Efficacy of the Nanodropper Device on Pupillary Dilation

NCT05274321

March 31, 2022

Clinical Research Protocol

RANDOMIZED TRIAL TO EVALUATE THE EFFICACY OF A SMALL VOLUME EYE DROP ADAPTER FOR PUPILLARY DILATION AND CYCLOPLEGIA IN CHILDREN

Protocol Number:	20-32530
Version Date:	1.0
Intervention:	Nanodropper Device (Nanodropper, Inc., Rochester MN)
IND Number:	N/A
Development Phase:	N/A
Sponsor:	N/A
Funding Organization:	Partial funding from the NIH-NEI EY002162 Core Grant for Vision Research. Three eye drop bottle adaptors were provided by Nanodropper, Inc.
Principal Investigator:	Name: Julius Oatts, MD Telephone: (415) 353-2800 Fax: N/A E-mail: Julius.Oatts@ucsf.edu
Medical Monitor:	N/A
Coordinating Center:	N/A

Approval:

_____ _____

PI or Sponsor Signature (Name and Title) *Date*

This confidential information about an investigational product is provided for the exclusive use of investigators of this product and is subject to recall at any time. The information in this document may not be disclosed unless federal or state law or regulations require such disclosure. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, with the obligation not to further disseminate this information.

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: #20-32530

Protocol Title: Randomized Trial to Evaluate the Efficacy of a Small Volume Eye Drop Adapter for Pupillary Dilation and Cycloplegia in Children

Protocol Date: 21 March 2022

_____ _____

Investigator Signature *Date*

_____

Print Name and Title

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LIST OF ABBREVIATIONS

µL	microliter
AE	adverse event
CFR	Code of Federal Regulations
CRF	case report form
D	diopter
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
PI	Principal Investigator
SAE	serious adverse experience
SE	spherical equivalent
SOC	standard of care

PROTOCOL SYNOPSIS

TITLE	Randomized Trial to Evaluate the Efficacy of a Small Volume Eye Drop Adapter for Pupillary Dilation and Cycloplegia in Children
SPONSOR	N/A
FUNDING ORGANIZATION	Partial funding from the NIH-NEI EY002162 Core Grant for Vision Research
NUMBER OF SITES	1
RATIONALE	Topical ophthalmic medications in the form of eye drops are widely used in pediatric ophthalmology clinics to achieve pupillary dilation and cycloplegia. The human eye can only absorb 7-10 μL of fluid, yet conventional eye drops are 50 μL. The extra medication contributes to waste, potential added systemic toxicity, and problems with medication durability, where patients run out of medication and are unable to obtain refills due to premature eye drop bottle exhaustion. This study aimed to directly compare the effect of small volume eye drops with standard of care eye drops on pupillary dilation and cycloplegia among pediatric patients.
STUDY DESIGN	This is a randomized, unblinded, non-inferiority study.
PRIMARY OBJECTIVE	To interpret a non-inferiority analysis of using the Nanodropper device for pupillary dilation and cycloplegia in pediatric patients.
SECONDARY OBJECTIVES	To interpret a non-inferiority analysis of using the Nanodropper device for intraocular pressure measurement in pediatric patients.
NUMBER OF SUBJECTS	50
SUBJECT SELECTION CRITERIA	Inclusion Criteria: Children ≤18 years of age who were having pupillary dilation performed as part of their routine eye examinations at the UCSF Pediatric Ophthalmology Clinic. Exclusion Criteria: Inability to cooperate with study interventions (eye drop administration, pupillometry, autorefraction); medication allergy to tropicamide, cyclopentolate, or phenylephrine; congenital or iatrogenic anterior segment abnormalities; anisocoria; not attending the scheduled appointment; or use of pupil altering topical or systemic medications.
TEST PRODUCT, DOSE, AND ROUTE	1% cyclopentolate at 10.4 μL dose 1% tropicamide at 10.4 μL dose

OF ADMINISTRATION	2.5% phenylephrine at 10.4 µL dose Product will be administered once with one drop of each of the above, topically through standard-sized eyedrop bottles with the Nanodropper adaptor affixed.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	1% cyclopentolate at standard -sized (approximately 50 µL) dose 1% tropicamide at (approximately 50 µL) dose 2.5% phenylephrine at (approximately 50 µL) µL dose Product will be administered once with one drop of each of the above, topically through standard-sized eyedrop bottles without any adaptor (standard of care).
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Participants will be on study for one clinic visit, approximately 40 minutes – 90 minutes. The total duration of the study is expected to be 6 months.
CONCOMMITANT MEDICATIONS	N/A
EFFICACY EVALUATIONS	N/A
PRIMARY OUTCOME(S)	• Intra-eye change in spherical equivalent from before and after dilation • Maximum pupil diameter after dilation • Change in pupil constriction percentage
SECONDARY ENDPOINTS	• Intraocular pressure after dilation
OTHER EVALUATIONS	N/A
SAFETY EVALUATIONS	N/A
PLANNED INTERIM ANALYSES	An interim analysis is planned after the enrollment of 20 participants for data collection quality and possible presentation of preliminary data at an academic conference.
STATISTICS **Primary Analysis Plan**	A non-inferiority analysis was done on the primary outcomes with pre-dilation measurements and treatment arm used as predictor variable and participants treated as random effect variable. A 10% margin on the SOC group was used to determine non-inferiority.

Rationale for Number of Subjects	Sample size was determined based on a power calculation to reach significance for one outcome at a p-value=0.05.

1 BACKGROUND

Instillation of a smaller volume eye drop has numerous advantages, including prolonging the use of medication bottles, reducing waste, and minimizing systemic absorption and local toxicity. Here, we evaluated the effectiveness of a novel small volume eye drop adapter, Nanodropper, which administers 10.4 μL eye drops when used for pediatric pupillary dilation and cycloplegia.

1.1 Overview of Non-Clinical Studies

There are two factors that coalesce to create the problem of premature bottle exhaustion. The first is patients regularly miss their eye when attempting to administer eye drops. One study determined that for every drop that makes it into a glaucoma patient's eye, seven drops are wasted during the instillation attempt.9 Second, prescription eye drop bottles elute drops that exceed the capacity of the human eye by five times.10 Therefore, every time a patient administers an eye drop, they lose approximately 80% of their medication to wasted overflow and/or systematic absorption.

1.2 Overview of Clinical Studies

Previous studies demonstrate that smaller eye drops used in the treatment of glaucoma are just as efficacious as their larger counterparts. Research on this topic dates back to 1980, beginning with a study conducted by File & Patton.20 The authors determined that 20 μL drops and 50 μL drops of 0.5% pilocarpine hydrochloride produced an equivalent miotic response in healthy volunteers. Additionally, it was noted that the 20 μL drops of the 0.5% drug solution produced fewer local symptoms (i.e., transient blurring of vision, some stinging upon administration, watering eyes, and mild redness) than the larger 50 μL drops.

2 STUDY RATIONALE

There has not yet been a study done to evaluate the efficacy of the Nanodropper device or the effect of small volume eye drops in pediatric patients.

2.1 Risk / Benefit Assessment

N/A

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to conduct an interpret a non-inferiority analysis of using the Nanodropper device for pupillary dilation and cycloplegia in a cohort of pediatric patients.

3.2 Secondary Objectives

The secondary objective is to conduct and interpret a non-inferiority analysis of using the Nanodropper device for intraocular pressure measurement in pediatric patients.

4 STUDY DESIGN

4.1 Study Overview

This is a single center, unblinded, randomized, simple, 1:1 trial. 100 eyes of 50 patients are planned. Each participant will have baseline autorefraction, pupillometry, and intraocular pressure measured at baseline. Each participant will be administered a single drop of 1% cyclopentolate, 1% tropicamide, and 2.5% phenylephrine in each eye for pupillary dilation and cycloplegia. One eye will receive the drops using standard-sized eye drop bottles and the other eye will receive drops using the same eye drop bottles, and with the Nanodropper adapter attached. 30 minutes after drop administration, each participant will have refraction, pupillometry, and intraocular pressure measured again.

Participants who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

Total duration of participation will be 40 minutes – 90 minutes. Total duration of the study is expected to be 6 months.

4.2 Primary Efficacy Outcome

The primary outcomes are 1) intra-eye change in spherical equivalent from before and after dilation, 2) maximum pupil diameter after dilation, 3) change in pupil constriction percentage.

4.3 Secondary Efficacy Outcome

The secondary outcome is intraocular pressure after dilation.

4.4 Safety Evaluations

We do not expect there to be additional safety evaluations related to this trial.

5 SUBJECT SELECTION

5.1 Study Population

Pediatric patients who were scheduled for routine pupillary dilation at the University of California, San Francisco Pediatric Ophthalmology clinic were eligible.

5.2 Inclusion Criteria

1. Male or female ≤18 years of age
2. Scheduled for routine pupillary dilation
3. Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.

5.3 Exclusion criteria

1. Inability to cooperate with study interventions (eye drop administration, pupillometry, autorefraction)

2. Medication allergy to tropicamide, cyclopentolate, or phenylephrine
3. Congenital or iatrogenic anterior segment abnormalities
4. Anisocoria
5. Not attending the scheduled appointment
6. Use of pupil altering topical or systemic medications
7. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.

6 CONCURRENT MEDICATIONS

N/A

6.1 Allowed Medications and Treatments

N/A

7 STUDY TREATMENTS

7.1 Method of Assigning Subjects to Treatment Groups

Example text: Up to 60 eligible patients will be randomly assigned receive eyedrops using the Nanodropper device in either the right or left eye, and standard of care drops in the other eye. Treatment groups (standard of care or Nanodropper) will be randomized in a 1:1 ratio using a web-based computer-generated randomization.

7.2 Blinding

Due to the nature of the study, investigators, research staff, and patients will be unblinded to the intervention.

7.3 Formulation of Test and Control Products

The intervention product is the Nanodropper adaptor (Nanodropper, Inc., Rochester, MN). The Nanodropper adaptor (right, Nanodropper, Rochester, MN) is comprised of three parts: the tip, base, and cap. The silicone tip tapers to a small diameter opening in order to reduce drop volume and is secured to the existing bottle with the base, which screws onto the eye dropper over the original cap. A plastic cap is kept in place to protect the tip in between drop administrations. The Nanodropper can be used for multiple uses but should not be removed from a bottle once attached.

7.4 Supply of Adaptors at the Site

Three Nanodropper adaptors have been provided by the manufacturer to the site for use in this study. The dedicated study eye drop bottles are located in the locked clinic office in the locked materials cabinet. Study staff will transport study eye drop bottles to and from clinic rooms for use.

7.4.1 Administration Instructions

Nanodropper adaptors will already be attached to eye drop bottles prior to use in the study. Administer the drops by gently squeezing eye drop bottles to elute one drop of medication into the patient's open eye. Repeat for all three topical ophthalmic medications denoted in this protocol.

7.4.2 Storage

Study adaptors should be stored by the study site at controlled room temperature.

8 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

8.1 Clinical Assessments

8.1.1 Demographics

Demographic information (date of birth, gender, eye color) will be recorded at Visit 1.

8.1.2 Baseline measurements

Baseline spherical power, cylindrical power, axis; maximum pupil diameter, minimum pupil diameter, pupil constriction percentage, pupil construction latency, and intraocular pressure will be recorded at Visit 1.

8.1.3 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop and times), outcome, treatment and relation to study intervention will be recorded in the notes section of the electronic data collection form.

9 EVALUATIONS BY VISIT

9.1 Visit 1

1. Review the study with the subject (subject's legal representative) and obtain electronic informed consent and HIPAA authorization and assent, if appropriate.
2. Assign the subject a unique screening number.
3. Record demographics data.
4. Record non-cycloplegic autorefraction, pupillometry, and tonometry.
5. Randomize Nanodropper to be given to right or left eye.
6. Administer dilating eye drops.
7. Record cycloplegic autorefraction, pupillometry, and tonometry.

9.2 Early Withdrawal

1. Record any Adverse Experiences and record reason for withdrawal.

10 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

10.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign, symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

10.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

10.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB), the site investigator will report SAEs to the IRB.

11 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

11.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation

12 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, study staff, or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Inappropriate administration of medication (too many eye drops)
- Failure to measure or record data

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The study investigator will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

13 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

13.1 Data Sets Analyzed

All eligible patients who are randomized into the study and receive the intervention of small volume eye drops will be included in the analysis. Outcome data will be analyzed an a by-eye level, not a by-patient level.

13.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized by intervention/control group: gender, age, eye color, refractive error.

13.3 Analysis of Primary Endpoint

We plan a non-inferiority analysis of the primary endpoints: spherical equivalent, maximum pupil diameter, and pupil constriction percentage. Change scores for each outcome will be calculated by subtracting post-dilation values from pre-dilation values for both the intervention and control groups. Absolute differences for each outcome will be calculated by subtracting standard of care and intervention change score. Confidence interval will be set at 95%. Analysis of covariance (ANCOVA) will be performed on each post-dilation outcome with pre-dilation measurements and treatment arms will be used as predictor variables. Participants will be considered as a random effect variable. The noninferiority margin will be determined by taking ten percent of the standard of care change score. Non-inferiority will be determined if the non-inferiority margin does not overlap with the regression coefficient's 95% confidence interval.

We will also analyze statistical significant differences between means of both groups for each outcome. We plan to use the Shapiro-Wilk test to analyze if the data is normally distributed. We will then plan to do a paired t-test or a Wilcoxon signed rank test to examine within-subject differences in the outcomes between standard of care and intervention groups. We plan to perform Welch's t-test and Mann Whitney U test to examine within-eye differences between standard of care and intervention eyes determined by the distribution results of Shapiro-Wilk test.

13.4 Analysis of Secondary Endpoints

Statistical analysis of the secondary endpoint, intraocular pressure, will be analyzed as above.

13.5 Interim Analysis

N/A

13.6 Sample Size and Randomization

Sample size was determined based on a power calculation to reach significance for one outcome at a p-value=0.05. A minimum of 100 eyes will be included.

DATA COLLECTION, RETENTION AND MONITORING

13.7 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) OR paper CRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database, but will be identified by a site number, subject number, and birthdate.

For eCRFs: If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. *For paper CRFs:* If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

13.8 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

13.9 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

13.10 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

13.11 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

13.12 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

13.13 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject birthdate will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

14 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

14.1 Protocol Amendments

Any amendment to the protocol will be written by the study investigator. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment

intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

14.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB of the participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

14.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent

from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

14.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

14.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX 1. STUDY VISIT SCHEDULE

	VISIT 1
Informed Consent	**X**
Demographics	**X**
Non-cycloplegic autorefraction	**X**
Non-cycloplegic pupillometry	**X**
Non-cycloplegic tonometry	**X**
Eye dilation using standard of care drops	**X**
Eye dilation using Nanodropper	**X**
Cycloplegic autorefraction	**X**
Cycloplegic pupillometry	**X**
Cycloplegic tonometry	**X**
Adverse Experiences	**X**