

Full Title:

Soft contact lenses to optimise vision in adults with idiopathic infantile nystagmus: a pilot parallel randomised controlled trial

Short Title:

Contact lenses in adults with idiopathic infantile nystagmus

Authors:

Maria Theodorou^{1,2}, Ana Quartilho^{2,3}, Wen Xing², Catey Bunce^{2,4,5}, Gary Rubin^{2,3}, Gillian Adams¹, Annegret Dahlmann-Noor^{1,2}

¹ Paediatric Ophthalmology and Strabismus, Moorfields Eye Hospital, London, UK

² National Institute for Health Research Biomedical Research Centre at Moorfields Eye Hospital, London, UK.

³ University College London, UCL Institute of Ophthalmology, London, UK

⁴ Kings College, University of London, London, UK

⁵ London School of Hygiene & Tropical Medicine, London UK

Correspondence to:

Maria Theodorou PhD, FRCOphth

Address: Paediatric Ophthalmology and Strabismus, Moorfields Eye Hospital,
162 City Road, London EC1V 2PD

Email: Maria.Theodorou@moorfields.nhs.uk

Mobile: 01144 7701 065 594

Abbreviations used in manuscript, tables and figures:

INS - Infantile Nystagmus Syndrome

CL – Contact Lens

BCVA – Best Corrected Visual Acuity

SCL – Soft Contact Lens

RGPL – Rigid Gas Permeable Lens

RCT – Randomised Control Trial

OCT – Optical Coherence Topography

NAFX – Expanded Nystagmus Acuity Function

IQR – Inter-Quartile Range

SD- Standard Deviation

CO – Confidence Interval

ANCOVA – Analysis of Co-Variance

C – Complete

W – Withdrew

LTFU-Lost to Follow Up

FC = Fully Corrective contact lenses

Pl = Plano contact lenses.

LFD – Longest Foveation Domain

MMV50 - Minimum Mean Velocity in a 50ms window

MMV100 -Minimum Mean Velocity in a 100ms window

Introduction

Infantile nystagmus syndrome (INS) is an involuntary, predominantly horizontal, oscillation of the eyes that develops at birth or shortly afterwards and persists throughout life. The prevalence of INS has been estimated to be 14 per 10000 (Sarvananthan et al, 2009). Reduced visual acuity is almost universal in INS, with impact on daily activities such as inability to reach visual standards for driving, particularly at times of increased psychological stress (Abadi and Bjerre, 2002; Abadi and Dickinson, 1986, Dell'Osso et al, 1974), although not necessarily increased visual demand (Tkalcevic and Abel, 2005; Wiggins et al, 2007).

At present there is no gold standard for the treatment of INS. Compared with glasses, it is anticipated that contact lenses (CL) may provide superior optical correction with a constantly moving eye as the patient would be expected to be viewing through the visual axis for a greater proportion of time, with reduced chromatic and spherical aberration as well as prismatic effect that may be induced with spectacles.

Furthermore, when a head posture is adopted to utilise a null point/zone, CLs allow fixation through the optically optimal area. However, these anticipated benefits may be offset if the movement causes a misaligned poorly fitting lens (Jayaramachandran et al, 2014). Unlike systemic medication such as gabapentin and memantine (Shery et al, 2006; McLean et al, 2007), CLs can be used across all age groups, including infants, young children and women of childbearing age. Risks associated with CLs are low and can be minimised with modifiable risk factors such as meticulous lens hygiene (Liesegang, 1997; Wagner et al, 2014). Many complications, such as allergy and non-sterile infiltrates, resolve with discontinuation of CL wear. The most serious potential adverse event is microbial keratitis, estimated at 2.44/10,000 presumed (1.8/10,000 culture proven) in contact lens wearers (all types) compared to

0.36/10,000 presumed (0.26/10,000 culture proven) in non contact lens wearers (Seal et al, 1999).

Lawson Smith first suggested over 40 years ago that CLs may also dampen ocular oscillations in INS, but published data is still scarce: Single case reports and small case series have suggested that refractive CLs improve vision and/or various nystagmus waveform parameters (Abadi, 1979; Allen and Davies, 1983; Bagheri et al, 2017; Biousse et al, 2004; Dell'Osso et al, 1988; Enoch and Windsor, 1968; Golubovic et al, 1989; Rutner and Ciuffreda, 2005; Taibbi et al, 2008). Most studies assessed the effect on best-corrected visual acuity (BCVA), assuming their effect to be mediated by correction of refractive error and additional vergence and accommodative effort (Abadi, 1979; Golubovic et al, 1989). Some studies suggest that damping of nystagmus may be mediated via proprioceptive signals from the surface of the eye (Abadi et al, 1980; Dell'Osso et al, 1988). Other INS treatment studies used rigid contact lenses (Allen and Davies, 1983; Bagheri et al, 2017; Golubovic et al, 1989; Jayaramachandran et al, 2014). However, soft CL are increasingly commonly used as they are considered more comfortable to wear and the newer types available offer correction of a wider range of refractive errors and astigmatism.

When we designed the present study, there wasn't any published data on the relative benefits and risks of soft versus rigid gas permeable CLs for INS, or feasibility data on contact lenses wear in adults with nystagmus. Tolerance was assumed and not specifically assessed, although Safran (Safran and Gambazzi, 1992) reports a single case of rebound phenomenon following contact lens wear. In addition, most of the published data did not have nystagmus recordings available. The present study aimed to provide this information.

Whilst the present study was enrolling participants, Jayaramachandran et al (2014) published a randomised cross over trial comparing spectacle wear with soft (SCL) and rigid gas permeable CL (RGPL). Surprisingly, this showed worsening of BCVA with SCLs, compared with baseline and with RGPLs, though the mean differences between groups were below 0.1 logMAR. Although the studies both assessed CL wear in INS, the aims differed (SCL v RGPL v glasses (baseline) and fully corrective SCL v plano SCL + glasses (baseline)), so we continued our study and present here data on feasibility and safety of SCL wear for INS, and further preliminary data on effect size based on visual acuity and nystagmus waveform parameters. The study was designed as a pilot study so primary outcomes were: recruitment rates, acceptability of and adherence to treatment and adverse events. Secondary outcomes were: change in best-corrected visual acuity and nystagmus parameters between baseline and two weeks from baseline.

Methods

Study Design

We carried out an unmasked pilot RCT comparing fully corrective soft contact lenses with plano soft contact lenses (+ refractive correction with spectacles if required) in adults with idiopathic INS. The study was performed in accordance with the Declaration of Helsinki, and was approved by the City Road and Hampstead Ethics Committee. It was registered on the UKCRN database. Written informed consent was obtained from all participants before randomization.

Participants & Clinical Assessments

Eligible participants were recruited between July 2013 and December 2014. They were identified from the ophthalmology clinics at Moorfields Eye Hospital, London and its outreach clinics; from electronic consultation letters and the Contact Lens database. Approaching consecutive eligible patients reduced selection bias. Inclusion and exclusion criteria are summarized in table 1.

Author MT took a detailed history and carried out a full ophthalmic assessment on all participants, including slitlamp examination of the anterior and posterior segment examination. Where appropriate patients underwent further investigations (including macula OCT and/or electrodiagnostic testing) to confirm a diagnosis of idiopathic infantile nystagmus syndrome. We recorded distance binocular and monocular BCVA in logMAR as measured by Early Treatment Diabetic Retinopathy Study chart at 4 metres and at near in a well-lit room.

Eye movements were recorded using an EyeLink 1000 video based eye tracker (SR Research) and sampled at 2ms intervals. Monocular and binocular recordings were

taken. The stimulus for eye movements consisted of a circular black target on a white background. The stimulus sequence consisted of cycles in which each target was shown for 10 seconds at 0, ± 5 , ± 10 and ± 15 degrees horizontally, and then repeated at ± 15 degrees vertically. The head was stabilized in the primary position with a chin rest.

Participants were assessed at baseline and two weeks (± 3 days) from baseline. As nystagmus waveforms and BCVA may be affected by tiredness, with worse findings in the late afternoon and evening, we scheduled all follow up study visits after 4pm to allow documentation of the maximum effect of contact lenses.

Randomization

Eligible participants were recruited and randomized into 2 groups on a 1:1 ratio. The randomization schedule was generated by a senior data manager in the Moorfields Research & Development department using random permuted blocks of varying sizes in STATA statistical software. The randomization allocation for each patient was provided by the data manager over the phone. The allocation list was kept by the senior data manager until the end of the trial and sent to the trial statistician for final analysis.

Trial Intervention: Contact Lens assessment & fitting

After randomization all participants underwent subjective refraction and measurements for CL fitting. Participants were issued a new spectacle prescription as appropriate, for full time wear to fully correct their refractive error.

21 participants were completely new to contact lens wear. All participants received individual instructions on CL handling and management by a CL practitioner. Where difficulties were encountered, further teaching sessions were organized until the participants were able to safely manage contact lens wear. All participants were given a diary to record daily wear in hours, and any adverse events, and contact details of author MT if there were any acute concerns.

Proclear SCL were issued (CooperVision Proclear). These CLs are made with phosphorylcholine, with a blue handling tint. They have an aspheric optic design and are available to correct up to 6 dioptres of astigmatism. CL fit was assessed at baseline and follow up visit. Misalignment of toric lenses by more than 5 degrees from the prescribed axis in either direction was classified as a poor fit, and CLs were remeasured and refitted.

Care after trial

Following completion of the 2-week observation period, participants had the option of continuing CL wear or to discuss alternative treatments.

Data Collection and Analysis

Feasibility

The number of eligible patients that agreed to participate was documented (including the number excluded due to other diagnoses made); number allocated to baseline group (plano CLs/specs) and fully corrective CLs; number lost to follow up; and the number that discontinued contact lens wear. The CL diary was reviewed at the follow up assessments, and any adverse effects documented and managed as appropriate.

Eye Movement Data

Calibration was performed offline so that the foveating periods of the waveform were fixated on the targets at 15 degrees. Underlying periodicities in the waveform were identified using the technique of periodic orbit analysis (Theodorou, 2009; Theodorou and Clement, 2007). This is based on non-linear dynamics allowing the repeatable part of the waveform to be selected with minimal observer bias. Application of this technique involves 4 stages: First, the velocity of the eye movement is thresholded and the intervals between threshold crossings calculated. Second, the intervals are concentrated onto the periodicity of the waveform by applying a transform based on a linear analysis of the changes in successive interval lengths. Third, the peak in a histogram of the transformed data is used to identify the underlying periodicity of the data. Finally, example cycles matching the periodicity are identified in the eye movement recordings. The width of the histogram bins used was 25ms. All cycles within ± 12.5 ms of the periodic orbit length were selected as example cycles as the datasets for each subject. The position of the cycle closest to the periodic orbit length was used to represent the underlying periodicity.

The eXpanded Nystagmus Acuity Function was calculated using the adaptable position and velocity parameters as described by Dell'Osso and Daroff (2002).

The waveform parameters in the datasets analyzed and compared between visits were: Amplitude (mean and minimum); Foveation Time (standard foveation window position $< \pm 0.5$ degrees and velocity < 4 degrees/second); Position (mean, minimum mean in a 50ms and 100ms foveation window, standard deviation); Velocity (mean, minimum mean in a 50ms and 100ms foveation window, standard deviation) and the eXpanded Nystagmus Acuity Function (NAFX).

The analysis routines (excluding the NAFX) were implemented in the software package Mathematica ® (Theodorou, 2009). The NAFX (Dell'Osso and Jacobs, 2002) was analyzed in Matlab using software from the Dell'Osso and Daroff lab (<http://www.omlab.org>).

Clinical data

Data were collected on paper case report forms and transferred to an electronic database for analysis.

Feasibility data were summarized descriptively. Analysis of secondary outcome measures was conducted on available data (complete case analysis).

Descriptive summary statistics are provided as mean and standard (SD) deviation for continuous approximately normally distributed variables, and median and interquartile ranges (IQR) for non-normally distributed continuous variables. For approximately normally distributed secondary outcome measures, mean difference between the two treatment groups at two weeks from baseline and respective 95% confidence interval (CI) were estimated using analysis of covariance (ANCOVA).

Pre-post treatment effect for each group was also estimated separately with respective 95% CI. For secondary outcomes not following a normal distribution, only descriptive summary statistics are presented. Main analysis was conducted by randomized treatment and a sensitivity analysis was conducted by treatment actually received.

Results

We randomized 38 participants. Baseline characteristics of all study participants are summarised in table 2 including: age; sex; allocated group; study status; subjective refraction; previous contact lens wear; previous treatment for nystagmus and/or strabismus, and the baseline ocular characteristics and waveform parameters in table 3. Mean (SD) BCVA with both eyes open for distance was 0.36 (0.14) in the plano CL group and 0.29 (0.16) in the corrective CL group; median near acuity was N6 in both groups. The mean (SD) spherical equivalent was -2.2 (3.5) and -2.6 (4.1) in the right and left eyes respectively in the plano CL group and +0.8 (3.3) and +1.2 (3.8) in the right and left eyes respectively in the corrective CL group.

Primary Outcomes: Feasibility

Eligible patients were identified from the ophthalmology clinics, electronic consultation letters and the Contact Lens database.

The flow through the study is summarized in the CONSORT flow diagram (Figure 1). 42 participants agreed to participate in the study: 1 was excluded (diagnosis of albinism) and 3 did not attend the agreed study appointments. 36/38 participants were recruited directly from ophthalmology clinics.

19 participants were randomized into each study group, although 3 of the 19 randomized to the fully corrective CLs were effectively plano (i.e. had no significant refractive error).

27 participants completed the study (71%, 16/19 in the plano CL group, 11/19 in the corrective CL group). All patients who withdrew (2/19 in each group, total n=4) were unable to insert their CL despite repeated teaching sessions. One patient from the plano CL group and 6 from the refractive CL group (of whom one had a plano CL)

were lost to follow-up.

Adverse events

CL discomfort was reported by 3/27 of the participants who completed the study (11%). This may have affected their BCVA and nystagmus waveform parameters. Two had no identifiable anterior segment pathology to account for the symptoms, while the third had signs of allergic eye disease, which responded well to treatment with G. olapatidine. All 3 completed the study.

We encountered three cases of CL tearing, which may be attributed to the thickness of the CL (0.065-0.35mm, dependent on power).

24 participants (89% of 27 who completed the study, and 63.2% of 38 randomized participants) who wore the CL until the follow-up assessment had no problems with CL tolerance. There were no cases of CL-associated keratitis in the study group.

Secondary Outcomes: Visual Acuity and Nystagmus parameters

Table 4 summarizes outcomes by study group. A representative example of waveform recording and outcome measures (in null) is shown in figure 2.

Visual acuity

In the following we present the results in those 27 participants who completed CL wear for at least two weeks. Mean improvement in BCVA (both eyes open) at two weeks from baseline was 0.07 (95% CI: 0.03 to -0.11) in the plano CL group and 0.06 (95% CI: 0.02 to 0.1) in the corrective CL group. The mean difference between the two treatments, adjusted for baseline values, was 0.01 (95% CI: -0.05 to 0.07) i.e. there was no evidence of a significant difference between plano and corrective CL at

two weeks from baseline.

Nystagmus parameters

Overall, effect estimates suggest an improvement in most waveform parameters in both the plano and the corrective CL group. In the plano group there was an improvement from baseline in all waveform parameters, but the effect estimate was only significant for the mean amplitude in degrees (1.19; 95% CI: 0.43 to 1.96). In the corrective CL group there were only significant improvements from baseline in velocity parameters (mean change in minimum mean velocity (degrees/second) in a 50ms window (2.67; 95% CI: 0.88 to 4.45); mean change in minimum mean velocity (degrees/second) in a 100ms window (3.41; 95% CI: 1.38 to 5.43) and NAFX (-0.05; 95% CI: -0.09 to -0.003). There was a worsening in position parameters, although none were statistically significant. Except for the position parameters, there was no evidence of significant differences between the 2 groups in terms of secondary outcome measures (see table 5).

For both primary and secondary outcomes, results were alike when conducting sensitivity analysis by treatment actually received (n = 18 plano CL group; n = 9 corrective CL group).

Sample Size for a future RCT

A sample size of 40 patients (20 per group) would allow 90% power to detect an improvement of 0.1 LogMAR in distance VA (measured with both eyes open) between treatment arms, at the 5% significance level. This sample size is based on a minimally clinically important difference of 1 line on the VA Chart i.e. 0.1 LogMAR which has been used in other trials; the observed pooled standard deviation of 0.16;

the observed lower limit of the 95% confidence interval 0.81 for the correlation 0.91; 95% CI: 0.81 to 0.96, between baseline and follow-up measurements. It is expected that 30% of patients will be lost to follow-up and therefore, the final sample size required for a definitive RCT using BCVA as the primary outcome measure would be 58 (29 per group). The observed correlation is high and is based on limited data therefore, it appears appropriate to base the sample size on the lower limit of the 95% CI.

Discussion

The key findings of the present pilot RCT are that 71% of randomized participants completed the two-week study period, CL treatment was well tolerated, and that the effect size in terms of BCVA improvement (and nystagmus parameters) is small. These findings and preliminary data will facilitate the design of a future full RCT on this topic.

To date, RCT evidence for treatment of INS is scarce; only four RCTs have been undertaken in this field. These have explored auditory biofeedback (Evans et al, 1998), pharmacological treatments (McLean et al, 2007; Hertle et al, 2015) and contact lenses (Jayaramachandran et al, 2014). Supplementary table 6 lists the main similarities and differences between the randomized CL trial (Jayaramachandran et al, 2014) and our study.

The principal limitation of this study was the non-masked design; in a full RCT, observers carrying out follow-up assessments should be masked to the allocated intervention. As this was a pilot RCT, with emphasis on feasibility outcomes, we felt that masking was not required. We reduced selection bias by approaching consecutive eligible patients. The small sample size and the fact that most participants did not have significant refractive errors or head postures mean we may have underestimated the effect of the CL on visual function and nystagmus parameters, our secondary outcomes. The refractive status of the 2 groups was also unexpectedly considerably different making interpretation of results difficult - stratification for refractive status should be considered in the design of a future RCT.

Strengths are the high quality of assessments and data, including clinical trials standard acuity measurements. We limited study inclusion to adults with idiopathic INS, minimizing any potential confounding factors.

We expect that our findings have high generalizability. A retention rate of 71% is not unusual for RCT, although we had expected a higher figure, as the trial observation period was only two weeks. Future studies may mitigate this problem by setting up regular contacts, for example via telephone, with participants, to offer support for any CL-related problems.

Interpretation

The present study provides further information to design future randomized treatment trials for INS. Of particular relevance for trials is the decision about primary outcome measures. In this study, the improvement in BCVA was small, less than 0.1 logMAR, which is within the test/retest variability of the ETDRS test. Nystagmus waveform parameters may be more appropriate in the primary as well as the null 'zone', as they are likely to detect clinically meaningful functional improvements which might not necessary translate into a clinically meaningful improvement in BCVA. The 2 earlier studies used visual acuity as their primary outcome measure (Evans et al, 1998; McLean et al, 2007), while the more recently published trials used waveform parameters as their primary outcome measures: NAFX (Hertle et al, 2014) and mean intensity in the null region viewing at 1.2m (Jayaramachandran et al, 2014). If clinically NAFX were to be selected as the meaningful parameter to assess treatment efficacy between arms (primary outcome), a sample size of 20 patients (10 per group) would allow 90% power to detect an improvement of 0.1 in NAFX between treatment arms, at the 5% significance level and assuming a 30% loss to follow-up. However, the sample size computed for NAFX is based on limited data (n = 11 for fully corrected CL group) where we observed little variation in terms of the NAFX parameter: 0.05 pooled standard deviation. As such, if higher variation were to be observed, a higher sample size would be required.

There remains much debate amongst nystagmus researchers as to the “best” objective outcome measure in nystagmus. The standard remains the NAFX, an acuity factor based on the NAF which takes extended foveation periods into account (Dell'Osso and Jacobs, 2002). However, velocity parameters may correlate more closely with high contrast visual acuity (Theodorou, 2006; Theodorou, 2009), and in the present study, velocity also improved in both treatment arms. There was also an improvement in amplitude which, although not correlating well with visual acuity (Bedell and Loshin, 1991), may play an important role in the psychosocial effects of nystagmus. Other measures of visual function, such as ‘time to see’ may be equally or even more relevant.

Whilst our study was not powered to detect significant changes in BCVA and waveform parameters, we observed a trend towards an improvement in visual function with CLs. This is in contrast to the recent randomized cross over trial⁹ which reported a reduction in BCVA with soft CL (although there was no significant difference in nystagmus parameters). Differences in contact lens type, and strict allowance for poor fit (only 5 degrees in this study), may have contributed to the different findings. Case reports and series reported improvements similar to the ones we report here (Abadi, 1979; Allen and Davies, 1983; Bagheri et al, 2017; Biousse et al, 2004; Dell’Osso et al, 1988; Enoch and Windsor, 1968; Golubovic et al, 1989; Rutner and Ciuffreda, 2005; Taibbi et al, 2008). A particularly interesting question for future trials is whether treatment effects may be greater in young children with INS, i.e. those in whom plasticity in the visual cortex is higher than in the adults included here. At least part of the visual deficit in INS is considered due to amblyopia (Feliuss and Muhanna, 2014; Fu et al, 2011).

Adverse events were rare, as expected in a small study. The incidence of CL-

associated keratitis is 2.44/10000 presumed, 1.8/10000 culture proven (Seal et al, 1999), and no case was observed here. One participant (1/27) completed the trial, but then abandoned CL wear due to recurrent exacerbation of allergic eye disease. Due to ocular surface changes, CL intolerance may be more common in patients with allergic eye problems.

The mechanism by which CL may improve visual function in INS, i.e. optical correction and/or proprioceptive mechanisms is not well understood. A full RCT is needed to determine whether CL which correct the refractive error are superior to plano CL plus glasses, although the results are suggestive of an additional proprioceptive mechanism. Previous studies on the effect of afferent stimulation of the trigeminal nerve have documented an immediate effect on INS (Dell'Osso et al, 1991; Sheth et al, 1995). In the present study, we chose a two-week follow-up to allow for optical adaptation, and assumed that any proprioceptive effect would be immediate. However, a later assessment at 4-6 months from baseline may allow the detection of desensitization, i.e. additional proprioceptive effects (Chen and Simpson, 2011).

Our data suggests a beneficial effect of CLs: visual acuity and nystagmus data suggests that it is the damping effect of the soft CL that improves visual function in people with nystagmus rather than superior refractive correction alone. This study provides preliminary evidence for the use of soft, even plano, CL in nystagmus.

However, a large randomised control trial is required to provide a safe evidence-based option for treatment in people of all ages, including children and women of childbearing age.

The study was designed primarily as a feasibility study and to estimate preliminary clinical parameters that would enable us to determine a sample size for a future study.

If we were to design a full RCT based on this study, a sample size of 58 patients (29 per group) would allow 90% power to detect an improvement of 0.1 LogMAR in distance VA (measured with both eyes open) between treatment arms, at the 5% significance level and assuming a 30% loss to follow-up. A pragmatic trial may also include participants with nystagmus types other than INS, as well as children.

Financial Support & Acknowledgements

This work was funded by the Nystagmus Network/Fight for Sight, Moorfields Eye Hospital Special Trustees and the National Institute for Health Research (NIHR) Biomedical Research Centre based at Moorfields Eye Hospital NHS Foundation Trust. The views expressed are those of the author(s) and not necessarily those of the funders, the NHS or the NIHR. The funding organizations had no role in the design or conduct of this research. No conflicting relationship exists for any author.

No conflict of interests exists for any author.

References

- Abadi RV. Visual performance with contact lenses and congenital idiopathic nystagmus. *British Journal of Physiological Optics*.1979;33:32-7.
- Abadi RV, Bjerre A. Motor and sensory characteristics of infantile nystagmus. *Br J Ophthalmol*. 2002; 86:1152–1160.
- Abadi RV, Carden D, Simpson J. A new treatment for congenital nystagmus. *British Journal Ophthalmology*. 1980; 64:2-6.
- Abadi RV, Dickinson CM. Waveform characteristics in congenital nystagmus. *Doc Ophthalmol*. 1986; 64:153–167.
- Allen ED, Davies PD. Role of contact lenses in the management of congenital nystagmus. *Br J Ophthalmol*. 1983; 67(12):834-6.
- Bagheri A, Abbasi H, Tavakoli M, Sheibanizadeh A, Kheiri B, Yazdani S. Effect of Rigid Gas Permeable Contact Lenses on Nystagmus and Visual Function in Hyperopic Patients with Infantile Nystagmus Syndrome. *Strabismus*. 2017;25(1):17-22.
- Bedell HE, Loshin DS. Interrelations between Measures of Visual Acuity and Parameters of Eye Movement in Congenital Nystagmus. *Investigative Ophthalmology & Visual Science*. 1991; 32(2): 416-421.
- Biousse V, Tusa RJ, Russell B, Azran MS, Das V, Schubert MS, et al. The use of contact lenses to treat visually symptomatic congenital nystagmus. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2004;75(2):314-6.
- Chen J, Simpson TL. A Role of Corneal Mechanical Adaptation in Contact Lens–Related Dry Eye Symptoms. *Cornea*. 2011; 52(3): 1200-5.
- Dell’Osso LF, Flynn JT, Daroff RB. Hereditary congenital nystagmus: an intrafamilial study. *Arch Ophthalmol*. 1974; 92:366–374.

Dell'Osso LF, Jacobs JB. An expanded nystagmus acuity function: intra- and intersubject prediction of best-corrected visual acuity. *Documenta Ophthalmologica*. 2002;104(3):249-76.

Dell'Osso LF, Leigh RJ, Daroff RB. Suppression of congenital nystagmus by cutaneous stimulation. *Neuro-ophthalmology*. 1991; 11: 173–175

Dell'Osso LF, Tracis S, Abel L, Erzurum SI. Contact lenses and congenital nystagmus. *Clinical Vision Sciences*. 1988; 3:229-32.

Enoch JM, Windsor CE. Remission of nystagmus following fitting contact lenses to an infant with aniridia. *American Journal of Ophthalmology*, 1968; 66(2):333-5.

Evans BJW, Evans BV, Jordahl-Moroz J, Nabee M. Randomised double masked placebo controlled trial of a treatment for congenital nystagmus. *Vision Research*. 1998; 38:2193-2202

Felius J, Muhanna ZA Visual Deprivation and Foveation Characteristics Both Underlie Visual Acuity Deficits in Idiopathic Infantile Nystagmus. *Investigative Ophthalmology & Visual Sciences*. 2013;54:3520-3525.

Fu VLN, Bilonick RA, Felius J et al. Visual acuity development of children with infantile nystagmus syndrome. *Investigative Ophthalmology & Visual Sciences*. 2011; 52:1404-11.

Golubovic S, Marjanovic S, Cvetkovic D, Manic S. The application of hard contact lenses in patients with congenital nystagmus. *Fortschritte der Ophthalmologie*. 1989; 86(5):535-9.

Hertle RW, Yang D, Adkinson T, Reed M. Topical brinzolamide (Azopt) versus placebo in the treatment of infantile nystagmus syndrome (INS). *Br J Ophthalmol*. 2015; 99(4):471-6.

Jayaramachandran P, Proudlock FA, Odedra N, Gottlob I, McLean RJ. A randomized

controlled trial comparing soft contact lens and rigid gas-permeable lens wearing in infantile nystagmus. *Ophthalmology*. 2014; 121(9):1827-36.

Liesegang TJ. Contact lens-related microbial keratitis: Part I: Epidemiology. *Cornea*. 1997; 16(2):125-31.

McLean R, Proudlock F, Thomas S, Degg C, Gottlob I. Congenital nystagmus: randomized, controlled, double-masked trial of memantine/gabapentin. *Ann Neurol*. 2007; 61(2):130-8.

Rutner D, Ciuffreda KJ. Soft contact lenses to improve motor and sensory function in congenital nystagmus: a case study. *Journal of Behavioral Optometry*. 2005;16(1):17-20

Saffran AB, Gambazzi Y. Congenital nystagmus: rebound phenomenon following removal of contact lenses. *British Journal Ophthalmology*. 1992; 76: 497-498.

Sarvananthan N, Surendran M, Roberts EO, Jain S, Thomas S, Shah N, et al. The prevalence of nystagmus: the Leicestershire nystagmus survey. *Investigative Ophthalmology & Visual Science*. 2009; 50(11):5201-6.

Seal DV, Kirkness CM, Bennett HG, Peterson M, Keratitis Study Group. Population-based cohort study of microbial keratitis in Scotland: incidence and features. *Contact Lens Anterior Eye*. 1999;22(2):49-57.

Shery T, Proudlock FA, Sarvananthan N, McLean R, Gottlob I. The effects of gabapentin and memantine in acquired and congenital nystagmus: a retrospective study. *Br J Ophthalmol*. 2006; 90(7): 839-43.

Sheth NV, Dell'Osso LF, Leigh RJ, Van Doren CL, Peckham HP. The effects of afferent stimulation on congenital nystagmus foveation periods. *Vision Research*. 1995; 35(16):2371-82.

Taibbi G, Wang ZI, Dell'Osso LF. Infantile nystagmus syndrome: Broadening the high-foveation-quality field with contact lenses. *Clinical Ophthalmology*. 2008;2(3):585-9

Theodorou M. Predicting visual acuity in early onset nystagmus. *Seminars in Ophthalmology*. 2006; 21 (2): 97-101.

Theodorou M. Nystagmus and Visual Acuity. PhD Thesis, Institute of Child Health, University College London. 2009.

Theodorou M, Clement RAC. Fixed point analysis of nystagmus. *Journal of Neuroscience Methods*. 2007; 161(1):134-41

Tkalcevic LA, Abel LA. The effects of increased visual task demand on foveation in congenital nystagmus. *Vision Res*. 2005;45:1139–1146.

Wagner H, Richdale K, Mitchell GL, Lam DY, Jansen ME, Kinoshita BT, Sorbara L, Chalmers RL; CLAY Study Group. Age, behavior, environment, and health factors in the soft contact lens risk survey. *Optom Vis Sci*. 2014; 91(3):252-61.

Wiggins D, Woodhouse JM, Margrain TH, Harris CM, Erichsen JT. Infantile nystagmus adapts to visual demand. *Invest Ophthalmol Vis Sci*. 2007; 48(5):2089-94.

Legends

Table 1: Inclusion and exclusion criteria for participants enrolled in study

Table 2: Baseline characteristics of all study participants including: age; sex; allocated group (0-plano, 1-corrective); Study Status (C-Complete, W-Withdrew, LTFU-Lost to Follow Up); Subjective Refraction; Previous Contact Lens Wear (N-No, Y-Yes); Previous treatment for nystagmus and/or strabismus.

Table 3. Baseline ocular characteristics of participants who completed the study, by randomised treatment. n-number, SD-standard deviation, IQR-Inter-Quartile Range. §-Missing data for one patient

Table 4. Comparison of visual acuity and nystagmus parameters pre-and post-treatment for each randomised treatment. Effect Estimate = Mean difference pre-post-treatment. CI- confidence interval, SD-standard deviation, n-number, NAFX-eXpanded Nystagmus Acuity Function. § - Missing data for one patient

Table 5. Comparison of visual acuity and nystagmus parameters by randomised treatment. SD = standard deviation. IQR = interquartile range. NAFX = eXpanded Nystagmus Acuity Function. Effect Estimate = Mean difference between the two treatments computed using ANCOVA (treatment effect adjusted for baseline values; reference group = Plain Contact lenses) . § -Missing data for one patient

Supplementary Table 6: Similarities and differences (in bold italic) between the current study and the recently published randomized crossover trial⁹

Figure 1: Flow of participants through study. FC = Fully Corrective contact lenses, Pl = Plano contact lenses.

Figure 2: Example of waveform recording recorded from subject 37 pre (A) and post

(B) contact lens wear. 5 second representative position profile shown in 15 degree right gaze (upper figure), straight ahead (middle) and 15 degree left gaze (lower figure). VA and waveform parameters in patients null (primary) shown. VA - LogMAR Visual Acuity with both eyes open; NAFX - eXpanded Nystagmus Acuity Function; MMV50 - Minimum Mean Velocity in a 50ms window; MMV100 -Minimum Mean Velocity in a 100ms window

Figure 1

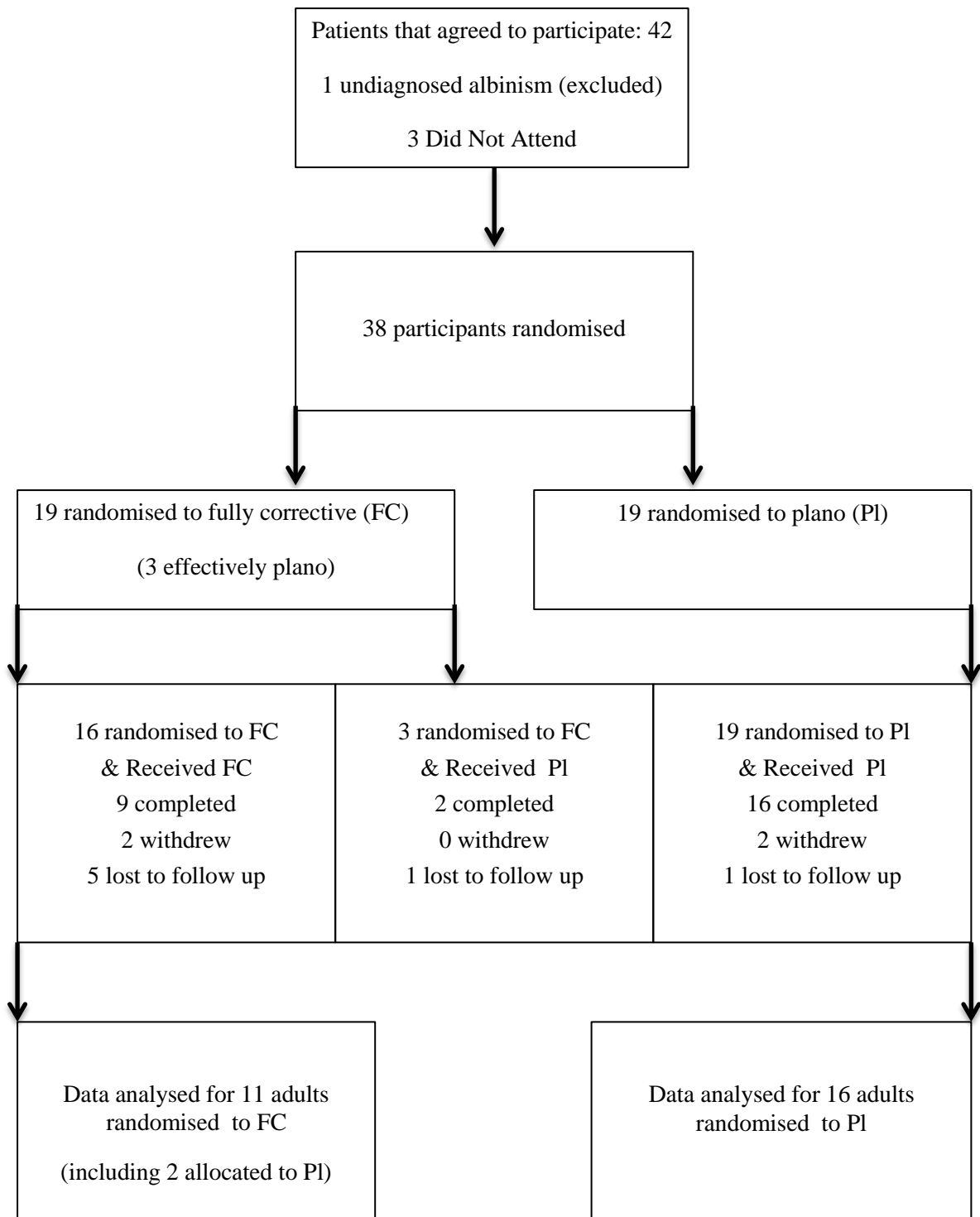


Figure 2

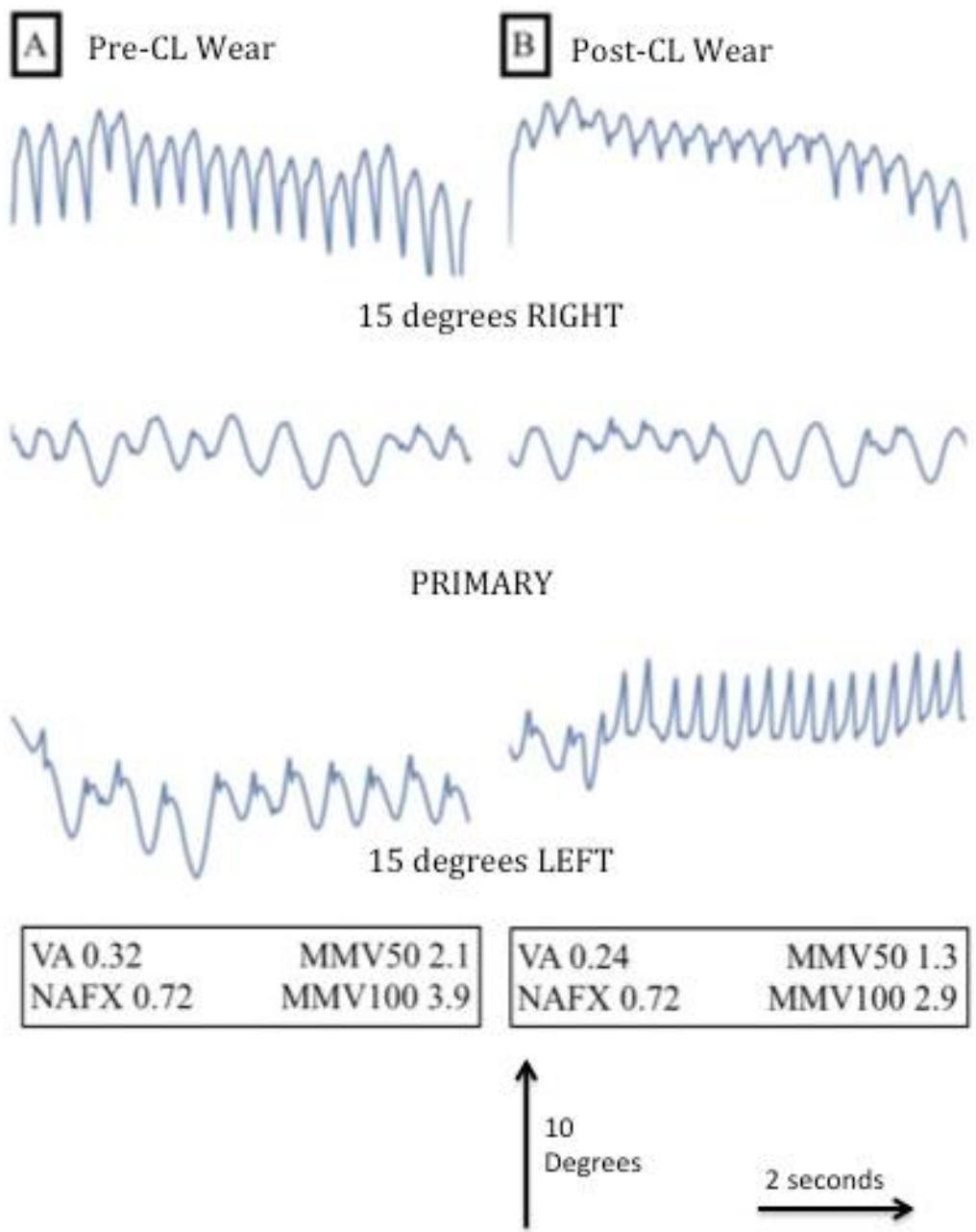


Table 1

Inclusion Criteria	Exclusion Criteria
Adults (aged 16 and above)	Children (under 16 years old)
Clinical diagnosis of INS without ocular/neurological co-morbidity	Nystagmus with other ocular/neurological co-morbidity
Able to give informed consent	Unable to give informed consent
Confirmation of waveforms consistent with INS (including those with a superimposed latent component).	Decelerating slow phase waveforms consistent with fusion maldevelopment nystagmus syndrome
	Periodic Alternating Nystagmus on prolonged eye movement recording (10mins)
	Any corneal pathology
	Unable to fit with contact lens
	Concurrent participation in other trials
	Imminent changes in neuroexcitatory or neuroinhibitory systemic medications during the trial duration,

Table 2

No	Age	Sex	Group	Status	DVA	Refraction R/L	Prev CL wear	Prev Treatment
1	18	M	0	W	0.6	-10/-2.5x30 -12.5/-2.25x15	N	Strabismus Surgery x1
2	29	M	0	C	0.56	+1/-3.5x180 +1/-3.5x180	Y	Nil
3	61	F	1	W	0.2	-0.75/-0.5x160 -1DS	Y	Nil
4	32	F	1	C	0.36	+6.5DS +7/-1x25	Y	Strabismus Surgeryx1
5	35	F	0	C	0.32	+1/-1x90 -1DS	N	Strabismus Surgeryx3
6	23	M	1	C	0.36	Plano plano	N	Nil
7	30	F	1	C	0.1	Plano Plano	N	Nil
8	50	M	0	C	0.36	+1.25/-1.5x7.5 +2/-2.5x167.5	N	Nil
9	42	M	1	LTFU	0.14	+0.5/-0.75x180 +2/-5x177.5	Y	Nil
10	34	M	0	C	0.6	+1.5/-3.25x180 +0.75/-1.75x155	Y	Nil
11	24	M	1	C	0.52	0.5/-1.5x165 plano	N	Nil
12	26	M	1	C	0.02	+4/-1x170 +6/-1x180	N	Nil
13	26	M	1	C	0.22	-1/-1x20 -0.5/-1x140	Y	Nil
14	52	F	0	C	0.44	-6/-1.5x25 -7/-1.5x80	Y	Nil
15	34	M	0	LTFU	0	Plano Plano	N	Multiple medications
16	40	M	1	C	0.54	-2.5/-2.5x100 -5.5/-1.5x150	Y	Strabismus Surgery x1
17	42	M	1	C	0.36	Plano/-0.25x35 +1.5/-2.5x145	N	Strabismus Surgery x1 Gabapentin
18	60	F	1	LTFU	0.76	-5.5/-2.5x5 -5.5/-1.5x175	N	Nil
19	30	M	0	C	0.2	Plano/-2x35 -0.50/-0.75x20	N	Nil
20	63	M	1	W	0.6	+1/-3x160 +1/-2x25	N	Nil
21	18	F	1	C	0.22	-6/-0.75x110 -5DS	N	Nil
22	27	M	1	LTFU	0.04	Plano Plano	Y	Strabismus Surgery x1
23	34	M	1	C	0.2	-6.5/-1.5x100 -6/-2.25x70	Y	Nil
24	32	M	1	C	0.12	+0.25/-2.75x110 plano/-3.25x7.5	Y	Gabapentin
25	41	M	0	C	0.42	-4.5/-4x160 -5.75/-2.50x180	Y	Nil
26	36	M	0	C	0.36	-5/-3x10 -7/-2.75x170	N	Nil

27	24	M	1	LTFU	0.68	+7/-4x170 +8/-4x17.5	N	Nil
28	33	F	0	C	0.52	-0.75/-1.5x145 plano/-2x35	N	Nil
29	26	F	1	C	0.48	-4.75/-1.25x25 -4.5/-2x170	N	Nil
30	26	M	1	C	0.46	+2/-4.25x25 +1.5/-3.5x170	Y	Baclofen
31	34	F	0	C	0.24	-0.5/-3x155 plano/-1.25x25	N	Nil
32	17	F	1	C	0.2	-2.75/-3x175 -3/-3.5x20	N	Nil
33	43	F	1	LTFU	0,1	Plano/-1.25x180 +0.50DS	N	Nil
34	20	F	1	C	0.22	-5/-3.75x170 -2.5/-5x180	Y	Nil
35	46	F	1	C	0.28	+3.5DS +5/-2x25	Y	Nil
36	16	M	1	LTFU	0.16	+2/-3x15 +2.25/-2.5x180	Y	Nil
37	64	M	0	C	0.32	-10.25/-0.50x20 -12.5/-0.75x160	Y	Nil
38	45	M	1	W	0.32	+2/-3.5x170 +1.75/-4x180	N	Nil

Table 3

	Plain CLs (n=16)	Fully corrective CLs (n=11)
Amblyopic Eye, n (%)	10 (62.5)	6 (54.6)
Distance Visual Acuity, Mean (SD)		
- Right Eye	0.45 (0.16)	0.32 (0.14)
- Left Eye	0.5 (0.21)	0.57 (0.49)
- Both Eyes	0.36 (0.14)	0.29 (0.16)
Near Visual Acuity, Mean (SD)		
- Both Eyes	6 (5, 8)	6 (5, 8) §
Spherical Equivalent, Mean (SD)		
- Right Eye	-2.2 (3.5)	0.8 (3.3)
- Left Eye	-2.6 (4.1) §	1.2 (3.8)
Cylinder, Mean (SD)		
- Right Eye	-2.2 (1.2)	-1.3 (1.4)
- Left Eye	-2.1 (1.3)	-1.4 (1.3)
Mean Amp, Mean (SD)	4 (1.6)	3.8 (2.7)
Foveation Time, Median (IQR)	0.0035 (0.001, 0.01)	0.012 (0.001, 0.018)
Position (standard foveation window), Mean (SD)	0.25 (0.08)	0.23 (0.05)
Velocity (standard foveation window), Mean (SD)	2.1 (0.2) §	2.1 (0.3)
Minimum mean position in a 50ms window, Mean (SD)	0.5 (1.1) §	0.2 (0.3)
Minimum mean position in a 100ms window, Mean (SD)	0.7 (1.1) §	0.4 (0.3)
Minimum mean velocity in a 50ms window, Mean (SD)	5.5 (6.9) §	5.2 (3.0)
Minimum mean velocity in a 100ms window, Mean (SD)	8.5 (8.2) §	7.6 (4.5)
NAFX, Mean (SD)	0.7 (0.08) §	0.7 (0.07)

Table 4

Pre-Post-treatment	Plain CLs Effect Estimate (95% CI) (N=16)	Fully corrective CLs Effect Estimate (95% CI) (N=11)
Distance VA		
- Right Eye	0.08 (0.04, 0.12) 0.07 (0.02, 0.11)	0.05 (-0.0002, 0.1) 0.03 (-0.02, 0.09)
- Left Eye	0.07 (0.03, 0.11)	0.06 (0.02, 0.1)
- Both Eyes		
Mean Amplitude	1.19 (0.43, 1.96)	0.85 (-0.24, 1.74)
Position (standard foveation window)	0.04 (-0.02, 0.1) §	-0.05 (-0.11, 0.01)
Velocity (standard foveation window)	0.03 (-0.16, 0.21) §	0.04 (-0.27, 0.35)
Minimum mean position in a 50ms window	0.44 (-0.16, 1.04) §	-0.06 (-0.34, 0.22)
Minimum mean position in a 100ms window	0.51 (-0.1, 1.11) §	-0.009 (-0.32, 0.3)
Minimum mean velocity in a 50ms window	1.38 (-2.93, 5.69) §	2.67 (0.88, 4.45)
Minimum mean position in a 100ms window	2.81 (-2.08, 7.71) §	3.41 (1.38, 5.43)
NAFX	-0.04 (-0.08, 0.005) §	-0.05 (-0.09, -0.003)

Table 5

Post-treatment	Plain contact lenses (N=16)	Fully corrective contact lenses (N=11)	Effect Estimate (95% CI)
Distance Visual Acuity, Mean (SD)			
- Right Eye	0.37 (0.14)	0.27 (0.18)	0.02 (-0.05, 0.09)
- Left Eye	0.44 (0.21)	0.54 (0.52)	0.03 (-0.04, 0.09)
- Both Eyes	0.29 (0.15)	0.23 (0.17)	0.01 (-0.05, 0.07)
Near Visual Acuity, Median (IQR)			
- Both Eyes	5.5 (5, 6)	5 (4.5, 8)	-
Mean Amp, Mean (SD)	2.8 (1.4)	2.9 (2.2)	0.27 (-0.75, 1.28)
Foveation Time, Median (IQR)	0.014 (0.004, 0.02)	0.01 (0.0013, 0.03)	-
Position (standard foveation window), Mean (SD)	0.22 (0.06) §	0.28 (0.08)	0.06 (0.004, 0.119)
Velocity (standard foveation window), Mean (SD)	2 (0.3) §	2.1 (0.4)	0.04 (-0.26, 0.33)
Minimum mean position in a 50ms window, Mean (SD)	0.1 (0.08) §	0.3 (0.3)	0.18 (0.02, 0.35)
Minimum mean position in a 100ms window, Mean (SD)	0.2 (0.1) §	0.4 (0.26)	0.19 (0.02, 0.36)
Minimum mean velocity in a 50ms window, Mean (SD)	4.1 (4.7) §	2.5 (1.0)	-1.6 (-4.6, 1.5)
Minimum mean velocity in a 100ms window, Mean (SD)	5.7 (5.2) §	4.2 (2.0)	-1.3 (-4.7, 2.1)
NAFX, Mean (SD)	0.8 (0.05) §	0.8 (0.07)	0.01 (-0.03, 0.05)

Supplementary Table 6

Similarities and differences (in bold italic) between the current study and the recently published randomized crossover trial⁷

	Current Study	Jayaramachandran et al ⁷
Study Type	Randomised <i>Control</i> Trial	Randomised <i>Crossover</i> Trial
Comparison	<i>1. Baseline(plano CL + spectacles)</i> <i>2. Fully corrective CL</i>	<i>1. Baseline (Spectacles)</i> <i>2. Fully corrective SCL</i> <i>3. Fully corrective RGP</i>
Inclusion criteria	Adult subjects (aged >16 years); Diagnosis idiopathic IN ; Confirmation of INS waveform (with/without latent component)	Adult subjects (aged >16 years); Diagnosis IN (idiopathic <i>or associated with albinism</i>); No simultaneous involvement in other trials.
Exclusion Criteria	Periodic alternating nystagmus;Any corneal pathology; Unable to fit with contact lenses; Waveforms consistent with a diagnosis of fusion maldevelopment nystagmus syndrome; concurrent participation in other trials	Periodic alternating nystagmus; Corneal trauma; Previous complications associated with contact lens wear.; Waveforms consistent with a diagnosis of fusion maldevelopment nystagmus syndrome
Randomisation	<i>Random permuted blocks of varying sizes in STATA statistical software.</i> Participants and investigator not masked to randomization.	<i>Computer generated stratified balanced (allocation ratio 1:1)randomization scheme with permuted block design.</i> Participants and investigator not masked to randomization.
Duration of treatment	2 weeks (+/- 3 days)	2-3 weeks
Contact lens type	Proclear soft (Coopervision Ltd)	Proclear soft (Coopervision Ltd) or <i>HydroCyl soft toric (Cantor and Nissel Ltd) & Quasar Aspheric RGPL (No & Contact Lens Ltd)</i>
Eye Movement Recordings	Eyelink Eyetracker, 500Hz. Horizontal stimuli 5deg apart, +/-15 degrees	Eyelink Eyetracker, 250Hz Horizontal stimuli 3deg apart, +/-30 degrees
Eye Movements Analysis	Analysis of randomly allocated file names to minimize bias. Dominant eye only analysed. <i>Calibration using best fit line to minimum mean position for primary and +/- 15 deg steps. Periodic waveform identified using period orbit analysis. All cycles within +/-12.5ms length selected.</i> Parameters analysed: amplitude, <i>foveation time, position (mean, min mean in 50/100ms window); velocity mean, min mean in 50/100ms window);</i> NAFX	Analysis of randomly allocated file names to minimize bias. Dominant eye only analysed. <i>Calibration using best fit line to mean position for each 3 deg step.</i> <i>Largest block of data without blinks (min 2 secs) analysed</i> Parameters analysed:amplitude, <i>frequency, intensity, NAFX, LFD (Longest Foveation Domain)</i>
Visual Outcomes	LogMAR BCVA (EDTRS optotypes), reading VA	LogMAR BCVA (EDTRS optotypes), reading VA <i>and critical print size</i>

Number randomised	38	24
Number completed study	27 (71%)	20 (83%)
Primary Outcomes	<i>Feasibility</i>	<i>Intensity</i>
Secondary Outcomes	VA & Various waveform parameters	VA & Various waveform parameters, tolerability
Results	High CL tolerability. <i>Good CL fit.</i> <i>Trend toward mean improvements in VA (not significant) and some nystagmus parameters.</i> Mean differences <1 LogMAR line <i>No differences between plano/corrective groups</i> <i>?suggestive of proprioceptive effect</i>	Tolerated well, <i>but misalignment with time?</i> <i>No significant differences for any nystagmus characteristic between groups. BCVA, reading and critical print size significantly worse for SCL.</i> Mean differences <1 LogMAR line.