STATISTICAL ANALYSIS PLAN

Study Protocol Number:	21-35793
Study Protocol Title:	Efficacy of Repeated Low-Level Red-Light Therapy in Myopia Control in Children: A Randomized Controlled Trial (RLRL Myopic Trial)
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ICH	International Conference on Harmonisation
RLRL	Repeated Low-level Red-Light
AL	Axial length
Ortho-K	Orthokeratology
RCT	Randomised Controlled Trial
RLRL	Low-Level Red-Light
SER	Spherical Equivalent Refraction
SVS	Single Vision Spectacle
CC	Corneal curvature
ACD	Anterior chamber depth
WTW	White to white
UCVA	Uncorrected visual acuity
BCVA	Best-corrected visual acuity
ChT	Choroidal thickness
OCT	Optical coherence tomography
AE	Adverse event
SAE	Serious adverse event
ITT	Intention-to-treat
PP	Per-protocol
SD	Standard deviation
CI	Confidence interval
ETDRS	Early Treatment Diabetic Retinopathy Study
DSMC	Data and Safety Monitoring Committee
CRF	Case report form

1. INTRODUCTION

Myopia, also known as short-sightedness or near-sightedness, is the most common eye disorder of school-aged children globally. Further progression towards severe myopia (also called high myopia, defined as -6.0 diopter or greater) that is associated with an increased risk of developing conditions that cause irreversible blindness, including myopic maculopathy, glaucoma or even retinal detachment. An effective treatment to control the progression of myopia is therefore critically important for childhood vision with preservation of eye health and quality of life as outcomes.

Current methods for controlling myopia progression have limitations for the global control of myopia. Based on our previous findings on the protective effects of increased light intensity of outdoor time, we are proposing an innovative solution, which in lieu of increasing ambient light illumination through outdoor light exposure, employs a device that creates direct local illumination on the ocular fundus. This strategy enables relatively higher energies of light to be delivered at much shorter durations of exposure to induce the myopia control effect. A successful 12-month multi-site randomized trial was conducted in China between 2019-2020 (Efficacy of repeated low-level red-light (RLRL) therapy in myopia control, Clinical trial registration: NCT04073238) and enrolled 264 school-aged children between 8-13 years old. The use of a home-based device (RLRL therapy, 3 minutes per session, twice per weekday, 12months) effectively controlled myopia progression, reaching 76.8% efficacy in controlling axial length elongation and 87.7% in spherical equivalent progression when the time of compliance to the treatment was 75%. More importantly, the study demonstrated that this novel intervention was safe and did not cause functional visual loss as indicated by best-corrected visual acuity or structural damage seen on retinal scans at each follow-up visit.

Given that the trial conducted in China was primarily in Chinese school-aged children, the currently proposed trial aims to confirm that the efficacy and safety of RLRL treatment are similar in the population that is representative of western countries, for example including Caucasian, Indian and Chinese patients. This study design is based on the hypothesis that whether the responses to RLRL treatment among various ethnic groups are similar remains unknown. In the current study, we propose to undertake trials in the USA to test the efficacy and safety of this novel treatment among African, Hispanic and Caucasian children.

1.1 Study Objectives

1.1.1 Primary Objective

- To assess the change from baseline in ocular axial length (AL) elongation among multi-ethnic children after RLRL treatment for 12-month

1.1.2 Secondary Objectives

- To assess the change from baseline in spherical equivalent refraction (SER) progression among multi-ethnic children after RLRL treatment for 12 months
- To assess the change from baseline in other ocular biometric parameters other than AL among multi-ethnic children after RLRL treatment for 12 months
- To assess the change from baseline in uncorrected visual acuity (UCVA) among multi-ethnic children after RLRL treatment for 12 months
- To assess the change from baseline in choroidal thickness (ChT) among multi-ethnic children after RLRL treatment for 12 months
- To assess the safety of RLRL treatment on self-reported adverse events (AE), best-corrected visual acuity (BCVA), and optical coherence tomography (OCT) scan for 12-month among multi-ethnic children

1.2 Study Design

This trial is a single-center, multi-ethnic, single-blind, parallel-group randomized controlled trial designed to evaluate the efficacy and safety of RLRL treatment on myopia among multi-ethnic schoolchildren.

This study will be conducted in the University of California, San Francisco (UCSF), and will enroll approximately 90 eligible children. The study period will be 12 months (1 year) and participants will be followed up at 1 month, 3 months, 6 months and 12 months.

Participants are aged 8-13 years old children with myopia cycloplegic SER of -1.00 to -5.00 D, astigmatism of 2.50 D or less, anisometropia of 1.50 D or less, and BCVA of 0.0 logarithm of the minimum angle of resolution or more (Snellen equivalent, 1.0 or 20/20) in either eye; with Hispanic, African or Caucasian ethnicity; without ocular abnormalities and prior myopic treatment in either eye, including but not limited to drugs, orthokeratology, progressive addition lenses, bifocal lenses, etc.

Eligible subjects will randomize in a 1:1 allocation ratio to either the RLRL treatment group or the single vision spectacles (SVS) control group. On top of wearing single vision spectacles, subjects in the RLRL treatment group will receive treatment twice a day from Monday to Friday, with each treatment lasting for 3 minutes at a minimal interval of 4 hours. The treatment will be carried out by the subjects themselves under thesupervision of their parents at home according to a standard protocol. The compliance will be monitored by an online log-in system built into the device that allows the users to log in with their username, with the system recording the day/time

and duration of each treatment session. Subjects in the SVS control group will wear single vision spectacles.

RLRL treatment device used in this study is a semi-conductor laser product (Eyerising International Pty Ltd, Melbourne, Australia), emitting low-level red-light with a wavelength of 650 ± 10 nm. Based on calculations done by the manufacturer, the device provides light at a power of 2.00 ± 0.50 mW. Instruction will be provided on how to use the device through a video demonstration to participants in the RLRL treatment group and the video will be provided to parents for review at any time.

A baseline visit will be conducted to obtain written informed consent from the participants (parents/guardians) and to assess the inclusion and exclusion criteria for the study. Eligible subjects who provide written informed consent will be randomly allocated to one of the two study groups (RLRL treatment or control). The baseline visit will also record date of birth, gender, ethnicity, medical history of ocular disease or surgery and perform visual acuity assessment, ocular biometric measurements via IOL Master, cycloplegia, cycloplegic auto-refraction, slit-lamp examination and optical coherence tomography.

At 1-month, 3-months, 6-months and 12-months follow-up and unexpected visits, a questionnaire on adverse events following the intervention will be administered to the subjects in the intervention group. Subjects and their parents/guardians will be asked if their health has changed since the last visit, including but not limited to short-term glare, flash blindness, and afterimages. The measurements at each follow-up visit are the same as the baseline assessments, including visual acuity assessment, ocular biometric measurements via IOL Master, cycloplegia, cycloplegic auto-refraction, slit-lamp examination and optical coherence tomography.

1.3 Study Timepoints

Participants will participate in this study for 12 months. Patients will attend the study site at Pre-screening and Visit 1 (baseline) for informed consent and confirmation of eligibility. The primary and secondary efficacy outcomes and safety outcomes for the study are assessed at 1month, 3 months, 6 months and 12 months.

The procedures to be performed throughout the study are outlined in the Schedule of Events in Table 1.

Table 1. Schedule of Events

	Pre-screening (Pre-consent)	Visit 1 (baseline examination)	Visit 2 (1-month±7)	Visit 3 (3-month±7)	Visit 4 (6-month±7)	Visit 5 (12-month±7)

Screening criteria		x					
Informed Consent			x				
Baseline questionnaire			x				
Randomization			x				
Control & Interventions ——Low-level red-light therapy			x	x	x	x	x
Treatment related questionnaire				x	x	x	x
Slit-lamp examination			x	x	x	x	x
Cycloplegia			x	x	x	x	x
Axial length assessment			x	x	x	x	x
Spherical equivalent assessment			x	x	x	x	x
Other ocular parameters	CC		x	x	x	x	x
	ACD						
	WTW						
Visual acuity	UCVA		x	x	x	x	x
	BCVA						
OCT			x	x	x	x	x
Supervision of project implementation			x	x	x	x	x
Adverse Events, Concomitant medications or treatment Reporting				x	x	x	x

2. STUDY POPULATIONS

A total of two populations will be used for all summaries and analyses. Subjects who have satisfied the population criteria will be classified in the designated population and will only be included in analyses for which they have available data.

Intention-to-Treat (ITT) Population

The ITT population is defined as all randomized subjects, regardless of when they withdrew from the study. The ITT population will be used to present all the efficacy data (including the primary and secondary efficacy outcomes) by randomized treatment group. Subjects will be summarized according to the group to which they are randomized, regardless of which treatment they actually receive.

Per-Protocol (PP) Population

The PP population consists of a subgroup of subjects of the ITT population who complete the trial without significant deviations from the protocol requirements. PP population excludes those participants who violate the protocol, including those who switch the allocation arm throughout the study, do not adhere to the assigned treatment or do not undergo scheduled assessments over time.

3. DEFINITIONS AND DERIVED VARIABLES

3.1 Demography and Baseline Characteristics

Age. Age will be calculated using the date of birth and the date of the baseline visit, and presented as age at last birthday as an integer.

3.2 Ocular parameters and visual acuity

Axial length (AL). AL is measured along the direction of the axis to obtain the distance of the optical path from the front surface of the cornea to the retinal pigment epithelium.

Spherical equivalent refraction (SER). SER is calculated by using the sum of the spherical power and half of the cylindrical power.

Corneal curvature (CC). Corneal radius of curvature is measured by the distance between corneal reflections.

Anterior chamber depth (ACD). ACD measurement is defined as the distance from the vertex of the anterior corneal surface to the anterior lens surface

White-to-white (WTW). WTW is determined by the corneal diameter.

Uncorrected Visual Acuity (UCVA) and Best-corrected visual acuity (BCVA). UCVA and BCVA are distance visual acuity measured by visual acuity chart.

Choroidal thickness (ChT). ChT is measured as the perpendicular distance from the outer portion of the hyperreflective line corresponding to the retinal pigment epithelium to the posterior edge of the choroid as demarcated by the hyperreflective line corresponding to the chorioscleral interface.

4. EFFICACY PARAMETERS

4.1 Primary Efficacy Outcome (Axial length)

The primary outcome is the change in AL measured at the 1-, 3-, 6-, and 12-month follow-up visits compared with baseline. Five measures of AL will be conducted on each eye prior to cycloplegia using partial coherence interferometry IOLMaster (Carl Zeiss 500, Meditec, Oberkochen, Germany) and averaged if the desired precision (i.e., < 0.05 mm) is achieved.

4.2 Secondary Efficacy Outcomes

The secondary efficacy outcome includes changes in cycloplegic spherical equivalent refraction (SER, myopia progression) measured at baseline compared to the 1-, 3-, 6- and 12-month follow-up visits.

4.2.1 Cycloplegic Spherical Equivalent Refraction

Refraction data will be measured at each eye using an autorefractor (KR-8800, Topcon, Tokyo, Japan) three times and averaged if the desired precision (i.e., spherical and cylindrical power < 0.25 D, axis < 5 degrees) is achieved. Cycloplegia will be achieved using 1 drop of 0.5% Alcaine (Alcon, Puurs, Belgium) followed by 3 drops of 1% cyclopentolate (Alcon, Puurs, Belgium) to each eye at 0, 5, and 20 minutes. Pupil light reflex and pupil diameter will be checked to confirm full cycloplegia. The SER is calculated by using the sum of the spherical power and half of the cylindrical power.

4.3 Other Outcomes

4.3.1 Biometric Parameters other than Axial Length

Other ocular biometric parameters (ACD, CC, and WTW corneal diameter) will be measured at the same session as AL measurement on each eye before cycloplegia by IOLMaster and were averaged if their desired precisions were achieved.

4.3.2 Uncorrected Visual Acuity

Uncorrected visual acuity (UCVA) will be assessed at 4 meters by trained optometrists using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart (Precision Vision, Villa Park, Illinois, USA). The examination protocol is the same as the protocol used in the Refractive Error Study in Children (which was a multi-country, population-based study in children organized by the World Health Organization).

4.3.3 Choroidal Thickness

For choroidal thickness (ChT), participants will undergo swept-source optical coherence tomography (SS-OCT, DRI-OCT Triton, Topcon, Tokyo, Japan) with pupil dilation and under standardized mesopic light conditions at the baseline examination and each follow-up visit. The DRI-OCT system uses an axial scan rate of 100,000 Hz using the laser wavelength of 1050 nm, yielding an 8-μm axial resolution and transverse resolution of 20 μm. Subjects will undergo 12 × 9 mm radial scans centered at the fovea. The quality of the scans is indicated by an automated display mode. The thickness (the distance between outer choroid-scleral margin and RPE-Bruch's complex) will be

obtained automatically with the assistance of SS-OCT software.

5. SAFETY PARAMETERS

5.1 Adverse Events

A questionnaire on adverse events following the intervention will be administered at each follow-up visit and unexpected visits for the subjects in the intervention group. Subjects and their parents/guardians will be asked about the adverse events, including but not limited to short-term glare, flash blindness, and afterimages.

5.2 Ocular Structural and Functional Parameters

5.2.1 OCT Structural Scan

The swept-source optical coherence tomography (SS-OCT, DRI-OCT Triton, Topcon, Tokyo, Japan) will be used to assess the anatomic changes of the fundus during the 12 months of follow-up.

5.2.2 Best Corrected Visual Acuity

Best corrected visual acuity (BCVA) will be used to assess the functional changes during the 12 months of follow-up. BCVA is assessed at 4 meters by trained optometrists using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart (Precision Vision, Villa Park, Illinois, USA). The examination protocol is the same as the protocol used in the Refractive Error Study in Children (which was a multi-country, population-based study in children organized by the World Health Organization).

6. STATISTICAL METHODOLOGY

6.1 Statistical and Analytical Issues

6.1.1 Statistical Methods

All statistical methods will be based on the International Conference on Harmonisation (ICH) E9 document “Statistical Principles for Clinical Trials”.

Data analysis will be performed under the intention-to-treat (ITT) principle. All subjects

who complete the protocol and those who fail to complete the protocol but do not withdraw from the study will be included in the analysis data set. For subjects who withdraw from the study, valid data collected before the withdrawal will be included in the analysis data set.

The eye that meets the inclusion criteria will be included in the analysis. If both eyes meet the inclusion criteria, and there is no statistical difference in ocular parameters between these two eyes, the right eye will be included in the analysis.

Descriptive statistics: For continuous variables, sample size, mean, standard deviation (SD), median, minimum, maximum, quartile and 95% confidence intervals (CIs) will be presented. For categorical variables, frequency distribution will be presented.

All statistical tests will be carried out at the 5% (2-sided) significance level unless otherwise specified.

Stata Statistical Software release 14 (StataCorp; College Station, TX, USA) will be used for statistical analysis.

6.1.2 Handling of Missing and Censored Data

Missing data on outcomes will not be imputed. Individuals who are switched to other myopia treatment methods, including orthokeratology or atropine eye drops, or those who discontinue RLRL treatment will be considered to be censored. They are included in the analysis, but only the data at the last visit before censoring will be used.

6.1.3 Determination of Sample Size

As a primary outcome, the RCT conducted in Guangzhou suggested that the mean±SD for 12-month changes in axial length were 0.12±0.21 mm and 0.36±.20 mm for the RLRL and control groups respectively. The averaged axial elongation in myopic children is assumed to be 0.36 mm/year with an SD of 0.2 mm/year from 8 to 13 years of age. The expected efficacy is assumed to be 42%. Hence, a sample of 76 can provide a power of 90% with a two-sided alpha of 0.05. Further, assuming a loss to follow-up of less than 15% per year leads to a total study sample size of 90 myopic children. Thus, 30 out of 90 study samples will be recruited for African, 30 for Hispanic and the remaining 30 for Caucasian.

Sample size justification: The expected difference between treatment and control groups is referred from a recently completed trial in Chinese school-aged children with the same inclusion and exclusion criteria.

6.2 Subject Characteristics

6.2.1 Subject Disposition

The subject disposition table will summarize the following and will be presented for all subjects by treatment group and overall.

- The number (%) of subjects randomized at the baseline visit
- The number (%) of subjects completed 1-month visit, 3-month visit, 6-month visit and 12-month visit
- The number (%) of subjects withdrawn at 1-month visit, 3-month visit, 6-month visit and 12-month visit
- The number (%) of subjects dropped out at 1-month visit, 3-month visit, 6-month visit and 12-month visit
- The number (%) of subjects in the ITT population
- The number (%) of subjects in the PP population

The number (%) of subjects who complete and withdraw from the study and the primary reason for withdrawal will be summarized by treatment group and overall for all subjects.

6.2.2 Protocol Violations

Protocol violations are defined as deviations from the procedures outlined in the protocol. All statistical analyses and summaries will be conducted on an ITT basis. The per protocol (PP) analysis strategy will furtherly validate the results. The PP population is defined as children who complete the treatment (SVS wear and RLRL treatment scheduled as 3 minutes per session, twice daily with a minimum interval of 4 hours, 5 days per week) and control (SVS wear) as originally allocated and who do not commit any major protocol violation.

6.2.3 Background and Demographic Characteristics

Demographic data presented will be age and gender. Baseline ocular characteristics (AL, SER, UCVA) will be reported.

Demographic and background data will be summarized using summary statistics for continuous variables (number of subjects, mean, SD, median, minimum and maximum) or by way of group frequencies and percentages for categorical variables, as appropriate. The ITT and PP population will be used to present these data.

6.2.4 Treatment exposure and compliance

Treatment compliance will be determined based on data from the automated diary function in the device system. Compliance is assigned as 100% if the date and times of treatment sessions suggested the participant complete all the assigned treatment

sessions (2 sessions a day, 5 days a week). Otherwise, compliance is calculated as a percentage of completed sessions divided by the total number of assigned treatment sessions during the whole treatment period.

Subjects will be asked at 1-month, 3-month, 6-month and 12-month visits whether they used any myopia treatment methods other than single vision spectacles and RLRL, e.g., orthokeratology, atropine, progressive addition lenses and bifocal lenses.

6.3 Efficacy Analysis

6.3.1 Primary Efficacy Analysis

The primary efficacy outcome is the change in AL assessed by IOL Master in 1-month, 3-month, 6-month and 12-month compared to baseline. Longitudinal mixed models will be used to demonstrate RLRL therapy efficacy on the progression of the primary outcome. An unstructured covariance matrix will be used along with a restricted maximum likelihood method, where the group, visit, and group-by-visit interaction will be added as fixed effects together with baseline age, sex, and baseline value as covariates. The subjects will be included as a random factor. The estimated mean treatment differences, corresponding 95% CIs, and two-sided P values will be calculated. Analysis will be conducted in the ITT population.

To measure the association between primary treatment efficacy and compliance on treatment, longitudinal mixed models where compliance is estimated as a percentage of the total number of assigned treatment sessions will be carried out.

Sensitivity analyses based on the per-protocol strategy will be performed to investigate the efficacy of RLRL therapy on the progression of the primary outcome (axial elongation) in the PP population. Sensitivity analyses will be further performed to assess efficacy of RLRL therapy in AL elongation control across different ethnic groups (Hispanic, African and Caucasian), different refraction groups and age groups.

6.3.2 Secondary Outcomes Analysis

The continuous secondary outcomes, including cycloplegic SER, ACD, CC, WTW corneal diameter and ChT will be analyzed in longitudinal mixed models where an unstructured covariance matrix will be used along with a restricted maximum likelihood method. The estimated mean treatment differences, corresponding 95% CIs, and two-sided P values will be calculated. Analysis will be conducted in the ITT population. Only the refraction data with full cycloplegia will be used for the analysis to ensure accuracy on refraction measurement.

Longitudinal mixed models where compliance is estimated as a percentage of the total number of assigned treatment sessions will be carried out, in order to measure

association between myopia control efficacy in SER and compliance on treatment.

Sensitivity analyses based on the per-protocol strategy will be performed to investigate the efficacy of RLRL therapy on the progression of the key secondary outcome (refraction progression) in the PP population. Sensitivity analyses will be further performed to assess efficacy of RLRL therapy in SER progression control across different ethnic groups (Hispanic, African and Caucasian), different refraction groups and age groups.

Changes in UCVA (an ordinal variable) will be categorized into 3 groups: worsening of 2 lines or more, no change (within 1 line), and improvement of 2 lines or more. Chi-square test will be used to explore the distribution of categorical secondary outcomes between two groups.

6.4 Safety Analysis

6.4.1 Adverse Events

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the adverse event form. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to an adequate resolution. Any medical condition that is present at the time that the participant is screened will be considered as a baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittently require documentation of onset and duration of each episode.

The masked treating physician will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization. All AEs should be followed until they are resolved or until a stable clinical endpoint is reached. Each AE is to be classified by the Investigator as SERIOUS (SAE) or NONSERIOUS (NSAE). All AEs must be reported from the time that the participant provides informed

consent through the last study visit.

A general summary table reporting the number (%) of subjects and the number of all AEs will be presented by the treatment group.

6.4.2 Ocular structure and function evaluation

For the ocular structure assessment, two ophthalmologists independently will review all OCT scans to identify possible structural damages. For ocular function evaluation, BCVA at 12 months will be categorized into meeting a 20/20 threshold and not meeting the threshold.

6.5 Interim Analysis

An interim analysis is planned to be performed at a three-month follow-up to assess the safety of the treatment and the preliminary efficacy of RLRL therapy. Based on the interim analysis results, the significance threshold will be adjusted to a P value of 0.048 after O'Brien–Fleming α-spending adjustment for the primary outcome.

6.6 Data Monitoring Committee Charter

The independent data and safety monitoring committee (DSMC) is established. The members of the committee include Leon Ellwein (chairman), Lei Zhang, and Robert Chang. The members are independent of the project team and there are no conflicts of interest. The members of the data and safety monitoring committee will regularly check the data collection process, storage, and analysis, and access the original data related to this clinical trial to determine the integrity, accuracy and consistency of the information with the original data. Relevant information will be available to members of the data and safety monitoring committee at any time. The data and safety monitoring committee will review informed consent and all data.

6.7 Analysis of Other Assessments

There will be no analysis of other assessments.

6.8 Analysis Performed

Should any of the planned statistical methods proposed prove unsuitable during the final analysis, more appropriate methods will be used, and any changes, including the rationale for use, will be documented in the clinical study report.

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