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Effectiveness of early spectacle intervention on visual outcomes in babies at risk of cerebral visual impairment: a parallel group, open-label, randomised clinical feasibility trial protocol

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Effectiveness of early spectacle intervention on visual outcomes in babies at risk of cerebral visual impairment: a parallel group, open-label, randomised clinical feasibility trial protocol

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ABSTRACT

Introduction Hypoaccommodation is common in children born prematurely and those with hypoxic ischaemic encephalopathy (HIE), with the potential to affect wider learning. These children are also at risk of longer-term cerebral visual impairment. It is also well recognised that early intervention for childhood visual pathology is essential, because neuroplasticity progressively diminishes during early life. This study aims to establish the feasibility and acceptability of conducting a randomised controlled trial to test the effectiveness of early near vision correction with spectacles in infancy, for babies, at risk of visual dysfunction.

Methods and analysis This is a parallel group, open-label, randomised controlled (feasibility) study to assess visual outcomes in children with perinatal brain injury when prescribed near vision spectacles compared with the current standard care—waiting until a problem is detected. The study hypothesis is that accommodation, and possibly other aspects of vision, may be improved by intervening earlier with near vision glasses. Eligible infants (n=75, with either HIE or <29 weeks preterm) will be recruited and randomised to one of three arms, group A (no spectacles) and two intervention groups: B1 or B2. Infants in both intervention groups will be offered glasses with +3.00 DS added to the full cycloplegic refraction and prescribed for full time wear. Group B1 will get their first visit assessment and intervention at 8 weeks corrected gestational age (B1) and B2 at 16 weeks corrected gestational age. All infants will receive a complete visual and neurodevelopmental assessment at baseline and a follow-up visit at 3 and 6 months after the first visit.

Ethics and dissemination The South-Central Oxford C Research Ethics Committee has approved the study. Members of the PPI committee will give advice on dissemination of results through peer-reviewed publications, conferences and societies.

Trial registration number ISRCTN14646770, NCT05048550, NIHR ref: PB-PG-0418-20006.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study will provide the preparation for a randomised controlled trial that may lead to important information on implementation of an early intervention screening programme and intervention strategy for infants at risk of hypoaccommodation and cerebral visual impairment.
⇒ The protocol has been carefully designed by a multidisciplinary team, including neonatology, optometry, ophthalmology, orthoptics, psychology, health economics and statisticians.
⇒ There has been extensive PPI throughout the study.
⇒ The ethics committee rejected placebo treatment (plano glasses) for the control arm; therefore, participants and healthcare providers will not be masked to the intervention.

INTRODUCTION

Vision is a primary sense and plays a major role in early developmental processes, learning and parent–infant transactions.[1] There are risks in all areas of development for infants with severely reduced or no vision.[2] The greatest risk is found in those with the most severe reduction of vision, particularly those with profound visual impairment (light perception at best).[3] This can lead to cumulative risks and adverse consequences in all aspects of learning, psychological and quality-of-life outcomes, unless infants and young children receive the optimal early interventions to support their vision and general development. One approach is to aim to intervene early to promote optimal vision and reduce the potential for visual impairment in 'at-risk' children, where feasible.

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For normal vision to develop in infancy, a child needs focused and clear images to be conveyed to the visual centres of the brain. There is a level of urgency in correcting childhood visual disorders as failure to do so before the end of the critical period (plasticity of visual system) results in permanently reduced vision.[4] The seminal work of Hubel and Wiesel in the 1960s showed the essential need for early rectification of visual impairment[5] due to this progressive diminishing of neuroplasticity during early life.[6 7]

Newborn babies are typically long-sighted (hyperopic) at birth[8] and emmetropise (become less long or short-sighted) over the first few months of life.[9] They also develop the ability to accommodate allowing them to change focus from a distant to a near target.[10] Accommodation is required to see clearly at near and, where hyperopia is significant, at distance as well. Reduced accuracy of accommodation (hypoaccommodation) is common in children with history of perinatal brain injury[11 12] and developmental disability.[13]

The aetiology of the increased prevalence of accommodation deficit in brain-injured children is unclear but a variety of mechanisms have been proposed.[11 12 14–16] Typically developing children demonstrate maturation of accurate accommodative responses in their first 2–4 months of life, when acuity, refractive error, disparity detection and vergence control are all rapidly maturing.[17] Children born prematurely often fail to show this normal pattern of visual development.[18] Current evidence also indicates that the majority of children with developmental disability do not emmetropise sufficiently[19 20] and hypoaccommodation is common. However, when provided with spectacles to correct hyperopia, accommodative status is improved.[21 22]

Hypoaccommodation is an accepted complication in children who are at risk of cerebral visual impairment (CVI).[12 23–26] CVI is caused by damage to the visual pathways (postchiasm) and/or the higher visual centres of the brain, in the absence of any major ocular disease,[27 28] and is the leading cause of childhood visual impairment in the UK[29] and childhood registration.[30 31] The condition has lifetime visual consequences that can range from blindness to subtle perceptual difficulties.[32] It can go unidentified even by targeted neurodevelopmental screening,[32] and has the ability to diminish children's educational outcomes[33] and quality of life.[34] Severe CVI is closely associated with child mortality and an increased risk of hospitalisation, socioeconomic deprivation and death in childhood.[35] The two major risk factors are prematurity and hypoxic ischaemic encephalopathy (HIE) and, due to advances in neonatal care, there is an increase in incidence of neurodevelopmental and visual impairment.[36]

The current standard of care is basic vision screening included within the national general screening programme known as the Newborn and Infant Physical Examination.[37] As per current National Health Service (NHS) guidelines, the next vision screening is recommended at 4–5 years of age. The lack of a mandate for vision screening in this age group means there are large inconsistencies in the availability of vision screening across the country, therefore, visual deficits can go undetected for many years. Referral to ophthalmology for more comprehensive visual assessment is only instigated if a problem is suspected.

Early intervention has the potential to benefit children's vision and other areas of development in children who are at risk of CVI[38] or who have diagnosed severe visual impairment from congenital disorders of the anterior visual system.[39] Although tolerance and compliance are often challenging,[40] a scoping review of published evidence concluded that spectacles had the highest level of evidence as an intervention for children with visual and neurodevelopmental impairment.[41] A conclusion is that all children with such dual impairment should be examined to assess their need for near and/or distance spectacles.[16 41]

Currently, evidence-based early intervention strategies for children at risk for poor visual outcomes following preterm birth and HIE are limited[38] and early intervention focussing directly on hypoaccommodation has not been investigated. It is known that babies' main visual stimuli for example, parental face and infants' hands occur at close range, and therefore, accurate focus of these targets is important for visual development. A study screening typically developing babies found that those with uncorrected hyperopia had increased risk of strabismus (squint) and poor visual acuity in later childhood.[42] Visuocognitive, spatial, visuomotor and visual attention deficits were also detected in the hypermetropic group and associated with hypoaccommodation. Our hypothesis is that accommodation and possibly other aspects of vision may be improved by intervening earlier with glasses and giving an overcorrection so that infants are in optimal focus for near targets.

While animal studies demonstrate that provision of spectacle correction can modify the 'active' element of emmetropisation,[43 44] there is limited equivocal evidence for human infants.[22 45] Three large studies of neurotypical infants showed that treating hypermetropia under the age of 1 year resulted in improved visual acuity, less strabismus and no inhibition of emmetropisation (though one study showed a slight delay in emmetropisation).[42 45 46] Current available evidence from studies of children with developmental disability indicate that normal emmetropisation mechanisms are not operative[21 22] so disruption of emmetropisation is of less concern than when considering neurotypical children. In addition to the benefits in visual acuity and visual development outlined above, early refractive correction (both of underlying refractive errors and hypoaccommodation) may lead to improved accommodation.[21 22] The need for near vision correction may be temporary if spectacles lead the child into learning to accommodate accurately themselves. In another population of infants who cannot accommodate accurately, those who have undergone cataract surgery in early life, early management with optical correction to compensate for the lack of accommodation is standard practice[47] to avoid amblyopia.

This study aims to test the feasibility, of conducting a randomised controlled trial (RCT) for a simple and safe

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early (8 or 16 weeks corrected gestational age (CGA)) intervention, namely spectacles for near vision, for children born preterm <29 weeks and/or children who have suffered HIE. Recent estimates of UK perinatal brain injury are 5.14 (4.97–5.32) per 1000 live births equating to nearly 4000 babies per year.[48] Therefore, if shown to be feasible and effective for reducing hypoaccommodation and improving vision, this simple and cheap intervention could have significant benefit in reducing long-term disability.

Aims

The study aims to establish the feasibility of recruiting to and conducting all planned aspects of the proposed RCT in this population. The primary outcome is to establish the feasibility of each measure and acceptance to babies and their parents of all aspects of the planned trial including the randomisation over the 10-month recruitment period. The acceptance of randomisation will be measured as the proportion of recruited parents who accept the offer of randomisation.

The secondary objectives, in relation to the feasibility of the planned RCT intervention in this group of children, are to establish:

- The feasibility of fitting and dispensing glasses with varying refractive corrections to infants aged 8 weeks vs 16 weeks CGA.
- Compliance with spectacle wear for parents and infants when dispensed at 8 weeks and 16 weeks CGA.
- The distribution of visual acuity at the 3-month and 6-month follow-ups compared with visual acuity at the first visit in all three arms.
- Retention rate in all three arms, which will be measured by the median number of infants reported per month.
- The distribution of refractive outcomes (measured in dioptres) at 3-month and 6-month follow-ups as compared with the first visit in all three groups.
- Evidence of impaired emmetropisation following administration of intervention. This will be measured by combining refractive error and visual acuity measures. The trial will not be feasible if there is a 2 SD difference in refractive error, at the 6-month follow-up versus baseline visit, without compensatory benefit (eg, two lines improvement in visual acuity).
- Determination of appropriate resource use data collection methods. A targeted paediatric client service receipt inventory (CSRI) form has been designed specifically for this population and will be used for the duration of the feasibility study.
- The distribution of accommodative outcomes (measured in dioptres) at 3-month and 6-month follow-ups as compared with the first visit in all three groups.
- Proportion of families completing phone questionnaire on spectacle compliance as a percentage of those in the intervention groups (B1 and B2).
- The absence of harm through mechanical trauma from prescribing glasses at these ages.
- Consent rate will be measured as the number of infants recruited vs number of infants, who fulfil the inclusion/exclusion criteria, approached.

Design and setting

This will be a single-centre, parallel group, three-arm study with a 1:1:1 equal allocation ratio. Recruitment, randomisation and research visits will be conducted in a specialised paediatric department at University College London Hospital (UCLH), a large tertiary hospital in London, UK.

Participants

Infants, who are either born <29 weeks preterm or those who have undergone therapeutic hypothermia for HIE, will be approached with the aim to recruit 75 infants over a 10-month period. Recruitment can occur at any time up to 8 weeks CGA prior to or after discharge. Each participant will be followed up for up to 6 months from the first baseline assessment at either 8 weeks or 16 weeks CGA depending on randomisation.

Sample size

The target sample of eligible babies is pragmatic as we estimate 100 (approximately 35 HIE and 70 preterm) babies will come through the UCLH neonatal intensive care unit (NICU) per year. For feasibility studies, sample sizes between 12 and 50 per group[49 50] have been recommended to estimate a chosen parameter. We predict 75% acceptance rate resulting in approximately 25 participants in each arm (A, B1 and B2). Selecting a sample of 100 from a population and determining that 75% of subjects would agree to recruitment would give 95% CI that between 65% and 83% of subjects in the population would agree to recruitment. This would help design the sample size needed for the full RCT.

Eligibility criteria

The research nurses/optometrist will screen infant's eligibility for inclusion on admission to the NICU. Eligible families will be approached to introduce the study, provide the parent/carer with an information leaflet and discuss the study procedure in detail. The research optometrist will obtain written, informed consent before any study procedures occur (see online supplemental appendix A for informed consent form).

Inclusion criteria

1. All term infants undergoing therapeutic hypothermia for HIE.
2. All preterm infants born at <29 weeks' gestational age. Evidence of hypoaccommodation is not required.

Exclusion criteria

1. Infants who are still an inpatient at 8 weeks CGA.
2. Infants with unrelated congenital or developmental ocular abnormality such as cataract requiring surgery, genetic retinal disease, coloboma. Retinopathy of prematurity will not be an exclusion criterion.

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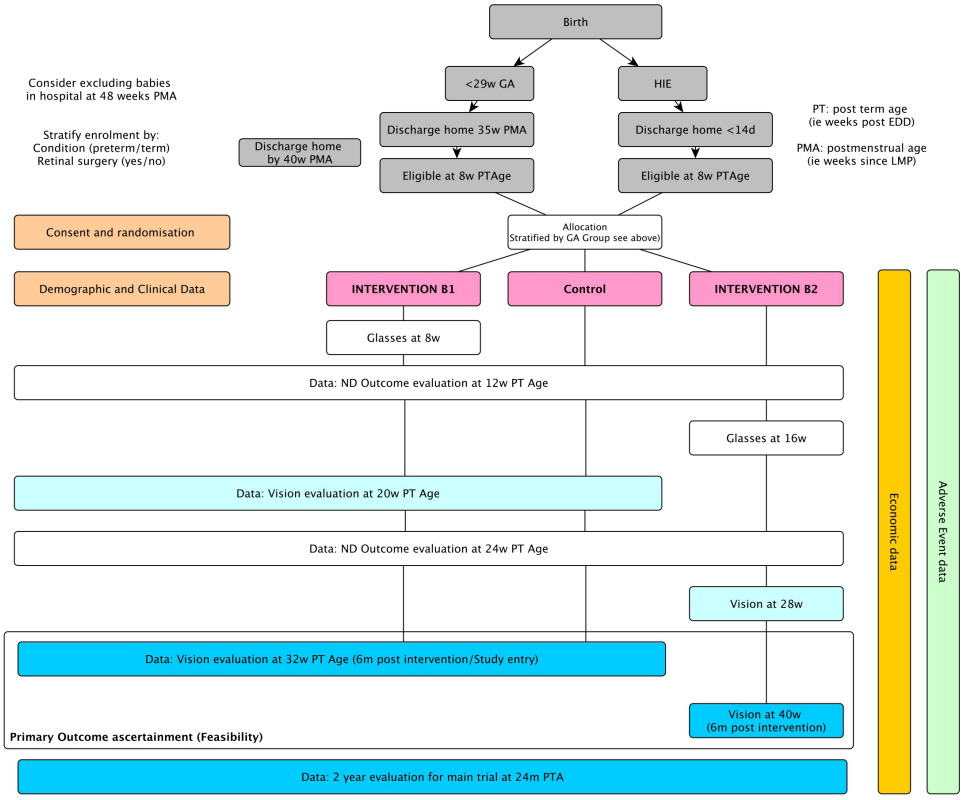

Figure 1 Flow of participation including the stages of recruitment, randomisation and intervention. GA, gestational age; HIE, hypoxic ischaemic encephalopathy. EDD = Expected date of delivery, LMP= last menstrual period, PT = post term age, PMA = postmenstrual age

3. Infants with severe refractive error (more than −6.00D spherical equivalent or +8.00D spherical equivalent).

Randomisation

The research optometrist will enrol and randomise participants using 'Sealed Envelope', an online randomisation service. Allocation concealment will be ensured, as randomisation will not be carried out until the patient has been recruited into the trial. This ensures that the assignment schedule is unpredictable.

Participants will be randomly assigned to one of three arms, group A, B1 or B2, with a 1:1:1 allocation as per a computer-generated randomisation schedule stratified by diagnosis (HIE or preterm) using random permuted blocks.

Intervention

Eligible children with consenting parents will undergo comprehensive assessments, including refractive error screening, visual, neurodevelopmental and functional broadband near infrared spectroscopy (fBNIRS) assessments at three prespecified time points. After visit 1, at either 8 weeks or 16 weeks depending on randomisation, each infant will be followed up after 3 months and 6 months (±3 weeks). The full details of flow of participants through the study and schedule of events are described in figure 1 and table 1, respectively.

Parents/carers of infants in the control group are advised of the full protocol and reassured that their infant will receive a full visual assessment much sooner than the current recommended guidelines, and if medical issues discovered, they would be referred promptly. If found to have residual refractive error at the end of the study, they will be referred to and followed up by appropriate NHS clinics. Refractive error screening will be carried out prior to randomisation (where possible) to avoid postrandomisation dropouts and unnecessary visits. Evidence of severe refractive error will also result in a referral and exclusion from the study due to the risk of associated ocular pathology.

Participants will be randomised to one of the following three arms:

Group A (control arm): First assessments at 8 weeks CGA. No glasses prescribed.

or to:

Group B1 (intervention arm): First assessments at 8 weeks CGA. Add +3.00 DS to the cycloplegic refraction and prescribe for full-time wear.

Or to:

Group B2 (intervention arm): First assessments at 16 weeks CGA. Add +3.00 DS to the cycloplegic refraction and prescribe for full-time wear.

Infants at 8 months and 10 months of age may be expected to have differences in visual acuity and refractive error relating their age and visual maturation, however, accommodative function has a more rapid postnatal maturation profile.[17]

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Table 1 Content for the schedule of enrolment, interventions and assessments

	Study period				
	Enrolment	Allocation	Postallocation		Close-out
Time point	$-t_{1Prestudy}$	$0_{Prestudy}$	$t_{1First\ visit}$	$t_{2Follow\ up\ 1}$	$T_{5Follow\ up\ 2}$
Enrolment					
Eligibility screen	X				
Informed consent	X				
Severe refractive error screen	X				
CSRI form			X	X	X
Demographics Questionnaire	X				
Allocation		X			
Interventions					
Group A			←	—	
Group B1			←	—	
Group B2				←	—
Assessments					
Ocular assessment			X	X	X
Neurodevelopmental assessment				X	X
fbNIRS			X	X	X
Non-serious/serious adverse event form	As needed throughout protocol				
Progress notes	X	X	X	X	X
Communication log	Every phone or in-person contact outside of regular visits				

fbNIRS, functional broadband near infrared spectroscopy.

There are three main areas of the assessment (see table 2 for detailed assessment breakdown).

1. Visual status (including visual acuity and refractive error) using age-appropriate methods.
2. General Development and Neurodevelopmental Delay using Bayley Scale of Infant Development, third edition.
3. Cortical responsiveness to visual stimuli using fBNIRS.

All assessments will be conducted aided (ie, with glasses if prescribed) and unaided for infants randomised to group B1 and B2.

Eligible families are advised that the study comprises three extra visits and reassured that if their circumstances change and it becomes challenging to attend the research appointments, they can withdraw from the study with no consequences to their medical care. The baseline assessment will only take place once the infant has been discharged and settled at home. The spectacle dispensing site was successfully changed from Great Ormond Street Hospital (GOSH) to UCLH; spectacles will be dispensed by the research optometrist at UCLH immediately after the visual assessment saving families an extra visit.

These tests cover the visual and developmental domains most commonly impaired in children following perinatal brain injury. The assessments are widely used and clinically validated.[51–53] The assessor will implement a standardised process for all assessments to enhance data quality and reduce bias. We are exploring the acceptability and feasibility of this set of measures in a population for whom there are no reported data for this battery of tests.

Adherence

To ensure full benefit from the spectacles, parents/carers are advised that spectacles are to be 'worn for all waking hours' though this will vary from one infant to another. While some infants develop to meet the age norms of their healthy peers, others may be suffering from multiple complications therefore the number of hours awake will vary enormously. Each parent/carer will receive a monthly telephone interview, on varying days of the week, based on a semistructured questionnaire (online supplemental appendix B). This will address tolerability, compliance issues and provide further education on spectacle use in groups B1 and B2. Reasons for not using the spectacles and simple strategies for enhancing adherence will be discussed and parents/carers will have an opportunity to ask questions at any time. The number of hours that each infant is awake and the number of hours the glasses are worn will be recorded.

Modifications to the protocol, which may affect patient safety, potential benefit of the patient, the conduct of the study (including changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects) will require a formal amendment to the protocol. Such amendment

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Table 2 Summary of assessments carried out in all three arms (group A, B1 and B2)

Visual status (research optometrist)	Atkinson's Battery for Child Development for Examining Functional Vision 1. Standard preferential looking visual acuity: Keeler cards @38 cm 2. Assessment of ocular alignment (corneal reflections) 3. Refraction and measurement of accommodation with PlusoptiX PowerRefractor and dynamic retinoscopy 4. Diffuse light reaction—orientation to light as an indicator of minimal visual function 5. Lateral tracking (saccadic or smooth pursuit) 6. Peripheral refixation—lateral fields; visual attention and extent of lateral visual fields 7. Sustained visual attention at a moderate distance 8. Pupil reactions to light and accommodative target 9. Retrieval of partially covered object and totally covered object, intermediate stages of object permanence 10. Batting and reaching. 11. Visually follows falling toy, development of object permanence 12. Defensive blink to approaching object 13. Convergence to approaching target, assessed with a torchlight 14. Dilation with Cyclopentolate 0.5% and phenylephrine 2.5% followed by funduscopy and cycloplegic refraction Near detection scale—near detection to standard 'lures'[54] on failure to obtain measurement with Keeler cards Hiding Heidi contrast test Ocular alignment assessment Fixes and/or smiles at parents/carer's face
	Length of time to complete assessments: 1 hour
General Development and Neurodevelopmental Delay (Neonatologist/other suitable clinician) Bayley Scale of Infant Development (BSID III)	1. The standardised age-appropriate visual items of the BSID III Parent/carer questionnaire to comprising eye contact (8 weeks), Social smile and regarding hands (3 months) and goal directed reach and bringing hands to midline (6 months)
	Length of time to complete assessments: 30 min–1 hour
Cortical responsiveness to visual stimuli (Neonatologist) Functional broadband near infrared spectroscopy	1. Identification of altered functional haemodynamic and metabolic response to visual stimulus 2. Assessment of changes in functional response in relation to response to glasses
	Length of time to complete assessment: 10 min

will be agreed on by the sponsor and approved by the ethics committee prior to implementation.

Statistical analysis

The time taken to recruit participants will be reported as a median with range. The proportion of patients who accept the offer of randomisation and the number of families who are lost to follow-up will be reported with a 95% CI computed using the exact binomial method. We will report the feasibility RCT in line with recommendations made within the Consolidated Standards of Reporting Trials extension for feasibility and pilot studies. Baseline characteristics will be reported by treatment allocation using means and SD for continuous data if approximately normally distributed (assessed by inspection of a histogram) or medians and IQRs for non-normally distributed continuous data. Categorical data will be reported as numbers and frequencies.

A table will be used to record details of all potential eligible babies including reasons for no consent, non-adherence (eg, discontinuation of intervention due to harms vs lack of efficacy) and non-retention (ie, consent withdrawn, lost to follow-up). This information will be used for the handling of missing data and interpretation of results (see online supplemental appendix C).

Health economic analysis

The feasibility of calculating the incremental cost per unit benefit of providing spectacles compared with treatment as usual in the control arm, over the period of the feasibility study, and from the perspective of the NHS and personal social services (PSS) in the first instance will be assessed.

This will include assessing the feasibility of collecting data on use of health and social care services by trial participants over the follow-up period of the trial, including hospital visits and admissions, accident and emergency (A&E) attendances, outpatient appointments, primary and community services, and medications, either via the NHS or where costs are borne privately by families. Information will also be collected on wider costs including time off work by the parents or other carers regarding loss of productivity. Costs to the NHS and PSS would be calculated by applying standard unit costs, and the productivity losses could be calculated using the human capital approach, in a future full trial. The feasibility of obtaining data on the cost of the intervention itself will also be assessed.

Regarding collecting effectiveness (benefit) data appropriate for an economic analysis within a future full trial, this is likely to match the future trial's primary clinical outcome. Measurement of quality of life in this very

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young population is not likely to be feasible, so clinical measures would instead be used as effectiveness measures. A number of possible effectiveness outcomes will be considered during the feasibility study, in line with the consideration of which is the most appropriate primary outcome to use in the main trial. Possibilities, therefore include, but are not limited to: (1) improvement in visual acuity at 6 months compared with visit one, (2) improvement in functional vision scale at 6 months compared with visit 1 or (3) improvement in defined visual developmental milestones at 6 months compared with the first visit. The incremental cost-effectiveness ratio of the future full trial would be expressed in terms of 'cost per unit improvement in clinical outcome', rather than in the more standard 'cost per additional quality-adjusted life-year (QALY) gained'. QALY is often used in studies with older children and adults where quality of life data are collected, either directly from participants of via proxy. The most appropriate type of analysis to be done will be explored as part of the feasibility study.

Safety and adverse events

An independent data monitoring ethics committee (IDMEC), trial steering committee (TSC) and trial management group (TMG) will oversee the conduct of this trial. The IDMEC will be instructed to look for any evidence of harm on a regular basis. The data to be collected and the procedures conducted at each visit will be reviewed in detail to ensure protocols are implemented consistently throughout the study.

GOSH/ICH research and development department are monitoring and auditing the conduct of the research. The impact of early correction will be closely monitored by measuring refractive error and accommodation, at 3 and 6 months after intervention. Expert ethical advice has been sought through the RDS to check on this dimension of potential harm (with a positive review) and it will also be monitored by the IDMEC using follow-up data as they come in case by case.

GOSH has been prescribing glasses to children of this age for decades (congenital cataract cases) and has not seen trauma (though it is very occasionally seen in slightly older children when they are more mobile). An expert paediatric dispensing optician will ensure the glasses are perfectly fitted and take into account the babies' developing features; the fit will be checked every few months.

Harms

The study will monitor for the following adverse effects through patient examination and chart review: hypoaccommodation, emmetropisation and mechanical harm.

All adverse events occurring after entry into the study and until the end of the trial will be reported as they occur on the case report form (CRF) and supported by an entry in the subject's file. Each event will be described in detail along with start and stop dates, severity, relation to the study (as judged by the research optometrist), action taken and outcome. Serious adverse events (SAEs) will be reported within 24 hours of first awareness of its occurrence. The investigators do not predict that there will be unexpected SAEs.

The sponsor has arranged for public liability insurance for participants enrolled into the study. This will include cover for additional healthcare, compensation or damages whether awarded voluntarily by the sponsor, or by claims pursued through the courts.

Masking

Due to the nature of the intervention, neither participants nor staff can be masked to allocation therefore the study set up is open label. The revealing of an infant's allocation to parents/carers will take place at the first visit.

Patient and public involvement

A patient and public involvement (PPI) committee has been assembled to be involved in all aspects of the study including, review of study materials, review of draft protocols, choice of outcomes, analysis and dissemination of results. Two parents of children with CVI, one visual impairment teacher, one affected young person, and one parent of an unaffected baby have agreed to form the PPI committee and will be offered training through the UCLH/BRC workshops.

Near study close, families will be informed of the results through personal feedback (via the research optometrist and meetings of the PPI committee) where they will be given the opportunity to discuss their experiences in the trial. The data from the feasibility trial will be used to inform decisions on study design for a subsequent definitive RCT. Members of the PPI committee will give advice on dissemination of results from feasibility study to the public and other professionals. Study outcomes will be published through peer-reviewed journals and presentations at CVI conferences and to the PPI committee.

Confidentiality

All information collected for the duration of the study will be confidential and only the research team will have access to it. Confidentiality will only be broken if there are health, safety or medical concerns, where referral to an appropriate specialist is required, and has been discussed with the parent/guardian in advance.

Data forms and data entry

For each subject enrolled, a CRF will be completed and signed by the investigator or authorised delegate from the study staff. Data collected during the study will be entered on CRFs and each participant will have a unique trial identifier specified to them. These forms will be entered electronically to the UCLH system, Epic and to UCL Data Safe Haven (DSH). The data entry screens will resemble the paper forms approved by the TMG.

Data management

Computerised data will be kept in password-protected encrypted systems and paper records will be kept in a locked cupboard and locked room at UCLH. All stored

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data will be suitably pseudoanonymised. Identifiable data will remain in the secure UCL DSH and anonymised data will be sent to London School of Hygiene and Tropical Medicine for analysis using encrypted memory sticks or encrypted email transmission.

ETHICS AND DISSEMINATION

The South Central Oxford C Research Ethics Committee and sponsor have reviewed and approved the protocol, consent form, patient information leaflet and other requested documents (ref 20/SC/0004).

Trial sponsor

GOSH

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COMMITTEES

Trial management group

Setup, routine running and analysis of the research.

Review the ongoing progress and conduct of the trial including progress of study and site opening, recruitment rate, site issues, data quality, return rate and protocol amendments.

PPI committee

Review of study design, materials and protocol. Choice of outcomes, analysis and dissemination of results.

Trial steering committee

Providing an independent, experienced opinion if any conflicts arise between any parties involved in the project.

Provide overall supervision for a project on behalf of the project's sponsor and funder.

To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments.

To provide advice to the investigators on all aspects of the project.

Independent data monitoring and ethics committee

Making recommendations to the steering committee on whether there are any ethical or safety reasons why the trial should not continue.

Report to the TSC.

Monitor the safety, rights and well-being of the trial participants case by case.

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Contributors RB (ophthalmologist) conceived the study and obtained grant funding. RB (optometrist), RB (ophthalmologist), SM and HSCT obtained ethical approval. RB (optometrist) will run the day-to-day activity of the project, draft the protocol and collect all data. CB provided statistical expertise in clinical trial design and will be conducting the primary statistical analysis. CSC provided expertise and advice in designing, planning and conducting health economic analyses alongside a clinical feasibility study. KS and AH have advised on design of study, implementation and technical aspects of measuring accommodation. LD has been involved in PPI and design of study. CW has provided clinical expertise in clinical research in CVI. NM has advised on timings of intervention in neonates and will have some oversight on study implementation. HSCT is the PPI lead for the project. ND has contributed to choosing the visual outcomes for the study. All authors contributed to refinement of the study protocol and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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Appendix A

Great Ormond Street Clinical and Academic department of Ophthalmology and Neonatal Unit, University College London Hospital

IRAS Reference: 265584
Patient Identification Number for this trial:

CONSENT FORM

Title of Project: Near vision spectacles for babies at risk of cerebral visual impairment: a feasibility study

Lead Researchers: Mr Richard JC Bowman MA MD FRCOphth, Consultant Ophthalmologist, Great Ormond Street Hospital, Dr Leigh Dyet, Consultant Neonatologist, University College London Hospital.

Please initial all boxes

1. I confirm that I have read and understand the information sheet dated [23/05/2020], [Version 2] for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that participation is voluntary and that we are free to withdraw at any time without giving any reason, without my child's medical care or legal rights being affected. ☐

3. I understand that relevant sections of my child's medical notes and data collected during the study may be looked at by individuals from NHS medical researchers from the above units, from regulatory authorities or from the NHS Trust, where it is relevant to our taking part in this research. I give permission for these individuals to have access to my child's records. ☐

4. I also give permission to store my child's data on the secure University Safe Haven database and for anonymized (non-identifiable) data to be shared with King's College Trial unit to analyse the results of the study. ☐

5. I agree to my GP being informed of our participation in the study. ☐

6. I am happy to be contacted in the future regarding the study. ☐

7. I agree for my child and I to take part in the above study for **both** the trial of the prescription glasses and the light based monitoring of brain activity. ☐

8. I agree for my child and I to take part only in the trial of the prescription glasses (**not** the light based montoring of brain activity). ☐

Name of Participant	Date	Signature

Name of Person Taking Consent	Date	Signature

One copy of the consent form will be retained by the researchers and one copy will be provided to the participants' parent/guardian.

Appendix B

Participant ID number		
Date of interview		
Date of diary data		
Notes – is baby awake / asleep / feeding etc.		Glasses on / off
	Midnight	
	1am	
	2am	
	3am	
	4am	
	5am	
	6am	
	7am	
	8am	
	9am	
	10am	
	11am	
	12noon	
	1pm	
	2pm	
	3pm	
	4pm	
	5pm	
	6pm	
	7pm	
	8pm	
	9pm	
	10pm	
	11pm	
Notes/ comments: reasons why glasses not worn all the time / problems etc.		

Appendix C

[free text]	[free text]	[free text]	[free text]	Participant ID
Choose an item.	Choose an item.	Choose an item.	Choose an item.	Is the infant eligible?
Choose an item.	Choose an item.	Choose an item.	Choose an item.	If not, why not eligible?
Choose an item.	Choose an item.	Choose an item.	Choose an item.	Was the infant recruited?
Choose an item.	Choose an item.	Choose an item.	Choose an item.	If not, why not recruited?
Choose an item.	Choose an item.	Choose an item.	Choose an item.	Have parents given consent?
[free text]	[free text]	[free text]	[free text]	Why not consented?
Choose an item.	Choose an item.	Choose an item.	Choose an item.	Has the infant been randomised?
Choose an item.	Choose an item.	Choose an item.	Choose an item.	If not, why not randomised?
Choose an item.	Choose an item.	Choose an item.	Choose an item.	Has the infant been allocated to intention to treat
Choose an item.	Choose an item.	Choose an item.	Choose an item.	Was intervention given?
Choose an item.	Choose an item.	Choose an item.	Choose an item.	If not, why not given intervention?
Choose an item.	Choose an item.	Choose an item.	Choose an item.	Is primary outcome available?
Choose an item.	Choose an item.	Choose an item.	Choose an item.	If not, why is primary outcome not available?