

CLINICAL STUDY PROTOCOL

A Randomized Controlled Trial of Gabor-Based Perceptual Learning for Adult Amblyopia

Item	Details
Lead Institution	Shanghai Eye Disease Prevention and Treatment Center / Shanghai Eye Hospital
Principal Investigators	Yan Xu; Haidong Zou
Study Design	Single-center, assessor-masked, 1:1 randomized, delayed-treatment-controlled superiority trial
Planned Sample Size	80 participants (40 immediate training; 40 delayed training)
Follow-up Duration	Week 24
Protocol Version	20250325.2.1
Version Date	16 July 2025

Protocol Synopsis

Item	Revised Protocol
Objective	To evaluate the superiority of Gabor training over delayed treatment for improving amblyopic-eye BCVA at week 12, together with safety, adherence, and potential predictors.
Study Design	Single-center, prospective, assessor-masked, 1:1 randomized, delayed-treatment-controlled study; randomization follows an 8–12-week optical-stability period.
Immediate-Training Group	Gabor training during weeks 0–12; study completion after week 12 endpoint assessment.
Delayed-Training Group	Best optical correction and observation during weeks 0–12; same 12-week Gabor training during weeks 12–24.
Primary Endpoint	Change from randomized baseline in amblyopic-eye ETDRS letters at week 12.
Key Secondary Endpoints	Proportions improving ≥ 10 and ≥ 15 letters at week 12; changes in contrast sensitivity and stereopsis; delayed-group pre/post training changes; safety and adherence.
Planned Sample Size	80 participants, 1:1 allocation. ANCOVA assumptions: 5-letter difference, SD 9 letters, baseline–week 12 correlation 0.60, two-sided $\alpha=0.05$, 80% power, and 15% attrition.
Primary Analysis	ITT principle; ANCOVA comparing week 12 change, adjusted for baseline BCVA and randomization stratification factors; MMRM as longitudinal supportive analysis.
Ethical Safeguards	Delay limited to 12 weeks with best optical correction and safety monitoring, followed by the same 12-week training; prespecified rescue and withdrawal criteria.

1. Background and Rationale

Amblyopia is a neurodevelopmental visual disorder caused by abnormal visual experience during the sensitive period of visual development. Common causes include anisometropia, strabismus, or both. Its defining feature is reduced best-corrected visual acuity that cannot be fully explained by ocular or visual-pathway pathology. A global systematic review and meta-analysis estimated a pooled prevalence of 1.44%, rising to 3.29% among people older than 20 years, indicating that visual impairment persists into adulthood in a substantial population [13]. Because spontaneous recovery is unlikely in adulthood, adult amblyopia represents a long-term burden of visual dysfunction.

Amblyopia is not simply a reduction in high-contrast acuity. Abnormal binocular experience may produce imbalanced interocular competition, suppression of amblyopic-eye input, abnormal spatial selectivity and binocular integration in the visual cortex, and impaired integration of local information into global perception [1]. In addition to reduced best-corrected distance and near acuity, patients may exhibit reduced contrast sensitivity, abnormal contour integration and crowding, impaired binocular fusion, and absent stereopsis. These deficits may affect detailed near work, reading, driving, spatial orientation, and stair negotiation. Therefore, high-contrast acuity alone cannot fully characterize treatment benefit; this study also evaluates near acuity, contrast sensitivity, stereopsis, and quality of life.

Traditional theory held that visual-system plasticity declines markedly after the childhood critical period, and amblyopia treatment consequently focused on children, leaving adults with limited perceived treatment opportunities. Conventional childhood treatment includes full optical correction, fellow-eye patching, or pharmacologic penalization, but this evidence cannot be directly extrapolated to adults. In a recent small prospective adult study, 2 hours of daily patching combined with near and distance visual activities produced an average improvement of approximately 0.17 logMAR after 12 weeks among nine completers, with concurrent improvement in contrast sensitivity [15]. Although this suggests that adults may benefit from treatment, the study was small, lacked a concurrent randomized control, and combined patching, computer tasks, and other visual activities, preventing attribution to individual components. The optimal treatment, true effect size, and likely responders in adult amblyopia therefore remain uncertain.

Basic and clinical research has progressively challenged the view that the adult visual system cannot be trained. Work by Levi and Polat showed measurable learning effects in adult amblyopic vision after training on specific visual tasks [2]. Perceptual learning refers to sustained improvement in the detection or discrimination of stimulus features through repeated, structured practice. Initial learning is often specific to the trained eye, retinal location, spatial frequency, or orientation, implicating early visual-cortical processing. Some effects, however, transfer to untrained clinical functions such as letter recognition, visual acuity, and contrast sensitivity, suggesting contributions from both low-level representational plasticity and higher-level decision, attention, and rule-learning processes [3,8].

Gabor stimuli are localized sinusoidal gratings whose spatial frequency, orientation, contrast, phase, and spacing can be precisely controlled. They are classical probes of spatial selectivity and lateral interaction in the primary visual cortex. In amblyopia, the balance of facilitation and inhibition between adjacent contours, long-range horizontal connections, and spatial integration may be abnormal. Gabor-based training typically presents targets and lateral masks near the individual threshold and adaptively

adjusts difficulty according to accuracy. Repeated practice may strengthen beneficial lateral facilitation, reduce inappropriate inhibition, and improve signal extraction, thereby enhancing contrast detection and letter recognition. Polat and colleagues observed approximately twofold gains in contrast sensitivity and letter-recognition performance following systematic low-level visual training in adults with amblyopia, demonstrating transfer from trained low-level tasks to higher-order visual functions [14].

Subsequent studies further support the potential benefit of perceptual learning in adult amblyopia. Zhou et al. assigned 23 adults with anisometropic amblyopia to different training conditions or a no-training group. Grating-detection training and repeated contrast-sensitivity training improved amblyopic-eye acuity and contrast sensitivity, whereas no corresponding improvement occurred without training; in a subset, approximately 90% of the acuity gain was retained for at least 1 year [4]. Pilot work by Chen et al. and extended training by Li et al. also reported improvements in adult amblyopic acuity or positional acuity [5,6]. Zhang et al. proposed that adult perceptual-learning gains may involve rule learning and cognitive compensation as well as early visual-cortical change [8]. In a clinical training setting, He et al. found that monocular near-threshold training improved acuity and contrast sensitivity and that early acuity change might predict final response, although substantial interindividual variability remained [10]. Reviews conclude that perceptual learning has therapeutic potential but do not yet support a single standardized regimen [3,9].

Important limitations remain. First, most adult studies are small, single-arm, or lack concurrent randomized controls, making it difficult to exclude optical adaptation, repeat-testing effects, natural fluctuation, and regression to the mean. Second, amblyopia type, age range, task, spatial frequency, number of sessions, and treatment duration vary considerably, leaving effect size and generalizability uncertain. Third, some studies focus on laboratory psychophysical outcomes and use nonuniform clinical measures of acuity, contrast sensitivity, and stereopsis. Fourth, adherence is often self-reported, and the relationship between actual completed dose and response is insufficiently validated. Fifth, patching, visual activities, and perceptual learning are sometimes combined, preventing attribution to a single mechanism. These issues hinder translation from laboratory evidence to routine care.

To address these gaps, this study uses a single-center, assessor-masked, randomized delayed-treatment-control design. All participants complete standardized optical correction and an 8–12-week stability period before randomization, with repeated ETDRS assessments on different dates to reduce bias from optical adaptation and baseline fluctuation. During randomized weeks 0–12, the immediate group receives standardized Gabor training while the delayed group continues stable optical correction without other amblyopia treatment, providing a concurrent control for estimation of the incremental effect of Gabor training. After the masked week 12 primary endpoint assessment, the delayed group receives the same 12-week training, ensuring that all participants can access the study intervention and allowing within-group replication of pre/post training changes.

The primary outcome is change in study-eye ETDRS letter score at 12 weeks after randomization. Best-corrected near acuity, contrast sensitivity, stereopsis, ocular deviation, safety, adherence, and quality of life are assessed concurrently. Software-recorded training logs enable exploration of associations among completed dose, baseline visual function, amblyopia type, age, and response. Through the stability period, allocation concealment, masked outcome assessment, standardized testing, and prespecified statistical analysis, this trial seeks to provide higher-quality exploratory randomized evidence for Gabor-based treatment of adult amblyopia and to inform effect-size

assumptions, endpoint selection, and target populations for future multicenter, active-controlled, or mechanistic studies.

Study Hypotheses

Primary hypothesis: At 12 weeks after randomization, the mean improvement from baseline in the amblyopic-eye ETDRS letter score will be greater in the immediate-training group than in the delayed-training group, with an adjusted between-group mean difference greater than 0.

Exploratory hypothesis: Completion of 12 weeks of Gabor training may improve contrast sensitivity and selected binocular visual functions, and the training effect may be associated with the completed training dose.

2. Study Objectives

Primary Objective

To evaluate the superiority of Gabor-based perceptual learning over 12 weeks of delayed treatment (optical correction alone) in improving amblyopic-eye best-corrected visual acuity (BCVA) in adults aged 18–55 years with amblyopia.

Secondary Objectives

- To evaluate the proportions of participants achieving improvements of ≥10 and ≥15 ETDRS letters.
- To evaluate changes in contrast sensitivity, near and distance stereopsis, and ocular deviation.
- To evaluate changes in the delayed-training group after 12 weeks of training.
- To evaluate training safety and adherence.

Exploratory Objectives

- To explore associations of age, amblyopia type, baseline BCVA, prior treatment history, degree of anisometropia, and training dose with treatment response.
- To explore changes in retinal/choroidal structure and blood-flow parameters; no confirmatory conclusions will be drawn from these analyses.
- To evaluate changes in amblyopia-related quality of life in adults.

3. Study Design

This is an investigator-initiated, single-center, prospective, assessor-masked, 1:1 randomized, delayed-treatment-controlled superiority clinical trial. Each participant will complete an 8–12-week optical-stabilization period and will be randomized after meeting the prespecified stability criterion. Participants in the immediate-training group will be followed for 12 weeks after randomization, and those in the delayed-training group for 24 weeks.

Phase	Immediate-Training Group	Delayed-Training Group	Primary Purpose
Optical-stability period (weeks –12/–8 to 0)	Best optical correction and repeated baseline	Best optical correction and repeated baseline	Exclude optical adaptation and unstable acuity

Phase	Immediate-Training Group	Delayed-Training Group	Primary Purpose
Randomized comparison (weeks 0–12)	12 weeks of Gabor training	Best optical correction; no Gabor training	Primary confirmatory between-group comparison
Delayed-treatment phase (weeks 12–24)	Study complete; no further follow-up	Receive 12 weeks of Gabor training	Assess delayed-group pre/post training changes

Study Flow

1. Screening, informed consent, comprehensive ophthalmic examination, and standardized optical correction.
2. Completion of an 8–12-week stability observation period, including at least two standardized ETDRS assessments on different dates.
3. After confirming eligibility and visual-acuity stability, randomization in a 1:1 ratio through a centralized randomization system.
4. Masked visual-function assessments, safety evaluations, and adherence recording according to the schedule of assessments.
5. Completion of blinded data review and finalization of the statistical analysis plan before database lock.

4. Study Population

Inclusion Criteria

1. Written informed consent; age 18–55 years inclusive at randomization.
2. Diagnosis of amblyopia, with amblyopic-eye BCVA of 20–70 ETDRS letters (decimal BCVA 0.05–0.5).
3. Amblyopia caused by anisometropia, strabismus, or both, meeting the following definitions:
 - Anisometropic amblyopia: interocular spherical-equivalent difference ≥ 1.00 D or astigmatic difference ≥ 1.50 D in any meridian, with no manifest strabismus at distance or near.
 - Strabismic amblyopia: strabismus at distance or near, or a history of strabismus surgery, without meeting the anisometropia criterion.
 - Combined-mechanism amblyopia: meeting both the strabismus and anisometropia criteria.
4. Completion of standardized optical correction and the 8–12-week stability period; absolute difference between week –4 and week 0 ETDRS scores < 5 letters, with no continuing pretreatment improvement trend.
5. Ability to use the study device for home training and accept electronic adherence monitoring.

Exclusion Criteria

1. Eccentric fixation, clinically significant nystagmus, or inability to complete reliable ETDRS testing.
2. Corneal, lenticular, retinal, macular, optic-nerve, or neurologic disease capable of explaining the visual-acuity reduction.
3. Study-eye spherical equivalent ≤ -8.00 D, or high refractive error judged by the investigator to compromise test reliability.
4. Recent intraocular surgery or ocular trauma, or extraocular-muscle surgery considered likely to affect outcomes.
5. Diplopia at baseline that interferes with safety evaluation, or an unacceptable training risk as judged by the investigator.
6. Patching, penalization, other visual training, or treatment likely to affect amblyopia outcomes within the prespecified period before randomization.
7. Inability to complete follow-up, understand the tasks, or participation in another clinical study likely to affect outcomes.

Determination of the Study Eye

For unilateral amblyopia, the amblyopic eye will be the study eye. If both eyes are eligible, the eye with worse BCVA will generally be selected; if BCVA is equal, one eye will be selected using a prespecified rule. The study eye may not be changed after designation. The fellow eye will serve as the safety-observation eye.

5. Randomization, Allocation Concealment, and Masking

Randomization

An independent statistician will generate a computer-based randomization sequence assigning participants 1:1 to immediate or delayed training. Variable block randomization will be stratified by baseline BCVA category (e.g., ≤ 50 vs > 50 letters) and amblyopia type (anisometropic vs other). Block sizes and the complete sequence will not be disclosed to recruitment or assessment personnel.

Allocation Concealment

After eligibility confirmation, stability determination, and baseline assessments, the study team will obtain assignment through an independent randomization system. The randomization sequence will not be stored in files accessible to recruitment personnel. Advance randomization and reservation of randomization numbers are prohibited.

Masking

Participants and training instructors cannot be masked to whether training has started; however, all BCVA, contrast-sensitivity, and binocular-function examiners will remain masked to assignment. Statisticians will use coded treatment groups until the primary analysis program is finalized. Before

each assessment, participants will be reminded not to disclose training status. Any unmasking will be documented with its reason, timing, and potential impact.

6. Interventions

Common Intervention: Best Optical Correction

All participants will undergo cycloplegic refraction and prescription confirmation during the stability period. Myopia and astigmatism should generally be fully corrected; hyperopia in the amblyopic eye should generally be fully corrected; undercorrection of hyperopia in the fellow eye must not exceed 2.00 D. Prescriptions must not be changed after randomization unless clinically necessary. Any change will be documented and addressed in sensitivity analyses.

Gabor-Based Perceptual Learning

Home-based training will use the RevitalVision visual perceptual-learning software. Training should be conducted in a dark or standardized low-illumination environment, with a calibrated computer display as the primary light source and a viewing distance of 1.5 m. Training modes include single-image, clarity, lateral-masking, and image-shift tasks, with parameters adaptively adjusted according to performance.

- Approximately 30 minutes per session, four sessions per week for 12 consecutive weeks. Allowable training windows and make-up-session rules will be specified in the operations manual.
- Participants will wear the study spectacle prescription during training. For unilateral amblyopia, the non-study eye will be occluded according to a standardized procedure. During the randomized comparison period, neither group may receive additional patching apart from occlusion required during Gabor training.
- The software will automatically record date, duration, completed tasks, stimulus parameters, and accuracy. Manual adherence records will be supplementary only.
- Training equipment, display size, resolution, luminance, and viewing distance must meet standardized requirements. The first training session will be supervised by trained personnel.

Management of the Delayed-Training Group During Weeks 0–12

Participants will continue wearing the prescription established during the stability period and will receive study contacts, visual-function assessments, and safety monitoring at the same frequency as the immediate-training group, but will not receive Gabor training or additional patching, penalization, or other visual training. After the masked primary endpoint assessment at week 12, they will begin 12 weeks of Gabor training.

Prohibited and Permitted Concomitant Treatments

After randomization, amblyopia training, patching, pharmacologic penalization, or any other intervention not specified in the protocol that could affect the primary outcome is prohibited. Clinically necessary treatment must not be delayed, must be fully documented, and will be reviewed by a masked adjudication committee to determine whether it constitutes a major protocol deviation.

7. Outcome Measures

Primary Outcome

Change from randomized baseline to week 12 in the study-eye ETDRS letter score. Randomized baseline will generally be the masked week 0 ETDRS result; the mean of weeks -4 and 0 will be used in a prespecified sensitivity analysis. Positive values indicate improvement.

Key Secondary Outcomes

1. Proportion with a ≥ 10 -letter improvement in study-eye BCVA at week 12.
2. Proportion with a ≥ 15 -letter improvement in study-eye BCVA at week 12.
3. Change in contrast sensitivity at week 12.
4. Changes in near and distance stereopsis at week 12.
5. Changes in BCVA, contrast sensitivity, and stereopsis in the delayed-training group from week 12 to week 24, after completion of 12 weeks of training.

Exploratory Outcomes

- Changes in ocular deviation, axial length, and refraction.
- Changes in OCT-derived retinal/choroidal thickness and blood-flow parameters.
- Change in quality-of-life questionnaire scores.
- Training dose–response relationship and potential predictors of treatment response.

Safety Outcomes

- A decrease of ≥ 10 ETDRS letters in fellow-eye BCVA.
- New or worsening diplopia, abnormal ocular alignment, visual fatigue, headache, nausea, or other training-related discomfort.
- Serious adverse events, adverse events leading to training discontinuation, and events judged by the investigator to be related to training.

8. Assessment Methods and Quality Control

Participant Information Collection

Questionnaire-based interviews will collect name, date of birth, sex, ethnicity, contact details, history of ocular disease or surgery, medical history, amblyopia treatment history (none, spectacle wear, patching, fellow-eye penalization, combined patching and penalization, or other), allergy history, and related information for entry into the electronic data capture (EDC) system.

Best-Corrected Distance Visual Acuity

BCVA will be measured letter by letter using a 4-m ETDRS chart under standardized illumination. Equivalent chart versions will be used to reduce memorization. Primary endpoint testing will be performed by a certified examiner masked to assignment. The better of two measurements must not be

selected. If repeat testing is required for quality control, the mean will be used or a third measurement obtained according to prespecified rules.

Best-Corrected Near Visual Acuity

Near visual acuity will be assessed with a standardized logarithmic near-vision chart conforming to GB/T 11533—2011 and using standard tumbling-E optotypes. The study and fellow eyes will be tested separately with best optical correction at a fixed distance of 25 cm. The chart will be positioned flat, with the optotype plane perpendicular to the line of sight, under uniform glare-free illumination.

Procedure: The participant will wear the study spectacle prescription, and the non-tested eye will be covered with an opaque occluder. Starting with larger optotypes, the participant will identify the orientation of each tumbling E until the smallest identifiable line is established. Directional prompting, shortening of the test distance, and squinting are not permitted. The decimal acuity corresponding to the smallest line read in full will be recorded.

Contrast Sensitivity

A uniform version of the FrACT (Freiburg Acuity and Contrast Test) automated visual-testing tool will be used. Developed in the laboratory of Michael Bach, FrACT uses anti-aliasing and dithering techniques and a PEST procedure to estimate the threshold.

Testing Procedure:

Calibrate the system in Settings before testing to ensure valid results.

A rotating tumbling E will be used as the contrast-sensitivity optotype.

Four orientations and 24 responses will be used; the test distance will be 50 cm.

Step 1: Open FrACT and adjust the display and test distance.

Step 2: Explain that this is a forced-choice test. Even if the participant reports seeing nothing, encourage the best possible guess. The software accounts for chance responses and presents items of similar difficulty. Encourage prompt responses; prolonged nonresponse will cause the software to advance automatically.

Step 3: Record the participant's response for the E orientation (up, down, left, or right) using the mouse or arrow keys. Test the left and right eyes sequentially.

Step 4: At completion, the software will generate the contrast-sensitivity result for recording.

Prism Cover–Uncover Test:

The participant will fixate near and distance targets. Cover–uncover testing will identify strabismus and determine the type and magnitude of deviation in prism diopters (PD).

Binocular Visual Function

Near and distance stereopsis will be assessed using Titmus and random-dot stereotests. Results will be converted to log arcsec. Examiners will remain masked to assignment.

Axial Length

Axial length will be measured using the IOLMaster (version 5.02; Carl Zeiss, Jena, Germany). The device will be calibrated with a model eye before measurement. The mean of three consecutive measurements will be used; testing will be repeated if any two measurements differ by >0.05 mm.

Refraction

After adequate cycloplegia, refraction in both eyes will be measured using an automated refractor (KR-8900; Topcon, Japan). The mean of three consecutive readings will be used. If any two readings differ by >0.50 D, measurement will be repeated.

OCT Examination

Swept-source OCT (DRI OCT-1 Atlantis; Topcon) using the 9-Line Radial follow-up mode will acquire fundus and tomographic images. Participants will rest briefly and avoid coffee and similar beverages before imaging. Axial magnification will be corrected, and imaging will be performed at a consistent time of day to reduce circadian variation in choroidal thickness. Automated choroidal-boundary segmentation will undergo manual review and correction. Choroidal thickness will be obtained at the subfovea and nine predefined regions across the inner, middle, and outer rings (superior, inferior, nasal, and temporal sectors as applicable).

OCT will be acquired at a consistent time of day whenever possible. Image-quality thresholds and masked manual segmentation review will be applied. Multi-region outcomes are exploratory and will be subject to multiplicity control.

9. Sample Size

The sample size is based on a superiority comparison of the change in ETDRS letters at week 12 between groups, with the primary analysis using ANCOVA adjusted for randomized baseline BCVA. Assumptions are a minimum clinically important between-group difference of $\Delta=5$ ETDRS letters, common standard deviation $\sigma=9$ letters, correlation between randomized baseline and week 12 BCVA $\rho=0.60$ based on the repeated-baseline design and preliminary adult data, two-sided $\alpha=0.05$, 80% power, and 1:1 allocation.

Using the approximate formula for comparison of two independent means:

$$n = 2 \times (Z_{1-\alpha/2} + Z_{1-\beta})^2 \times \sigma^2 \times (1-\rho^2) / \Delta^2$$

Substitution of $Z_{1-\alpha/2}=1.96$, $Z_{1-\beta}=0.842$, $\sigma=9$, $\rho=0.60$, and $\Delta=5$ gives approximately 32.6 participants per group, rounded up to 33 participants completing the primary endpoint. Allowing for 15% dropout or missing primary endpoints gives $33 \div (1-0.15)=38.8$, rounded up to 39 per group. To facilitate 1:1 randomization and retain a small margin, 80 participants (40 per group) will be enrolled. Approximately 68 participants (34 per group) are expected to complete the primary endpoint, providing slightly more than 80% power under these assumptions.

10. Statistical Analysis

General Principles

All tests will be two-sided, with $\alpha=0.05$ for the primary outcome. Continuous variables will be summarized using mean, standard deviation, median, quartiles, and range; categorical variables using counts and percentages. Primary results will include effect estimates, 95% confidence intervals, and P values rather than within-group significance alone. A standalone SAP will be finalized before database lock.

Analysis Populations

- Intention-to-treat/full analysis set (ITT/FAS): all randomized participants analyzed according to randomized assignment; the primary analysis population.
- Per-protocol set (PP): participants without major protocol deviations who meet prespecified minimum intervention/observation requirements; used for sensitivity analyses.
- Safety set: participants who receive at least one training session or complete at least one post-randomization safety assessment; summarized according to treatment actually received.

Primary Outcome Analysis

ANCOVA will compare the week 12 change in ETDRS letters between groups. The model will include treatment group, randomized baseline BCVA, and randomization stratification factors. The primary effect will be the adjusted mean difference (immediate minus delayed training) with 95% CI.

Longitudinal and Secondary Outcomes

A mixed model for repeated measures (MMRM) will analyze BCVA across visits, including treatment group, visit, group-by-visit interaction, baseline BCVA, and stratification factors, with a prespecified within-participant covariance structure. Binary responder outcomes will preferably use robust Poisson regression to estimate relative risks, with logistic regression if necessary. Skewed stereopsis outcomes will use suitable transformations, generalized models, or rank-based methods.

Delayed-Treatment Phase Analysis

Post-week 12 analyses will evaluate only within-group changes after 12 weeks of training in the delayed-training group. No maintenance follow-up is planned for the immediate-training group. Because the delayed group switches to treatment, week 12–24 findings cannot replace the randomized between-group comparison during weeks 0–12. Paired analyses or segmented mixed models may be used as supportive analyses.

Missing Data

The primary ANCOVA will be performed after multiple imputation or according to the primary strategy prespecified in the SAP. MMRM under a missing-at-random assumption will be a longitudinal supportive analysis. Participants with missing responder outcomes will be treated as nonresponders, with multiple-imputation sensitivity analysis. Delta adjustment or tipping-point analysis will assess the impact of missing-not-at-random assumptions.

Multiplicity

The primary outcome will be tested separately at two-sided $\alpha=0.05$. Key secondary outcomes will use a prespecified hierarchical procedure or Holm adjustment to control the family-wise error rate. Other secondary and exploratory outcomes will report unadjusted results and, where appropriate, false-discovery-rate adjustments, with their exploratory status clearly stated.

Subgroups and Predictors

Prespecified subgroups will be limited to age, amblyopia type, baseline BCVA, and prior treatment history. Heterogeneity will be evaluated through treatment-by-subgroup interaction terms. Predictor models will limit the number of candidate variables and may use penalized regression with bootstrap internal validation. Data-driven stepwise selection will not support primary conclusions.

Sensitivity Analyses

- PP analysis;
- Use of the mean of week -4 and week 0 BCVA as baseline;
- Exclusion of participants whose optical prescription changes after randomization;
- Alternative primary-endpoint visit-window definitions;
- Adjustment for actual training dose;
- Alternative missing-data assumptions.

11. Safety, Rescue Treatment, and Withdrawal

Rescue Criteria During the Delay Period

During weeks 0–12, rescue evaluation will be initiated if BCVA in the study or fellow eye decreases by ≥ 10 letters from randomized baseline and is confirmed on repeat testing, if persistent diplopia or a clinically significant alignment change occurs, or if continued delay is judged to pose clinical risk. The delay period may be terminated early and clinically necessary treatment given; masked outcome follow-up should still be completed whenever possible, and the participant will remain in the randomized group for ITT analysis.

Training Interruption or Discontinuation

- New persistent diplopia or intolerable visual symptoms.
- Confirmed decrease of ≥ 10 letters in fellow-eye BCVA.
- A serious adverse event or unacceptable risk from continued training as judged by the investigator.
- Withdrawal of consent.

Stopping training does not constitute withdrawal from follow-up. Unless the participant explicitly refuses, the study team should continue collecting primary outcome and safety data. Reasons for withdrawal must be categorized and documented.

12. Data Management and Quality Control

- A unified EDC system will be used, with logic checks, audit trails, access controls, and data backup.
- Before study initiation, the center will complete training and certification in the protocol, ETDRS, FrACT, stereopsis testing, randomization system, and adverse-event reporting.
- Informed consent, eligibility, source data, randomization, primary endpoints, and serious adverse events will be monitored regularly.
- Training logs will be uploaded automatically; manual changes must retain an audit trail.
- Masking status and any unmasking of primary endpoint assessors will be monitored.
- Protocol-deviation classification and blinded data review will be completed before database lock.

Conflicts of Interest and Independence

The sponsor or software supplier may not access the randomization sequence, unilaterally modify the protocol, SAP, or database, or control publication decisions. Publications will fully disclose equipment, software, funding, data ownership, and investigator conflicts of interest. The primary statistical analysis should preferably be performed by an independent statistician.

13. Ethical Considerations and Trial Registration

The study will comply with the Declaration of Helsinki, applicable Good Clinical Practice requirements, and the center's ethics requirements. All participants will provide written informed consent before any study-specific procedure.

A delayed-treatment rather than long-term untreated control is used because evidence for patching alone in adults is limited, the true incremental benefit of Gabor training remains uncertain, and a concurrent 12-week control is needed to separate optical adaptation and measurement effects. After primary endpoint assessment, the delayed group will receive the same 12-week training as the immediate group, with continued safety monitoring and prespecified rescue treatment.

The study will be publicly registered before the first randomization, including the primary outcome, time point, sample size, groups, and statistical principles. Protocol reporting will follow SPIRIT and trial reporting will follow CONSORT, including a participant flow diagram.

十四、14. Schedule of Assessments

Item	Week -12/-8	Week -4	Week 0	Week 6	Week 12	Week 18	Week 24
Informed consent / screening	√						
Standardized refraction / spectacles	√	As needed	Confirm				As needed
Eligibility criteria	Initial screen	Review	Confirm				
Randomization			√				
ETDRS BCVA	√	√	√	Both	Both	D	D
Contrast sensitivity	√		√		Both		D
Alignment / stereopsis	√		√		Both		D
Axial length / refraction	√		√		Both		D
OCT (exploratory)	√		√		Both		D
Quality of life			√		Both		D
Training instruction			I		D		
Training logs / adherence			I (start)	I (ongoing)	I (complete) / D (start)	D (ongoing)	D (complete)
Adverse events / concomitant treatment			Both	Both	Both	D	D
Primary Endpoint					★		

Note: I=immediate-training group; D=delayed-training group; Both=both groups assessed; ★=randomized between-group primary endpoint. Post-randomization on-site visits occur at weeks 6 and 12; after delayed training begins, visits occur at weeks 18 and 24. The immediate group completes the study after the week 12 primary endpoint assessment, without maintenance follow-up; the delayed group continues through week 24. Training logs are collected continuously by the software. Remote safety and adherence contacts occur every 2–4 weeks between on-site visits, with unscheduled visits for warning signs. Each on-site visit has a prespecified window, and the acceptable primary-endpoint window will be defined in the SAP.

15. Study Organization and Responsibilities

Institution	Investigators	Primary Responsibilities
Shanghai Eye Disease Prevention and Treatment Center / Shanghai Eye Hospital	Yan Xu; Haidong Zou	Overall oversight, recruitment, study conduct, quality control, and safety management

Before study initiation, names and responsibilities of recruitment staff, masked assessors, training instructors, data-management staff, the independent statistical lead, and the safety-reporting contact will be documented, ensuring separation of recruitment/intervention duties from primary endpoint assessment.

16. Prespecified Protocol Deviations

- Randomization despite failure to meet key eligibility criteria;
- Primary endpoint assessor aware of assignment without possible remediation;
- Delayed group receives nonprotocol visual training or patching during weeks 0–12;
- Immediate group receives no training;
- Primary endpoint outside the prespecified visit window;
- Incorrect study eye or primary outcome measurement not compliant with certified procedures.

Major protocol deviations will be adjudicated before database lock without knowledge of primary analysis results. All randomized participants will remain in the ITT analysis.

17. References

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Appendix: Amblyopia Quality of Life Questionnaire

Amblyopia Quality of Life Questionnaire

Name

Sex

Date of Birth

____ / ____ / ____
(MM/DD/YYYY)

Ethnicity

Instructions

Please answer based on your actual experience during the past 7 days. For each question, check the box (☐) next to the response that best applies to you. Select only one response for each question. If you are unsure, choose the response that most closely reflects your experience.

Part 1 Visual Function

1. During the past 7 days, have objects appeared increasingly blurred when you looked at them while wearing appropriate corrective glasses?

A ☐ All the time B ☐ Most of the time C ☐ Sometimes D ☐ Not at all

2. During the past 7 days, have objects appeared to overlap, or have you seen two images of the same object?

A ☐ All the time B ☐ Most of the time C ☐ Sometimes D ☐ Not at all

3. During the past 7 days, have you had difficulty judging the depth of or distance to objects in front of you?

A ☐ All the time B ☐ Most of the time C ☐ Sometimes D ☐ Not at all

4. During the past 7 days, when looking straight ahead at an object, have you been unable to see objects above, below, or to either side of it?

A ☐ All the time B ☐ Most of the time C ☐ Sometimes D ☐ Not at all

Part 2 Vision-Related Daily Activities

5. During the past 7 days, when reading a book or magazine, have the words appeared blurred or been difficult to distinguish?

A ☐ All the time B ☐ Most of the time C ☐ Sometimes D ☐ Not at all

6. During the past 7 days, when writing, have you had difficulty keeping your writing in a straight line?

A ☐ All the time B ☐ Most of the time C ☐ Sometimes D ☐ Not at all

7. During the past 7 days, when watching videos or playing games on an electronic device, have images appeared blurred or been difficult to see clearly? (For example, on a computer, tablet, smartphone, or electronic learning device.)

A ☐ All the time B ☐ Most of the time C ☐ Sometimes D ☐ Not at all

8. During the past 7 days, when reading or typing on an electronic device, have words appeared blurred or been difficult to see clearly? (For example, on a computer, tablet, smartphone, or electronic learning device.)

A ☐ All the time B ☐ Most of the time C ☐ Sometimes D ☐ Not at all

9. During the past 7 days, have you had difficulty recognizing distant objects or reading distant text while wearing appropriate corrective glasses?

A ☐ All the time B ☐ Most of the time C ☐ Sometimes D ☐ Not at all

10. During the past 7 days, when taking part in sports such as football (soccer), basketball, badminton, or table tennis, have you had difficulty judging the position of the ball? (For example, being unable to catch or return the ball accurately.)

A ☐ All the time B ☐ Most of the time C ☐ Sometimes D ☐ Not at all

11. During the past 7 days, have you had difficulty picking up a small object on the first attempt? (For example, a button or paper clip.)

A ☐ All the time B ☐ Most of the time C ☐ Sometimes D ☐ Not at all

12. During the past 7 days, when going up or down stairs without using a handrail, have you missed a step, stumbled, or fallen?

A ☐ All the time B ☐ Most of the time C ☐ Sometimes D ☐ Not at all

Part 3 Broader Impact on Life and Health

13. During the past 7 days, when studying or working, have you been unable to concentrate for more than 15 minutes?

A ☐ All the time B ☐ Most of the time C ☐ Sometimes D ☐ Not at all

14. During the past 7 days, did you take part in social activities or meet and spend time with friends?

A ☐ Every day B ☐ Most of the time C ☐ Sometimes D ☐ Not at all

15. During the past 7 days, have you felt lacking in confidence or discouraged?

A ☐ All the time B ☐ Most of the time C ☐ Sometimes D ☐ Not at all

Scoring and Source Information

Item Scoring Rules

Items 1–13 and 15: A=4 points, B=3 points, C=2 points, and D=1 point. Item 14 is positively worded and is reverse-scored: A=1 point, B=2 points, C=3 points, and D=4 points. The total score is the sum of the scores for all 15 items (range: 15–60 points). A higher score indicates more pronounced related symptoms or a greater impact on quality of life.

Reference

Webber A, Randhawa S, Felizzi F, et al. The Amblyopia Quality of Life (AmbQoL): Development and Content Validation of a Novel Health-Related Quality of Life Instrument for Use in Adult and Pediatric Amblyopia Populations. *Ophthalmology and Therapy*. 2023;12:1281–1313.

Supplementary Table 1 of the article (conceptual framework for the AmbQoL adult/adolescent, child, and caregiver versions).