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 (Babies in Glasses BIG)

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STATISTICAL & HEALTH ECONOMIC ANALYSIS PLAN

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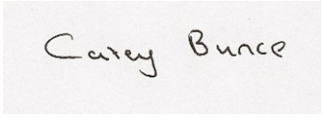
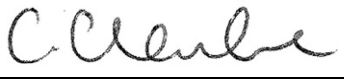
Prof Catey Bunce	Statistics co-applicant		8/8/2024
Dr Caroline Clarke	Health economics co-applicant		11/9/2024
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1. Summary

1.1 Null hypothesis

There is no difference in visual outcome between children with perinatal brain injury when prescribed near vision spectacles compared with the current standard care – waiting until a problem is detected.

*** This null hypothesis is not being formally tested by this exploratory feasibility trial

1.2 Study aim

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.

1.3 Study design:

This is an exploratory, single-centre randomised parallel-group feasibility clinical trial in babies at risk of cerebral visual impairment. The “treatments” under comparison in this study are:

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

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

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

1.4 Schedule of assessments

	STUDY PERIOD					
	Enrolment	**Allocation**	**Post-allocation**			**Close-out**
TIMEPOINT**	$-t_1$	**0**	t_1	t_2	t_3	T_4
ENROLMENT:						
Eligibility Screen	X					
Informed consent	X					
Severe Refractive Error Screen	X					
CSRI Form			X	X	X	X
Demographics Questionnaire	X					
Allocation		X				
INTERVENTIONS:						
Group A			♦—	—	—♦	
Group B1			♦—	—	—♦	
Group B2				♦—	—	—♦
ASSESSMENTS:						
Ocular assessment			X	X	X	X
Neurodevelopmental assessment				X	X	
fbNIRS			X	X	X	X
Non-serious/ Serious Adverse Event Form	**As Needed Throughout Protocol**					
Progress notes	X	X	X	X	X	X
Communication log	**Every phone or in-person contact outside of regular visits**					

CSRI = Client Service Receipt Inventory; fbNIRS = functional broadband near infrared spectroscopy

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2. Outcome measures

2.1 Primary outcome measure (feasibility)

The acceptance of randomisation measured by the proportion of recruited parents who accept the offer of randomisation.

2.2 Secondary outcome measures

Feasibility

2.2.1 The feasibility of fitting and dispensing glasses with varying refractive corrections to infants aged 8 weeks versus 16 weeks CGA

2.2.2 Compliance with spectacle wear for parents and infants when dispensed at 8 weeks and 16 weeks CGA.

2.2.3 The retention rate in all 3 arms, which will be reported descriptively on our CONSORT flow diagram. (This is a change to the published protocol which stated it would be reported by the median number of infants reported per month as it was agreed by investigators that this was likely to confuse readers).

2.2.4 The proportion of families completing phone questionnaire on spectacle compliance as a percentage of those in the intervention groups (B1 & B2).

Clinical

2.2.5 The distribution of visual acuity at the 3 and 6-month follow ups compared with visual acuity at the first visit in all 3 arms.

2.2.6 The distribution of refractive outcomes (measured in dioptres) at 3 and 6-month follow ups as compared to the first visit in all 3 groups.

2.2.7 The distribution of accommodative outcomes (measured in dioptres) at 3 and 6-month follow ups as compared to the first visit in all 3 groups.

2.2.8 Evidence of impaired emmetropisation following administration of intervention. This will be monitored carefully on a case-by-case basis for each child.

2.2.9 The absence of harm through mechanical trauma from prescribing glasses at these ages. This will be monitored carefully on a case-by-case basis for each child.

2.2.10 The distribution of ABCDEFV scores at baseline, 3 and 6 months. Each subtest will be scored as a binary pass fail and these will be totalled (possible 0-14).

Economic

2.2.10. Determination of appropriate resource-use data collection methods. A targeted paediatric Client Service Receipt Inventory (CSRI) form has been modified for this population and will be used for the duration of the feasibility study.

3 Sample size calculation

The target sample of eligible babies is pragmatic as we estimate 100 (approximately 35 with hypoxic ischaemic encephalopathy [HIE] and 70 pre-term [<29 weeks]) babies will come through the University College Hospitals London (UCLH) neonatal intensive care unit per year. For feasibility studies, sample sizes between 12 and 50 per group [1], [2] have been recommended to estimate a chosen parameter. We predict 75% acceptance rate resulting in approximately 25 participants in each arm (A, B1, B2). Selecting a sample of 100 from a population and determining that 75% of subjects would agree to recruitment would give 95% confidence that between 65% and 83% of subjects in the population would agree to recruitment. This would provide enough confidence to proceed to a subsequent definitive randomised controlled trial (RCT).

4. 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 pre-term) using random permuted blocks.

5. Statistical Data Analysis

5.1. Analysis Principles

5.1.1 ITT or PP: Analyses will be in accordance with the intention-to-treat (ITT) principal where all patients are analysed as per the groups to which they are randomised and not per-protocol (PP), to retain the validity of the randomisation process.

5.1.2 Significance levels of tests: All statistical tests will use a 2-sided p-value of 0.05, unless otherwise specified. All confidence intervals presented will be 95% and two-sided.

5.1.3 Baseline comparability: Baseline characteristics will be summarised by randomised group and diagnosis. Summary measures for the baseline characteristics of each group will be mean and standard deviation for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables. Where numbers are small, we may simply report raw data.

5.1.4 Adjustment for design factors: Since randomisation was stratified by diagnosis (HIE or pre-term) analyses of outcomes will also be stratified.

5.1.5 Follow-up and losses to follow-up: missing data: It is inevitable that some patients will be lost to follow-up. Sample size estimation assumed 10% of patients would not provide an evaluable 6-month outcome. If this rate is observed, data for many patients will be only partially observed. Reasons for missingness may be important and these will be examined. This is a feasibility study and imputation for missing data will not be conducted.

5.2 Planned Analysis:

5.2.1 Primary Analysis: We will report the proportion of participants who accept the offer of randomisation as a proportion with a 95% confidence interval computed by the exact binomial method.

5.2.2 Secondary Endpoint Analysis

Summary statistics will be provided for all secondary outcome measures by treatment group and diagnosis. Summary measures will be mean and standard deviation for continuous (approximately) normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables. Treatment differences may be estimated and estimates presented with 95% confidence intervals where appropriate. Where numbers within groups are too small for meaningful summaries patient listings by time point will be tabulated. Scatter graphs will also be included.

5.3 Toxicity / Symptoms

The number of new serious complications occurring before the end of six months will be reported by treatment and diagnosis group.

6. Health Economic Analysis

6.1 Aim and objective of economic analysis

The aim is to assess the feasibility of calculating the incremental cost per unit benefit of providing spectacles compared with treatment as usual in the control arm in a future full RCT, from the perspective of the NHS and Personal Social Services (PSS).

The objective of this feasibility study is to determine and pilot appropriate resource-use data collection methods for a future full RCT. A targeted paediatric CSRI form has been designed specifically for this population and will be used in this feasibility study.

6.2 Reporting of resource use and cost information

Descriptive statistics will be reported for resource use items and their levels of completion, and for costs calculated from these, by randomised group and by diagnosis, and no formal comparisons across groups will be made.

Resource use information will be collected via the resource use questionnaire developed for this feasibility study based on the Client Service Receipt Inventory (CSRI).

Standard unit costs for NHS and PSS (but not productivity losses) will be applied to resource items and these will also be reported descriptively, by randomised group and by diagnosis.

Resource use items or categories will be summarised as frequencies and percentages, and costs will be summarised as means and standard deviations (as this is the format required for summing costs), and medians and interquartile ranges and max-min ranges (as the costs are not usually normally distributed, so this format can be more informative).

The CSRI includes 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.

The feasibility of obtaining data on the cost of the intervention itself will also be assessed, and reported as estimated costs of providing the intervention, by randomised group and by diagnosis.
Information was also collected on time off work by the parents or other carers and this will also be reported as descriptive statistics (number of days), as it would be used in a future full trial to assess productivity losses.

6.3 Consideration of effectiveness data (no further analysis here)

A future full trial would require collection of effectiveness (benefit) data, and this feasibility study allows consideration of what type of effectiveness data would be most appropriate in this future context.

To explain further: the standard measurement of benefit for a health economic analysis would use patient-reported information on quality of life, but this is not feasible in this very young population, so clinical measures would instead be used as effectiveness measures for a future health economic analysis.

Previous studies by one of the study co-applicants (Naomi Dale) have demonstrated the importance of developmental acceleration of improvement in visual acuity in infancy and by one year of age and across the preschool years [3], [4]

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: (i) improvement in visual acuity at 6 months compared to visit one, (ii) improvement in accommodation or refraction at 6 months compared to visit one, or (iii) improvement in defined visual developmental milestones at 6 months compared to the first visit.

The incremental cost-effectiveness ratio (ICER) in a future full trial would then be expressed in terms of “incremental cost per unit improvement in clinical outcome”, rather than in the more standard “incremental cost per additional quality-adjusted life-year (QALY) gained” which is often used in studies with older children and adults where quality of life data are collected, either directly from participants or via proxy.

These measures are covered in the statistical part of the analysis as described above, and possible use of these measures as future health economic effectiveness measures will be discussed as part of the reporting for this feasibility study.

7. Appendices - Dummy tables

Table 1: Baseline characteristics of the study patients by treatment and diagnostic group (HEI or pre-term)

Table 2: Ocular characteristics at baseline of the study patients by treatment and diagnostic group (HEI or pre-term)

Table 3: Pre-specified progression criteria and observed results

Table 4: Clinical outcomes at first, 3 month and 6 month visit by treatment and diagnostic group (HEI or pre-term)

Table 5: Harms by treatment and diagnostic group (HEI or pre-term)

Table 6: Challenges met during feasibility study and how definitive study will address

8. References

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