate familiarity with the protocol and patient follow-up procedures. To prepare for the certification, the Clinic Coordinator must demonstrate command of the CLEK Study protocol as described in this Operations Manual, Chapters 2, 3, 4, 5, 6, and 13.

After satisfactory completion of all requirements, verification of certification is issued and forwarded from the Chairman’s Office to the Coordinating Center and the Executive Committee. To keep certification current, the task must be satisfactorily completed on at least 10 Study patients in a calendar year.
12.10 Certification for Contact Lens Verification

Certification requirements for contact lens verification are:

- To read the CLEK Operations Manual, Section 9.5 on contact lens parameter verification; and

- To complete a practical examination measuring 3 masked CLEK Study trial lenses, supplied through the Chairman’s Office.
Chapter 13
Chairman’s Office and Participating Clinic Operations

13.1 Chairman’s Office Functions

The Chairman’s Office is at The Ohio State University College of Optometry in Columbus, Ohio, under the direction of Dr. Karla Zadnik. The CLEK Study Chairman’s Office Coordinator is Jodi M. Malone.

The Chairman’s Office oversees the Participating Clinics, the CLEK Photography Reading Center (CPRC), the CLEK Topography Reading Center (CTRC) and the Coordinating Center. The Study Chairman is the liaison between the Executive Committee and the Participating Clinics. In particular, the Chairman’s Office is primarily responsible for two functions that directly affect day-to-day Participating Clinic operations.

13.1.1 Per-Patient Payment to Participating Clinics

Per-patient payment to Clinics and to CLEK Study patients is administered through the Chairman’s Office. The Coordinating Center issues quarterly reports to the Chairman’s Office of patients whose data were submitted in that quarter, along with the visit date and type. The Chairman’s Office processes a check for that quarter’s visits at the rates specified in Table 13-1.

13.1.2 Per-Patient Payment to Patients

At the time that Patient X is seen in Clinic Y, Patient X is given a Patient Reimbursement form and a self-addressed, business reply envelope to the Chairman’s Office. He or she completes the form and mails it. Receipt of this form at the Chairman’s Office triggers the sending of a welcome letter to the patient, Then, a check for $20 per visit is processed by the Chairman’s Office and mailed directly to the patient. This method nominally reimburses the patient for CLEK Study-related expenses and ensures annual, centralized patient address update by the Chairman’s Office. If they so choose, patients can decline the individual payment, but they may still wish to send their addresses to the Chairman’s Office to be included on the central CLEK Study mailing list.

Additionally, the Chairman’s Office will send out stamped postcards addressed to the Chairman’s Office at the six-month interval between Study Visits for CLEK Study patients to return for address update.
Table 13-1. Per-Patient Payment to Participating Clinics and to Patients.

<table>
<thead>
<tr>
<th>Visit Type</th>
<th>Payment to Clinic</th>
<th>Payment to Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual Visit 2</td>
<td>$300</td>
<td>$20</td>
</tr>
<tr>
<td>Annual Visit 3</td>
<td>$300</td>
<td>$20</td>
</tr>
</tbody>
</table>

13.2 CLEK Study Newsletters

One CLEK Study patient newsletter is distributed each year. This newsletter provides Study-related information to give the patients a sense of the national perspective of the study, provide health information relevant to CLEK Study patients, and highlight achievements—professional and personal—of CLEK Study personnel. The newsletters are designed to maintain contact with the patients and to promote esprit de corps. The newsletter is distributed to all CLEK Study personnel, all CLEK Study patients, and referring doctors as requested by the Participating Clinics. One of the two semi-annual issues includes a tear-out, addressed postcard for the patient to mail back to the Chairman’s Office for address verification. CLEK Study patients will also receive reprints of all pertinent publications.

13.3 Introduction to Participating Clinic Operations

The organization of a CLEK Clinic varies across Participating Clinics.

The Clinic Principal Investigator is the Clinician, who is responsible for on-site management of the project and for interaction with the CLEK Study Chairman, the Coordinating Center, and the CLEK Photography Reading Center.

The Clinic coordination, clerical, and correspondence tasks are the responsibility of the Clinic Principal Investigator, but each Clinic must have someone certified for coordination duties. How these duties will be handled — whether they will be delegated to a departmental secretary, work study student, or ophthalmic technician, for example — is determined by the individual Clinic Principal Investigator.

The Study measurement tasks, visual acuity, refraction, keratometry, slit lamp examination, corneal photography, application of trial lenses to the First Definite Apical Clearance Lens with fluorescein photography of the First Definite Apical Clearance Lens and the lens 0.2 mm flatter than the First Definite Apical Clearance Lens, and fluorescein photography of the patient’s habitual lenses (in rigid lens wearers only), can be completed by as few as two (Clinician and Back-up Clinician with one of them performing Clinic coordination duties) and as many as five (Clinician, Back-up Clinician, Technician, Photographer, and Clinic Coordinator) people; however, funding is only provided for travel to the training meeting for three people per Clinic.
Table 13-2 shows which measurements can be performed by the various Participating Clinic personnel.

**Table 13-2. CLEK Study Tasks.**

<table>
<thead>
<tr>
<th>Task</th>
<th>Who Can Perform Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity</td>
<td>Clinician, Technician*</td>
</tr>
<tr>
<td>Contact lens fit assessment</td>
<td>Clinician</td>
</tr>
<tr>
<td>Refraction</td>
<td>Clinician, Technician*</td>
</tr>
<tr>
<td>Keratometry, videokeratography</td>
<td>Clinician, Technician, Photographer</td>
</tr>
<tr>
<td>Slit lamp examination</td>
<td>Clinician</td>
</tr>
<tr>
<td>Corneal and fluorescein photography</td>
<td>Clinician, Photographer</td>
</tr>
<tr>
<td>FDACL</td>
<td>Clinician, Technician*</td>
</tr>
</tbody>
</table>

*As long as these tasks as performed by technicians are legal in the individual Participating Clinic’s state.

### 13.4 Eligibility

When a prospective CLEK Study patient is identified by any member of the Study team, a referring center, or an outside clinician, an Eligibility Form is completed. If the patient is eligible according to the entry criteria in Chapter 3 of this Operations Manual and the patient provides informed consent, he or she is seen immediately or scheduled for a Baseline Visit.

### 13.5 Baseline Visit

Each CLEK Study Visit uses the same protocol. The order of testing is incorporated in the CLEK Examination Form.

The following sequence of events is initiated:

1. The Clinician completes the CLEK Examination Form with ancillary testing (eg, visual acuity, photography, topography) performed by personnel as he or she designates.

2. The corneal and fluorescein photographs are taken according to the protocol in Chapter 11 of this Operations Manual, and the fundus examination and tonometry are performed.

3. After all forms are completed by the Clinician, the original forms are mailed to the Coordinating Center. The Clinic retains a copy of the forms on-site.

4. The Clinic Principal Investigator sends the exposed fluorescein photography and corneal photography film to the CLEK Photography Reading Center by regular mail in the CLEK Study mailer within 24 hours.
(5) The Clinic Principal Investigator sends the TMS topography data (if applicable) on disk to the Chairman’s Office by regular mail in the CLEK Study mailer within 24 hours.

13.6 Annual Visits

Follow-up Annual Visits are scheduled each year for eight years, using the Baseline Visit date as the reference date (Section 5.5 of this Operations Manual). Procedures for the Annual Visits are identical to those for the Baseline Visit (Table 13-3).

Table 13-3. Examinations, tests and measures scheduling.

<table>
<thead>
<tr>
<th>VISIT</th>
<th>TESTS AND MEASURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, Annual Visits 1-8, Presurgical Visit, Revisit</td>
<td>Quality of life, history, visual acuity, in rigid contact lens wearers: current contact lens fit evaluation with fluorescein photography, manifest refraction, keratometry/corneal videokeratography, slit lamp examination, corneal photography, first definite apical clearance trial lens with fluorescein photography of this lens and the lens 0.2 mm flatter in rigid contact lens wearers.</td>
</tr>
</tbody>
</table>

13.7 Repeat Visits

Early in the CLEK Study, 100 patients (approximately 8 per Participating Clinic) are selected at random by the Coordinating Center to participate in a study of CLEK Study protocols and their measurement reproducibility.

Each Participating Clinic will receive notification as to which CLEK Study patients have to be examined a second time within one month of their Baseline Visit. These patients are called by the Clinic and scheduled for this Repeat Visit within two weeks of notification by the Coordinating Center. These patients will undergo the identical protocol as outlined for the Baseline Visit above.

13.8 Completion of the Patient-Completed Forms and the Medical History Portion of the CLEK Examination Form

The CLEK Patient History form should be completed to the best of the patient’s abilities and knowledge. It is not designed as a questionnaire where any CLEK Clinic personnel interpret the questions or assist the patient with assessment of the questions.

The CLEK Quality of Life Form is the MOS 36-Item Short-Form Health Survey (SF-36) and as such is a standardized instrument for the assessment of quality of life. Patients should complete the form to the best of their abilities and knowledge, and
Study personnel should urge the patients to interpret the questions as best they can, without urging the patients in any specific direction.

The Systemic Disease question on the CLEK Examination Form attempts to assess the association between keratoconus and a long list of systemic diseases, some very rare, that have been traditionally linked to keratoconus. Many of the diseases are unfamiliar to the patient, but they should be asked whether they have each of them by specific name anyway. For example, if a patient has something as unusual as Ehlers-Danlos Syndrome, he or she will presumably know it and will answer the question as such.

The Previous Eye Trauma question on the CLEK Examination Form is not meant to include corneal abrasions.

The Eye Rubbing question on the CLEK Examination Form must be answered simply as stated to the best of the patient’s abilities, separately for each eye.

The question about Current Contact Lens Wear on the CLEK Examination Form refers to whether contact lenses are currently prescribed. If the patient does not wear his or her contact lenses in to the CLEK Study Visit, he or she should not be urged by CLEK Study personnel to wear them for the examination. Remember, the purpose is to assess keratoconus patients with as little intervention from the Study as possible.
Chapter 14
CLEK Photography Reading Center (CPRC) Procedures

14.1 Organization of the CLEK Photography Reading Center

The CPRC performs an important research function with respect to objectively recording two of the critical measures in the CLEK Study: (1) corneal scarring (corneal photography), (2) contact lens fit (fluorescein photography of rigid contact lens wearers), and (3) First Definite Apical Clearance Lens fluorescein photograph reading.

The organization of the CLEK Photography Reading Center is shown in Figure 14-1.

The personnel at the CLEK Photography Reading Center are:

CPRC Director - Joseph T. Barr, O.D., M.S.
CPRC Coordinator - Gloria Scott-Tibbs, B.S.
Three CPRC Photograph Readers - Gilbert Pierce, O.D., Ph.D. Marjorie Jeandervin, O.D., M.S., and Roanne Flom, O.D.
CPRC Computer Programmer - Matt Gilbert
CPRC Slide Labeling and Filing Technicians

The CPRC Director organizes the CLEK Photography Reading Center and hires, trains, and certifies the CPRC staff. The CLEK Photography Reading Center Coordinator is responsible for assuring that the day-to-day operations run according to protocol. The CLEK Photograph Readers perform all photograph grading. The CLEK Photography Reading Center Computer Programmer programs the local area computer network and trains the staff on use of the network. Detailed descriptions of these activities are contained in the CLEK Photography Reading Center Operations Manual.

The CLEK Photography Reading Center Director, along with Timothy B. Edrington, OD MS, Consultant to the CPRC, train and certify CLEK Clinic personnel at central meetings and conduct site visits when necessary to the CLEK Clinics to insure that the Photographers and the Clinicians in the CLEK Clinics are qualified to perform the CLEK Study.
14.2 Photography Schedules for Participating Clinics

Fluorescein pattern photography is performed on all CLEK Study patients at each Study Visit to document the “First Definite Apical Clearance Lens,” except on eyes that have undergone penetrating keratoplasty or other corneal surgery.

Fluorescein pattern photography is performed on all rigid contact lens-wearing CLEK Study patients at each Study Visit to document their habitual rigid contact lens fit.

Additional fluorescein photography is performed by the CLEK Clinic when the CLEK Photography Reading Center directs the Clinic to rephotograph a patient due to poor photograph quality in the original photographs.

Corneal photography is performed at all Study Visits. After reading the photographs, the CLEK Photography Reading Center sends photography outcome data to the Coordinating Center.
The cornea is also photographed whenever the CLEK Photography Reading Center directs the CLEK Clinic to rephotograph the cornea due to poor photograph quality.

The fluorescein pattern photography protocol is in Chapter 10, and the corneal photography protocol is found in Chapter 11 of this Operations Manual. Both protocols are also in the CLEK Photography Reading Center Operations Manual.

### 14.3 CLEK Photography Reading Center Procedures

The CLEK Photography Reading Center Coordinator purchases Kodak Ektachrome ASA 100 film and stores it in a secure cabinet. Prior to the beginning of the CLEK Study and at six-month intervals thereafter, or as necessary, the CLEK Photography Reading Center Coordinator sends rolls of film to each of the CLEK Clinics. Only film from the CPRC may be used. CPRC film is reserved for CLEK Study patients. The CLEK Photography Reading Center Coordinator maintains a log of this activity.

The CLEK Photography Reading Center Coordinator receives film from the CLEK Clinic, logs the receipt of the film onto the film log, and delivers it to the processing laboratory within two working days.

The CPRC Director or his designated reader determines if the slides are of adequate quality to be graded. The CLEK Photography Reading Center Coordinator or Slide Labeling Technician labels the slides, the CPRC Coordinator arranges the slides in carousel slide projector trays as directed in the CPRC Operations Manual. The Coordinator informs a CPRC Reader that the slides are ready to be read.

The CPRC Readers read the slides, recording slide quality and grading outcomes on the computer screen. The Reader reads photographs without knowledge of the patient, condition, Clinic, etc. After determining that all the data are complete and entered accurately, the Reader stores the results on the computer. The Reader may also place notes in the file with suggestions to improve photography that are conveyed to the Clinic by the CPRC Director.

### 14.4 Repeat Photography

In the event of poor quality fluorescein or corneal photographs, repeat photography is necessary.
The CPRC Director informs the Clinic Principal Investigator if a set of fluorescein or corneal photographs is not gradable and conveys any specific recommendations on methods to improve photograph quality that the Reader may have noted in the file (Section 14.3 above). The Study patient is immediately rescheduled for an appointment within 14 days for repeat photography. The new exposed film is mailed to the CLEK Photography Reading Center on the same day as the repeat photography.

14.5 Certification of CLEK Photography Reading Center Personnel

14.5.1 Certification of Photograph Readers

The CLEK Photography Reading Center must have certified Photograph Readers. Certification requirements for the CLEK Photography Readers are:

1. Attend training sessions conducted by the Director of the CLEK Photography Reading Center concerning the design of the CLEK Study, the methods for fluorescein photography, the methods of fluorescein photograph reading and documentation, the methods for corneal photography, and the methods of corneal photograph reading and documentation;

2. Study and know in detail the CLEK Operations Manual, especially Chapters 2, 10, 11, and 14, and the CLEK Photography Reading Center Operations Manual;

3. Complete a written examination for the Photograph Reader;

4. Read 100 teaching slides (50 fluorescein, 50 cornea) as specified in the CLEK Photography Reading Center Operations Manual, under the direction of the CPRC Director;

5. Independently and correctly read 20 apical touch fluorescein patterns and 20 apical clearance fluorescein patterns to the satisfaction of the CPRC Director;

6. Independently and correctly read photographs from 20 slightly scarred eyes and 20 nonscarred eyes to the satisfaction of the CPRC Director.

Documentation of completion of each of these requirements is submitted to the Project Manager at the Coordinating Center. The CPRC Director and the Coordinating Center Director are responsible for recommending certification. After the training session and examination (steps 3 and 4 just above), provisional certification is awarded to the CLEK Photograph Reader. After satisfactory
completion of all requirements at the CLEK Photography Reading Center, a
certification number is issued by the Project Manager to the CLEK Photograph
Readers.

Probationary certification is granted in the event of unsatisfactory
performance. Full certification must be restored within a reasonable period of
time, or termination from the Study should be considered.

Annual recertification is granted after examination by the CLEK
Photography Reading Center Director.

14.5.2 Certification of CLEK Photography Reading Center Coordinator

Certification requirements for the CLEK Photography Reading Center
Coordinator are as follows:

(1) Attend training sessions conducted by the Director of the CPRC
concerning the design of the CLEK Study, the methods for fluorescein
photography, the methods of fluorescein photograph reading and
documentation, the methods for corneal photography, and the methods for
cornea photograph reading and documentation;

(2) Study and know in detail the CLEK Operations Manual, especially
Chapters 2, 10, 11, and 14, and the CPRC Operations Manual;

(3) Complete a written examination for the CLEK Photography Reading
Center Coordinator as presented by the CPRC Director and the Coordinating
Center Director; and

(4) Demonstrate understanding of the CPRC computer system, the flow of
materials and data between the CPRC and the Clinics, film log recording, slide
labeling, organizing slides for reading, performance of data entry and report
generation, sending data to the Coordinating Center, and slide storage.

All documentation is submitted to the Project Manager at the
Coordinating Center. The CPRC Director and the Coordinating Center Director
are responsible for recommending certification. After the written examination,
provisional certification is awarded to the CPRC Coordinator. After satisfactory
completion and demonstration of all requirements at the CPRC, a certification
number is issued by the Project Manager to the CPRC Coordinator.
Probationary certification is granted in the event of unsatisfactory performance. Full certification must be restored within a reasonable period of time, or termination from the Study should be considered.

Annual recertification is granted after examination by the CPRC Director and the Coordinating Center Director.
14.6 Summary of CLEK Photography Reading Center Procedures

The CLEK Photography Reading Center Operations Manual provides complete details on the following procedures:

(1) Responsibilities of the CLEK Photography Reading Center Director, the CPRC Coordinator, the Readers, the CPRC Slide Labeling Technician, the CPRC Computer Programmer;

(2) Training and certification of the CPRC staff, the CLEK Clinicians, and the CLEK Clinic Photographers;

(3) Scheduling of fluorescein and corneal photography;

(4) Fluorescein and corneal photography protocols (also in Chapters 11 and 12 of this Operations Manual);

(5) Retakes of photographs;

(6) Routing and processing of photographs;

(7) Reading of photographs;

(8) Internal quality control by the CPRC;

(9) External quality control by the CPRC;

(10) CPRC reports; and

(11) CPRC forms.
15.1 Introduction

The Coordinating Center is the joint effort of the Department of Ophthalmology and Visual Sciences and the Division of Biostatistics of Washington University School of Medicine. The Coordinating Center collaborates with the Study Chairman’s Office, the Executive Committee, the CLEK Study Group and the Data Monitoring and Oversight Committee in the design and implementation of the CLEK Study. This includes coordinating the efforts of investigators, monitoring protocol adherence, receiving, managing, and storing all CLEK Study data, analyzing CLEK Study data, and preparing reports and publications. The staff of the Coordinating Center consists of the Director, the Co-Director, the Project Manager, the Statistician, the Project Assistant, and the Senior Research Analyst.

Figure 15-1 The Coordinating Center’s Organizational Scheme

The objective of the Coordinating Center’s work changes greatly depending on the phase of the study. The objectives of the Coordinating Center are summarized in each of the phases depicted in Table 15-1.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Beginning Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol Development</td>
<td>Funding of Coordinating Center, Chairman’s Office</td>
</tr>
<tr>
<td>Recruitment/Follow-up</td>
<td>Start enrollment and follow-up</td>
</tr>
<tr>
<td>Patient Closeout</td>
<td>Complete follow-up, closeout</td>
</tr>
<tr>
<td>Study Termination</td>
<td>Final data analysis, publications</td>
</tr>
</tbody>
</table>
15.2 Protocol Development Phase

This phase begins at funding of the Coordinating Center and represents a set of activities that must be completed before Study patients can be enrolled.

The Coordinating Center plays an active role—along with the Chairman’s Office, the Executive Committee, and the CLEK Study Group—in the development of the CLEK Study protocol. This includes the following:

- Complete sections of the CLEK Operations Manual that require further refinement and development;
- Pretest and refine forms and data entry/editing/management programs for study administration (patient logs) and data collection at Clinics. Forms have been field tested at 5 clinics and revised once. The forms continue to be refined. Procedures for training and certification of CLEK Study personnel is developed from this experience base. Programs are completed for generating recurrent reports, trial administration and database management;
- Certify Coordinator and Readers at the CLEK Photography Reading Center on the CLEK Study protocol;
- Conduct a dry run of non-study photographs at the CLEK Photography Reading Center to test each phase of the operation from logging data and grading to transmitting data to the Coordinating Center;
- Supply Clinics with forms and documentation for the purpose of study administration (scheduling, logs) data collection, entry and editing at the time of the initial training meetings; and
- Prepare the first report to Data Monitoring and Oversight Committee.

15.3 Recruitment and Follow-up Phase

15.3.1 Activities

This phase is the heart of the study and is projected to cover five years from the time of initial patient recruitment up to completion of follow-up visits (closeout). This phase includes the following:

- Patient eligibility determination and enrollment;
• Coordination and preparation of agendas for CLEK Study standing committees;

• Administrative and scientific support to the Clinics and to the CLEK Photography Reading Center;

• Monitor the flow of patient visits and data from the point of collection at the Clinic to deposition in a master database at the Coordinating Center. The Coordinating Center generates dates for scheduled patient visits from the time of enrollment. Monitoring reports summarize the data quality (missing and erroneous data) and timeliness of patient visits and transmittal of forms to the Coordinating Center;

• Assist the Clinic staff in interpreting the CLEK Operations Manual and implementing the protocol. For this purpose, electronic mail will be used as much as possible;

• Receive, edit, and store data files from the Clinics and from the CLEK Photography Reading Center;

• Analyze data for baseline publications and develop the analysis plan for testing primary hypotheses;

• Prepare reports on the clinical and methodological findings and innovations of the CLEK Study.

15.3.2 Quality Assurance

The Executive Committee and the Data Monitoring and Oversight Committee advise in selecting what “reportable protocol violations” are monitored and reported monthly. Procedures for protecting the scientific integrity of the CLEK Study include:

• Initial training and certification for Clinic personnel on the protocol, examination procedures, and forms completion;

• Monitoring of Clinic data;

• Weekly telephone trouble-shooting calls with Clinics for the first month after Clinic start-up and monthly thereafter;

• Initial site visit to the CLEK Photography Reading Center and site visits to Clinics on an as needed basis (estimated at four per Study year) for the purposes of monitoring data integrity; and
• Maintain an on-going certification database for Clinic staff, Reading Center staff and the Coordinating Center.
15.3.3 Reports Prepared by the Coordinating Center

Quarterly Coordinating Center Report

This report is for the Coordinating Center for the purpose of self-monitoring and includes the following information:

- Number and types of forms received;
- Number, date and type of edit checks initiated by the Coordinating Center and the time to resolution of edit checks overall and by Clinic;
- Time intervals between patient visit date, form transmittal, and pass data edit, overall and by Clinic;
- Missing data rate by variable and form type reported overall and by clinic;

Quarterly Report to CLEK Photography Reading Center

The Coordinating Center report includes:

- Intra-rater reliability (at least a 10% stratified random sample selected by the Coordinating Center will be regraded by the CLEK Photography Reading Center by the same Reader).

Monthly Report to Clinics

This report provides the following information:

- Number of eligible patients who are enrolled, overall and by Clinic.

Semi-Annual Report to Clinics

- Baseline demographic and clinical characteristics of enrolled patients, i.e., age, gender, race, keratometry readings, and other reports as requested by the Executive Committee or the Data Monitoring and Oversight Committee;
- Percent and number of each visit outside time window, overall and by Clinic;
Semi-Annual Data Monitoring and Oversight Committee Report

- At 6 month intervals and upon request, the Coordinating Center completes extensive monitoring reports for the Data Monitoring and Oversight Committee.

- Report to the Data Monitoring and Oversight Committee includes a summary of recurrent reports to the Clinics, to the CLEK Photography Reading Center, and to the Coordinating Center as well as quality assurance reports, recruitment and retention reports, and activity reports for the Resource Centers.

- Monitoring data for validity of sample size assumptions; and

- Variability in keratometry readings and visual acuity measurements between Clinics and within patients as an index for quality control.

15.4 Analysis of Baseline Data

- Monitor sample size assumptions;

- Monitor inter-grader and intra-grader reliability at the CPRC;

- Determine the agreement between Clinician and CPRC gradings for habitual fit, corneal scarring, and FDACL;

- Analysis of Specific aims based on baseline data:

  - characterize the association between best-corrected visual acuity and visual quality of life;

  - determine which measurement of visual acuity, best-corrected or habitual, is most associated with visual quality of life;

  - determine if the better eye, the worse eye, or bilateral habitual visual acuity correlates with visual quality of life;

  - characterize the association between corneal curvature as measured by keratometry and corneal irregularity, corneal scarring, patient’s age, whether the patient wears spectacles or contact lenses, and type of contact lenses;
–describe the relationship among corneal scarring as determined by 
photography and corneal curvature, age, visual acuity (high and low 
contrast, best-corrected and habitual), whether the patient wears 
spectacles or contact lenses and the type of contact lens worn, and the First 
Definite Apical Clearance Lens base curve.

15.5 Patient Closeout Phase

The role of the Coordinating Center in closeout includes:

• Monitoring procedures for patient closeout;

• Assisting in the preparation of papers;

• Developing plans for final data editing and storage;

• Arranging closeout of the Clinics, the CLEK Photography Reading Center, 
  and the Coordinating Center; and

• Determine final disposition of data files.

15.6 Termination Phase

During the termination phase, study datasets have essentially undergone final 
editing. This is a very active period for writing papers and completing analyses 
supporting ancillary questions. This phase includes the following:

• Completing scheduled data analyses and writing of papers;

• Placing data files and study documents in selected archives; and

• Serving as the CLEK Study communications center.

15.7 Form Design

Forms for the CLEK Study have been designed, field tested and revised during 
the planning phase. However, our general policy is pretest, pretest and pretest. Forms 
are pretested in another subset of Clinics during the Protocol Development Phase 
(Section 15.2). The Coordinating Center will prepare and distribute study forms to the 
Participating Clinics. The following guidelines will be observed in the generation of 
forms:
(1) Forms are be self-contained, when possible. Their completion should not require reference to separate instruction manuals or tables of codes for completion. The instructions necessary for the completion of a form are routinely printed on the forms.

(2) Individual items are self-explanatory. Compactness of the forms is sacrificed to achieve clarity when necessary.

(3) Forms include only that information which is available at a given point in time. Information which is collected at a later date is incorporated into another form.

(4) Each person responsible for data collection and/or data entry will be identified along with relevant dates of processing. This increases our ability to manage the data collection/data entry aspects of the study and to identify staffing or quality control problems.

15.8 Records Flow Within the Coordinating Center

Within one working day of receipt, the Project Assistant manually checks agreement between the form type, the patient identification number, and visit date with the Transmittal Log. When the transmittal log and the data received do not agree, disagreements are resolved when possible. Unresolved disagreements are flagged with an edit code when the data clerk enters Transmittal Log information. Additional manual checks conducted by the data clerk include checking for the correct number of pages, the patient identification number, and the date on the form. The Project Manager performs a manual scan of forms before they are bundled by form type for key data entry. The Project Assistant then bundles forms by type, stamps a unique batch number on each page of the forms and stamps the batch number on the corresponding transmittal log. Forms with serious problems are not sent to data entry pending resolution of the problem.

Frequently, problems of protocol adherence are noted at this stage, and remedial actions are initiated. The Coordinating Center response to problems with protocol adherence range from discussions with the Clinic to a discussion with the Study Chairman and the Executive Committee about possible changes to the protocol. Another action to be considered is scheduling a site visit to the Clinic.

Key to disk entry of data is performed off-site by a subcontractor. Data are picked up by courier daily. Data are keyed to disk by two different key operators, with the second operator performing verification. The turnaround time for data to be received on disk from time of pick-up by courier is three working days.

The data entry contractor completes a problem report for each batch of forms processed. In this manner, the Coordinating Center is able to distinguish data errors
that escape detection by the Coordinating Center from errors that were introduced in data entry.

Each form type is a different file where the file name consists of the batch number and form code.

Batch editing of data files consists of three phases beginning with a check for consistency of form type within a file and the number of pages for each form. The second phase of editing consists of core edits that are conducted for all forms. These edit checks include identification of missing values, out-of-range values, illegal characters, verifying correction of patient identification numbers, certifications, and visit windows. Form specific edits consist of edits that are unique to that form type.

Errors in the data are reported by issuing an edit report that is mailed to the Clinic. The edit report states the patient identification number, visit date, and form type, and the item number and type of error for each problem detected, i.e., missing value, range check, illegal character, etc. An edit report also is issued for forms that pass all edits without errors. Computer-generated flags are attached to records for form with errors to document the status of the record. Records with errors or questionable items are marked as such and remain in a temporary file until final correction and verification. Records that pass editing are transferred to the master database on a regular basis.

15.8 Data Management

The SAS system is used for virtually all of the computer processing within the Coordinating Center. We have considerable experience with SAS on a variety of hardware platforms and have contributed to the development of SAS to meet the needs of the Coordinating Center (Miller, 1977; Roesti et. al., 1984; Achtenberg, 1989). The use of only a single integrated software system provides better utilization of the Coordinating Center and Clinic manpower. The use of SAS also allows the use of a single software system across a broad spectrum of hardware platforms.

Over the course of the CLEK Study, significant changes will occur in the cost/performance curves for computers. SAS’s flexibility across hardware platforms allows a balance between the stability of existing hardware systems with the economies of newly available hardware. All Coordinating Center staff have a PC available for their use with necessary SAS software. In addition, all of the PCs are connected to the Division of Biostatistics’ UNIX machines, and to the university-wide ethernet for rapid and reliable file transfer, for the receipt of electronic mail, and for connecting to other computers for the execution of those SAS tasks which require a shared use computer.

In the CLEK Study database, all instances of each type of form are grouped together as a single SAS dataset cross-indexed by patient ID. The entire collection of
datasets (a SAS library) resides on a single shared-use disk on a Biostatistics server. Monthly “snapshot” copies of the data library are made for the production of those management reports which the Executive Committee, the Coordinating Center, and the Data Monitoring and Oversight Committee jointly develop. Other programs extract analysis subsets for interim analyses and quality control monitoring. This freezing of the dataset allows for more consistent analyses than continually making the analytic runs from a live database which is constantly changing as new forms are added and corrections are made. As appropriate, only forms which have passed all edit checks are included in analyses.

Forms are entered and initially edited at the Clinic, transmitted, received and re-edited at the Coordinating Center. Attached to each observation are flags indicating the stage of processing for that form. Along with these flags are the relevant dates so that aged management reports can track forms flow.

15.9 Dataset Backup

Daily archives of the library are made with weekly backups stored off-site as protection against disaster.

15.9.1 Data Security

As the central repository of information for the study, the Coordinating Center has particular responsibilities towards the security of the data. The Coordinating Center protects the data from all hazards including disasters and unauthorized access. The computer room in the Division of Biostatistics is locked to access except by staff and contains fire and heat sensors which are connected to alarms at the guard’s desk located about 30 feet away. The computer system is backed up for file integrity purposes weekly, and the monthly backups are stored in a remote facility. The data for this study are also separately backed up and stored in a safety deposit vault at a nearby bank. Additional security in the form of an electronic card-access system is being installed in 1995.

To guard against unauthorized access to the data, all shared use computer systems are protected with passwords which are changed frequently. Only individuals with a particular “need to know” are given access and system privileges are carefully restricted. All of the PCs to be used in the Coordinating Center are located within a secure area and the area is locked when not in use. SAS itself supports passwords for its data sets which makes it more difficult to access information in an intelligible fashion. Each participating staff member requiring access to study datasets receives a password with an associated “security level.” Those whose need-to-know is limited to reports will have the lowest access privileges, “reports only.” Those who need to review information on a patient-by-patient basis receive “BROWSE” privileges. Individuals performing data entry and editing have “ENTRY” privilege. And a single person at
each site has “supervisory” privileges, including the ability to change the passwords for other staff members. Systems connected to the ethernet are carefully controlled and all systems without ethernet access control (e.g. PCs) are insulated from the backbone by bridges or routers. The ethernet cable itself is routed only through secure passageways.

15.10 Electronic Mail

Electronic mail facilitates communications among the various components of the study, provides a record of interactions, facilitating the documentation of decisions affecting the study, encourages the distribution of information exchanged between individuals to all those who should be kept abreast of the discussion.

E-mail is often more efficient than telephone calls because it allows for the work to be scheduled into the workload of the Clinic rather than being an unscheduled disruption at the convenience of the Coordinating Center.

In order to support the use of electronic mail among CLEK Study sites, a very early task is to survey each of the participants to ascertain their current utilization of e-mail. Our previous experience leads us to believe that much greater acceptance of the use of e-mail is obtained when a user needs to know only a single system and has local support for the use of that mail system. Washington University is well situated on both BITNET and the Internet (NSFNET) so most probably, mechanisms already exist for transferring mail from a particular site to the Coordinating Center and to other Study participants. If the particular Study participant does not use e-mail, but their institution does provide well supported e-mail services on one of the academic networks, then we will work with the user to obtain services from that institution.

15.11 References


Chapter 16
Study Organization and Policy Matters

16.1 Introduction

The resource centers for the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study are:

(1) CLEK Clinics;
(2) Coordinating Center;
(3) CLEK Photography Reading Center;
(4) CLEK Topography Reading Center;
(4) Study Chairman’s Office; and
(5) National Eye Institute Program Office.

The organizational structure of the CLEK Study links resource centers together in a productive network (Figure 1-1). The organization must be self-sufficient, stable, and self-renewing in order to achieve the Study goals.

16.1.1 CLEK Clinics

Chapter 13 of this Operations Manual outlines the CLEK Clinic Operations.

Each Clinic is responsible for screening potential CLEK Study patients, for recruiting an adequate number of eligible patients, and for following patients according to the protocol until the termination of the Study. Each Clinic has at least one certified Clinician and one certified Back-up Clinician and at most those staff members plus one certified Technician, one certified Photographer, and one certified Study Coordinator. All Clinics are reimbursed for CLEK Study participation on a per-patient basis from the CLEK Study Chairman’s Office.

16.1.2 Coordinating Center

Chapter 16 of this Operations Manual contains the Coordinating Center’s operating plan.

The Coordinating Center at Washington University Medical School (St. Louis) is responsible for:

(1) Development and implementation of the study design;
(2) Receiving, editing, processing, analyzing and storing the data generated in the CLEK Study;

(3) Coordinating data generation activities of the Clinics and the CLEK Photography Reading Center; and

(4) Implementing and maintaining quality assurance procedures to minimize bias and error.

The Coordinating Center personnel include the Director, the Co-Director, the Project Manager, the Project Assistant, the Statistician, and the Senior Research Analyst.

16.1.3 CLEK Photography Reading Center (CPRC)

Chapter 14 of this Operations Manual and the CLEK Photography Reading Center Operations Manual describe the goals and day-to-day operations of the CPRC in detail.

The CLEK Photography Reading Center, located at The Ohio State University College of Optometry, is responsible for receiving all fluorescein photographs and corneal photographs and grading them according to specific procedures and criteria described in the CLEK Photography Reading Center Operations Manual, maintaining records of photography data, and transmitting grading results to the Coordinating Center. The CLEK Photography Reading Center consists of the CPRC Director, the CPRC Coordinator, and two Readers.

16.1.4 CLEK Topography Reading Center (CTRC)

Chapter 8 of this Operations Manual and the CLEK Topography Reading Center Operations Manual describe the goals and day-to-day operations of the CTRC in detail.

The CLEK Topography Reading Center, located at the University of Illinois at Chicago Department of Ophthalmology and Visual Sciences, is responsible for receiving all videokeratographic images and grading them according to specific procedures and criteria described in the CLEK Topography Reading Center Operations Manual, maintaining records of videokeratography data, and transmitting grading results to the Coordinating Center. The CLEK Topography Reading Center consists of the CTRC Director, the CTRC Programmer, the CTRC Technician, and the CTRC Biostatistician.

16.1.5 CLEK Executive Committee and the Study Chairman
The CLEK Executive Committee consists of five people: Karla Zadnik, OD PhD, of The Ohio State University College of Optometry, the CLEK Study Chairman, Joseph T. Barr, OD MS, of The Ohio State University College of Optometry, Director of the CLEK Photography Reading Center, Mae O. Gordon, PhD, of Washington University, Department of Ophthalmology and Visual Sciences and the Division of Biostatistics, Timothy B. Edrington OD MS of the Southern California College of Optometry, Consultant to the CLEK Photography Reading Center, and Donald F. Everett, MA, National Eye Institute, Project Officer. Dr. Zadnik as Study Chairman and the Executive Committee are responsible for the overall scientific conduct of the CLEK Study and maintaining the CLEK Study organization as an effective collaborative group. The staff at the Study Chairman’s Office consists of the Study Chairman and the Study Coordinator.

16.1.5 National Eye Institute Program Office

The National Eye Institute Program Office is responsible for administration and monitoring of the CLEK Study. The Program Office participates in the general organizational and scientific guidance of the study. The National Eye Institute appoints the Data Monitoring and Oversight Committee.

16.2 Study Administration

The administration of the CLEK Study is provided by key standing committees which are as follows:

- Executive Committee
- Data Monitoring and Oversight Committee

Each of these committees is described in the sections which follow. These committees are expected to function throughout the lifetime of the CLEK Study.

16.3 Executive Committee

The Executive Committee has overall responsibility for directing CLEK Study activities and formulating policy for the Study, except for responsibilities specifically assigned to other committees.

The Executive Committee meets in person at least once each year and by telephone conference weekly. Additional meetings may be called by any member of the Executive Committee.
16.3.1 Executive Committee Membership

The following individuals are permanent voting members of the Executive Committee:

- Study Chairman
- Director of the Coordinating Center
- Director of the CLEK Photography Reading Center
- Consultant to the CLEK Photography Reading Center
- Director of the CLEK Topography Reading Center
- National Eye Institute Project Officer

The Study Chairman may appoint other individuals to the committee for one-year terms as she deems necessary to assure the scientific quality of the deliberations.

Any member who misses two consecutive meetings of the Executive Committee is subject to replacement by the Study Chairman. All members are expected to file statements with the Study Chairman describing any personal or professional involvement with manufacturers or others who might benefit financially from the findings of the CLEK Study.

16.3.2 Executive Committee Functions

Some of the specific functions of the Executive Committee are:

- To deal with day-to-day operational matters which do not involve changes in the Study protocol or policy;
- To assign priorities for Study activities;
- To perform administrative and logistic functions for the CLEK Study, including scheduling meetings, scheduling site visits, etc.; and
- To coordinate preparation of progress reports to the National Eye Institute Director.

16.4 Data Monitoring and Oversight Committee

Responsibility for monitoring the conduct of the Study and for monitoring the accumulating data is assigned to the Data Monitoring and Oversight Committee. This committee provides recommendations to the Director of the National Eye Institute and to the CLEK Executive Committee regarding when
findings from the CLEK Study may be released to the Study investigators, to Study patients, and to the vision community. This committee also oversees the informed consent process, major changes to the protocol, and Participating Clinic performance.

The Data Monitoring and Oversight Committee meets once a year for discussion of accumulating data. Additional meetings are scheduled as necessary.

16.4.1 Data Monitoring and Oversight Committee Membership

The voting members of the Data Monitoring and Oversight Committee are not otherwise involved in the conduct of the Study. They are:

- One biostatistician/epidemiologist
- One optometrist
- One ophthalmologist

The voting members are appointed by the Director of the National Eye Institute, with input from the CLEK Executive Committee. Members who miss two consecutive meetings are subject to replacement. All members are expected to file statements with the Study Chairman describing any personal or professional involvement with manufacturers or others who might benefit financially from the findings of the Study.

In addition to the voting members, the Data Monitoring and Oversight Committee also includes non-voting members who serve by virtue of their roles in the Study. These are:

- Study Chairman
- Director of the Coordinating Center
- National Eye Project Officer

The Chairman of the Data Monitoring and Oversight Committee may invite other individuals to attend one or more meetings in order to advise the Data Monitoring and Oversight Committee on the Study design and procedures when necessary for proper interpretation of the data.

16.4.2 Data Monitoring and Oversight Committee Functions

The specific functions of the Data Monitoring and Oversight Committee are to make recommendations to the Director of the National Eye Institute and to the CLEK Executive Committee regarding issues such as:
• Reviewing the design of the CLEK Study, including methods of patient recruitment, the informed consent process, and data collection procedures;

• Evaluating the accumulating data at regular intervals;

• Determining when the data are sufficiently convincing to answer Study questions of interest;

• Determining when data collected should be released to the Study investigators, to Study patients, and to the ophthalmic community;

• Evaluating recruitment and monitoring overall performance of the Resource Centers and Participating Clinics;

• Recommending to the Executive Committee changes in the Study protocol based on periodic data analysis;

• Evaluating data and protocols for patient protection; and

• Protecting the operational and scientific integrity of the Study, including evaluation of ancillary studies.

16.5 Patient Consent

The CLEK Study requires that written consent be obtained from each patient prior to enrollment into the Study. The patient should be asked to sign the consent form only after eligibility has been established and after patient education has been completed (see Chapters 3 and 4 of this Operations Manual for details). The signed consent form should be kept in the Clinic. The Data Monitoring and Oversight Committee and the Project Manager may review consent forms from time to time to assure adherence to minimum standards.

Each Clinician is responsible for obtaining approval of the consent form from his or her local institutional review board. (See sample Human Subjects application and informed consent form at the end of Chapter 4 of this Operations Manual.) A copy of each Clinic’s approved consent form and documentation of approval must be submitted to the Coordinating Center before patients can be enrolled in the CLEK Study.

16.6 Patient Costs
CLEK Study patients are not billed for Study-related visits and are reimbursed $20 for each Study Visit for personal expenses. Usual and customary fees apply for non-Study-related eye and vision care, including contact lens and surgical care.
16.7 Publicity

All publicity and press releases for the CLEK Study are to have prior approval of the Executive Committee. Study investigators who are approached by the press for information concerning the Study should refer these inquiries to the CLEK Executive Committee.

It is recognized that when information is sought from an individual investigator by the local press in his own community, it is sometimes necessary or desirable for the investigator to handle the request him/herself. In such an event the participating investigator should speak as an individual and not as the official representative of the CLEK Study Group. This fact should be made clear to the press; however, the information given out should be accurate and should reflect the general policy and views of the group. The Study Chairman should be informed of all local presentations to the press and be sent a copy of the material published.

16.8 Editorial Policy

16.8.1 Publication of Study Design, Methods, and Findings

The Executive Committee will review all written reports prepared for publication. All reports from the CLEK Study will list the Collaborative Evaluation of Keratoconus (CLEK) Study Group as the last author. The primary endpoint paper and selected other major papers will list only the CLEK Study Group as the primary author in a manner consistent with the publication policy of the selected journal. Other publications will list the primary author and co-authors and the CLEK Study Group. All professional participants of CLEK, including those at the central units and Participating Clinics, will be listed at the end of each paper and are considered as authors or contributors. In major papers, all study personnel, past and present, will be listed with the approval of the Clinic Principal Investigator for whom they have worked.

Conflicts regarding authorship are resolved by the Executive Committee. General guidelines for authorship are: active participation in the production of the manuscript or other important contribution. Authorship rights are not available for membership on the writing committee only, use of data only, or signing the copyright form. If the timeline for a paper has expired with no substantial evidence of progress, authorship rights are assumed to have expired. The Coordinating Center will contact the primary author, and leadership of the paper will be negotiated. The Executive Committee will be informed of changes in lead authorship. An individual may be given an acknowledgment for reading and providing critical comments on the manuscript. An investigator at the
Coordinating Center will be added to the author list on all papers which require his or her statistical input.

The Executive Committee establishes writing committees for principal papers from among the CLEK investigators. Investigators may volunteer for writing assignments and suggest additional topics where appropriate. A representative of the Coordinating Center will be appointed to writing committees on papers or presentations requiring study data. Investigators may volunteer for writing assignments and suggest additional topics where appropriate.

The investigator should submit an abstract and a short description of the proposed paper including co-authors, data to be reported and timeline for drafts and submission (Appendix 16A). This information should be sent to the Study Chairman. The Executive Committee is responsible for reviewing the proposal’s merit and deciding if it should be an CLEK Study publication. This review process is intended to insure the quality of study publications and to refine the proposal. The Executive Committee is responsible for determining priorities (timeline and order of preparation) of proposed papers/presentations. Upon approval of the proposed paper/presentation, a detailed analysis plan and timetable are developed with the Coordinating Center.

The Coordinating Center is responsible for maintaining a database that tracks proposed and approved study publications and presentations. A list of approved study publications and presentations will be distributed to all CLEK investigators on a regular basis. Interested CLEK investigators are invited to contact the primary author to add their name to the writing group.

Should the workload associated with the preparation of papers exceed the resources of the Coordinating Center, it will be the responsibility of the Coordinating Center in conjunction with the Executive Committee to establish priorities. It will be the responsibility of the Coordinating Center to contact primary authors when timelines are not met. Major problems in the preparation of manuscripts are referred to the Executive Committee.

The primary author is responsible for coordinating all activities related to the writing and submission of papers and abstracts. This includes arranging conference calls, discussing analytic plans with the Coordinating Center, assigning writing responsibilities to co-authors, maintaining timeliness, determining the order of authorship, circulating drafts to co-authors, and circulating final drafts to the Executive Committee and as needed, to the Data Monitoring and Oversight Committee. Upon circulation of the draft, there will be a two-week period during which members can make comments about the paper.
If the focus of the paper changes as it moves from abstract to the manuscript stage, the primary author will notify the Study Chairman in writing. The Study Chairman will be responsible for insuring that the revised proposal receives appropriate review.

Each publication must acknowledge National Eye Institute support as follows: “This study was supported by grants from the National Eye Institute, National Institutes of Health, Bethesda, MD.”

Copies of principal papers from CLEK are sent (before publication) to all Participating Clinic Principal Investigators, to all members of the Executive Committee, and to the Data Monitoring and Oversight Committee. Reprints of published papers are mailed to each Participating Clinic for distribution among the staff and to outside consultants. Five reprints of each paper are sent to the Coordinating Center for the CLEK library.

The Study Chairman will send a letter of approval with all manuscripts when they are submitted for publication. Some journals require that all individuals listed as members of the study group sign the copyright waiver form. If so, the writing committee will enlist the assistance of the Study Chairman’s Office to obtain these signatures.

All major study publications and presentations must receive approval of the Data Monitoring and Oversight Committee prior to submission to any professional journal or presentation at a meeting.

16.8.2 Presentations

Oral presentations and abstracts to be printed must be approved in advance by the Executive Committee. No unpublished CLEK Study results may be used for oral presentations, local or otherwise, unless a specific exception is granted by the Executive Committee and the Data Monitoring and Oversight Committee. Study results include all data collected for the CLEK Study. The above restrictions do not apply to local presentations of the design of the Study, provided these presentations contain no unpublished Study results. Such presentations are encouraged to stimulate patient recruitment.

16.8.3 Publications from Ancillary Studies

Manuscripts dealing with ancillary studies carried out in conjunction with the CLEK Study must be sent to the Executive Committee for review before
submission for publication. Investigators may not independently use Study data collected at their Clinic.
16.8.4 **Publications Concerning Methodology**

The Executive Committee encourages the investigators at the Coordinating Center and the CLEK Photography Reading Center to publish methods employed at those Resource Centers to carry out their CLEK Study functions. For example, publications from the Coordinating Center investigators may deal with methods used for data management, statistical analysis, quality assurance, or other procedures for which that Center has primary responsibility.

Papers concerning methodology developed at the Resource Centers may be published in conventional authorship format. However, CLEK Clinics, investigators, and the National Eye Institute must be recognized. Review and approval by the Executive Committee are required before manuscripts concerning methodology are submitted for publication. The authors are responsible for distributing copies of methodological publications to the Executive Committee and other CLEK investigators. Five reprints of all such publications should be sent to the Coordinating Center for the CLEK library.

16.9 **Ancillary Studies**

16.9.1 **Introduction**

Individual investigators who desire to carry out ancillary studies are encouraged to do so. Ancillary studies may greatly enhance the value of the CLEK Study and ensure the continued interest of all investigators. However, to protect the integrity of the Study, ancillary studies must be reviewed and approved by the CLEK Executive Committee before their inception, whether or not they require supplemental funds.

No additional tests or measures can be made on CLEK Study patients without prior approval by the Executive Committee. Data analysis, unless of special interest to one of the Coordinating Center investigators, is the responsibility of the ancillary study investigators.

16.9.2 **Definition of an Ancillary Study**

An ancillary study is a research project that requires either:

1. Supplemental observations or procedures to be performed on any CLEK Study patient according to a set protocol or

2. Additional work to be done by or information to be obtained from either the Coordinating Center or the CLEK Photography Reading Center.
16.9.3 **Rationale for Approval Requirement**

Everyone involved in the CLEK Study is entitled to prior assurance that no ancillary study will:

- Complicate the interpretation of CLEK Study results;
- Adversely affect patient cooperation or recruitment;
- Jeopardize the public image of the Study; or
- Create a serious diversion of Study resources locally, at the Coordinating Center, or at any other of the Resource Centers serving the whole CLEK Study Group.

16.9.4 **Preparation of Approval Request for Ancillary Study**

The request for approval of an ancillary study involves two steps. The first requires a brief description of the proposed ancillary study in narrative form stating the primary hypothesis and a brief description of the study which addresses the issues in Section 16.10.3 (above). This brief description is sent to the Study Chairman and reviewed by the Executive Committee within one month of receipt. If approved for further consideration, a detailed description should be submitted in narrative form following the standard PHS-398 format and must provide information on the additional patient burden imposed by the ancillary study informed consent procedure, extra time, extra visits, etc. It should contain a description of the objectives, methods, and significance of the ancillary study. Full details should be given concerning any procedures to be carried out on any CLEK Study patients, such as laboratory tests, psychiatric interviews, psychological testing, etc. Mention should be made of any substances to be injected or otherwise administered to the patients. Any observations to be made or procedures to be carried out on a patient outside of the Clinic should be described.

Detailed information should be given concerning the extent to which the ancillary study will require blood or other specimens. If specimens are to be obtained from the patients, mention should be made of all procedures to be carried out on these specimens.

If access to CLEK Study data is required, the investigator must specify what data are needed, on whom it is needed, and the timetable for access to such data. Access to CLEK Study data requires approval by the Data Monitoring and Oversight Committee.
All ancillary studies must have local IRB approval for the CLEK Participating Clinics involved.
16.9.5 Procedures for Obtaining Ancillary Study Approval

The investigator proposing an ancillary study should send a written request (described just above in Section 16.11.4) to the Study Chairman, who is responsible for distributing copies to all members of the Executive Committee. Within a reasonable time the Study Chairman summarizes questions and/or objections raised by members of the Executive Committee and sends this summary to the applicant for amplification, clarification, or withdrawal of the request. The members of the Executive Committee have another opportunity to review the request. If the Executive Committee then approves the ancillary study proposal, the Chairman prepares a statement of the Executive Committee consensus, including any remaining reservations or objections, and makes a recommendation to the Data Monitoring and Oversight Committee, which is responsible for review and recommendation of ancillary studies. The Chairman then notifies the investigator proposing the ancillary study of the decision.

16.9.6 Funding of Ancillary Studies

If no additional funds are required, the investigator may proceed with the ancillary study as soon as it has been approved by the Executive Committee and the Data Monitoring and Oversight Committee. If additional funds are needed, the investigator may prepare and submit a new research grant application to the potential sponsor for review in the same manner as any other new research grant application. Copies of the grant application are sent to the Study Chairman, the investigator is not to accept the grant or activate the ancillary study until approval has been received from the CLEK Executive Committee.

16.9.7 Publication of Ancillary Study Results

All manuscripts of presentations for scientific meetings based on ancillary study data must be reviewed and approved by the Executive Committee before publication or presentation. Such review pertains only to the impact on CLEK Study objectives, and not to the ancillary study’s scientific merit.

After publication, 35 reprints of the ancillary study report should be sent to the Study Chairman’s Office for distribution to the Executive Committee, and five copies should be sent to the Coordinating Center for the CLEK library.

16.9.8 Progress Reports

The Principal Investigator of each ancillary study is expected to report to the Study Chairman at six-month intervals on the progress of the ancillary study.
This report may be prepared as a letter. The Study Chairman reports on the status of all ancillary studies to the Executive Committee at each meeting.

16.10 Access to Study Information

16.10.1 Study Documents

The CLEK Operations Manual and copies of the data collection forms used in the CLEK Study will be placed in a suitable repository, such as that maintained by the National Technical Information Service, for access by any interested party. These documents may be referenced without prior approval once they have been placed in the repository. The Coordinating Center Director replaces documents in the archives with updated copies whenever substantive changes are made in the procedures or methods, as determined by either the Executive Committee or the Data Monitoring and Oversight Committee.

In general, the following documents may not be released to any group or individual outside the CLEK Study Group:

- Minutes of CLEK Study meetings;
- Performance monitoring reports for CLEK Clinics and Resource Centers;
- and
- Data Monitoring and Oversight Committee reports.

16.10.2 CLEK Study Data

Access to CLEK Study data on individual patients is prohibited to unauthorized persons, whether on file in a Clinic, in the Coordinating Center, or in the CLEK Photography Reading Center. The identity of individual CLEK Study patients may not be revealed in any public report or presentation.