

Objective Assessment of Visual Performance Using Optokinetic Nystagmus in Young Children

PROJECT CO-ORDINATING CENTRE

Auckland Bioengineering Institute (ABI)
UniServices House
Level 7, 70 Symonds Street
The University of Auckland
Auckland, New Zealand

Principal Investigator: Dr. Jason Turuwhenua

Project Co-ordinator: Dr. Lily Yu-Li Chang

STEERING GROUP COMMITTEE MEMBERS

Dr. Jason Turuwhenua

Auckland Bioengineering Institute (ABI)
Telephone: +64 9 373-7599 ext. 81742

A/Prof. Benjamin Thompson

University of Waterloo
200 University Avenue West
Waterloo, ON, Canada
Telephone: 519-888-4567 ext. 39398

Dr. Eileen E Birch

Retina Foundation of the Southwest
9600 North Central Expressway
Suite 200, Dallas, TX 75231, USA
Telephone: +1 214-363-3911

Dr. Shuan Dai

Eye Doctors, Auckland, NZ
Telephone: +64 9 520-9689

Dr. Christine Nearchou

The University of Melbourne
Parkville VIC 3010, Australia
Telephone: +61 390359899

Dr. Lily Yu-Li Chang

Auckland Bioengineering Institute (ABI)
Telephone: +64 9 373-7599 ext. 81689

STUDY CENTRES

Dr. Jason Turuwhenua

Dr. Peng Guo

Dr. Lily Yu-Li Chang

Dr. Shuan Dai

Eye Doctors (Ascot) in correspondence
to: Auckland Bioengineering Institute
70 Symonds Street
The University of Auckland
Auckland, New Zealand

Dr. Eileen Birch
Dr. Krista R Kelly

Retina Foundation of the Southwest
9600 North Central Expressway
Suite 200, Dallas, TX 75231, USA
+1 214-363-3911

Dr. Christine Nearchou

University of Melbourne Eye Care Clinic
2/800 Swanston St
University of Melbourne
VIC 3010

Dr. Ben Thompson

University of Waterloo
200 University Avenue West
Waterloo, ON, Canada

CO-ORDINATING CENTRE STAFF

The National Institute for Health Innovation
Tamaki Building 730
Level 4, Room 477
Tamaki Campus Gate 1, 261 Morrin Rd
Auckland, New Zealand
Telephone: +64 9 373-7599 ext. 82337

Lead Data Manager: Michelle Jenkins, m.jenkins@auckland.ac.nz

Senior Project Manager: Angela Wadham, a.wadham@auckland.ac.nz

Senior Biostatistician: Yannan Jiang, y.jiang@auckland.ac.nz

STUDY MANAGEMENT COMMITTEE MEMBERS

Dr. Jason Turuwhenua

Dr. Lily Yu-Li Chang

Dr. Peng Guo

Angela Wadham

Michelle Jenkins

Dr. Yannan Jiang

PROJECT SPONSORS

The University of Auckland is the Sponsor for 2 sites, Eye Doctors (Ascot) in New Zealand and the Retina Foundation of the Southwest in USA, with funding obtained from the Ministry of Business, Innovation and Employment and MedTech CoRE

Objective Acuity Limited is the Sponsor for 1 site at the University of Melbourne Eye Auckland, New Zealand

SOURCE OF STUDY DEVICE

The study device is designed by Dr. Jason Turuwhenua, and consists of multiple components: a stimulus display unit, infrared (IR) camera for optokinetic nystagmus (OKN) video recording, IR illumination, and a computer. Data collection will be done with a prototype device by Objective Acuity Ltd, a UniServices (University of Auckland) start-up company co-founded by Lead investigator, Dr. Jason Turuwhenua, and A/Prof. Ben Thompson.

SIGNATURES PAGE

This Agreement is executed by a duly authorised representative of each Party.

SIGNED BY THE PRINCIPAL INVESTIGATOR ON THIS _____ DAY OF _____ 2017

_____ Signature

Dr. Jason Turuwhenua, Ph.D
Principal Investigator
Auckland Bioengineering Institute (ABI)
University of Auckland

SIGNED BY THE CO-INVESTIGATORS ON THIS _____ DAY OF _____ 2017

_____ Signature

A/Prof. Benjamin Thompson, Ph.D.
Co-Investigator
University of Waterloo

Protocol Revision Chronology	Date	Type
Visual Function OKN Protocol Version 1	20 October 2016	Original
Visual Function OKN Protocol Version 2	06 March 2017	1 st amendment
Visual Function OKN Protocol Version 3	04 April 2017	2 nd amendment
Visual Function OKN Protocol Version 4	29 September 2017	3 rd amendment
Visual Function OKN Protocol Version 5 (draft)	14 November 2017	4 th amendment

TABLE OF CONTENTS

PROJECT CO-ORDINATING CENTRE	2
STEERING GROUP COMMITTEE MEMBERS.....	2
STUDY CENTRES.....	2
CO-ORDINATING CENTRE STAFF	3
STUDY MANAGEMENT COMMITTEE MEMBERS	3
PROJECT SPONSORS	3
SOURCE OF STUDY DEVICE	4
SIGNATURES PAGE	5
TABLE OF CONTENTS	6
1. OVERVIEW.....	8
2. BACKGROUND	8
3. RATIONALE FOR THE PRESENT STUDY.....	8
4. RELEVANCE TO HEALTH.....	9
5. STUDY GOALS AND OBJECTIVES	9
5.1 Primary Objective.....	10
5.2 Secondary Objectives.....	10
6. STUDY DESIGN.....	10
6.1 Eligibility Criteria.....	10
6.2 Sample Size	11
7. STUDY PLAN SCHEMATIC	13
8. RECRUITMENT.....	14
9. DATA COLLECTION	14
9.1 Registration and assessments	14
9.2 Schedule of visits and procedures	15
10. STATISTICAL CONSIDERATIONS	17
10.1 Sample Size.....	17
10.2 Statistical Analyses.....	18
10.2.1 Patient registration and demographics.....	18
10.2.2 Visual acuity and visual impairment	18
10.3 Data management.....	18
11. ETHICAL APPROVAL AND CONSENT.....	19
11.1 Ethics Committee	19
11.2 Informed Consent	19
11.3 Withdraw from participation	19
11.4 Incidental Findings.....	19

12.	CLINICAL DEVICE	19
13.	DISSEMINATION OF RESULTS.....	20
	13.1 Study registration	20
	13.2 Participants and public	20
	13.3 Academic/professional colleagues.....	20
	13.4 Health service funders and providers.....	20
	13.5 Iwi/ Maori	20
14.	ADMINISTRATIVE SECTION.....	21
	14.1 Adherence to the Protocol	21
	14.2 Protocol Revisions	21
	14.3 Data confidentiality and security	21
	14.4 Monitoring	21
	14.5 Reporting schedule.....	21
	14.6 Record retention policy	21
	14.7 Insurance	22
	14.8 Ownership and Management of the OKN dataset.....	22
	14.9 Publication policy.....	22
15.	REFERENCES.....	22
	Appendix 1 – Abbreviations	24
	Appendix 2 – Study Centre Investigator Signature Sheet	25
	Appendix 3 – Summary of Protocol Amendments	27

1. OVERVIEW

If eye problems occur in early childhood, they can affect the development of the brain areas that are responsible for sight and cause lifelong visual impairment. In addition, vision problems can affect the development of fine control over arm and hand movements and, in older children, impact on education. Many of the eye problems that affect young children can be treated effectively, however detecting these problems is challenging. Young children find it difficult to complete standard tests of vision because these tests require high levels of attention. Many tests also involve recognising shapes and letters and are therefore not suitable for young children.

To address this problem we are developing a new computer-based vision test suitable for use with children as young as 2-years old. The test is simple and easy to use; carefully designed moving patterns are shown to the child that causes a reflexive, involuntary movement of the eyes if the child is able to see the pattern. At the same time we record the movement of the eyes with a video camera attached to a computer and the software we are developing will identify whether the child is able to see the pattern or not. Finally, the visibility of the pattern will be varied to measure how well the child can see.

In this project, we will develop and perform clinical tests in ophthalmology and optometry clinics in New Zealand, the USA and Australia. The overall aim of this research is to produce a device that can be used to rapidly and accurately test visual acuity in young children to allow for the early detection and treatment of vision problems. The device will be appropriate for use in eye-care clinics and school screenings as well as settings such as community support services for children's health (e.g. Plunket rooms in NZ) and pre-schools.

2. BACKGROUND

Recent research by A/Prof. Ben Thompson and his colleagues conducted at the Auckland Super Clinic in South Auckland, found that only 33% of children referred for further assessment by the national B4 School screening program had a diagnosed vision problem (5572 screened, 698 referred, 230 diagnosed) (Langeslag-Smith, Vandal, Briane, Thompson, & Anstice, 2015). This high false-positive referral rate (67%) is due to difficulties in measuring vision in young children (in this case 4 year olds) and places a significant burden on paediatric ophthalmology services nationwide. False positive referrals are associated with significant health care costs and cause significant stress for families with young children. They are also the number one reasons cited by primary care health workers for not conducting vision screening. The objective vision testing system that we have developed has the potential to improve this situation.

3. RATIONALE FOR THE PRESENT STUDY

The earlier in life a vision problem can be detected, the better the treatment

outcomes for the child in terms of vision, educational performance, neurological development, motor function and quality of life. However, at present there are no reliable, objective and clinically usable tests available that allow for the measurement and detection of vision problems in young children, a particularly challenging group to measure. In this project, we will address this global problem by developing a low-cost, portable, clinically applicable device that assesses visual acuity by inducing and measuring an involuntary, reflexive eye movement known as optokinetic nystagmus (OKN). This eye movement only occurs when a moving target is visible. By using our device to automatically detect the presence, absence and direction of OKN, as young children freely view carefully designed drifting stimulus patterns; we will determine measures of visual acuity.

4. RELEVANCE TO HEALTH

Detection and subsequent treatment of vision problems in young children can prevent the development of amblyopia (“lazy eye”), a neurodevelopmental disorder of visual brain areas that often results in life-long visual impairment (Holmes & Clarke, 2006). Amblyopia affects visuo-motor development, reduces career options, disproportionately affects people from lower socioeconomic groups and almost doubles the lifetime risk of legal blindness (Wong, 2012). Amblyopia also has significant economic implications. For example, untreated amblyopia is associated with a US\$7.4 billion loss of GDP in the USA (Membreno, Brown, Brown, Sharma, & Beauchamp, 2002), which equates to a loss of approximately NZ\$110 million in New Zealand. The proposed research will benefit New Zealanders by helping to address the economic and social burdens caused by amblyopia.

More generally, the proposed research will also benefit commercially oriented, cross-disciplinary health care research in New Zealand. The study brings together multiple New Zealand institutions including the University of Auckland, the National Institute for Health Innovation, Callaghan Innovation and the Medical Technologies Centre for Research Excellence (MedTech CoRE). Furthermore, collaborations with leading international research institutes such as the Retina Foundation of the Southwest and the University of Waterloo (where A/P Thompson holds his primary appointment) will establish lasting collaborations that will increase capacity in New Zealand for optometry and ophthalmology oriented research. In addition, the development of an objective test of vision in young children will directly benefit paediatric ophthalmologists and optometrists who currently rely on tests that are often inaccurate and difficult to administer.

5. STUDY GOALS AND OBJECTIVES

The overall research goal is to develop and validate an OKN device (consisting of a stimulus display and eye tracking system) for the assessment of visual acuity in young children who are incapable of completing visual acuity testing using the gold-standard ATS-HOTV eye chart.

5.1 Primary Objective

To assess the sensitivity and specificity of the OKN device for detecting uncorrected monocular visual acuity impairment caused by strabismic amblyopia, anisometric amblyopia or refractive error in developmentally normal children from 3-6-years of age. The ATS-HOTV test delivered using the Electronic Visual Acuity (EVA) system will be used as the gold-standard comparison.

Uncorrected monocular visual acuity impairment will be defined using the ATS-HOTV test in the absence of refractive correction according to age-specific visual acuity cutoffs for vision screening provided by the American Association for Pediatric Ophthalmology and Strabismus (AAPOS, 2014): 36-47 months, >0.4 LogMAR; 48-59 months, >0.3 LogMAR; 60-83 months, >0.2 LogMAR.

5.2 Secondary Objectives

Testability of the OKN device (proportion of completed measurements vs. attempts) compared to the ATS-HOTV test. A complete measurement is defined as a visual acuity measurement at the age-appropriate cut-off LogMAR level for each eye separately.

To assess the specificity and sensitivity of OKN in the detection of impaired visual acuity for pre-specified subgroups, if sufficient number of children can be recruited for each category:

- Study sites (NZ vs USA vs Australia vs Canada)
- Age groups (36-47, 48-59, 60-83 months of age)
- Sex (Male, Female)
- Hyperopes vs. Myopes
- High astigmatism vs. low/no astigmatism
- Strabismic vs. non-strabismic

6. STUDY DESIGN

Multi-country cross sectional observational study, using OKN eye movement as a novel way of assessing visual acuity in children aged 3-6 years old compared to gold standard ATS-HOTV test.

6.1 Eligibility Criteria

Children will be eligible for *inclusion* if they meet the following criteria:

- Aged 3-6 years old (36-83 months at the time of registration)
- Have parent(s)/guardian(s) willing to provide informed consent
- Had paediatric eye examination, including cycloplegic refraction within the past 12 months (clinical scenario 1 in section 8) OR is a child for whom the parent consents to having a paediatric eye examination including cycloplegic refraction at the time of registration (clinical scenario 2 in section 8)

Potentially eligible children will be excluded if they have any of the criteria below:

- Infantile nystagmus syndrome
- Eye muscle surgery within the past 6 months
- Current eye disease
- Developmental delay (known or suspected)
- Systemic disease or syndrome

6.2 Stages of Study

Stage one: the study commenced recruitment on 6th March 2017, and eligibility criteria was as described above. We had a recruitment target of a total of 200 eligible children from the study centres. The OKN test consisted of a compulsory test (10 trials per eye, for both eyes), and an additional test (15 trials per eye, for both eyes) if child was able to maintain attention. This was described in section 9 of the study protocol version 3.0. The inclusion criteria stated that the child must have had a paediatric eye examination, including cycloplegic refraction within the past 6 months OR the parent consents to having a paediatric eye examination including cycloplegic refraction at the time of registration.

At the steering group meeting in June 2017, the need of an interim analysis was discussed and the steering group agreed that it would inform us of data quality, and design of the OKN test.

Interim analysis stage: interim analysis was conducted by Dr. Yannan Jiang and the data suggested the OKN test was too long for children to maintain attention. The data was therefore not of sufficient quality for calculating the study objectives. There had been 96 children registered in REDCap at this stage. Recruitment was therefore temporarily paused.

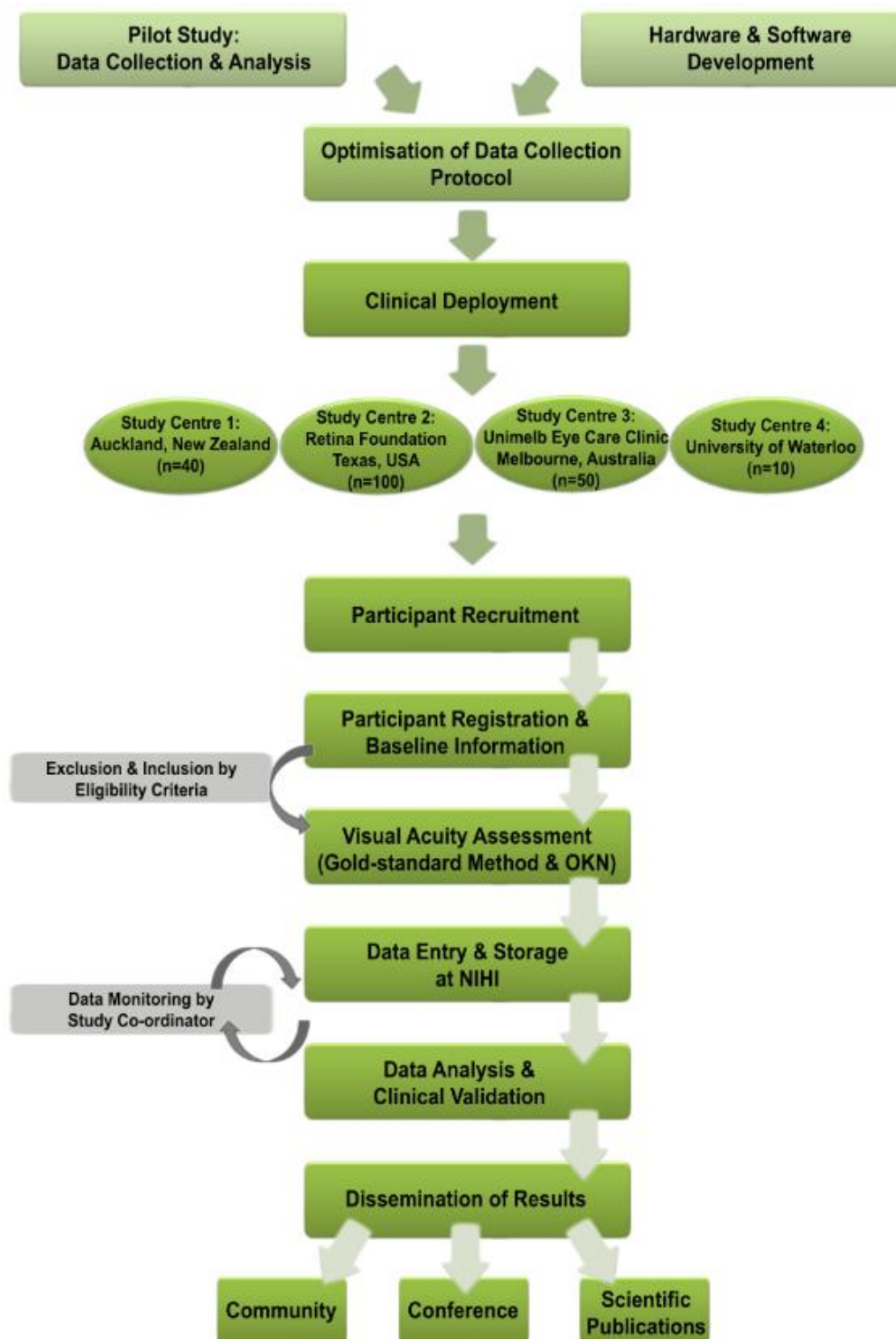
Pilot stage: the study team led by Dr. Jason Turuwhenua redesigned the OKN test and the steering group agreed on a shorted test on September 13th 2017 (described in section 9 below).

Stage two: the study will recommence recruitment, using the shortened study protocol and updated software for the OKN device. We will invite those children who participated in Stage one of the study to participate in Stage two. These children will be treated as new participants and therefore a new consent form will be signed by the parents/caregivers, and a new registration number will be assigned. The inclusion criteria now states that the child must have had a paediatric eye examination, including cycloplegic refraction within the past 12 months OR the parent consents to having a paediatric eye examination including cycloplegic refraction at the time of registration.

6.3 Sample Size

Up to 200 eligible children will be recruited to the study from the study sites for stage two of the study, to optimise the power of the study when calculating primary and secondary study objectives.

7. STUDY PLAN SCHEMATIC



*

*Eye Doctors (Ascot) and The University of Auckland Optometry clinic will be recruiting in parallel for the Auckland Study Centre.

*Target sample size for each study centre is provided as a guide – the overall target is 200 children across all sites.

8. RECRUITMENT

Participants aged 3-6 years old will be recruited by referral from pediatric ophthalmologists to Eye Doctors (Ascot), and Retina Foundation of the Southwest. The Auckland site will also recruit participants aged 3-6 years old from University of Auckland Optometry clinic. The University of Melbourne Eye Care Clinic site will recruit participants aged 3-6 years old from its Paediatrics and Binocular Vision Clinic.

If recruitment in Auckland, NZ based on clinical referrals does not provide a sufficient number of children with no strabismus, anisometropia, and significant refractive error*, recruitment of children from the community will commence. The study will be advertised at the University of Auckland and the University of Auckland clinics and information will be provided to the parents of children who attend routine eye examinations at the university of Auckland clinics. Siblings of study participants with a clinical referral will also be invited to participate. If recruitment at the Retina Foundation of the Southwest site is not providing sufficient numbers, the Retina Foundation of the Southwest will also begin screening onsite at a local paediatric ophthalmology clinic.

A recruitment monitoring report will be compiled by National Institute for Health Innovation (NIHI) once 50% of the target sample size has been reached to assess whether recruitment from the community, or through screening at local ophthalmology clinics is necessary.

*Anisometropia is defined as ≥ 1.00 D difference between eyes. Significant refractive error is defined as $> +3.00$ D hyperopia, > -1.00 D myopia.

Recruitment from study sites - there may be two clinical scenarios:

1. The participant is approached by a clinician, and enrolls into the study on the day of gold-standard paediatric eye examination by an ophthalmologist or optometrist. All measures will be completed on day 1-14 of the study (Table 2).
2. A potential participant is referred to the study by a paediatric ophthalmologist or optometrist who had conducted a gold-standard paediatric eye examination for the participant within the last 6 months (180 days). The participant is approached by the researcher at the local site for eligibility assessment, informed consent, and enrolment on day 1. Visual acuity by ATS-HOTV and OKN may be completed on day 1-14 (Table 3).

9. DATA COLLECTION

9.1 Registration and assessments

Children must meet the eligibility criteria, and their parent(s)/guardian(s) must give informed consent. Three clinical record forms (CRFs) will be used to collect registration/demographics information (Form A), gold-standard paediatric eye examination (Form B), and visual acuity by ATS-HOTV and OKN (Form C).

Form A - All participants will be assessed for their eligibility to participate, and have their registration and demographics information collected.

Form B - All participants will have a gold standard comprehensive medical eye examination with the paediatric ophthalmologist, including monocular visual acuity assessment, cover test, ocular motility, cycloplegic refraction, and ocular health assessment. The assessment will include age-appropriate binocular vision testing. Strabismus may be measured using the simultaneous prism cover test, modified Krimsky test or Hirschberg's test. Stereoacuity may be measured using the Randot preschool test or the Lang stereotest.

Form C – All participants will have monocular visual acuity (unaided, without refractive correction) measured and recorded by LogMAR, using the ATS-HOTV crowded test (EVA testing system) at standard viewing distance. OKN assessment will be conducted using the clinical device.

Form D – All participants' OKN eye movement videos will be analysed offline under the supervision of Dr. Jason Turuwhenua and Dr. Peng Guo (masked from information within Form B and C). Videos will be analysed by an automated image-analysis algorithm. The videos will also be analysed by a human observer. The presence or absence of OKN eye movement, the direction of OKN eye movement, and reasons that may inhibit post-analysis will be recorded.

9.2 Schedule of visits and procedures

On the day or within 14 days of enrollment into the study, a trained examiner will conduct 2 separate tests: 1) gold-standard, uncorrected, monocular visual acuity testing using the ATS-HOTV crowded test (EVA testing system) and 2) screening by OKN using the study device. Children will sit on their own or be seated on a parent's lap. The OKN device is placed 1.5 m from the child, and the lighting condition is as specified in the manual of procedures. An opaque eye patch is placed over the eye not being tested, and the child is encouraged to focus on the dots at the centre of the moving stimulus pattern.

Monocular unaided visual acuity of the child by ATS-HOTV and OKN are mandatory measurements for this study. **Please note that both ATS-HOTV and OKN must be done PRIOR to cycloplegia.**

Visual acuity screening by OKN will involve a minimum of two stimulus sizes being presented to each eye depending on the age of the child (Table 1), as a better visual acuity level (a smaller LogMAR) is expected in older children (AAPOS, 2014). General screening will be done at LogMAR 0.7 for all children. The expected visual acuity cut-off for children are LogMAR 0.4 for 36-47 months, 0.3 for 48-59 months, and 0.2 for 60-83 months (AAPOS, 2014). Children with visual acuity above these cut-off values are considered to have failed the screening test. The thickness of the strokes of the OKN stimulus were designed in accordance with the design of standard ETDRS visual

acuity (VA) chart (Bailey & Lovie, 1976). OKN results will be analysed offline using custom software.

Age of child	Stimulus size equivalent to LogMAR 0.7	Stimulus size equivalent to LogMAR 0.5	Stimulus size equivalent to LogMAR 0.4	Stimulus size equivalent to LogMAR 0.3	Stimulus size equivalent to LogMAR 0.2
36-47 months	✓		✓		
48-59 months	✓			✓	
60-83 months	✓				✓

Table 1. Stimulus sizes presented to children divided into 3 age groups. LogMAR levels tested are marked by a tick.

Measures	Study Visit 1 (day 1)	Study Visit 2 (day 1-14, rescheduled visit for those unable to do ATS-HOTV visual acuity at study visit 1)
1. Informed Consent	✓	
2. Demographics	✓	
3. Gold standard paediatric medical eye examination (including visual acuity, refraction, binocular vision, ocular health)	✓	
4. Diagnosis of child's visual impairment based on gold standard exam	✓	
5. Child's compliance with gold standard exam	✓	
6. Visual acuity assessment by OKN and ATS-HOTV	✓	✓

Table 2. Schedule of procedures for clinical scenario 1: OKN is done on the same day as gold standard paediatric medical eye examination.

Measures	Study Visit 1 (day -1 to -180 days)	Study Visit 2 (day 1)	Study Visit 2 (day 2-14, rescheduled visit for those unable to do ATS-HOTV visual acuity at study visit

			1)
1. Informed Consent		✓	
2. Demographics		✓	
3. Gold standard paediatric medical eye examination (including visual acuity, refraction, binocular vision, ocular health)	✓		
4. Diagnosis of child's visual impairment based on gold standard exam	✓		
5. Child's compliance with gold standard exam	✓		
6. Visual acuity assessment by ATS-HOTV and OKN		✓	✓

Table 3. Schedule of procedures for clinical scenario 2: OKN is done ≤ 6 months (180 days) from the date of gold standard paediatric medical eye examination.

If the child is unable to do ATS-HOTV test for visual acuity on day 1, he/she is to continue with OKN assessment, and may return for a rescheduled visit within 14 days to have both ATS-HOTV and OKN assessed. If ATS-HOTV cannot be completed at the rescheduled visit, or the child fails to attend the appointment, the OKN data collected at this visit will contribute towards testability calculations as described in section 5.2 and test-retest measures if sufficient data are available. If the child completes ATS-HOTV test on day 1, but OKN assessment could not be completed due to failure to attempt the test, or technical issues affecting the study device, he/she will be invited to return for a rescheduled visit within 14 days to have both ATS-HOTV and OKN assessed. Failure to complete OKN assessment at the rescheduled visit, or failure to attend the appointment will have the child's data contribute towards testability calculations in section 5.2. Children who do not complete both ATS-HOTV and OKN assessment at the same visit will not contribute towards sensitivity and specificity calculation in section 5.1.

Please note that both ATS-HOTV and OKN must be done PRIOR to cycloplegia.

10. STATISTICAL CONSIDERATIONS

10.1 Sample Size

200 children across all sites will be recruited and included for sensitivity and specificity calculation in section 5.1, if both ATS-HOTV and OKN can be completed at the same visit. This is based on the following rationale. A standard vanishing optotype chart (the Cardiff cards) in elderly patients who were also able to complete acuity testing on a Snellen chart as a gold standard reference, had a sensitivity of 92%, and a specificity of 91% for detecting reduced visual acuity (Johansen, White, & Waraisch, 2003). With an estimated prevalence of reduced visual acuity of 60%, a

total sample size of 200 will provide 120 children with a visual deficit and 80 children without, and will allow for sensitivity and specificity to be calculated with a precision (margin of error) of 0.05 for sensitivity and 0.06 for specificity.

10.2 Statistical Analyses

Statistical analysis will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.3 (R Foundation for Statistical Computing). All statistical tests will be two-sided at 5% significance level. The STROBE statement will be used as the guidelines for reporting observational studies.

10.2.1 Patient registration and demographics

Patient registration will be reported in STROBE flow diagram (Von Elm et al., 2007). Demographic information on all eligible participants and their families and households, will be summarised descriptively by study sites and overall. Continuous variables will be presented as the numbers observed and missing, mean and standard deviation, median and interquartile range. Categorical variables will be presented as frequencies and percentages.

10.2.2 Visual acuity and visual impairment

Visual acuity and other clinical measurements assessed by the gold-standard eye examination and OKN, will first be summarised descriptively by study sites and overall. Testability of the OKN device will be evaluated. For those measured by two methods, correlation and level of agreement will be estimated with 95% confidence intervals and two-sided p-values. Specificity and sensitivity of OKN in the detection of visual impairment will be calculated. Logistic regression will be used to evaluate the predictive effect of OKN assessment on visual acuity impairment, adjusting for important baseline demographics. The odds ratio and receiver operating characteristic (ROC) curves will be calculated. The analysis will also be conducted on children in pre-defined subgroups, with sufficient sample sizes.

10.3 Data management

Study forms will be used to collect individual participants' data at the scheduled visits. Data will be entered into a secure electronic database at NIHI and extracted to SAS for final analysis. Data quality checks will be carried out by the data manager and statistician prior to data lock. If data is collected from a child who is later found to be ineligible for this study, data will be retained and a separate analysis will be done by the researchers.

11.ETHICAL APPROVAL AND CONSENT

11.1 Ethics Committee

Ethical approval of the study protocol and protocol-related documents will be sought from the University of Auckland Human Participants Ethics Committee, UT Southwestern Medical Center Institutional Review Board, The University of Melbourne Human Ethics Advisory Group, and The Office of Research Ethics, University of Waterloo.

11.2 Informed Consent

As participants in this study will be under 7 years of age. Written informed consent will be obtained from their parents, guardians or caregivers by the investigator at the baseline visit or the responsibility can be designated to the research assistant.

11.3 Withdrawal from participation

Participants have the right to withdraw from the research at any time without giving a reason.

Participants have the right to withdraw their data from the research up to one month from the date of participation.

11.4 Incidental Findings

During this observational study incidental ocular conditions diagnosed will be managed by standard clinical procedures under the care of the participant's paediatric ophthalmologist.

12.CLINICAL DEVICE

The clinical device (otherwise referred to as the OKN device) is a prototype designed by Dr. Jason Turuwhenua, which consists of a computer, stimulus display unit, an IR video camera and background IR illumination.

Stimulus display unit - dynamic stimulus pattern designed to induce OKN are presented on a 24" inch monitor. At least two stimulus sizes as described in section 9 will be presented to each eye. There are 5 trials per stimulus size, and each trial is shown to the participant over 5 seconds during which the stimulus drifts leftwards or rightwards at a constant speed.

IR video camera – videos of participant's eyes and face are recorded for OKN analysis. The camera lens is positioned at the plane of the monitor, and the lens was set to capture the region of the face. Camera resolution was set to 640 × 480 pixels, at 30 Hz refresh rate. Appropriate IR lighting is used to provide optimal illumination of the participant's eyes to aid image analysis.

The recording of the video is synchronized to the presentation of the stimulus on the monitor using Matlab in the master computer.

13. DISSEMINATION OF RESULTS

13.1 Study registration

The study will be registered on the Australian New Zealand Clinical Trials Registry, which is a World Health Organization compliant public domain trials register.

13.2 Participants and public

At the end of the study, all participants will receive a letter of thanks for participating in the study, a brief summary of the study results and their significance, and any future research plans. The public will be informed of results via the news page on The University of Auckland School of Optometry & Vision Science Website, and the Auckland Bioengineering Institute website.

13.3 Academic/professional colleagues

The new knowledge generated by this research will be disseminated through peer-reviewed journal articles that will be made publically available through the University of Auckland's journal article repository. Descriptions of the research and research results will also be presented at national and international conferences.

13.4 Health service funders and providers

Descriptions of the research and research results will be posted on the applicant's University websites and will be communicated to eye-care professionals through articles in trade magazines such as NZ Optics and national and international conferences, such as the New Zealand National Eye Centre Seminars, and the MedTech CoRE conference.

13.5 Iwi/ Maori

The PI is an active member of the Māori community, serves as Associate Dean Māori at the Auckland Bioengineering Institute and is a member of the Interim Māori Working Party for the National Science Challenge 10. The PI has discussed Māori community involvement in the proposed research with Dr. Diana Siew (National Sector Manager – MedTech) who has an established relationship with Waipareira Trust Māori Health through their subsidiary Whānau Tahī Limited that is linked to Callaghan Innovation's Māori Health and Social Services team. Members of Whānau Tahī have expressed interest in participating in the proposed research by facilitating deployment of prototype OKN devices within the Māori community.

14.ADMINISTRATIVE SECTION

14.1 Adherence to the Protocol

Except for changes to eliminate an immediate hazard to participants, the approved protocol will be followed as specified. Any significant protocol deviation will be documented in the Study Log.

14.2 Protocol Revisions

All revisions will be discussed with, and approved by, the Steering Committee.

If the revision is a substantial amendment, the principal investigator will submit it to the appropriate Ethics Committee for their consideration.

14.3 Data confidentiality and security

Paper records will be stored in a locked file cabinet at study centres. Electronic data will be stored and backed-up on the NIHI servers. Only members of the project management team, study centres, and co-ordinating centre will have access to these records.

14.4 Monitoring

The project co-ordinator will oversee and monitor study conduct at each centre to ensure that the study protocol is being adhered to.

14.5 Reporting schedule

The principal investigator will provide annual reports of the progress, or completion, termination or discontinuation of the study to the UOA Ethics Committee and to the funder of this study.

14.6 Record retention policy

Essential documents including paper forms or electronic files (participant data and consent forms) will be retained for six years. Electronic data will be kept on a password protected UoA computer, backed up by a UoA server. Physical data will be kept in a locked cabinet in the office or the project co-ordinator. Research staff involved in the study at the study centres will not destroy any records associated with the study during the record retention period. After the record retention period, the data will be destroyed in a confidential manner (i.e. permanently delete electronic data from all computers and servers and shredding of physical data).

If the principal investigator or any co-investigators withdraw from the study (e.g. relocation, retirement), any records they hold will be transferred to a mutually agreed upon designee (e.g. another co-investigator). Notice of such transfer will be given in writing to Auckland Bioengineering Institute.

14.7 Insurance

New Zealand site (Eyedoctors, Ascot) – Participants in this study residing in New Zealand may be entitled to compensation from the Accident Compensation Corporation (ACC) for personal injury suffered as a result of treatment given as part of the study (section 32 (4) of the Injury, Prevention, Rehabilitation and Compensation Act 2001 and section 13 of the Injury, Prevention, Rehabilitation and Compensation Amendment Act (No 2) 2005).

Texas site (Retina Foundation of the Southwest) - There is a Professional Liability Insurance Policy for the Retina Foundation of the Southwest and its staff in the conduct of medical research.

Compensation for an injury resulting from participation in this research is not available from the University of Texas Southwestern Medical Center at Dallas or the Retina Foundation of the Southwest.

Melbourne site (University of Melbourne Eye Care Clinic) – The clinical trial is covered by The University of Melbourne Combined Liability insurance (Policy No: AUS16889313B/C).

14.8 Ownership and Management of the OKN dataset

- The OKN dataset is owned by Auckland UniServices Ltd.
- NIHI has responsibility for the storage, protection and analysis of study data.
- The Steering Committee has responsibility for the safe guardianship and use of the data.
- Individual study data remains the property of study participants.

14.9 Publication policy

Publications are encouraged from this study and will include appropriate acknowledgements and co-authorship of the personnel and funder(s) involved. Due to the prospective commercialisation of the OKN device and the license agreement between Objective Acuity Ltd (co-founders Dr. Jason Turuwhenua and A/Prof. Ben Thompson) and UniServices, University of Auckland, the proposed publication will be supplied to Objective Acuity Ltd and UniServices for review at least 30 days prior to its submission or presentation. The Reviewing Party may, within 30 days of such delivery, object to the Publication on the grounds that it would involve the disclosure of the Reviewing Party's confidential information, or because there is patentable subject matter in which the Reviewing Party has an interest which needs protection. Any commercially sensitive information will need to be removed, or delayed for publication for 90 days in order to permit the filing of patent applications. Publication of a dissertation/thesis may be subject to an embargo for a period of time to be agreed amongst the thesis author and study management team.

15. REFERENCES

- AAPOS. (2014, 2016). Vision Screening Recommendations: Techniques for Pediatric Vision Screening. Retrieved 05/10, 2016, from <https://aapos.org/terms/conditions/131>
- Bailey, I. L., & Lovie, J. E. (1976). New Design Principles for Visual Acuity Letter Charts*. *Optometry & Vision Science*, 53(11), 740-745.
- Holmes, J. M., & Clarke, M. P. (2006). Amblyopia. *The Lancet*, 367(9519), 1343-1351.
- Johansen, A., White, S., & Waraisch, P. (2003). Screening for visual impairment in older people: validation of the Cardiff Acuity Test. *Archives of gerontology and geriatrics*, 36(3), 289-293.
- Langeslag-Smith, M. A., Vandal, A. C., Briane, V., Thompson, B., & Anstice, N. S. (2015). Preschool children's vision screening in New Zealand: a retrospective evaluation of referral accuracy. *BMJ open*, 5(11), e009207.
- Membreno, J. H., Brown, M. M., Brown, G. C., Sharma, S., & Beauchamp, G. R. (2002). A cost-utility analysis of therapy for amblyopia. *Ophthalmology*, 109(12), 2265-2271.
- Von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., Vandenbroucke, J. P., & Initiative, S. (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Preventive medicine*, 45(4), 247-251.
- Wong, A. M. F. (2012). New concepts concerning the neural mechanisms of amblyopia and their clinical implications. *Canadian Journal of Ophthalmology/Journal Canadien d'Ophthalmologie*, 47(5), 399-409.

Appendix 1 – Abbreviations

ABI	Auckland Bioengineering Institute
ATS	Amblyopia Treatment Study
ETDRS	Early treatment of diabetic retinopathy study
EVA	Electronic visual acuity
IR	Infrared
MedTech CoRE	Medical Technology Centre of Research Excellence
NIHI	National Institute for Health Innovation
OKN	Optokinetic nystagmus
PI	Principal Investigator
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
UoA	University of Auckland
VA	Visual acuity

Appendix 2 – Study Centre Investigator Signature Sheet

By signing below, I confirm that I have received, read and understood the protocol Version 5, dated 14 November 2017, for the study titled “Objective assessment of visual performance using optokinetic nystagmus in young children”.

I agree to adhere to the current protocol except where necessary to protect the safety, rights, or welfare the participant.

I will conduct this clinical study according to Good Clinical Practice (ICH GCP) and local legal and regulatory requirements.

I will ensure that the OKN device supplied by the Objective Acuity Ltd, UniServices will be used only for administration to participants included in this study protocol and for no other purpose without written permission from the Principal Investigator.

If other personnel at my centre are involved in the study I will provide and discuss the protocol with them to ensure that they are fully informed about the OKN device and the study.

I understand that the protocol may be revised at any time and I undertake to ensure the most current version is adhered to at all times.

I understand that the study may be terminated or enrolment suspended at any time if it becomes necessary to protect the best interests of the study participants.

Investigator’s Name (print): Dr. Shuan Dai

Centre Name: Eye Doctors (Ascot Hospital)

Investigator’s Signature: _____

Date of Signature: _____

Study Centre Investigator Signature Sheet

By signing below, I confirm that I have received, read and understood the protocol Version 5, dated 14 November 2017, for the study titled "Objective assessment of visual performance using optokinetic nystagmus in young children".

I agree to adhere to the current protocol except where necessary to protect the safety, rights, or welfare the participant.

I will conduct this clinical study according to Good Clinical Practice (ICH GCP) and local legal and regulatory requirements.

I will ensure that the OKN device supplied by the Objective Acuity Ltd, UniServices will be used only for administration to participants included in this study protocol and for no other purpose without written permission from the Principal Investigator.

If other personnel at my centre are involved in the study I will provide and discuss the protocol with them to ensure that they are fully informed about the OKN device and the study.

I understand that the protocol may be revised at any time and I undertake to ensure the most current version is adhered to at all times.

I understand that the study may be terminated or enrolment suspended at any time if it becomes necessary to protect the best interests of the study participants.

Investigator's Name (print): Dr. Eileen Birch

Centre Name: Retina Foundation of the Southwest, Texas, USA

Investigator's Signature: _____

Date of Signature: _____

Study Centre Investigator Signature Sheet

By signing below, I confirm that I have received, read and understood the protocol Version 5, dated 14 November 2017, for the study titled "Objective assessment of visual performance using optokinetic nystagmus in young children".

I agree to adhere to the current protocol except where necessary to protect the safety, rights, or welfare the participant.

I will conduct this clinical study according to Good Clinical Practice (ICH GCP) and local legal and regulatory requirements.

I will ensure that the OKN device supplied by the Objective Acuity Ltd, UniServices will be used only for administration to participants included in this study protocol and for no other purpose without written permission from the Principal Investigator.

If other personnel at my centre are involved in the study I will provide and discuss the protocol with them to ensure that they are fully informed about the OKN device and the study.

I understand that the protocol may be revised at any time and I undertake to ensure the most current version is adhered to at all times.

I understand that the study may be terminated or enrolment suspended at any time if it becomes necessary to protect the best interests of the study participants.

Investigator's Name (print): Dr. Christine Nearchou

Centre Name: University of Melbourne Eye Care Clinic

Investigator's Signature: _____

Date of Signature: _____

Appendix 3 – Summary of Protocol Amendments

Page	Section heading	Amendment / (Reason)
1-28	Footer	<ul style="list-style-type: none"> Protocol Version 5.0 Dated 17 November 2017.
3	Study centres	<ul style="list-style-type: none"> University of Waterloo added as study centre 4.
10	Secondary objectives	<ul style="list-style-type: none"> University of Waterloo participants may be compared with other sites as part of secondary outcome analysis.
10	Eligibility criteria	<ul style="list-style-type: none"> Children who had paediatric eye examination, including cycloplegic refraction within the past 12 months are eligible to participate.
11	Study stage 2	<ul style="list-style-type: none"> We will invite those children who participated in Stage one to participate in Stage two. These children will be treated as new participants.
13	Schematic	<ul style="list-style-type: none"> University of Waterloo added as study centre 4.
17	Sample size	<ul style="list-style-type: none"> Change of wording that 200 children across all sites will be recruited.
19	Ethics	<ul style="list-style-type: none"> Local ethics approval will be sought from The Office of Research Ethics, University of Waterloo.