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Protocol for a parallel assignment prospective, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of 0.01% atropine for near work-induced transient myopia and myopic progression

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Complete List of Authors:	Qin, Guanghao; He Eye Specialist Hospital, Ophthalmology Chen, Jiayan; He Eye Specialist Hospital, Ophthalmology Hu, Lan; He Eye Specialist Hospital Qi, Yifan; He Eye Specialist Hospital, Ophthalmology Xu, Ling ; He Eye Specialist Hospital, Ophthalmology He, Wei; He Eye Specialist Hospital, Ophthalmology Yu, Sile; He Eye Specialist Hospital, Ophthalmology; He University Pazo, Emmanuel Eric; He Eye Specialist Hospital, Ophthalmology He, Xingru; He Eye Specialist Hospital, Ophthalmology; He University
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Protocol

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Names protocol contributors: Guanghao Qin [1], Jiayan Chen [1], Lan Hu[1], Yifan Qi[1], Ling Xu[1], Wei He [1], Sile Yu [1,2], Emmanuel Eric Pazo [1]*, Xingru He [1,2]*

1 He Eye Specialist Hospital, Shenyang, China.

2 He University, Shenyang, China.

*** Correspondence:**

1. Emmanuel Eric Pazo, Department of Ophthalmology, He Eye Specialist Hospital, Shenyang, China.11003

ericpazo@outlook.com

2. Xingru He, School of Public Health, He University, Shenyang, China.110034

hexingru@hsyk.com.cn

ABSTRACT

Introduction: Near work-induced transient myopia (NITM) is important in permanent myopia (PM) development and progression. Atropine eye drop is beneficial in reducing initial NITM and slowing down myopic progression.

Methods and analysis: Participants will be randomly assigned in a 1:1 ratio to receive 0.01% atropine or placebo eye drop once nightly bilaterally for one year. Initial NITM, cycloplegic refraction, axial length (AL), best-corrected visual acuity (BCVA), intraocular pressure (IOP), and pupil diameter will be measured at baseline, 4-week, 12-week, 24-week, 36-week, and 48-week. Visual Function Questionnaire will be administered at baseline and each follow-up visit. Adverse events also will be monitored and documented at each subsequent follow-up visit.

Discussion: This study investigates the efficacy of 0.01% atropine in the treatment of NITM and its possible association with the progression of refractive change in Chinese myopic children.

Ethics and dissemination: A parallel assignment prospective, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of 0.01% atropine for near work-induced transient myopia and myopic progression registered on 10 September 2023. Ethics approval number: IRB (2023) K025.01. The study's findings will be shared regardless of the effect's direction.

Registration number: NCT06034366.

Keywords: Myopia, near work-induced transient myopia, 0.01% atropine, RCT

Strengths and limitations of this study:

- The trial is designed to be embedded into routine clinical practice regarding myopia treatment.
- The protocol promotes understanding of the mechanism, enabling credible inference about benefits.
- A large RCT has not been conducted to understand the benefits of 0.01% atropine in the treatment of NITM and the relationship between NITM and refractive change after treatment in the long term.
- The limitation of the research is that it's a single-center study.
- The study is limited to 1-year follow-up.

INTRODUCTION

Background and rationale {6a}

Myopia is a common condition that develops primarily during childhood and early adulthood when excessive elongation of the eye results in images of distant objects coming into focus in front of the retina, which leads to blurred distance vision.[1] Myopia is the most common ocular disorder worldwide, with increasing prevalence over the past decades, predominantly in East Asia.[2,3] Previous studies suggested that environmental factors, such as near-work demands, likely play an important role in myopia development in the younger population.

Near work is a major environmental component in establishing and progressing permanent myopia (PM), induced via near work-induced transient myopia (NITM). In

contrast to PM, NITM refers to the prolonged period required for the accommodation of the eyes to revert to a normal level after performing a persistent near task.[4] It was proposed some years ago that NITM, which produces minor and chronic retinal defocus, may be one of many possible environmentally-based, myopigenic, contributory factors to permanent myopia.[5,6]

As a nonselective muscarinic antagonist, atropine eye drops with different concentrations have been reported to slow down the myopic progression in myopes.[7,8] Recently, a two-week study assessed the efficacy of a low-concentration of atropine (0.01%) on the initial NITM magnitude among Chinese myopic children.[9] The results suggested 0.01% atropine reduced the initial NITM magnitude. However, the long-term efficacy of 0.01% atropine in treating NITM and the relationship between NITM and refractive change after treatment is still unclear.

This study aimed to investigate the efficacy of 0.01% atropine in treating NITM and its possible association with the progression of refractive change in Chinese myopic children.

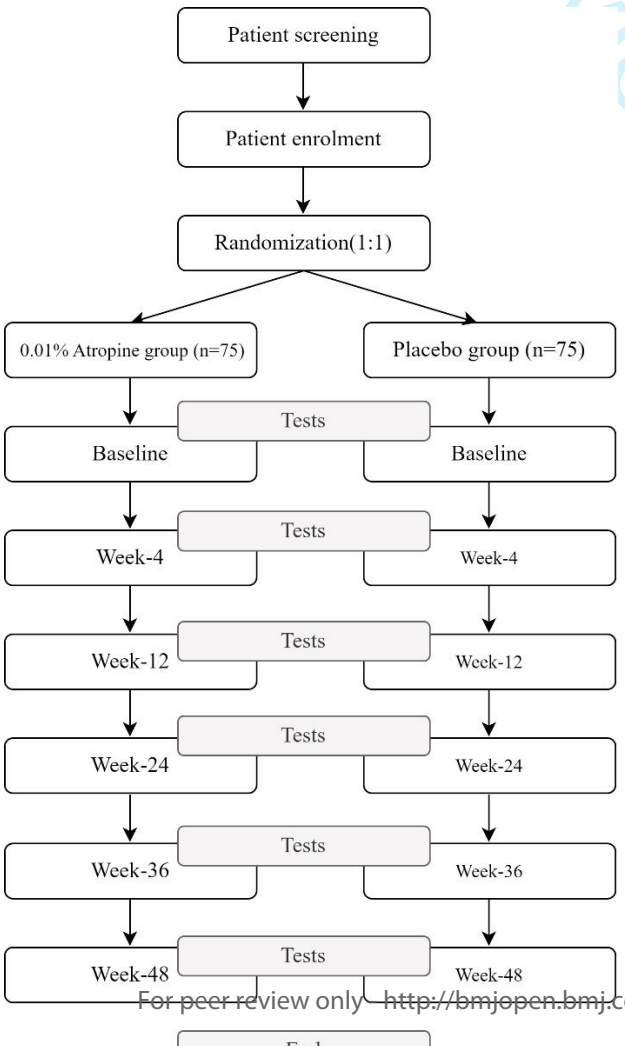
Objectives {7}

The primary objective of this study is to investigate the efficacy of 0.01% atropine in the treatment of NITM and its possible association with the progression of refractive change in Chinese myopic children.

Trial design {8}

This is a prospective, randomized, double-blind, placebo-controlled trial performed at He Eye Specialist Hospital [ethics approval number: IRB (2023) K025.01]. The study adheres to the tenets of the Declaration of Helsinki and is registered at ClinicalTrails.gov (NCT06034366) using the SPIRIT reporting guidelines[10]. Randomization will be performed using a web-based, online, sealed envelope-based system (https://www.sealedenvelope.com). Specific study information sheets will be provided to patients prior to being consented. Following a dedicated screening and randomization visit for eligible patients, participants will be randomized to one of two trial arms. (Figure 1)

Figure 1. Study flow chart



Methods: Participants, interventions, and outcomes

Study setting {9}

This study will be conducted between Oct 1, 2023, and May 30, 2025. Participants will be recruited at the Department of Ophthalmology, He Eye Specialist Hospital, Shenyang, China.

Patient and Public Involvement

Patients and the public will not be involved in this study's design, implementation, reporting, or dissemination plans.

Eligibility criteria {10}

Inclusion criteria:

1. Age 6 to 12 years
2. Subjects and their guardians agreed to participate in this study
3. Best-corrected visual acuity (BCVA) 0.1 (log minimum angle of resolution, LogMAR) or better.
4. Initial NITM (spherical equivalent) ≤ -0.25 D
5. Myopic refractions ≥ −1.0 D and astigmatism ≤ 2.5 D in both eyes.

Exclusion criteria:

1. Children with systemic diseases or ocular diseases.

2. Previous experiences with myopia control therapy
3. A history of allergies to atropine.
4. Patients were deemed inappropriate for trial participation by the lead investigator.

Informed consent {26a}

Trained and experienced clinicians will seek informed permission from prospective participants and guardians.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

This trial does not involve collecting biological specimens.

Interventions

The explanation for the choice of comparators {6b}

After enrollment in the study, treatments will be initiated immediately after randomization. Participants in the study group will use 0.01% atropine (3 ml unit-concentration, preservative-free) once nightly in both eyes for 48 weeks, while those in the control group will utilize placebo eye drops (0.9% sodium chloride, 3 ml unit-concentration, preservative-free) once nightly in both eyes for 48 weeks. All eye drops will be prepared by He Eye Specialist Hospital, Co, LTD, Shenyang, China, with the same packaging.

Intervention description {11a}

In this study, patients receive either 0.01% atropine or placebo eye drops for 48 weeks based on the group they are placed in. Five follow-up visits will be performed at week 4, week 12, week 24, week 36, and week 48 in both groups; a pediatric ophthalmologist will conduct comprehensive eye exams, including primary outcomes, secondary outcomes, and safety evaluation.

Criteria for discontinuing or modifying allocated interventions {11b}

After enrollment in the study, participants will receive one drop of 0.01% atropine or placebo eye drops once nightly in both eyes for 48 weeks. In case of allergic reactions or adverse events (AE) related to the study drug, the principal investigator (PI) (Emmanuel Eric Pazo) will decide if participants can continue further. Participants who onset other serious diseases or refuse to continue participating in the study will be stopped from using the designated eye drops.

Strategies to improve adherence to interventions {11c}

Participants and guardians will be reminded by phone and email every week, and appointments will be booked in advance based on their availability time. Patients will be provided a medication record booklet and their medication status will be verified at each follow-up session to enhance adherence.

In the event of non-compliance, such as absence, participants will be contacted by phone or email to ask if they want to continue or discontinue the study.

Relevant concomitant care permitted or prohibited during the trial {11d}

Subjects are allowed to use single-vision lenses during treatment. Any other treatment or therapy for myopia control will be prohibited during the course of this study, including the Orthokeratology lens, multifunctional defocus lens, and red-light feeding instrument. Besides, any eye drops and systemic medications that may affect the outcome were prohibited

Provisions for post-trial care {30}

The placebo group will be transferred to the atropine group for treatment in the following year.

Outcomes {12}

Table 1 displays the timeline for data collection and site visits. The assessments will be conducted in accordance with a predetermined order. A trained physician (GHQ) will do an in-person medical examination and lifestyle-related information interview. Comprehensive eye exams will be conducted by an ophthalmologist, including assessments mentioned below at baseline, week 4, week 12, week 24, week 36, and week 48.

Primary Outcome

Initial NITM will be evaluated by an open-field infrared autorefractor (WAM-

5500; Grand Seiko, Japan), including the following steps.[11]

Pre-task: Subjects will be taught to binocularly fixate on a photopic high-contrast Maltese cross target situated at 5 m, and their accommodative response will be monitored dynamically for 10s.

Task: Subjects will complete a 5-minute near-work task with a 5D accommodating demand. To guarantee that subjects pay attention to the near target, we will utilize pairs of high-contrast black-and-white photographs with 10 small differences in each pair, and they will be instructed to discover as many differences as possible throughout the 5-minute task. Two pairs of targets will be used, with a different pair employed for each experimental session. The targets will be displayed on a digital screen (iPad mini6, Apple Inc., Cupertino, CA; 8.3in.). To get a satisfactory instrument alignment with the visual axis, both targets are closely placed, one above the other.

Post-task: The near work task will be swiftly removed after the 5-minute near work activity, and subjects will be instructed to focus for a 3-minute period on the photopic high-contrast Maltese cross target positioned at 5 m.

The primary dependent variables are the magnitude of accommodation during the 5-minute task, the initial NITM, and the decay duration. The NITM dioptric magnitude will be the mean spherical equivalent of the post-task minus pre-task values. This measure will be computed over 18 10-second intervals (i.e., 3-minute post-task). The first 10-s interval is referred to as the initial NITM. Following data collection, the mean spherical equivalent (MSE of all measurements for each 10 s time bin interval) will be determined. After the data acquisition, the mean spherical equivalent (MSE of all

measurements for each time bin interval of 10 s) will be calculated. The initial NITM dioptric magnitude is represented by the MSE of the post-task minus pre-task value.

Secondary outcomes

All students will receive a cycloplegic autorefraction (WAM-5500; Grand Seiko Co., Ltd. Hiroshima, Japan) after NITM testing during each visit, whereas the parents will receive a non-cycloplegic autorefraction (ARK-1, NIDEK, Japan) during the baseline examination. Cycloplegic autorefraction will be performed 20 min after instilling three drops of cyclopentolate 1% (Cyclogyl, Alcon). Three readings will be obtained in each eye and averaged within and across each group.

Ocular axial length (AL) will be measured on a Zeiss IOL Master 700 (Carl Zeiss Meditec Inc, Dublin, CA) based on non-contact partial coherence interferometry.

A validated Chinese version of the 25-item National Eye Institute Visual Function Questionnaire will be provided to all subjects to determine the impact of different treatment groups on the vision-related quality of life.[12]

Safety evaluation

BCVA in the logarithm of the minimum angle of resolution (logMAR) will be assessed by an optometrist.

Intraocular pressure (IOP) will be evaluated using a non-contact tonometer (NT-510, NIDEK, Japan).

Mesopic pupil size and photopic pupil size will be measured with the OPD-Scan III (Nidek, Gamagori, Japan).

Anterior segment examination will be performed by Slit-lamp biomicroscopy and

indirect ophthalmoscopy through a dilated pupil.

Participant timeline {13}

The schedule for data collection and visits is shown in Table 1. After registration for this study, the assigned treatment intervention will be administered for 48 weeks. Furthermore, the effect of eyedrops will be examined at the week 4, week 12, week 24, week 36, and week 48 follow-ups (Figure 1).

Table 1. The schedule of enrolment, interventions, and assessments of this trial

		STUDY PERIOD							
	Enrolment	Allocation	Post-allocation						Close-out
TIMEPOINT:	**October -23**	**2023**	**Day 0**	**4 weeks**	**12 weeks**	**24 weeks**	**36 weeks**	**48 weeks**	**End-2025**
ENROLMENT:									
Eligibility screen	×								
Informed consent	×								
Allocation		×							
INTERVENTIONS:									
[0.01% atropine eye drops]		×	×	×	×	×	×	×	
[placebo eye drops]		×	×	×	×	×	×	×	
ASSESSMENTS:									
[The baseline variables]	×	×							
[The primary outcome]		×	×	×	×	×	×	×	
[The secondary outcome]		×	×	×	×	×	×	×	
[Safety evaluation]			×	×	×	×	×	×	

Sample size {14}

The sample size calculation is based on the primary outcome measures of initial NITM to establish the superiority of the 0.01% atropine group compared to the placebo group in terms of the changes in the mean from the baseline in the initial NITM at week 48. We took the estimated initial NITM for 0.01% atropine and placebo groups to be -0.076 and -0.41D.[9] The expected standard deviation within a group was assumed to be 0.2 D. A sample size of 16 subjects could achieve 90% power at a 0.05 significance level. According to Chinese《preparation supervision measures for the administration of medical institutions》(2005), the number of participants should be at least 60. Considering a maximum dropout rate of 20%, the sample size required is 150 (75 per group).

Recruitment {15}

This study will be conducted between Oct 1, 2023, and May 30, 2025. This clinical study will be done in a single site, with participants blinded to the treatment assignment. This research is open to children who met the inclusion criteria at He Eye Specialist Hospital's Department of Ophthalmology. Participants will be recruited using adverts in the distribution pamphlets, the website, and social media postings. Participants' demographic information will be collected during the first (screening) appointment.

Assignment of interventions: Allocation

Sequence generation {16a}

A web-based randomization application will be used (https://www.project-redcap.org/). Allocation will be done using block randomization and stratified according to age (allocation factor: 12 years ≥ age 6 years). (Known only to the statistical team, not stated here to maintain masking). Participants will be in a 1:1 allocation ratio to 0.01% atropine or placebo groups.

Concealment mechanism {16b}

The block size will be concealed from other researchers, and the randomization table will not be available for assessment by anyone involved in the study [13]. An independent biostatistician performs randomization. The biostatistician is the only one who has access to check the file. The allocation list is kept in a separate file on a different computer.

Implementation {16c}

Opaque and sealed (A randomization list for each stratum) envelopes containing serial numbers will be prepared by an independent statistician and delivered to the clinical trial center.

An independent researcher will distribute the envelopes to participants and allocate them into study groups at 1:1 without implementing stratification.

Before the random assignment, all participants will be informed that they will be allocated to one of two groups. Random allocation will be conducted at visit 2. Random numbers with corresponding participants will be determined in the order of the time of

the second visit. They will be opened by the clinician prescribing the eye drops (0.01% atropine or placebo eye drop). The allocation result will not be announced to the participants until the end of the data collection phase of the trial. Researchers collecting and analyzing data related to this trial will be blinded to the participant allocation results.

Assignment of interventions:

Blinding {17a}

The treatment assignment for the study will be triple-masked. Participants in the research would be unable to recognize the contents. A masked examiner for all clinical assessments will not be involved in this research's data collection or group allocation procedure. The investigator will not be aware of the three groups. Participants will be randomly assigned to 0.01% atropine group or placebo group. The box containing ampoules will be labeled with a batch number, including the study reference number, participant ID, contact number, investigator name, site address, the expiration date of the eye drops, storage instructions, and a statement informing the participant that the eye drops are for use only in clinical trials and should not be ingested. The PI will determine and perform the circumstances and procedures under which unblinding is permissible.

Procedure for unblinding if needed {17b}

The PI will determine and perform the circumstances and procedures under which unblinding is permissible.

Participant withdrawal

Based on the following criteria, patients will be removed from the research.

1. When it is deemed challenging to continue, the study is owing to the emergence of new ailments.
2. The participant who lost to follow-up.
3. When participants or their legal guardians want to end their participation in a study.
4. When the participant's caretaker cannot guarantee their participation in the study.
5. When the research project has concluded.
6. When the lead investigator and sub-investigators believe it is acceptable to cease the study due to adverse events.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Data administration is the responsibility of Jiayan Chen, Department of Clinical Research, as chosen by the PI. This research will collect data using a proprietary EMR case report form and management application. Following the database lock, the individual responsible for the statistical analysis will get the locked data following the database. The data management handbook will provide the details on any specific information. At the end of the study, a report on the implementation and the status of data management will be compiled and sent to the PI with the locked research data.

Plans to promote participant retention and complete follow-up {18b}

Informed consent will include information regarding follow-up assessments for all participants. If participants discontinue or deviate from intervention protocols, the study team will initiate contact and prioritize addressing any concerns that may be impacting their adherence to the intervention protocols. If these concerns cannot be resolved, the participants will be requested to complete subsequent self-assessment questionnaires online.

Data will be gathered during pre-randomization, termination, and follow-up periods at week 4, week 12, week 24, week 36, and week 48. The method of data collection for this study will involve the use of clinical tests and self-report questionnaires, which will be administered through an online platform. To guarantee the completeness and accuracy of the gathered data, the online questionnaires will be encoded in a manner that necessitates respondents to provide comprehensive responses to all inquiries before submitting their answers.

Data management {19}

Separately experienced staff members at He Eye Specialist Hospital, Department of Clinical Research, performed data collection and entry. Supervision and double confirmation were performed by Guanghao Qin, along with weekly backup, to ensure data quality.

Confidentiality {27}

Each participant's personal information will be kept confidential in the same way as their medical histories in the hospital before, during, and after the trial.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not Applicable-There will be no biological specimens collected.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Unless otherwise mentioned, this study's significance level is set to 5% two-sided, and the confidence coefficient is set to 95%. The background of the study's subjects will be tabulated by calculating the mean and standard deviation for continuous variables and the frequency and percentage for categorical variables. Suppose the continuous variables do not follow a normal distribution. In that case, they will be converted appropriately by logarithmic transformation or other means and aggregated with the mean and standard deviation, or the median and interquartile range will be utilized as descriptive statistics. For the primary endpoint, between-group comparisons using baseline as a covariate and an analysis of covariance will be made to produce the adjusted mean, its 95% confidence interval, and the p-value. A paired t-test will be used to make within-group comparisons. To ensure participant safety, frequencies and proportions will be computed for each group and item, and comparisons between

groups will be made using Fisher's exact probability test or the $\chi 2$ statistic. Correlation analysis will be used to assess the relationship between NITM and myopic progression.

Interim analyses {21b}

Not applicable- no anticipated problems are detrimental to the participant, so interim analysis is not warranted.

Methods for additional analyses (e.g., subgroup analyses) {20b}

Subgroup analyses are not planned for this study.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

After accounting for loss to follow-up and missing data in sample-size calculations, using a two-tailed t-test of difference between means with a power of 90% and a significance level of 5%, we allowed a dropout rate of 20%.

Plans to give access to the complete protocol, participant-level data, and statistical code {31c}

The datasets analyzed during the current study and statistical code are available from the corresponding author on reasonable request, as is the complete protocol.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The subject leader and the project manager will form the Steering Committee (SC). The SC is accountable for managing the whole project. The SC appoints the Monitor Group's (MG) inspectors. The MG will oversee the entire research procedure in compliance with the Good Clinical Practice (GCP) requirements. The inspector will analyze the investigator's adherence to the protocol, the protection of participants' rights and interests, the quality of the Case report form (CRF), and the investigators' understanding of different standards before submitting inspection reports to the SC.

Composition of the data monitoring committee, its role and reporting structure {21a}

Due to the projected low frequency of adverse events and the modest numbers in each location, no data monitoring committee has been convened for this trial. The database will be constructed using Excel (Microsoft, USA 2022 version), and regular data monitoring will be undertaken per the sponsor's standard operating procedures. The steering committee will have oversight and access to the trial under the supervision of the trial manager at any time during the study.

Adverse event reporting and harms {22}

Adverse events are unanticipated indications, symptoms, or illnesses seen during a clinical study, regardless of their relationship to the treatment. There may be local, general, and psychological unwanted effects. If any discomfort or new changes in

condition during the study period, or any unexpected situation, whether related to the study or not, one should promptly notify the doctor, who will make a judgment and give appropriate medical treatment. According to the results, the doctor will evaluate the eye health status at the end of each examination. If the condition deteriorates or is no longer suitable for the study, the study may be terminated early. At the same time, the doctor will provide other treatment options ideal for the current situation to ensure health to the greatest extent. If major adverse events occur, He Eye Specialist Hospital Certified Review Board will be notified; experimental treatments will be discontinued promptly, and appropriate therapies will be offered.

Frequency and plans for auditing trial conduct {23}

The study will be reviewed and evaluated weekly by an independent supervisor unrelated to the PI and sponsors.

Plans for communicating significant protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

If there are modifications to eligibility criteria, outcomes, or analyses, a revised protocol will be submitted for approval to the He Eye Specialist Hospital Medical Ethics Committee.

Dissemination plans {31a}

The study's findings will be shared regardless of the effect's direction. All possible

beneficiaries of the research, including patients, caretakers, family, doctors, advisory boards, and medical boards, will receive trial data. Publications in high-impact, open-access medical journals and talks at national and international medical conferences will serve this purpose.

Trial status

Recruitment began on Oct 1, 2023, and the approximate date when recruitment will be completed in March 2023. Protocol version 2.0 was approved in August 2022.

Abbreviations

NITM: Near work-induced transient myopia; PM: Permanent myopia; AL: axial length; BCVA: Best-corrected visual acuity; IOP: Intraocular pressure; RCT: Randomized control trial; AE: Adverse events; PI: principal investigator; MSE: mean spherical equivalent; SC: Steering Committee; GCP: Good Clinical Practice; CRF: Case report form

Declarations

Acknowledgments

The authors would like to express their appreciation for the effort of all personnel involved in this trial.

Authors' contributions {31b}

Conception and design of the research: GQ, JC, LH, YQ, LX, WH, SY, XH, and EEP; analysis and interpretation of the data: GQ, JC, EEP; writing original draft preparation: GQ; critical revision of the manuscript (reviewing and editing): GQ and EEP; supervision: XH, SY, and EEP.

Funding statement {4}

This study was entirely funded and sponsored by He Eye Specialist Hospital, Shenyang, China, which included study design, data collection, analysis, interpretation, and manuscript writing. No support was received for the publication of this article.

Availability of data and materials {29}

Any data required to support the protocol can be supplied on request.

Ethics and dissemination {24}

The study was registered with the trial number NCT06034366 and was conducted in compliance with the tenets of the Declaration of Helsinki and the Institutional Review Board of the He Eye Specialist Hospital, Shenyang, China: IRB (2023) K025.01. Documented informed consent was obtained from all participants in this study. In the present study, all components with any individually identifiable information have been removed from the dataset.

Consent for publication {32}

Not applicable - no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The

participant information materials and informed consent form are available from the corresponding author on request.

Competing interest statement {28}

The authors declare that they have no competing interests.

Authors' information

1 He Eye Specialist Hospital, Shenyang, China.

2 He University, Shenyang, China.

Figure legends

Figure 1. Study flow chart

Word count: 4078

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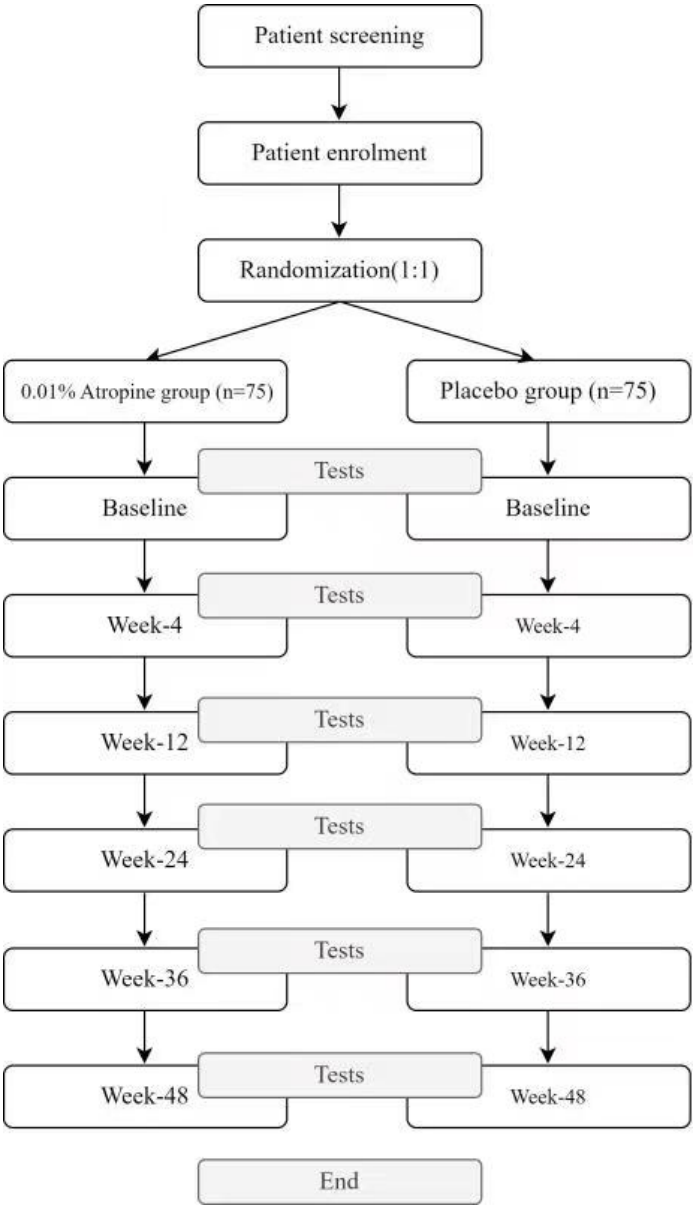

Figure 1. Study flow chart

162x282mm (72 x 72 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (P1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (P2)
	2b	All items from the World Health Organization Trial Registration Data Set (P2)
Protocol version	3	Date and version identifier (P2)
Funding	4	Sources and types of financial, material, and other support (P23)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (P1)
	5b	Name and contact information for the trial sponsor (P9)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (P23)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (P20)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (P4)
	6b	Explanation for choice of comparators (P8)
Objectives	7	Specific objectives or hypotheses (P4)
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (P5)

Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (P6)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (P7)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (P8)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (P9)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (P9)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (P9)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (P10)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (P12)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (P8)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (P14)
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions (P14)

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned (P14)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (P15)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (P14)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial (P16)
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (P17)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols (P17)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (P18)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol (P19)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (P19)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) (P20)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (P21)

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial (P19)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct(P21)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (P22)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (P24)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (P22)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (P18)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (P18)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (P24)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators(P24)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (P22)
	31b	Authorship eligibility guidelines and any intended use of professional writers (P23)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (P20)

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates(P24)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (P33)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol for a parallel assignment prospective, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of 0.01% atropine for near work-induced transient myopia and myopic progression in China

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Protocol

Title: Protocol for a parallel assignment prospective, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of 0.01% atropine for near work-induced transient myopia and myopic progression in China

Names protocol contributors: Guanghao Qin [1], Jiayan Chen [1], Lan Hu[1], Yifan Qi[1], Ling Xu[1], Wei He [1], Sile Yu [1,2], Emmanuel Eric Pazo [1]*, Xingru He [1,2]*

1 He Eye Specialist Hospital, Shenyang, China.

2 He University, Shenyang, China.

*** Correspondence:**

1. Emmanuel Eric Pazo, Department of Ophthalmology, He Eye Specialist Hospital, Shenyang, China.11003

ericpazo@outlook.com

2. Xingru He, School of Public Health, He University, Shenyang, China.110034

hexingru@hsyk.com.cn

ABSTRACT

Introduction: Assessment of near work-induced transient myopia (NITM) is important for permanent myopia (PM) development and progression. Atropine eye drop has been reported to be beneficial in reducing initial NITM and slowing down myopic progression. This study aimed to investigate the efficacy of 0.01% atropine in treating NITM and its possible association with the progression of refractive change in Chinese myopic children.

Methods and analysis: The study is designed as a parallel assignment prospective, randomized, double-blinded, placebo-controlled trial conducted at He Eye Specialist Hospital in Shenyang, China. One hundred fifty participants will be randomly assigned in a 1:1 ratio to receive 0.01% atropine or placebo eye drop once nightly bilaterally for one year. Initial NITM, cycloplegic refraction, axial length, best-corrected visual acuity, intraocular pressure, and pupil diameter will be measured at baseline, 4-week, 12-week, 24-week, 36-week, and 48-week. Visual Function Questionnaire will be administered at baseline and each follow-up visit. Adverse events also will be monitored and documented at each subsequent follow-up visit.

Ethics and dissemination: A parallel assignment prospective, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of 0.01% atropine for near work-induced transient myopia and myopic progression registered on Sept 10, 2023. Ethics approval number: IRB (2023) K025.01. The study's findings will be shared regardless of the effect's direction.

Trial registration number: NCT06034366.

Strengths and limitations of this study:

- This study is a parallel assignment prospective, randomized, double-blinded, placebo-controlled trial.
- One hundred fifty participants participants will be randomly assigned in a 1:1 ratio to receive 0.01% atropine or placebo eye drop once nightly bilaterally for one year.
- An evaluation of Initial NITM, cycloplegic refraction, axial length, best-corrected visual acuity, intraocular pressure, and pupil diameter will be performed.
- The limitation of the research is that it's a single-center study.
- The study is limited to 1-year follow-up.

INTRODUCTION

Background and rationale {6a}

Myopia is a common condition that develops primarily during childhood and early adulthood when excessive elongation of the eye results in images of distant objects coming into focus in front of the retina, which leads to blurred distance vision.[1] Myopia is the most common ocular disorder worldwide, with increasing prevalence over the past decades, predominantly in East Asia.[2,3] Previous studies suggested that environmental factors, such as near-work demands, likely play an important role in myopia development in the younger population.

Near work is a major environmental component in establishing and progressing permanent myopia (PM), induced via near work-induced transient myopia (NITM).

[4,5]In contrast to PM, NITM refers to the prolonged period required for the accommodation of the eyes to revert to a normal level after performing a persistent near task.[6] Some years ago, it was proposed that NITM, which produces minor and chronic retinal defocus, may be one of many possible environmentally-based, myopigenic, contributory factors to permanent myopia.[7,8]Initial NITM magnitude is one of the key parameters used to characterise the accommodative response following a sustained near-work task, which is defined as the dioptric difference between the immediate pre- and immediate post-near task distance refractive state.[9,10] Previous studies reported that initial NITM was increased in myopes than in hyperopes or emmetropes.[4,11]

As a nonselective muscarinic antagonist, atropine eye drops with different concentrations have been reported to slow down the myopic progression in myopes.[12,13] Recently, a two-week study assessed the efficacy of a low concentration of atropine (0.01%) on the initial NITM magnitude among Chinese myopic children.[14] The results suggested that 0.01% atropine reduced the initial NITM magnitude. However, the long-term efficacy of 0.01% atropine in treating NITM and the relationship between NITM and refractive change after treatment is still unclear.

This study aimed to investigate the efficacy of 0.01% atropine in treating NITM and its possible association with the progression of refractive change in Chinese myopic children.

Objectives {7}

The primary objective of this study is to investigate the efficacy of 0.01% atropine

in the treatment of NITM and its possible association with the progression of refractive change in Chinese myopic children.

Trial design {8}

This is a prospective, randomized, double-blind, placebo-controlled trial performed at He Eye Specialist Hospital [ethics approval number: IRB (2023) K025.01]. The study adheres to the tenets of the Declaration of Helsinki and is registered at ClinicalTrails.gov (NCT06034366) using the SPIRIT reporting guidelines[15]. Randomization will be performed using a web-based, online, sealed envelope-based system (https://www.sealedenvelope.com). Specific study information sheets will be provided to patients prior to their consent. Following a dedicated screening and randomization visit for eligible patients, participants will be randomized to one of two trial arms. (Figure 1)

Methods: Participants, interventions, and outcomes

Study setting {9}

This study will be conducted between Oct 1, 2023, and May 30, 2025. Participants will be recruited at the Department of Ophthalmology, He Eye Specialist Hospital, Shenyang, China.

Patient and Public Involvement

Patients and the public will not be involved in this study's design, implementation,

reporting, or dissemination plans.

Eligibility criteria {10}

Inclusion criteria:

1. Age 6 to 12 years
2. Subjects and their guardians agreed to participate in this study
3. Best-corrected visual acuity (BCVA) 0.1 (log minimum angle of resolution, LogMAR) or better.
4. Initial NITM (spherical equivalent) ≤ -0.25 D
5. Cycloplegic refractions ≥ −1.0 D and astigmatism ≤ 2.5 D in both eyes.
6. Anisometropia in both eyes ≤ 1.5 D

Exclusion criteria:

1. Children with existing systemic diseases including asthma, collagen disease, immune system disorders, prostate hypertrophy, spastic paralysis, Down's syndrome, severe cardiac, pulmonary, hepatic, and renal dysfunction.
2. Patients with glaucoma or high intraocular pressure, ocular inflammatory diseases, strabismus, amblyopia, corneal diseases, diseases of lens, retinal and optic neuropathy.
3. Regular use of medications that may affect the efficacy of 0.01% atropine, including hairy fruit rutabaga eye drops, tropicamide eye drops, anticholinergic drugs such as pirenzepine and tropicamide, and cholinergic drugs such as carbachol and hairy fruit rutabaga.

4. Previous experiences with myopia control therapy.

5. A history of allergies to atropine.

6. Patients were deemed inappropriate for trial participation by the lead investigator.

Informed consent {26a}

Trained and experienced clinicians will seek informed permission from prospective participants and guardians.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

This trial does not involve collecting biological specimens.

Interventions

The explanation for the choice of comparators {6b}

After enrollment in the study, treatments will be initiated immediately after randomization. Participants in the study group will use 0.01% atropine (3 ml unit-concentration, preservative-free) once nightly in both eyes for 48 weeks, while those in the control group will utilize placebo eye drops (0.9% sodium chloride, 3 ml unit-concentration, preservative-free) once nightly in both eyes for 48 weeks. All eye drops will be prepared by He Eye Specialist Hospital, Co, LTD, Shenyang, China, with the same packaging.

Intervention description {11a}

In this study, patients receive either 0.01% atropine or placebo eye drops for 48 weeks based on the group they are placed in. Five follow-up visits will be performed at week 4 (±3 days), week 12 (±7 days), week 24(±7 days), week 36(±7 days), and week 48(±7 days) in both groups; a pediatric ophthalmologist will conduct comprehensive eye exams, including primary outcomes, secondary outcomes, and safety evaluation.

Criteria for discontinuing or modifying allocated interventions {11b}

After enrollment in the study, participants will receive one drop of 0.01% atropine or placebo eye drops once nightly in both eyes for 48 weeks. In case of allergic reactions or adverse events (AE) related to the study drug, the principal investigator (PI) (Emmanuel Eric Pazo) will decide if participants can continue further. Participants who onset other serious diseases or refuse to continue participating in the study will be stopped from using the designated eye drops.

Strategies to improve adherence to interventions {11c}

Participants and guardians will be reminded by phone and email every week, and appointments will be booked in advance based on their availability time. Patients will be provided a medication record booklet and their medication status will be verified at each follow-up session to enhance adherence.

In the case of outside the allowance, participants will be contacted by phone or email to make sure if they want to continue or discontinue the study. Subjects who

could not complete the follow-up inside the allowance were removed from this study.

Relevant concomitant care permitted or prohibited during the trial {11d}

Subjects are allowed to use single-vision lenses during treatment. Any other treatment or therapy for myopia control will be prohibited during the course of this study, including the Orthokeratology lens, multifunctional defocus lens, and red-light feeding instrument. Besides, any eye drops and systemic medications that may affect the outcome were prohibited, including hairy fruit rutabaga eye drops, tropicamide eye drops, anticholinergic drugs such as pirenzepine and tropicamide, and cholinergic drugs such as carbachol and hairy fruit rutabaga.

Provisions for post-trial care {30}

The placebo group will be transferred to the atropine group for treatment in the following year.

Outcomes {12}

Supplementary Table 1 displays the timeline for data collection and site visits. The assessments will be conducted in accordance with a predetermined order. A trained physician (GHQ) will do an in-person medical examination and lifestyle-related information interview. Comprehensive eye exams will be conducted by an ophthalmologist, including assessments mentioned below at baseline, week 4, week 12, week 24, week 36, and week 48.

Primary Outcome

Initial NITM will be evaluated by an open-field infrared autorefractor (WAM-5500; Grand Seiko, Japan), including the following steps.[16]

Pre-task: Subjects will be taught to binocularly fixate on a photopic high-contrast Maltese cross target situated at 5 m, and their accommodative response will be monitored dynamically for 10s.

Task: Subjects will complete a 5-minute near-work task with a 5D accommodating demand. To guarantee that subjects pay attention to the near target, we will utilize pairs of high-contrast black-and-white photographs with 10 small differences in each pair, and they will be instructed to discover as many differences as possible throughout the 5-minute task. Two pairs of targets will be used, with a different pair employed for each experimental session. The targets will be displayed on a digital screen (iPad mini6, Apple Inc., Cupertino, CA; 8.3in.). To get a satisfactory instrument alignment with the visual axis, both targets are closely placed, one above the other.

Post-task: The near work task will be swiftly removed after the 5-minute near work activity, and subjects will be instructed to focus for a 3-minute period on the photopic high-contrast Maltese cross target positioned at 5 m.

The NITM dioptric magnitude will be the mean spherical equivalent of the post-task minus pre-task values. This measure will be computed in the first 10-s interval . The first 10-s interval is referred to as the initial NITM. The initial NITM dioptric magnitude is represented by the MSE of the post-task minus pre-task value.

Secondary outcomes

All students will receive a cycloplegic autorefraction (WAM-5500; Grand Seiko Co., Ltd. Hiroshima, Japan) after NITM testing during each visit, whereas the parents will receive a non-cycloplegic autorefraction (ARK-1, NIDEK, Japan) during the baseline examination. Cycloplegic autorefraction will be performed 20 min after instilling three drops of cyclopentolate 1% (Cyclogyl, Alcon). Three readings will be obtained in each eye and averaged within and across each group.

Ocular axial length (AL) will be measured on a Zeiss IOL Master 700 (Carl Zeiss Meditec Inc, Dublin, CA) based on non-contact partial coherence interferometry.

A validated Chinese version of the 25-item National Eye Institute Visual Function Questionnaire will be provided to all subjects to determine the impact of different treatment groups on the vision-related quality of life.[17]

Safety evaluation

BCVA in the logarithm of the minimum angle of resolution (logMAR) will be assessed by an optometrist.

Intraocular pressure (IOP) will be evaluated using a non-contact tonometer (NT-510, NIDEK, Japan).

Mesopic pupil size and photopic pupil size will be measured with the OPD-Scan III (Nidek, Gamagori, Japan).

Anterior segment examination will be performed by Slit-lamp biomicroscopy and indirect ophthalmoscopy through a dilated pupil.

Participant timeline {13}

The schedule for data collection and visits is shown in Supplementary Table 1. After registration for this study, the assigned treatment intervention will be administered for 48 weeks. Furthermore, the effect of eyedrops will be examined at the week 4, week 12, week 24, week 36, and week 48 follow-ups (Figure 1).

Sample size {14}

The sample size calculation is based on the primary outcome measures of initial NITM to establish the superiority of the 0.01% atropine group compared to the placebo group in terms of the changes in the mean from the baseline in the initial NITM at week 48. We took the estimated initial NITM for 0.01% atropine and placebo groups to be -0.076 and -0.41D.[14] The expected standard deviation within a group was assumed to be 0.20 D. A sample size of 16 subjects could achieve 90% power at a 0.05 significance level. According to Chinese《preparation supervision measures for the administration of medical institutions》(2005), the number of participants should be at least 60. Considering a maximum dropout rate of 20%, the sample size required is 150 (75 per group).

Recruitment {15}

This study will be conducted between Oct 1, 2023, and May 30, 2025. This clinical study will be done in a single site, with participants blinded to the treatment assignment.

This research is open to children who met the inclusion criteria at He Eye Specialist Hospital's Department of Ophthalmology. Participants will be recruited using adverts in the distribution pamphlets, the website, and social media postings. Participants' demographic information will be collected during the first (screening) appointment.

Assignment of interventions: Allocation

Sequence generation {16a}

A web-based randomization application will be used (https://www.project-redcap.org/). Allocation will be done using block randomization and stratified according to age (allocation factor: 12 years ≥ age 6 years). (Known only to the statistical team, not stated here to maintain masking). Participants will be in a 1:1 allocation ratio to 0.01% atropine or placebo groups.

Concealment mechanism {16b}

The block size will be concealed from other researchers, and the randomization table will not be available for assessment by anyone involved in the study [18]. An independent biostatistician performs randomization. The biostatistician is the only one who has access to check the file. The allocation list is kept in a separate file on a different computer.

Implementation {16c}

Opaque and sealed (A randomization list for each stratum) envelopes containing

serial numbers will be prepared by an independent statistician and delivered to the clinical trial center.

An independent researcher will distribute the envelopes to participants and allocate them into study groups at 1:1 without implementing stratification.

Before the random assignment, all participants will be informed that they will be allocated to one of two groups. Random allocation will be conducted at visit 2. Random numbers with corresponding participants will be determined in the order of the time of the second visit. They will be opened by the clinician prescribing the eye drops (0.01% atropine or placebo eye drop). The allocation result will not be announced to the participants until the end of the data collection phase of the trial. Researchers collecting and analyzing data related to this trial will be blinded to the participant allocation results.

Assignment of interventions:

Blinding {17a}

The treatment assignment for the study will be triple-masked. Participants in the research would be unable to recognize the contents. A masked examiner for all clinical assessments will not be involved in this research's data collection or group allocation procedure. The investigator will not be aware of the three groups. Participants will be randomly assigned to 0.01% atropine group or placebo group. The box containing ampoules will be labeled with a batch number, including the study reference number, participant ID, contact number, investigator name, site address, the expiration date of the eye drops, storage instructions, and a statement informing the participant that the

eye drops are for use only in clinical trials and should not be ingested. The PI will determine and perform the circumstances and procedures under which unblinding is permissible.

Procedure for unblinding if needed {17b}

The PI will determine and perform the circumstances and procedures under which unblinding is permissible.

Participant withdrawal

Based on the following criteria, patients will be removed from the research.

1. When it is deemed challenging to continue, the study is owing to the emergence of new ailments.
2. The participant who lost to follow-up.
3. When participants or their legal guardians want to end their participation in a study.
4. When the participant's caretaker cannot guarantee their participation in the study.
5. When the research project has concluded.
6. When the lead investigator and sub-investigators believe it is acceptable to cease the study due to adverse events.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Data administration is the responsibility of Jiayan Chen, Department of Clinical Research, as chosen by the PI. This research will collect data using a proprietary EMR case report form and management application. Following the database lock, the individual responsible for the statistical analysis will get the locked data following the database. The data management handbook will provide the details on any specific information. At the end of the study, a report on the implementation and the status of data management will be compiled and sent to the PI with the locked research data.

Plans to promote participant retention and complete follow-up {18b}

Informed consent will include information regarding follow-up assessments for all participants. If participants discontinue or deviate from intervention protocols, the study team will initiate contact and prioritize addressing any concerns that may be impacting their adherence to the intervention protocols. If these concerns cannot be resolved, the participants will be requested to complete subsequent self-assessment questionnaires online.

Data will be gathered during pre-randomization, termination, and follow-up periods at week 4, week 12, week 24, week 36, and week 48. The method of data collection for this study will involve the use of clinical tests and self-report questionnaires, which will be administered through an online platform. To guarantee the completeness and accuracy of the gathered data, the online questionnaires will be encoded in a manner that necessitates respondents to provide comprehensive responses to all inquiries before submitting their answers.

Data management {19}

Separately experienced staff members at He Eye Specialist Hospital, Department of Clinical Research, performed data collection and entry. Supervision and double confirmation were performed by Guanghao Qin, along with weekly backup, to ensure data quality.

Confidentiality {27}

Each participant's personal information will be kept confidential in the same way as their medical histories in the hospital before, during, and after the trial.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not Applicable-There will be no biological specimens collected.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Unless otherwise mentioned, this study's significance level is set to 5% two-sided, and the confidence coefficient is set to 95%. The background of the study's subjects will be tabulated by calculating the mean and standard deviation for continuous variables and the frequency and percentage for categorical variables. Suppose the continuous variables do not follow a normal distribution. In that case, they will be

converted appropriately by logarithmic transformation or other means and aggregated with the mean and standard deviation, or the median and interquartile range will be utilized as descriptive statistics. For the primary endpoint, between-group comparisons using baseline as a covariate and an analysis of covariance will be made to produce the adjusted mean, its 95% confidence interval, and the p-value. A paired t-test will be used to make within-group comparisons. To ensure participant safety, frequencies and proportions will be computed for each group and item, and comparisons between groups will be made using Fisher's exact probability test or the $\chi 2$ statistic. Correlation analysis will be used to assess the relationship between NITM and myopic progression.

Interim analyses {21b}

Not applicable- no anticipated problems are detrimental to the participant, so interim analysis is not warranted.

Methods for additional analyses (e.g., subgroup analyses) {20b}

Subgroup analyses are not planned for this study.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

After accounting for loss to follow-up and missing data in sample-size calculations, using a two-tailed t-test of difference between means with a power of 90% and a significance level of 5%, we allowed a dropout rate of 20%.

Plans to give access to the complete protocol, participant-level data, and statistical code {31c}

The datasets analyzed during the current study and statistical code are available from the corresponding author on reasonable request, as is the complete protocol.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The subject leader and the project manager will form the Steering Committee (SC). The SC is accountable for managing the whole project. The SC appoints the Monitor Group's (MG) inspectors. The MG will oversee the entire research procedure in compliance with the Good Clinical Practice (GCP) requirements. The inspector will analyze the investigator's adherence to the protocol, the protection of participants' rights and interests, the quality of the case report form (CRF), and the investigator's understanding of different standards before submitting inspection reports to the SC.

Composition of the data monitoring committee, its role and reporting structure {21a}

Due to the projected low frequency of adverse events and the modest numbers in each location, no data monitoring committee has been convened for this trial. The database will be constructed using Excel (Microsoft, USA 2022 version), and regular data monitoring will be undertaken per the sponsor's standard operating procedures.

The steering committee will have oversight and access to the trial under the supervision of the trial manager at any time during the study.

Adverse event reporting and harms {22}

Adverse events are unanticipated indications, symptoms, or illnesses seen during a clinical study, regardless of their relationship to the treatment. There may be unwanted local, general, and psychological effects. If any discomfort or new changes in condition during the study period, or any unexpected situation, whether related to the study or not, one should promptly notify the doctor, who will make a judgment and give appropriate medical treatment. According to the results, the doctor will evaluate the eye health status at the end of each examination. If the condition deteriorates or is no longer suitable for the study, the study may be terminated early. At the same time, the doctor will provide other treatment options that are ideal for the current situation to ensure health to the greatest extent. If major adverse events occur, He Eye Specialist Hospital Certified Review Board will be notified; experimental treatments will be discontinued promptly, and appropriate therapies will be offered.

Frequency and plans for auditing trial conduct {23}

The study will be reviewed and evaluated weekly by an independent supervisor unrelated to the PI and sponsors.

Plans for communicating significant protocol amendments to relevant parties (e.g.,

trial participants, ethical committees) {25}

If there are modifications to eligibility criteria, outcomes, or analyses, a revised protocol will be submitted for approval to the He Eye Specialist Hospital Medical Ethics Committee.

Dissemination plans {31a}

The study's findings will be shared regardless of the effect's direction. All possible beneficiaries of the research, including patients, caretakers, family, doctors, advisory boards, and medical boards, will receive trial data. Publications in high-impact, open-access medical journals and talks at national and international medical conferences will serve this purpose.

Trial status

Recruitment began on Oct 1, 2023, and the approximate date when recruitment will be completed in March 2023. Protocol version 2.0 was approved in August 2022.

Ethics and dissemination {24}

The study was registered with the trial number NCT06034366 and was conducted in compliance with the tenets of the Declaration of Helsinki and the Institutional Review Board of the He Eye Specialist Hospital, Shenyang, China: IRB (2023) K025.01. Documented informed consent was obtained from all participants in this study. In the present study, all components with any individually identifiable

information have been removed from the dataset.

Abbreviations

NITM: Near work-induced transient myopia; PM: Permanent myopia; AL: axial length; BCVA: Best-corrected visual acuity; IOP: Intraocular pressure; RCT: Randomized control trial; AE: Adverse events; PI: principal investigator; MSE: mean spherical equivalent; SC: Steering Committee; GCP: Good Clinical Practice; CRF: Case report form

Declarations

Acknowledgments

The authors would like to express their appreciation for the effort of all personnel involved in this trial.

Authors' contributions {31b}

Conception and design of the research: GQ, JC, LH, YQ, LX, WH, SY, XH, and EEP; analysis and interpretation of the data: GQ, JC, EEP; writing original draft preparation: GQ; critical revision of the manuscript (reviewing and editing): GQ and EEP; supervision: XH, SY, and EEP.

Funding statement {4}

This study was entirely funded and sponsored by He Eye Specialist Hospital,

Shenyang, China, which included study design, data collection, analysis, interpretation, and manuscript writing. No support was received for the publication of this article.

Availability of data and materials {29}

Any data required to support the protocol can be supplied on request.

Consent for publication {32}

Not applicable - no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent form are available from the corresponding author on request.

Competing interest statement {28}

The authors declare that they have no competing interests.

Authors' information

1 He Eye Specialist Hospital, Shenyang, China.

2 He University, Shenyang, China.

Figure legends

Figure 1. Study flow chart

Word count: 4111

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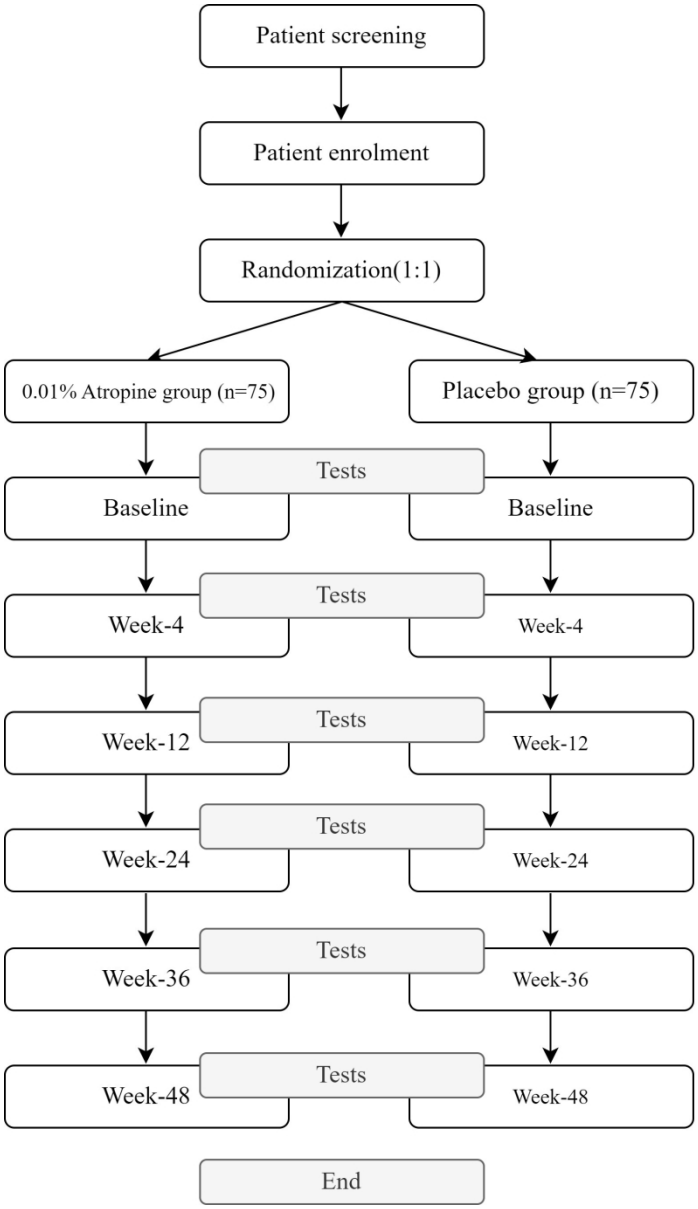

Figure 1. Study flow chart

132x228mm (300 x 300 DPI)

Table 1. The schedule of enrolment, interventions, and assessments of this trial

		STUDY PERIOD							
	Enrolment	Allocation	Post-allocation						Close-out
Windows:	**October -23**	**2023**	**Day 0**	**4W ± 3D**	**12 W ± 3D**	**24W ± 3D**	**36W ± 3D**	**48 W ± 3D**	**End-2025**
ENROLMENT:									
Eligibility screen	×								
Informed consent	×								
Allocation		×							
INTERVENTIONS:									
[0.01% atropine eye drops]		×	×	×	×	×	×	×	
[placebo eye drops]		×	×	×	×	×	×	×	
ASSESSMENTS:									
[The baseline variables]	×	×							
[The primary outcome]		×	×	×	×	×	×	×	
[The secondary outcome]		×	×	×	×	×	×	×	
[Safety evaluation]			×	×	×	×	×	×	

W: Weeks; D: Days

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (P1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (P2)
	2b	All items from the World Health Organization Trial Registration Data Set (P2)
Protocol version	3	Date and version identifier (P2)
Funding	4	Sources and types of financial, material, and other support (P23)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (P1)
	5b	Name and contact information for the trial sponsor (P9)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (P23)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (P20)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (P4)
	6b	Explanation for choice of comparators (P8)
Objectives	7	Specific objectives or hypotheses (P4)
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (P5)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (P6)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (P7)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (P8)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (P9)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (P9)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (P9)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (P10)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (P12)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (P8)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (P14)

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions (P14)

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned (P14)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (P15)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (P14)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial (P16)
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (P17)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols (P17)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (P18)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol (P19)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (P19)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) (P20)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (P21)

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial (P19)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct(P21)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (P22)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (P24)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (P22)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (P18)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (P18)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (P24)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators(P24)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (P22)
	31b	Authorship eligibility guidelines and any intended use of professional writers (P23)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (P20)

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates(P24)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (P33)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol for a parallel assignment prospective, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of 0.01% atropine for near work-induced transient myopia and myopic progression in China

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Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Research methods
Keywords:	Paediatric ophthalmology < OPHTHALMOLOGY, Clinical Trial, China

Protocol

Title: Protocol for a parallel assignment prospective, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of 0.01% atropine for near work-induced transient myopia and myopic progression in China

Names protocol contributors: Guanghao Qin [1], Jiayan Chen [1], Lan Hu[1], Yifan Qi[1], Ling Xu[1], Wei He [1], Sile Yu [1,2], Emmanuel Eric Pazo [1]*, Xingru He [1,2]*

1 He Eye Specialist Hospital, Shenyang, China.

2 He University, Shenyang, China.

*** Correspondence:**

1. Emmanuel Eric Pazo, Department of Ophthalmology, He Eye Specialist Hospital, Shenyang, China.11003

ericpazo@outlook.com

2. Xingru He, School of Public Health, He University, Shenyang, China.110034

hexingru@hsyk.com.cn

ABSTRACT

Introduction: Assessment of near work-induced transient myopia (NITM) is important for permanent myopia (PM) development and progression. Atropine eye drop has been reported to be beneficial in reducing initial NITM and slowing down myopic progression. This study aimed to investigate the efficacy of 0.01% atropine in treating NITM and its possible association with the progression of refractive change in Chinese myopic children.

Methods and analysis: The study is designed as a parallel assignment prospective, randomized, double-blinded, placebo-controlled trial conducted at He Eye Specialist Hospital in Shenyang, China. One hundred fifty participants will be randomly assigned in a 1:1 ratio to receive 0.01% atropine or placebo eye drop once nightly bilaterally for one year. Initial NITM, cycloplegic refraction, axial length, best-corrected visual acuity, intraocular pressure, and pupil diameter will be measured at baseline, 4-week, 12-week, 24-week, 36-week, and 48-week. Visual Function Questionnaire will be administered at baseline and each follow-up visit. Adverse events also will be monitored and documented at each subsequent follow-up visit.

Ethics and dissemination: A parallel assignment prospective, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of 0.01% atropine for near work-induced transient myopia and myopic progression registered on Sept 10, 2023. Ethics approval number: IRB (2023) K025.01. The study's findings will be shared regardless of the effect's direction.

Trial registration number: NCT06034366.

Strengths and limitations of this study:

- This study is a parallel assignment prospective, randomized, double-blinded, placebo-controlled trial.
- One hundred fifty participants participants will be randomly assigned in a 1:1 ratio to receive 0.01% atropine or placebo eye drop once nightly bilaterally for one year.
- An evaluation of Initial NITM, cycloplegic refraction, axial length, best-corrected visual acuity, intraocular pressure, and pupil diameter will be performed.
- The limitation of the research is that it's a single-center study.
- The study is limited to 1-year follow-up.

INTRODUCTION

Background and rationale {6a}

Myopia is a common condition that develops primarily during childhood and early adulthood when excessive elongation of the eye results in images of distant objects coming into focus in front of the retina, which leads to blurred distance vision.[1] Myopia is the most common ocular disorder worldwide, with increasing prevalence over the past decades, predominantly in East Asia.[2,3] Previous studies suggested that environmental factors, such as near-work demands, likely play an important role in myopia development in the younger population.

Near work is a major environmental component in establishing and progressing permanent myopia (PM), induced via near work-induced transient myopia (NITM).

[4,5]In contrast to PM, NITM refers to the prolonged period required for the accommodation of the eyes to revert to a normal level after performing a persistent near task.[6] Some years ago, it was proposed that NITM, which produces minor and chronic retinal defocus, may be one of many possible environmentally-based, myopigenic, contributory factors to permanent myopia.[7,8]Initial NITM magnitude is one of the key parameters used to characterise the accommodative response following a sustained near-work task, which is defined as the dioptric difference between the immediate pre- and immediate post-near task distance refractive state.[9,10] Previous studies reported that initial NITM was increased in myopes than in hyperopes or emmetropes.[4,11]

As a nonselective muscarinic antagonist, atropine eye drops with different concentrations have been reported to slow down the myopic progression in myopes.[12,13] Recently, a two-week study assessed the efficacy of a low concentration of atropine (0.01%) on the initial NITM magnitude among Chinese myopic children.[14] The results suggested that 0.01% atropine reduced the initial NITM magnitude. However, the long-term efficacy of 0.01% atropine in treating NITM and the relationship between NITM and refractive change after treatment is still unclear.

This study aimed to investigate the efficacy of 0.01% atropine in treating NITM and its possible association with the progression of refractive change in Chinese myopic children.

Objectives {7}

The primary objective of this study is to investigate the efficacy of 0.01% atropine

in the treatment of NITM and its possible association with the progression of refractive change in Chinese myopic children.

Trial design {8}

This is a prospective, randomized, double-blind, placebo-controlled trial performed at He Eye Specialist Hospital [ethics approval number: IRB (2023) K025.01]. The study adheres to the tenets of the Declaration of Helsinki and is registered at ClinicalTrails.gov (NCT06034366) using the SPIRIT reporting guidelines[15]. Randomization will be performed using a web-based, online, sealed envelope-based system (https://www.sealedenvelope.com). Specific study information sheets will be provided to patients prior to their consent. Following a dedicated screening and randomization visit for eligible patients, participants will be randomized to one of two trial arms. (Figure 1)

Methods: Participants, interventions, and outcomes

Study setting {9}

This study will be conducted between Oct 1, 2023, and May 30, 2025. Participants will be recruited at the Department of Ophthalmology, He Eye Specialist Hospital, Shenyang, China.

Patient and Public Involvement

Patients and the public will not be involved in this study's design, implementation,

reporting, or dissemination plans.

Eligibility criteria {10}

Inclusion criteria:

1. Age 6 to 12 years
2. Subjects and their guardians agreed to participate in this study
3. Best-corrected visual acuity (BCVA) 0.1 (log minimum angle of resolution, LogMAR) or better.
4. Initial NITM (spherical equivalent) ≤ -0.25 D
5. Cycloplegic refractions ≥ −1.0 D and astigmatism ≤ 2.5 D in both eyes.
6. Anisometropia in both eyes ≤ 1.5 D

Exclusion criteria:

1. Children with existing systemic diseases including asthma, collagen disease, immune system disorders, prostate hypertrophy, spastic paralysis, Down's syndrome, severe cardiac, pulmonary, hepatic, and renal dysfunction.
2. Patients with glaucoma or high intraocular pressure, ocular inflammatory diseases, strabismus, amblyopia, corneal diseases, diseases of lens, retinal and optic neuropathy.
3. Regular use of medications that may affect the efficacy of 0.01% atropine, including hairy fruit rutabaga eye drops, tropicamide eye drops, anticholinergic drugs such as pirenzepine and tropicamide, and cholinergic drugs such as carbachol and hairy fruit rutabaga.

4. Previous experiences with myopia control therapy.
5. A history of allergies to atropine.
6. Patients were deemed inappropriate for trial participation by the lead investigator.

Informed consent {26a}

Trained and experienced clinicians will seek informed permission from prospective participants and guardians.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

This trial does not involve collecting biological specimens.

Interventions

The explanation for the choice of comparators {6b}

After enrollment in the study, treatments will be initiated immediately after randomization. Participants in the study group will use 0.01% atropine (3 ml unit-concentration, preservative-free) once nightly in both eyes for 48 weeks, while those in the control group will utilize placebo eye drops (0.9% sodium chloride, 3 ml unit-concentration, preservative-free) once nightly in both eyes for 48 weeks. All eye drops will be prepared by He Eye Specialist Hospital, Co, LTD, Shenyang, China, with the same packaging.

Intervention description {11a}

In this study, patients receive either 0.01% atropine or placebo eye drops for 48 weeks based on the group they are placed in. Five follow-up visits will be performed at week 4 (±3 days), week 12 (±7 days), week 24(±7 days), week 36(±7 days), and week 48(±7 days) in both groups; a pediatric ophthalmologist will conduct comprehensive eye exams, including primary outcomes, secondary outcomes, and safety evaluation.

Criteria for discontinuing or modifying allocated interventions {11b}

After enrollment in the study, participants will receive one drop of 0.01% atropine or placebo eye drops once nightly in both eyes for 48 weeks. In case of allergic reactions or adverse events (AE) related to the study drug, the principal investigator (PI) (Emmanuel Eric Pazo) will decide if participants can continue further. Participants who onset other serious diseases or refuse to continue participating in the study will be stopped from using the designated eye drops.

Strategies to improve adherence to interventions {11c}

Participants and guardians will be reminded by phone and email every week, and appointments will be booked in advance based on their availability time. Patients will be provided a medication record booklet and their medication status will be verified at each follow-up session to enhance adherence.

In the case of outside the allowance, participants will be contacted by phone or email to make sure if they want to continue or discontinue the study. Subjects who could

not complete the follow-up inside the allowance were removed from this study.

Relevant concomitant care permitted or prohibited during the trial {11d}

Subjects are allowed to use single-vision lenses during treatment. Any other treatment or therapy for myopia control will be prohibited during the course of this study, including the Orthokeratology lens, multifunctional defocus lens, and red-light feeding instrument. Besides, any eye drops and systemic medications that may affect the outcome were prohibited, including hairy fruit rutabaga eye drops, tropicamide eye drops, anticholinergic drugs such as pirenzepine and tropicamide, and cholinergic drugs such as carbachol and hairy fruit rutabaga.

Provisions for post-trial care {30}

The placebo group will be transferred to the atropine group for treatment in the following year.

Outcomes {12}

Supplementary Table 1 displays the timeline for data collection and site visits. The assessments will be conducted in accordance with a predetermined order. A trained physician (GHQ) will do an in-person medical examination and lifestyle-related information interview. Comprehensive eye exams will be conducted by an ophthalmologist, including assessments mentioned below at baseline, week 4, week 12, week 24, week 36, and week 48.

Primary Outcome

Initial NITM will be evaluated by an open-field infrared autorefractor (WAM-5500; Grand Seiko, Japan), including the following steps.[16]

Pre-task: Subjects will be taught to binocularly fixate on a photopic high-contrast Maltese cross target situated at 5 m, and their accommodative response will be monitored dynamically for 10s.

Task: Subjects will complete a 5-minute near-work task with a 5D accommodating demand. To guarantee that subjects pay attention to the near target, we will utilize pairs of high-contrast black-and-white photographs with 10 small differences in each pair, and they will be instructed to discover as many differences as possible throughout the 5-minute task. Two pairs of targets will be used, with a different pair employed for each experimental session. The targets will be displayed on a digital screen (iPad mini6, Apple Inc., Cupertino, CA; 8.3in.). To get a satisfactory instrument alignment with the visual axis, both targets are closely placed, one above the other.

Post-task: The near work task will be swiftly removed after the 5-minute near work activity, and subjects will be instructed to focus for a 3-minute period on the photopic high-contrast Maltese cross target positioned at 5 m.

The NITM dioptric magnitude will be the mean spherical equivalent of the post-task minus pre-task values. This measure will be computed in the first 10-s interval . The first 10-s interval is referred to as the initial NITM. The initial NITM dioptric magnitude is represented by the MSE of the post-task minus pre-task value.

Secondary outcomes

All students will receive a cycloplegic autorefraction (WAM-5500; Grand Seiko Co., Ltd. Hiroshima, Japan) after NITM testing during each visit, whereas the parents will receive a non-cycloplegic autorefraction (ARK-1, NIDEK, Japan) during the baseline examination. Cycloplegic autorefraction will be performed 20 min after instilling three drops of cyclopentolate 1% (Cyclogyl, Alcon). Three readings will be obtained in each eye and averaged within and across each group.

Ocular axial length (AL) will be measured on a Zeiss IOL Master 700 (Carl Zeiss Meditec Inc, Dublin, CA) based on non-contact partial coherence interferometry.

A validated Chinese version of the 25-item National Eye Institute Visual Function Questionnaire will be provided to all subjects to determine the impact of different treatment groups on the vision-related quality of life.[17]

Safety evaluation

BCVA in the logarithm of the minimum angle of resolution (logMAR) will be assessed by an optometrist.

Intraocular pressure (IOP) will be evaluated using a non-contact tonometer (NT-510, NIDEK, Japan).

Mesopic pupil size and photopic pupil size will be measured with the OPD-Scan III (Nidek, Gamagori, Japan).

Anterior segment examination will be performed by Slit-lamp biomicroscopy and indirect ophthalmoscopy through a dilated pupil.

Participant timeline {13}

The schedule for data collection and visits is shown in Supplementary Table 1. After registration for this study, the assigned treatment intervention will be administered for 48 weeks. Furthermore, the effect of eyedrops will be examined at the week 4, week 12, week 24, week 36, and week 48 follow-ups (Figure 1).

Sample size {14}

The sample size calculation is based on the primary outcome measures of initial NITM to establish the superiority of the 0.01% atropine group compared to the placebo group in terms of the changes in the mean from the baseline in the initial NITM at week 48. We took the estimated initial NITM for 0.01% atropine and placebo groups to be -0.076 and -0.41D.[14] The expected standard deviation within a group was assumed to be 0.20 D. A sample size of 16 subjects could achieve 90% power at a 0.05 significance level. According to Chinese《preparation supervision measures for the administration of medical institutions》(2005), the number of participants should be at least 60. Considering a maximum dropout rate of 20%, the sample size required is 150 (75 per group).

Recruitment {15}

This study will be conducted between Oct 1, 2023, and May 30, 2025. This clinical study will be done in a single site, with participants blinded to the treatment assignment.

This research is open to children who met the inclusion criteria at He Eye Specialist Hospital's Department of Ophthalmology. Participants will be recruited using adverts in the distribution pamphlets, the website, and social media postings. Participants' demographic information will be collected during the first (screening) appointment.

Assignment of interventions: Allocation

Sequence generation {16a}

A web-based randomization application will be used (https://www.project-redcap.org/). Allocation will be done using block randomization and stratified according to age (allocation factor: 12 years ≥ age 6 years). (Known only to the statistical team, not stated here to maintain masking). Participants will be in a 1:1 allocation ratio to 0.01% atropine or placebo groups.

Concealment mechanism {16b}

The block size will be concealed from other researchers, and the randomization table will not be available for assessment by anyone involved in the study [18]. An independent biostatistician performs randomization. The biostatistician is the only one who has access to check the file. The allocation list is kept in a separate file on a different computer (as described in Chen et al.).[19]

Implementation {16c}

Opaque and sealed (A randomization list for each stratum) envelopes containing

serial numbers will be prepared by an independent statistician and delivered to the clinical trial center.

An independent researcher will distribute the envelopes to participants and allocate them into study groups at 1:1 without implementing stratification.

Before the random assignment, all participants will be informed that they will be allocated to one of two groups. Random allocation will be conducted at visit 2. Random numbers with corresponding participants will be determined in the order of the time of the second visit. They will be opened by the clinician prescribing the eye drops (0.01% atropine or placebo eye drop). The allocation result will not be announced to the participants until the end of the data collection phase of the trial. Researchers collecting and analyzing data related to this trial will be blinded to the participant allocation results.[19]

Assignment of interventions:

Blinding {17a}

The treatment assignment for the study will be triple-masked. Participants in the research would be unable to recognize the contents. A masked examiner for all clinical assessments will not be involved in this research's data collection or group allocation procedure. The investigator will not be aware of the three groups. Participants will be randomly assigned to 0.01% atropine group or placebo group. The box containing ampoules will be labeled with a batch number, including the study reference number, participant ID, contact number, investigator name, site address, the expiration date of

the eye drops, storage instructions, and a statement informing the participant that the eye drops are for use only in clinical trials and should not be ingested. The PI will determine and perform the circumstances and procedures under which unblinding is permissible.

Procedure for unblinding if needed {17b}

The PI will determine and perform the circumstances and procedures under which unblinding is permissible.

Participant withdrawal

Based on the following criteria, patients will be removed from the research.

1. When it is deemed challenging to continue, the study is owing to the emergence of new ailments.
2. The participant who lost to follow-up.
3. When participants or their legal guardians want to end their participation in a study.
4. When the participant's caretaker cannot guarantee their participation in the study.
5. When the research project has concluded.
6. When the lead investigator and sub-investigators believe it is acceptable to cease the study due to adverse events.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Data administration is the responsibility of Jiayan Chen, Department of Clinical Research, as chosen by the PI. This research will collect data using a proprietary EMR case report form and management application. Following the database lock, the individual responsible for the statistical analysis will get the locked data following the database. The data management handbook will provide the details on any specific information. At the end of the study, a report on the implementation and the status of data management will be compiled and sent to the PI with the locked research data.[19]

Plans to promote participant retention and complete follow-up {18b}

Informed consent will include information regarding follow-up assessments for all participants. If participants discontinue or deviate from intervention protocols, the study team will initiate contact and prioritize addressing any concerns that may be impacting their adherence to the intervention protocols. If these concerns cannot be resolved, the participants will be requested to complete subsequent self-assessment questionnaires online.

Data will be gathered during pre-randomization, termination, and follow-up periods at week 4, week 12, week 24, week 36, and week 48. The method of data collection for this study will involve the use of clinical tests and self-report questionnaires, which will be administered through an online platform. To guarantee the completeness and accuracy of the gathered data, the online questionnaires will be encoded in a manner that necessitates respondents to provide comprehensive responses

to all inquiries before submitting their answers.

Data management {19}

Separately experienced staff members at He Eye Specialist Hospital, Department of Clinical Research, performed data collection and entry. Supervision and double confirmation were performed by Guanghao Qin, along with weekly backup, to ensure data quality.

Confidentiality {27}

Each participant's personal information will be kept confidential in the same way as their medical histories in the hospital before, during, and after the trial.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not Applicable-There will be no biological specimens collected.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Unless otherwise mentioned, this study's significance level is set to 5% two-sided, and the confidence coefficient is set to 95%. The background of the study's subjects will be tabulated by calculating the mean and standard deviation for continuous variables and the frequency and percentage for categorical variables. Suppose the

continuous variables do not follow a normal distribution. In that case, they will be converted appropriately by logarithmic transformation or other means and aggregated with the mean and standard deviation, or the median and interquartile range will be utilized as descriptive statistics. For the primary endpoint, between-group comparisons using baseline as a covariate and an analysis of covariance will be made to produce the adjusted mean, its 95% confidence interval, and the p-value. A paired t-test will be used to make within-group comparisons. To ensure participant safety, frequencies and proportions will be computed for each group and item, and comparisons between groups will be made using Fisher's exact probability test or the $\chi 2$ statistic. Correlation analysis will be used to assess the relationship between NITM and myopic progression.

Interim analyses {21b}

Not applicable- no anticipated problems are detrimental to the participant, so interim analysis is not warranted.

Methods for additional analyses (e.g., subgroup analyses) {20b}

Subgroup analyses are not planned for this study.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

After accounting for loss to follow-up and missing data in sample-size calculations, using a two-tailed t-test of difference between means with a power of 90% and a significance level of 5%, we allowed a dropout rate of 20%.

Plans to give access to the complete protocol, participant-level data, and statistical code {31c}

The datasets analyzed during the current study and statistical code are available from the corresponding author on reasonable request, as is the complete protocol.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The subject leader and the project manager will form the Steering Committee (SC). The SC is accountable for managing the whole project. The SC appoints the Monitor Group's (MG) inspectors. The MG will oversee the entire research procedure in compliance with the Good Clinical Practice (GCP) requirements. The inspector will analyze the investigator's adherence to the protocol, the protection of participants' rights and interests, the quality of the case report form (CRF), and the investigator's understanding of different standards before submitting inspection reports to the SC.[19]

Composition of the data monitoring committee, its role and reporting structure {21a}

Due to the projected low frequency of adverse events and the modest numbers in each location, no data monitoring committee has been convened for this trial. The database will be constructed using Excel (Microsoft, USA 2022 version), and regular data monitoring will be undertaken per the sponsor's standard operating procedures.

The steering committee will have oversight and access to the trial under the supervision of the trial manager at any time during the study.

Adverse event reporting and harms {22}

Adverse events are unanticipated indications, symptoms, or illnesses seen during a clinical study, regardless of their relationship to the treatment. There may be unwanted local, general, and psychological effects. If any discomfort or new changes in condition during the study period, or any unexpected situation, whether related to the study or not, one should promptly notify the doctor, who will make a judgment and give appropriate medical treatment. According to the results, the doctor will evaluate the eye health status at the end of each examination. If the condition deteriorates or is no longer suitable for the study, the study may be terminated early. At the same time, the doctor will provide other treatment options that are ideal for the current situation to ensure health to the greatest extent. If major adverse events occur, He Eye Specialist Hospital Certified Review Board will be notified; experimental treatments will be discontinued promptly, and appropriate therapies will be offered.[19]

Frequency and plans for auditing trial conduct {23}

The study will be reviewed and evaluated weekly by an independent supervisor unrelated to the PI and sponsors.

Plans for communicating significant protocol amendments to relevant parties (e.g.,

trial participants, ethical committees) {25}

If there are modifications to eligibility criteria, outcomes, or analyses, a revised protocol will be submitted for approval to the He Eye Specialist Hospital Medical Ethics Committee.

Trial status

Recruitment began on Oct 1, 2023, and the approximate date when recruitment will be completed in March 2023. Protocol version 2.0 was approved in August 2022.

Ethics and dissemination {24}

The study was registered with the trial number NCT06034366 and was conducted in compliance with the tenets of the Declaration of Helsinki and the Institutional Review Board of the He Eye Specialist Hospital, Shenyang, China: IRB (2023) K025.01. Documented informed consent was obtained from all participants in this study. In the present study, all components with any individually identifiable information have been removed from the dataset.

The study's findings will be shared regardless of the effect's direction. All possible beneficiaries of the research, including patients, caretakers, family, doctors, advisory boards, and medical boards, will receive trial data. Publications in high-impact, open-access medical journals and talks at national and international medical conferences will serve this purpose.[19]

Abbreviations

NITM: Near work-induced transient myopia; PM: Permanent myopia; AL: axial length; BCVA: Best-corrected visual acuity; IOP: Intraocular pressure; RCT: Randomized control trial; AE: Adverse events; PI: principal investigator; MSE: mean spherical equivalent; SC: Steering Committee; GCP: Good Clinical Practice; CRF: Case report form

Declarations

Acknowledgments

The authors would like to express their appreciation for the effort of all personnel involved in this trial.

Authors' contributions {31b}

Conception and design of the research: GQ, JC, LH, YQ, LX, WH, SY, XH, and EEP; analysis and interpretation of the data: GQ, JC, EEP; writing original draft preparation: GQ; critical revision of the manuscript (reviewing and editing): GQ and EEP; supervision: XH, SY, and EEP.

Funding statement {4}

This study was entirely funded and sponsored by He Eye Specialist Hospital, Shenyang, China, which included study design, data collection, analysis, interpretation, and manuscript writing. No support was received for the publication of this article.

Availability of data and materials {29}

Any data required to support the protocol can be supplied on request.

Consent for publication {32}

Not applicable - no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent form are available from the corresponding author on request.

Competing interest statement {28}

The authors declare that they have no competing interests.

Authors' information

1 He Eye Specialist Hospital, Shenyang, China.

2 He University, Shenyang, China.

Figure legends

Figure 1. Study flow chart

Word count: 4111

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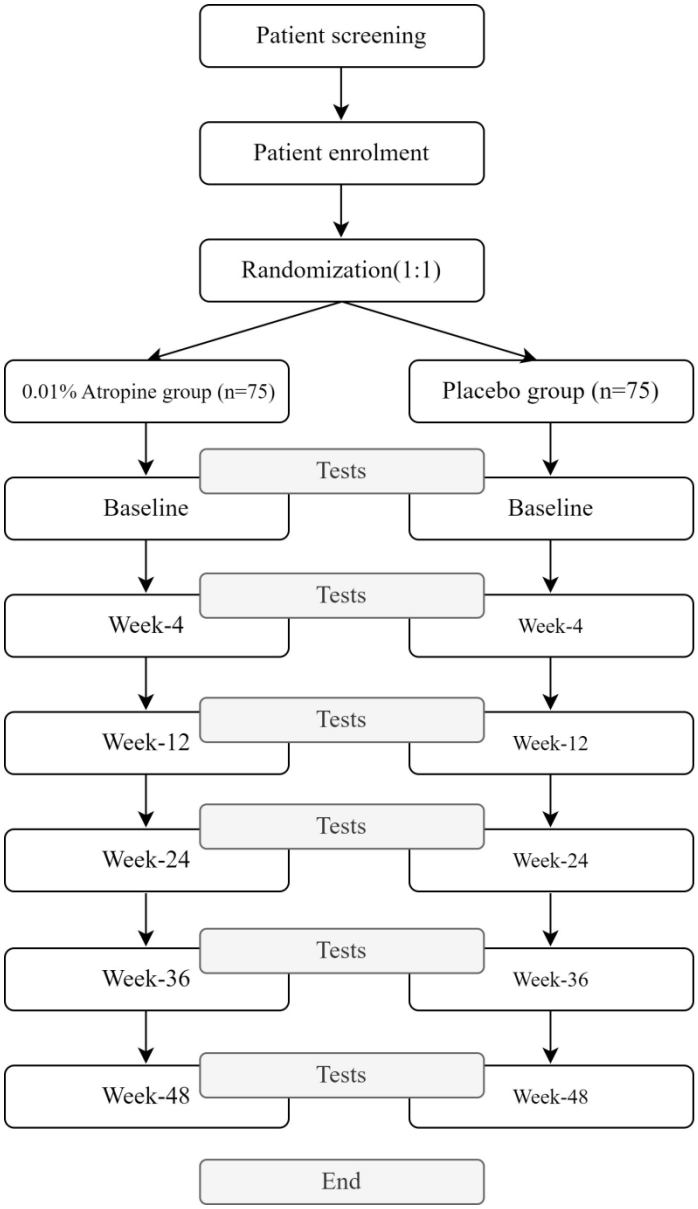

Figure 1. Study flow chart

132x228mm (300 x 300 DPI)

Supplementary Table 1. The schedule of enrolment, interventions, and assessments of this trial

		STUDY PERIOD							
	Enrolment	Allocation	Post-allocation						Close-out
Windows:	**October -23**	**2023**	**Day 0**	**4W ± 3D**	**12 W ± 3D**	**24W ± 3D**	**36W ± 3D**	**48 W ± 3D**	**End-2025**
ENROLMENT:									
Eligibility screen	×								
Informed consent	×								
Allocation		×							
INTERVENTIONS:									
[0.01% atropine eye drops]		×	×	×	×	×	×	×	
[placebo eye drops]		×	×	×	×	×	×	×	
ASSESSMENTS:									
[The baseline variables]	×	×							
[The primary outcome]		×	×	×	×	×	×	×	
[The secondary outcome]		×	×	×	×	×	×	×	
[Safety evaluation]			×	×	×	×	×	×	

W: Weeks; D: Days

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (P1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (P2)
	2b	All items from the World Health Organization Trial Registration Data Set (P2)
Protocol version	3	Date and version identifier (P2)
Funding	4	Sources and types of financial, material, and other support (P23)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (P1)
	5b	Name and contact information for the trial sponsor (P9)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (P23)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (P20)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (P4)
	6b	Explanation for choice of comparators (P8)
Objectives	7	Specific objectives or hypotheses (P4)
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (P5)

Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (P6)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (P7)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (P8)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (P9)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (P9)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (P9)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (P10)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (P12)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (P8)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (P14)
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions (P14)

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned (P14)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (P15)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (P14)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial (P16)
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (P17)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols (P17)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (P18)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol (P19)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (P19)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) (P20)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (P21)

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial (P19)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct(P21)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (P22)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (P24)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (P22)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (P18)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (P18)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (P24)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators(P24)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (P22)
	31b	Authorship eligibility guidelines and any intended use of professional writers (P23)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (P20)

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates(P24)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (P33)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.