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Phase 2a randomised controlled feasibility trial of a new 'balanced binocular viewing' treatment for unilateral amblyopia in children age 3–8 years: trial protocol

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ABSTRACT

Introduction Treatments for amblyopia, the most common vision deficit in children, often have suboptimal results. Occlusion/atropine blurring are fraught with poor adherence, regression and recurrence. These interventions target only the amblyopic eye, failing to address imbalances of cortical input from the two eyes ('suppression'). Dichoptic treatments manipulate binocular visual experience to rebalance input. Poor adherence in early trials of dichoptic therapies inspired our development of balanced binocular viewing (BBV), using movies as child-friendly viewable content. Small observational studies indicate good adherence and efficacy. A feasibility trial is needed to further test safety and gather information to design a full trial.

Methods/analysis We will carry out an observer-masked parallel-group phase 2a feasibility randomised controlled trial at two sites, randomising 44 children aged 3–8 years with unilateral amblyopia to either BBV or standard occlusion/atropine blurring, with 1:1 allocation ratio. We will assess visual function at baseline, 8 and 16 weeks. The primary outcome is intervention safety at 16 weeks, measured as change in interocular suppression, considered to precede the onset of potential diplopia. Secondary outcomes include safety at other time points, eligibility, recruitment/retention rates, adherence, clinical outcomes. We will summarise baseline characteristics for each group and assess the treatment effect using analysis of covariance. We will compare continuous clinical secondary endpoints between arms using linear mixed effect models, and report feasibility endpoints using descriptive statistics.

Ethics/dissemination This trial has been approved by the London-Brighton & Sussex Research Ethics Committee (18/LO/1204), National Health Service Health Research Authority and Medicines and Healthcare products Regulatory Agency. A lay advisory group will be involved with advising on and disseminating the results to non-professional audiences, including on websites of funder/participating institutions and inputting on healthcare professional audience children would like us to reach. Reporting to clinicians and scientists will be via internal and external meetings/conferences and peer-reviewed journals.

Trial registration number NCT03754153.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Novel sensitive and child-friendly methods will allow monitoring of suppression/interocular balance as a measure of safety for the first time in a dichoptic treatment trial.
⇒ Input from children and families into the development of the intervention should lead to improved acceptability and adherence.
⇒ Home-based administration of treatment requires input and supervision from parents and carers, which may affect adherence.

INTRODUCTION

Amblyopia ('lazy eye') is the most common vision deficit in children, affecting 2%–4%.[1 2] It is a developmental defect of binocular vision, that is, a disruption of the equal processing of information from both eyes. An imbalance of cortical input from the two eyes results in the brain suppressing information from the amblyopic eye, causing a range of defects in vision and gaze stability, including reduced acuity, poor stereo-vision and vulnerability to crowding (the disruptive influence of clutter on recognition).[3 4] It can affect hand-eye co-ordination and fine motor skills.[5–8] Loss of vision in the better-seeing eye can affect quality of life, even in adulthood.[9–11] The two main causes for amblyopia are a difference in spectacle prescription between the two eyes (anisometropia) and the eyes not being straight (squint, strabismus). Children

may have both, giving three types of amblyopia: anisometropic, strabismic and combined mechanism.

Current treatment consists of corrective glasses, if indicated, followed by either occlusion (patching) of the better-seeing ('fellow') eye, or blurring with atropine eyedrops. Only two-thirds of children achieve near-normal vision in the amblyopic eye.[12 13] Poor adherence is a significant factor.[14] In addition, vision regresses to pretreatment levels in 30%,[15] and amblyopia recurs in 25% within a year of cessation of treatment.[16] Both treatments enforce monocular vision, which can hinder the restoration of stereo-vision.[17] There is an urgent need for treatments that are both engaging/acceptable to children and that address the underlying problem of imbalance between the eyes.

New treatments aim to balance the cortical input from the two eyes ('dichoptic treatment') and gradually reduce the suppression of input from the amblyopic eye. Previously tested methods involved games such as the Tetris falling block game, with image aspects split across the two eyes and those shown to the fellow eye having reduced contrast. Early clinical trials suffered from poor adherence,[18–20] likely because the content did not sustain children's interest.[21] A new approach using an adventure game is in early evaluation,[22 23] but requires children to wear red/green anaglyph glasses on top of their own glasses, which may be inconvenient.

We have developed a novel dichoptic treatment, balanced binocular viewing (BBV), which involves children watching three-dimensional movies for 1 hour a day. The image shown to the better-seeing eye is blurred to the same level as the vision in the amblyopic eye.[24] Together with children and families, we have developed an extensive movie library that children can choose from. Preliminary studies with 22 children aged 3–11 years using BBV for 8–24 weeks showed that children used the treatment on average 89% (SD 24) of the prescribed daily time, and that visual acuity in the amblyopic eye improved by a mean of 0.27 logMAR (SD 0.22).[24]

Concerns have been raised that reducing inter-ocular suppression by means of dichoptic treatment risks inducing double vision (diplopia) in people with strabismus. A previous dichoptic treatment trial observed transient or intermittent diplopia in 16% of participants, but no cases of permanent diplopia.[18] It is widely held that diplopia arises rarely during standard treatment; it is considered a risk only if treatment is started in individuals with strabismus, and after the end of the 'critical period' of vision development. In clinical practice, amblyopia treatment is usually offered up to the age of 7–8 years, although the 'critical period' continues up to the age of around 8–12 years.[25] Strabismus is considered a risk factor for intractable diplopia, if amblyopia treatment reduces suppression; suppression is therefore carefully monitored. However, there are no robust incidence data for the onset of diplopia during amblyopia treatment. A survey of head orthoptists in the UK estimated 4.4 cases per year.[26] A UK-wide case ascertainment study of intractable diplopia across all age groups and causes estimated an incidence of 53–63 cases per year, but none following or during primary amblyopia treatment. All cases occurred after surgical procedures.[27] A retrospective case review found intractable diplopia only after strabismus surgery in adults who had had previous strabismus surgery in childhood.[28]

Changes in suppression are believed to precede the onset of diplopia. In observational studies of conventional and binocular treatments, no consistent change in suppression has been observed with improvements in vision.[24 29] No previous clinical trial has measured suppression, possibly because conventional tests lack sensitivity, particularly for children. Recently developed tests are both more sensitive and more child-friendly.[30–34]

Other safety concerns are the potential loss of visual acuity in the better-seeing eye, onset of new manifest strabismus or worsening of pre-existing strabismus. With conventional treatment, a loss of acuity in the better-seeing eye of 0.1 logMAR has been observed in 12% of children, and a loss of 0.2 logMAR in 0.53%; with dichoptic treatment, in 6.6% and 0.55%, respectively.[18] New-onset manifest strabismus or worsening of pre-existing strabismus has been reported in 6% of children receiving conventional occlusion treatment, and in 9% with dichoptic treatment.[18] Neither occurred in our previous studies of BBV treatment.[24]

Specific objectives

As this will be the first randomised controlled trial (RCT) of a dichoptic treatment for amblyopia in the UK, with uncertainty surrounding eligibility and enrolment rates,[35] we will first carry out a feasibility trial. The primary objective is to evaluate the safety of the experimental intervention, using a novel 'VacMan suppression test' of interocular balance that varies the contrast of elements presented to each eye,[24 31] as a measure of change in suppression/interocular balance at 16 weeks from baseline.

Secondary objectives are those pertinent to a feasibility trial: to evaluate recruitment and retention rates, adherence with the allocated intervention, safety at other time points, and clinical measures of visual function (such as best-corrected visual acuity (BCVA)). These outcomes will inform the design of a future phase 3 RCT to evaluate efficacy and provide further data on safety.

METHODS AND ANALYSIS

Trial design

We will carry out an observer-masked parallel-group phase 2a feasibility RCT, randomising 44 children with unilateral amblyopia to either BBV or standard occlusion/atropine blurring (figure 1).

Patient and public involvement

Parents of children (ages 3–8 years) with amblyopia, undergoing standard care, were involved in informing

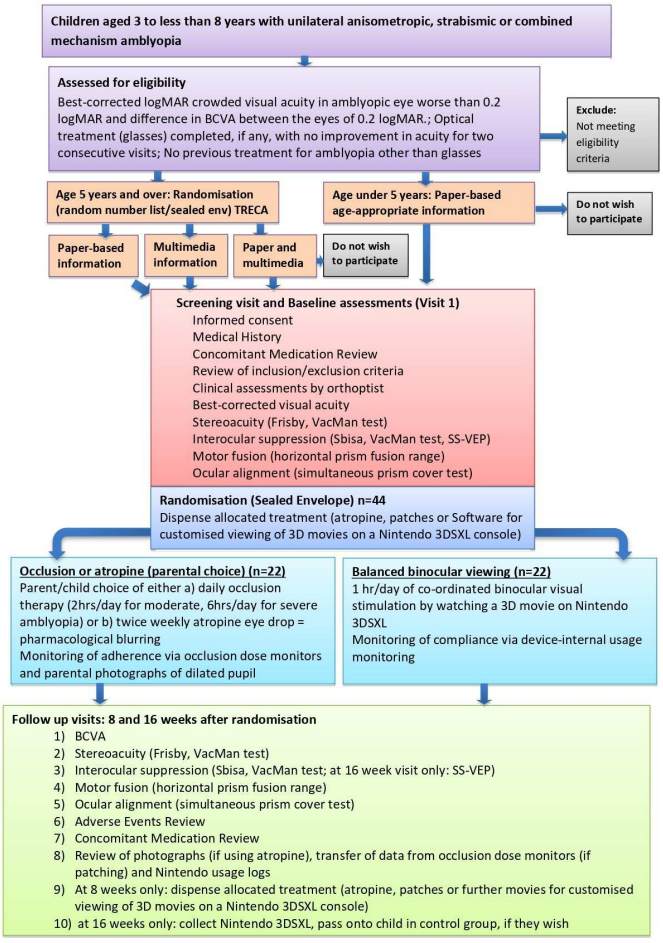

Figure 1 Participant flow chart. 3D, three dimensions; BCVA, best-corrected visual acuity; SS-VEP, Steady-state visually evoked potentials.

the feasibility and design of the study, including a discussion about the use of a tool to measure health-related quality of life[36]; the outcomes from which are reported in line with the consensus Guidance for Reporting Involvement of Patients and the Public short form (table 1).[37]

Study setting

Moorfields Eye Hospital clinics at City Road and St George's Hospital, and Cambridge Community Services National Health Service (NHS) Trust community clinics in Bedfordshire will be the two study sites.

Participant eligibility criteria

Inclusion criteria:

- Age between 3 and 8 years (inclusive) (figure 1).
- Unilateral anisometropic, strabismic or combined mechanism amblyopia (see definitions below).
- BCVA in the amblyopic eye worse than 0.20 logMAR, with a difference between the eyes of 0.20 logMAR or more.
- Completion of optical treatment prior to inclusion in the trial, if applicable.
- No prior treatment (including occlusion or atropine), other than optical treatment.

Definitions

Strabismic amblyopia: amblyopia in the presence of esotropia (in-turn squint) with near deviation up to 10 prism dioptres, with or without previous surgical correction, and no significant refractive error (ie, hypermetropia of less than 1.50 dioptre sphere (DS); American Academy of Ophthalmology, http://www.aao.org/pediatric-center-detail/types-of-amblyopia).

Refractive/anisometropic amblyopia: amblyopia in the presence of anisometropia (difference in glasses prescription between the two eyes) of ≥0.5 DS of spherical equivalent or ≥1.50 dioptre cylinder (DC) of difference in astigmatism in any meridian which persists after optical adaptation, with no measurable heterotropia (manifest misalignment) at distance or near fixation.

Combined mechanism amblyopia: amblyopia in the presence of either an esotropia at distance and/or near fixation or a history of strabismus surgery, as well as anisometropia of ≥1.0 DS of spherical equivalent or ≥1.50 DC of difference in astigmatism in any meridian, which persists after optical adaptation.

Exclusion criteria

- Ocular cause for reduced visual acuity other than amblyopia.
- Inability/unwillingness to cooperate with the assessment tests.
- Developmental disorders, learning or neurological disabilities likely to impact adherence to treatment.
- Photosensitive epilepsy.
- Prior intraocular surgery.
- Myopia with spherical equivalent of greater than −6.0 DS.
- Manifest strabismus greater than 10 prism dioptre with distance or near fixation.

Interventions

Active intervention

BBV therapy, presented on a handheld games console (Nintendo 3DS) with autostereographic display, allowing for delivery of different movie images to each eye without glasses (using a parallax barrier). Various commercial, age-appropriate movies will be viewed for a dose of 1 hour per day, either in a single 60 min or 2×30 min sessions. Depending on the interocular difference in visual acuity at baseline, movies will be presented with high, medium or low blur level to the less affected eye. The level of blur is defined as the standard deviation (σ, expressed in minutes of arc) of the two-dimensional Gaussian filter-kernel the image is convolved with:

$$G(x,y) = \frac{1}{2\pi^2} + e^{-\frac{x^2+y^2}{2^2}}$$

The blur levels to be applied are: high (σ=32.0 pixels=49.2 arc min), medium (σ=8.0 pixels=12.3 arc min), and low (σ=2.0 pixels=3.1 arc min).

Table 1 GRIPP2 Short Form Reporting Checklist. After Staniszewska *et al*[37]

Section and topic	Item
1: Aim	1. To understand the acceptability of the BALANCE protocol to families and the feasibility of integrating the study into their daily routine 2. To understand whether children would be willing to use the Nintendo 3DSXL
2: Methods	Two rounds of 1:1 interviews with parents of children (aged 3–8 years) undergoing standard of care treatment for amblyopia recruited via the clinic (eight families). Interviews were conducted with each family in a private space away from the clinic and waiting area. Participants were volunteers. Responses were recorded anonymously: 1. Round 1: up to 30 min interviews with three families about the BALANCE protocol design 2. Round 2: up to 60 min interviews with five families about the usability of the Nintendo 3DSXL (including observation of the children with the device)
3: Results	Round 1: 1. All families were happy for 1 hour of screen time a day; two families preferred 2×30 min sessions 2. Two families prefered monitoring visits every 8 weeks over monthly; one family preferred more frequent monitoring 3. Two families thought it was acceptable to return the device after a proposed 6 month treatment period; whereas one family felt their child would want to keep it Round 2: 1. All families had negative experiences with patching and said the device would be a welcome alternative if effective 2. All families felt it would be possible to integrate the device into the daily routine for the 2–3 months treatment period and would be willing to extend 3. Three families felt they would need to use incentivisation to help children to concentrate on the device for the treatment period; one family felt young children (3–5 years) would struggle to concentrate 4. All families felt monitoring visits every 8 weeks was acceptable 5. Four families felt their child would be happy to pass the device onto another child at the end of the treatment regimen 6. Four families were in favour of refreshing the content on the device at follow-up visits 7. Three families did not feel the proposed use of the Children Health Utility (CHU9D, Stevens *et al*)—a paediatric generic preference-based measure of health-related quality of life—was appropriate for the study 8. All children engaged with the device; four children (ages 6–8 years) engaged for the longest (up to 10 mins) while the 3-year-old was less engaged; two children almost deleted the content from the device
4: Discussion and conclusions	1. Families were positive about the development of a new treatment approach and favourable of the proposed study and agreed that it would be possible to integrate it into the family routine 2. Families informed feasibility and directly influenced the final design: possibility of 2×30 min sessions; reduced duration of follow-up from monthly to every 8 weeks; to replace CHU9D with a series of follow-up questions asked at monitoring appointments (as suggested by one family) 3. Overall it was felt children could engage with the intervention but younger children in particular might be less engaged; access to the device settings would need to be secured
5: Reflections/critical perspective	1. We did not directly involve children in the design of the study. At the time we were advised that children from this age group may not be able to engage cognitively with the study. The team at the time did not have experience of children's involvement or access to an appropriate children's and young people's advisory group (YPAG) to support this work. We have since established a children and young people's advisory group (Eye YPAG) who can provide support for the future 2. One family in each round did not have English as a first language and appeared to find engagement with the study more difficult, suggesting access to a translator may be required to support study delivery

Control

Occlusion or atropine, depending on parental choice. The prescribed dose of occlusion will depend on the severity of amblyopia, as per current clinical practice[38 39]: 6 hours/day for severe amblyopia (amblyopic eye BCVA worse than 0.6 logMAR) or 2 hours/day for moderate amblyopia (amblyopic eye acuity between 0.2 and 0.6 logMAR). Dosage for atropine 1% will be one drop to the better-seeing eye twice a week, regardless of amblyopia severity, as per clinical standard practice. We are not planning any dosage modification during the study period of 16 weeks.

Outcomes

Primary outcome

We will measure changes in suppression/interocular balance (considered to precede double vision) at 16 weeks from baseline, using a novel VacMan Suppression test of interocular balance that varies the contrast of elements presented to each eye.[24 31]

Secondary outcomes

Feasibility outcomes

- Enrolment/retention:
  We will keep an electronic log (stored in a secure Microsoft Office Excel file) of families approached

about taking part, which type of information material was provided (as part of TRECA, see below), whether the family consented to take part, or, if they are willing to provide this information, why they declined to take part. We will also keep a log of families withdrawing from the trial and reasons for withdrawal.

- Adherence
  Intervention group: The Nintendo-device keeps a record of daily use of the device, indicating how long different applications were used for, which will serve as activity log. Parents will need to ensure that the device is only accessible to children participating in the trial.
  Control group—occlusion: we will insert a temperature sensor (occlusion dose monitor, ODM) between two standard adhesive eye patches; the proximity to the warm skin is recorded by the sensor.
  Control group—atropine: twice weekly photo of pupils acquired by parents; the research orthoptist will review these photographs on the parent's device during the study visits, and record on the paper-based case report form (CRF) on how many of these photos the pupil of the fellow eye was dilated.
  For each group, we will calculate adherence as proportion of prescribed treatment received: (1) BBV: percentage of prescribed hours. We will also compute the proportion of days on which BBV treatment was used post randomisation. (2)Occlusion: percentage of prescribed hours and (3) Atropine: percentage of photos showing enlarged pupil
- Safety measured using other tests and at other time points
  We will measure changes in suppression/interocular balance from baseline, using: (1) Clinical Sbisa red filter bar (at 8 and 16 weeks), with absorption level of the filter as outcome measure[26 29] Click or tap here to enter text;[40] (2) VacMan interocular balance test of suppression at 8 weeks and (3) Steady-state visual evoked potentials, with the Fourier amplitude at the stimulus flicker frequency as outcome measure (SSVEP, at 16 weeks only, as this test extends the assessment time and requires specialised equipment)[30]

Clinical measures of visual function and intervention acceptability

We will measure BCVA on a clinical trials standard acuity testing system, using a validated ATS-HOTV testing protocol[41] Click or tap here to enter text.via Precision Vision VA testing software, either by naming or by matching letter. With this protocol, a change of greater than 0.18 logMAR is taken to reflect a true change in acuity, though we note that this test slightly overestimates amblyopic eye acuity.[42]

We will measure stereoacuity, with true change defined as a change of at least two octaves from baseline.[43 44] Measurements will be taken using the Frisby test, which can be performed by young children and is sensitive enough to detect low levels of stereopsis, as well as our gamified 'VacMan' stereo-test.[4]

We will also document motor fusion (horizontal prism fusion range test) and ocular alignment (alternative prism cover test).

Lastly, we will collect data on acceptability/impact of all treatments on the family, and acceptability of the current BBV movie library and content (questions to children and parents/carers).

Participant timeline

Potentially eligible children will be identified among new patients with strabismus or anisometropia. Optical adaptation will be commenced as appropriate. Families will be approached about trial participation when an interocular acuity difference of at least 0.2 logMAR persists after completion of optical adaptation. This study contributes to the TRECA trial (Trials Engagement in Children and Adolescents, ISRCTN (international standard randomised controlled trial number): 73136092, IRAS (integrated research application system) 212761, REC (research ethics committee) 17/YH/0082). The aim of the TRECA trial is to determine whether the presentation of trial information material in either paper-based or multimedia format has an impact on families' decision to take part in a trial. If a child aged 5 years and older, and their parents/carers, express an interest to learn more about the BALANCE trial, we will then use a randomisation list generated in a statistical software package (SPSS version 28) to randomise them to receive either:

- Trial-specific multimedia interventions (MMI) designed to improve the quality of decision making about recruitment to clinical trials involving children and young people only.
- MMI in addition to the paper-based participant information material.
- The conventional paper-based participant information material only, age-appropriate for under 6 and 6–8 years old children, and for parents/carers.

Only children aged 5 years and older are eligible to take part in the TRECA trial, while for BALANCE, the minimum age is 3 years. Families of eligible children younger than 5 years will be provided with age-appropriate paper-based information material, without randomisation.

After answering any questions about the BALANCE trial, the research orthoptist will obtain written informed consent from parents/carers and verbal or written assent from children (figure 1).

Assessments will be carried out at baseline, and 8 and 16 weeks after randomisation (table 2).[45]

Recruitment

Both trial sites provide services for children who have failed the school vision screening, that is, they are the first point of contact for optical adaptation and occlusion/atropine treatment for amblyopia. Participation in the

Table 2 Schedule of assessments. After Chan et al, SPIRIT 2013[45]

Study parameter	Visit 1 Baseline (Day 0)	Visit 2 8 Weeks (±1 week)	Visit 3 16 Weeks (±1 week)
Review of inclusion/exclusion criteria	X		
Medical History	X		
Concomitant Medication Review	X	X	X
Informed consent	X		
Randomisation	X		
Adverse Event Review		X	X
Dispense allocated treatment	X	X	
Review of photographs (atropine group), transfer of data from occlusion dose monitors and Nintendo usage logs		X	X
Collect allocated treatment (Software for customised viewing of 3D movies on a Nintendo 3DSXL console)		X	X
Clinical assessments by orthoptist masked to allocated treatment			
BCVA	X	X	X
Stereoacuity (Frisby, VacMan stereo-test)	X	X	X
Interocular suppression (Sbisa, VacMan suppression test)	X	X	X
Interocular suppression (SS-VEP)	X		X
Motor fusion (horizontal prism fusion range)	X	X	X
Ocular alignment (alternate prism cover test)	X	X	X

BCVA, best-corrected visual acuity; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; SS-VEP, Steady-state visually evoked potentials.

TRECA trials with provision of multimedia information may also enhance recruitment.

Sample size

The sample size was calculated on the visual acuity endpoint, which is critical to inform the design of the future phase 3 trial. A sample size of 44 evaluable patients provides 90% power with 5% two-sided alpha, to detect a difference in the change of 0.225 logMAR in visual acuity between the two treatment arms, assuming an SD of the change of 0.22.[24] We are expecting a drop-out rate of 10%.

Randomisation

All sites will use the web-based Sealed Envelope system for sequence generation. Children will be randomised to either BBV or standard occlusion/blurring with a 1:1 allocation ratio, stratified by parental choice of control treatment, level of interocular acuity difference and type of amblyopia, using minimisation with a random element to ensure that the researcher randomising the patient will not know what the next treatment allocation will be.

Implementation

An unmasked observer will enrol participants, complete the web-based randomisation and give the allocated intervention to the participant.

Masking

It will not be possible to mask participants or their parents. At each site, a masked orthoptist will carry out the study assessments. We will ask the families not to disclose their allocated intervention to the masked orthoptist. In order to maintain masking in the atropine group, we will ask families to discontinue this treatment 2 weeks prior to the study visits at 8 and 16 weeks from baseline. There are no plans for unmasking the masked observer.

Data collection methods

Paper-based CRFs will be designed using the sponsor's CRF template. The masked research orthoptist will complete the CRF at each study visit.

Data management methods

The delegation log will identify all those personnel with responsibilities for data collection (masked research orthoptists) and handling, including those who have access to the trial database. A data officer will enter data onto the web-accessible database within 1 week of CRF completion. The senior data manager—within the sponsor organisation—will independently ask the IT team to run missing data queries and perform range check, logic check and data quality checks at defined time points. Data queries will be sent to the trial manager or assigned data officer for clarification and confirmation before data lock and analysis.

Statistical methods

The primary analysis will be conducted using the intention-to-treat principle where all randomised patients with available outcome data are analysed in their allocated group, whether or not they receive their randomised treatment. Baseline characteristics will be summarised for each treatment group, but no formal statistical comparisons will be made at baseline. Continuous data will be summarised using means and SD, if data appear Gaussian, or medians and IQRs if not. Categorical data will be reported as frequencies and percentages.

The primary outcome at 16 weeks will be compared between the groups using analysis of covariance. Continuous primary and secondary outcomes will be analysed using linear mixed-effects models to estimate mean difference between treatments while adjusting for respective baseline value and randomisation stratification factors (parental choice of control treatment, degree of interocular acuity difference, type of amblyopia as a fixed effect and site as a random effect—if a model does not converge, site will be fitted as a fixed effect). For binary outcomes, mixed-effects logistic regression will be used to estimate OR.

The recruitment rate will be calculated as number of children enrolled divided by number of families approached. The retention rates at 8 and 16 weeks calculated as number of families retained divided by number of families enrolled.

We will compare binary and categorical outcomes—such as the reason for stopping treatment and the proportion of children experiencing adverse events—in the two groups using Fisher's exact test. All statistical tests will use a two-sided p value at the 5% significance level unless otherwise specified. All confidence intervals presented will be 95% and two sided. No formal interim analysis is planned.

Subgroups for analysis are the three types of amblyopia: unilateral anisometropic, strabismic or combined mechanism amblyopia. We will carry out an additional subgroup analysis of the groups of parental choice of control treatment (occlusion or atropine).

Missing values for baseline covariates will be dealt with using mean imputation. Missing observations in primary and secondary outcomes will not be imputed for the main analysis, however, further supportive analysis where missing primary outcome data are imputed will be undertaken by supportive analysis to assess how robust the main analysis is to missing data assumptions. Reasons for missingness will be investigated using logistic regression of covariates on an indicator of missingness. Withdrawn patients with full available data will only be included in analysis if they have not switched treatment between withdrawal and respective follow-up.

Data monitoring

A trial management group will meet on a regular basis, to monitor all aspects of the conduct and progress of the trial, to ensure that the protocol is adhered to and to take appropriate action to safeguard participants and the quality of the trial itself. The group will meet to discuss any issues with data quality, and any concerns will be discussed at the trial steering committee (TSC).

An independent data monitoring committee (IDMC) will monitor trial progress and patient safety data, at intervals, while the clinical trial is ongoing. The IDMC will make recommendations to the TSC regarding continuation, stopping or any modification to the trial. For this study the IDMC and TSC will meet together and the committees will be formed of one group.

The TSC will provide the overall supervision of the trial and ensure that it is being conducted in accordance with the principles of Good Clinical Practice and the relevant regulations. The TSC will have an independent chair and include members (including one lay member) who are independent of the investigators, their employing organisations, funders and sponsors. The TSC will agree the trial protocol and any protocol amendments, monitor trial and conduct, advise on scientific credibility and provide advice to the investigators on all aspects of the trial. The TSC will consider and act, as appropriate, on the recommendations of the IDMC or equivalent and will carry the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy. As above it is to be noted that the TSC and IDMC will meet together as a joint committee.

Harms

All adverse events (AE) and serious AEs (SAE) will be recorded in the medical records and CRF following consent. The chief or principal investigator will complete the sponsor's SAE form and the form will be emailed to the sponsor immediately (or within 24 hours but certainly no later than three calendar days) of becoming aware of the event. The chief or principal investigator will respond to any SAE queries raised by the sponsor as soon as possible. The investigator shall keep detailed records of all AEs and device deficiencies relating to the clinical trial which are reported to them by trial participants or users. The investigator shall document all relevant information on sponsor provided AE logs, SAE forms and device deficiency forms.

Auditing

The sponsor will perform two on-site monitoring visits conducted by an independent monitor following the first patient recruited at each site and at study close out at each site. The monitor will review 10% source data verification and carry out a full document check, consent form check, AE and trial master file review at the sponsor site.

ETHICS AND DISSEMINATION

This trial has been approved by the London - Brighton & Sussex Research Ethics Committee (18/LO/1204), the NHS Health Research Authority and the Medicines and Healthcare products Regulatory Agency.

Protocol amendments

In collaboration with the Investigator(s), amendments will be documented and submitted for ethical and regulatory approval (as required) prior to implementation.

Confidentiality

All data will be handled in accordance with the UK Data Protection Legislation. The CRFs will not bear the participant's name or other personal identifiable data. On enrolment into the study, participants will be assigned a trial identification number, composed of a digit indicating the site, followed by a sequential number starting with one indicating the participant. The study site will maintain a master Participant Identification Log.

Access to data

A data officer will enter CRF data into a web-accessible database hosted on Moorfields Eye Hospital servers. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

Ancillary and post-trial care

After the end of the trial, participants will return to standard care for further management.

Dissemination policy

A lay advisory group will be involved with advising on and disseminating the results to non-professional audiences, including reporting on the websites of funder and participating institutions, as well as inputting on healthcare professional audiences children would like us to reach with the results. Reporting to clinicians and scientists will be via internal and external meetings/conferences and peer-reviewed journals. Individual-level data will be made available on request to the principal investigator.

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Contributors AHD-N, SCD, JAG, DB and AS developed the initial trial protocol and applied for the funding award, with AHD-N as lead applicant, JAG and AS as coapplicants, and SCD and DB as named collaborators. SL and AD contributed to protocol refinement and implementation. H-MD reviewed and updated sample size and statistical aspects during the COVID-19 pandemic.

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