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Abstract

Paediatric visual impairment and blindness has emotional, social and economic impacts for the individual, their family, and the wider community. Causes of visual impairment in children are multifarious and include prematurity, structural abnormalities, inherited conditions, infective diseases, and nutritional deficiencies. A large number of paediatric ocular conditions are avoidable, being either preventable or treatable. Thus, early detection through screening programs and accurate assessment is essential to improve long term outcomes for children through timely management and treatment.

Retinopathy of prematurity (ROP) is a disease that affects low birth weight and extremely premature infants. Screening to detect ROP which requires treatment is recommended for all at-risk infants by the World Health Organization. However, worldwide the numbers of infants at-risk of ROP is increasing and the number of ophthalmologists willing to screen is decreasing. The development of wide-field digital imaging (WFDI) as a potential alternative for ROP screening may alleviate the current workflow challenge. The Auckland Regional Telemedicine ROP network (ART-ROP) is one of the first programs worldwide to exclusively use WFDI to detect and manage ROP. A large review of all infants screened by ART-ROP between 2006 and 2015 was undertaken revealing no infant with treatment-requiring ROP was missed by this screening method. A cohort of these children were prospectively recruited to further assess the efficacy of ART-ROP by evaluating long term ophthalmic structural and visual outcomes of children who were previously screened for ROP in our telemedicine system. No new cases of ROP-related retinal changes were detected indicating the safety and reliability of ART-ROP screening. Of note, no visual difference was noted between premature children with and without a history of ROP.

With the efficacy of WFDI established in premature infants, the potential of it being used as a screening method for all infants was investigated. Universal newborn eye screening (UNES) utilised WFDI of the anterior and posterior eye to detect the prevalence of congenital ocular abnormalities including birth-related retinal haemorrhages in a prospective cohort of newborns. Importantly, ocular abnormalities were detected in a significant number of infants. Retinal haemorrhages were the most common with 94% of these resolved by six-week follow up examination. However, the impact of retinal haemorrhages, in particular those that are long-standing or that affect the macula, are unknown. Other
key observations included congenital cataract, optic nerve hypoplasia, and other retinal lesions, indicating that UNES with WFDI is a successful screening tool for detecting congenital ocular abnormalities.

A paediatric visual field screening technique called the Saccadic Vector Optokinetic Perimeter (SVOP) has been recently developed for young children or those with neuro-disabilities. SVOP utilises infra-red eye tracking to potentially overcome some of the challenges with current paediatric visual field techniques such as Goldmann perimetry or the confrontation method. The clinical applicability of SVOP was evaluated in children with both normal and impaired vision. The majority of children were able to complete SVOP, with good agreement observed between SVOP, Goldmann, and the confrontation visual field method in children with normal vision. SVOP was also significantly faster to perform. Therefore, SVOP is a potential screening tool for visual fields in children who are unable to perform standard techniques due to neuro-disabilities, complex needs, or mobility issues.

The field of paediatric visual impairment is extensive but extremely important. The inter-related research studies contained within this PhD thesis aim to improve screening and assessment techniques of newborns, both premature and full-term, and children. Improvements and novel developments in these areas, as identified in this thesis, may help to eliminate the significant burden of avoidable visual impairment in the paediatric population.
Acknowledgements

A thesis is not a lone pursuit and it is only through the great support I have had both professionally and personally that this work has reached completion. There are many people that deserve thanks, and I would like to take this opportunity and honour all who made this achievement possible, there is not space to thank everyone individually but there are a few people I would like to specifically mention.

Firstly I am indebted to my outstanding supervisory team; Professor Charles McGhee, Dr Shuan Dai, and Dr Stuti Misra. They have all been there from conception to completion, and all the experiences in between. Their invaluable input has shaped my thesis, my career, and my future. I am blessed to have such incredible mentors, and now friends, in these three individuals.

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<tr>
<td>ADHB</td>
<td>Auckland District Health Board</td>
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<tr>
<td>AP-ROP</td>
<td>Aggressive posterior retinopathy of prematurity</td>
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<tr>
<td>ART-ROP</td>
<td>Auckland Regional Telemedicine Retinopathy Of Prematurity screening network</td>
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<tr>
<td>BIO</td>
<td>Binocular indirect ophthalmoscopy</td>
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<tr>
<td>BLENNZ</td>
<td>Blind and Low Vision Education Network New Zealand</td>
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<td>BW</td>
<td>Birth weight</td>
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<td>CHRPE</td>
<td>Congenital hypertrophy of the retinal pigment epithelium</td>
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<td>CMDHB</td>
<td>Counties Manukau District Health Board</td>
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<tr>
<td>CVI</td>
<td>Cerebral visual impairment</td>
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<tr>
<td>DS</td>
<td>Dioptrre sphere</td>
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<tr>
<td>ETROP</td>
<td>Early treatment for retinopathy of prematurity</td>
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<td>GA</td>
<td>Gestational age</td>
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<tr>
<td>HVFA</td>
<td>Humphrey visual field analyser</td>
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<tr>
<td>ICROP</td>
<td>International classification of retinopathy of prematurity</td>
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<tr>
<td>IOP</td>
<td>Intra-ocular pressure</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>NICU</td>
<td>Neonatal intensive care unit</td>
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<td>PMA</td>
<td>Post menstrual age</td>
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<td>ROP</td>
<td>Retinopathy of prematurity</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SITA</td>
<td>Swedish interactive thresholding algorithm</td>
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<td>SVOP</td>
<td>Saccadic vector optokinetic perimeter</td>
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<td>UNES</td>
<td>Universal Newborn Eye Screening</td>
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<tr>
<td>WDHB</td>
<td>Waitemata District Health Board</td>
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<td>WFDI</td>
<td>Wide-field digital imaging</td>
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## Co-Authorship Form

This form is to accompany the submission of any PhD that contains published or unpublished co-authored work. **Please include one copy of this form for each co-authored work.** Completed forms should be included in all copies of your thesis submitted for examination and library deposit (including digital deposit), following your thesis Acknowledgements. Co-authored works may be included in a thesis if the candidate has written all or the majority of the text and had their contribution confirmed by all co-authors as not less than 65%.

Please indicate the chapter/section/subjects of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work.

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The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate’s contribution to this work, and the nature of the contribution of each of the co-authors; and
- that the candidate wrote all or the majority of the text.

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Chapter 1:

Normal development and common pathologies of the newborn and paediatric eye
1.1 Introduction

Prevention of childhood visual impairment is of international significance with the World Health Organization naming it as one of the priorities of the VISION 2020 – The Right to Sight initiative. There are numerous causes of childhood visual impairment, both congenital and acquired, with vast regional variations.\(^1\)\(^2\) Regardless of the cause of visual impairment the associated emotional, social and economic costs are profound and life-long, affecting the individual, their family, and the wider community. Many of the causes of visual impairment are preventable or treatable, thus are deemed avoidable by the World Health Organization.\(^1\)

The visual system begins developing in the third week post-conception. By birth, the visual system is still immature and continues to develop throughout childhood. Clear visual input in infancy is essential for normal visual development with any interruption to this process potentially causing permanent visual loss unless timely diagnosis and treatment is instigated.\(^1\)\(^2\)

1.2 Normal eye development

1.2.1 Embryology

The ocular structures are formed from ectoderm and mesenchyme with one tissue inducing the next to form the complexity which is the eye. In the third week post conception the first glimpse of the future eyes can be detected as subtle indentations on the widest aspect of the neural fold, known as the optic sulci.\(^3\) The optic sulci evaginate to form optic pits,\(^4\) which continue to deepen with the distal end dilating to form the optic vesicle, whilst the proximal portion constricts to form the optic stalk, Figure 1-1.\(^3\) The optic vesicles sink in upon themselves to form a double layered optic cup, which inferiorly remains open as the choroidal fissure, accepting migrating mesenchyme and the hyaloid artery (Figure 1-1).\(^4\)\(^5\) Embryonic ocular vascularisation is complex with progressing and regressing supplies to mirror the development of the eye.\(^3\) By four weeks post conception individual structural components of the eye are beginning to form.\(^3\) Figure 1-2 details the structures of the developed eye, these structures and their relevant development will be described below.
Figure 1-1- The early embryological development of the eye. Reproduced with permission from Clinical Anatomy of the Eye (1998) Wiley and Sons Inc.⁴

Figure 1-2 - Gross anatomy of the eye
1.2.2 Ocular adnexa

The most anterior aspect of the eye, are the eyelids which protect the eye and assist with tear distribution on the anterior surface (Figure 1-3).\textsuperscript{6} The eyelids are formed by surface ectoderm that grows towards the centre of the eye where they fuse at approximately three months of intra-uterine development, they remain so until the fifth month.\textsuperscript{4} The separation results in the intra-palpebral fissure between the upper and lower eye lid, through which the eye can be visualised, see Figure 1-3.\textsuperscript{6}

![Figure 1-3 - Anterior structures of the eye including eyelids, cornea, iris, conjunctiva, and sclera. White arrow indicates intra-palpebral fissure.](image)

1.2.3 Cornea

The cornea comprises the anterior one-sixth of the eye and is optically transparent and avascular, see Figure 1-2.\textsuperscript{7,8} The cornea originates from surface ectoderm and neural crest cells, and is one of the final processes in eye development.\textsuperscript{4} The three corneal layers, epithelium, stroma, and endothelium,
are present in their elementary form by five to six weeks gestation. The underlying endothelium controls the hydration of the cornea, maintaining the clear, transparent media, which is the main refractive component of the eye. The clear cornea allows more posterior ocular structures, such as the iris, to be visualised directly (Figure 1-3).

1.2.4 Conjunctiva and sclera

The remaining five-sixths of the eye are comprised of the tough, fibrous sclera which protects the eyeball. The sclera is formed from condensed mesenchyme. The sclera can be visualised anteriorly through the clear conjunctiva, see Figure 1-3. The conjunctiva is a thin mucus membrane divided into two main portions, the palpebral covering the internal aspect of the eye lids, and the bulbar conjunctiva which overlies the anterior surface of the eyeball except for the cornea. Goblet cells in the conjunctiva secrete mucus to maintain the moisture of the ocular surface.

1.2.5 Uvea

Inside the protective fibrous layer of the eye is the uveal tract, derived from mesenchyme. The uvea is the vascular and pigmented layer of the eye consisting of the iris, ciliary body, and choroid (Figure 1-2). The choroid nourishes the overlying outer retinal layers and absorbs excess light. The ciliary body's primary roles are the suspension of the lens within the anterior chamber and the production of aqueous humour that fills the anterior chamber. The iris is the most anterior uveal component and is formed from mesenchyme and ectoderm. It can be visualised through the transparent cornea as displayed in Figure 1-3 and is anterior to the lens. The iris creates the aperture of the eye's optical system, the pupil, with the muscles of the iris, the dilator pupillae and the sphincter pupillae, dilating and constricting the pupil in response to light. The pupil can also be pharmacologically dilated or constricted by the use of pharmacological agents when required for examination or surgery.

1.2.6 Lens development

The crystalline lens is a clear, avascular, biconvex structure located posterior to the iris (Figure 1-2). It is responsible for approximately one third of the power of the adult eye. The lens develops from
surface ectoderm which overlies the optic cup, this thickens becoming the lens placode, which invaginates to form the lens vesicle (Figure 1-1). The lens vesicle then detaches from the surface ectoderm to sit within the optic cup. The transient hyaloid artery branches from the primitive dorsal ophthalmic artery and forms the tunica vasculosa lentis which surrounds the lens, allowing its rapid growth in utero. Meaning that by birth the lens has an equatorial diameter of 6.5mm about two thirds that of an adult. In the first two to three decades of life the lens reaches its maximum diameter of 9 to 10mm, however the lens depth will continue to thicken throughout life.

The lens sits in a capsule that is attached to the surrounding ciliary muscle by suspensory ligaments called zonules. The zonules tighten or loosen to either flatten or steepen the lens, this process is known as accommodation. When the lens accommodates the dioptic power changes allowing the eye to focus near or distant objects.

1.2.7 Vitreous

The optic cup and the lens are separated by the primary vitreous body. The secondary vitreous develops between the primary vitreous and the retina and is a complex structure comprised of collagen fibres, extracellular matrix, and other substances. The vitreous fills the large vitreous cavity that comprises four fifths of the globe (Figure 1-2) and is essential for metabolism in the eye. An S-shaped channel remains in the vitreous from the regression of the hyaloid artery during development. In some individuals remnants of the hyaloid artery remain after birth, known as persistent foetal vasculature.

1.2.8 Retinal development

The retina is a multi-layered neurosensory tissue, comprised of neural, glial and vascular components. The double layered optic cup is the precursor for the inner sensory retina and the outer retinal pigmented epithelium. In the second month of gestation, differentiation of retinal cells begins at the optic nerve head, migrating peripherally. Retinal vessels mimic this pattern of development with spindle-shaped cells stemming from the optic nerve at 14 to 15 weeks gestation.

Retinal vessel development is initially by vasculo-genesis to form the primordial vessels of the central inner plexus. Angiogenesis is then responsible for the remaining vascularisation of the retina including
outer plexus and periphery. The timing of angiogenesis across the retina is in concordance with physiological induced hypoxia, for example the foveal area is vascularised coincident to eyelid opening and the first visually evoked potential. The intricacies of the retina including the photoreceptor cells continue developing into the seventh month of gestation, whilst full retinal vascularisation is not achieved until 37 to 38 weeks gestation.

In the case of preterm delivery the retina is not completely differentiated or vascularised, which can lead to subsequent visual impairment or the development of retinopathy of prematurity. The fundus, which includes the retina, optic nerve head and macula, can be visualised through retinal photography or ophthalmoscopy. A healthy newborn fundus with full retinal vascularisation and differentiation is illustrated in Figure 1-4.
1.2.9 Ocular growth

At birth neonatal eyes have a mean axial length of 17.3mm,\textsuperscript{13} reaching 24mm by adulthood. Not only does the eye grow in size but also in visual capability. The macula is histologically immature at birth with the foveal pit continuing to develop with maturation occurring between 15 to 45 months of age, whilst optic nerve myelination is occurring until two years of age.\textsuperscript{14} Visual acuity increases concurrently with these developments. A newborn infant has acuity of approximately 6/240, reaching 6/18 by 6 months of age, continuing to improve until adult acuity is attained.\textsuperscript{14} Normative visual experience is essential for this visual maturation to occur, failure of this can lead to amblyopia. Amblyopia is treatable within the visually sensitive period in the first 7 to 8 years of life, after which it is associated with permanent visual morbidity and impairment. Therefore, early detection and treatment is paramount in paediatric ocular disorders.

1.3 Neonatal and infant ocular pathology

Visual impairment in children varies across the globe with regional disparities due to ocular disease rates, nutrition, and health resource availability.\textsuperscript{1, 2, 15} Worldwide the leading causes of childhood blindness and severe visual impairment include corneal scarring, retinal disorders, cataract, and cerebral visual impairment.\textsuperscript{1, 2} Corneal scarring is uncommon in developed nations like New Zealand due to the underlying causes such as vitamin A deficiency, measles, and ophthalmia neonatorum being uncommon or appropriately treated.\textsuperscript{1} Thus, in high income countries, such as New Zealand, the leading causes of childhood visual impairment or blindness are: cerebral visual impairment, retinopathy of prematurity (ROP), retinal dystrophies, optic nerve atrophy, and optic nerve hypoplasia.\textsuperscript{2}

Early detection of ocular abnormalities in the neonatal period may result in improved long term outcomes with timely management and treatment. Ocular abnormalities that potentially may be detected include: congenital cataract, retinoblastoma, optic nerve hypoplasia and ROP.

1.3.1 Congenital Cataract

Congenital cataract, an opacification of the lens, is an avoidable cause of childhood blindness affecting approximately 1-4/10,000 children in developed nations.\textsuperscript{1, 16} Congenital cataracts have many underlying
causes including hereditary, chromosomal, systemic or metabolic abnormality, or intrauterine infection. Inherited cases are generally autosomal dominant, but X-linked and autosomal recessive cases have also been reported.

Visual impairment as a result of cataract can be minimised with early surgical intervention and appropriate post-surgical visual rehabilitation. Current recommendations indicate surgery should occur in the first six weeks of life, to prevent potentially irreversible amblyopia. The key aspect of managing congenital cataract is timely detection to allow appropriate treatment and prevent unnecessary visual impairment.

1.3.2 Retinoblastoma

Retinoblastoma is the most common malignant ocular tumour occurring in childhood, with an incidence of approximately 1 in 18,000 live births. Retinoblastoma initiates in embryonic retinal cells and normally occurs prior to the age of four. With early diagnosis and modern treatments, these ocular tumours can be very successfully treated and have survival rates of more than 95%. However, in cases where retinoblastoma is detected late, or not at all, mortality rates can be as high as 70%, indicating that early detection is essential to save lives.

1.3.3 Optic nerve hypoplasia

Optic nerve hypoplasia is a congenital and non-progressive disease characterised by an under-development of the optic nerve head in one or both eyes, see Figure 1-5.

The aetiology of optic nerve hypoplasia is unknown, however it has been associated with primiparity, young maternal age, and recreational drug and alcohol use. Optic nerve hypoplasia has a prevalence of 1 in 10,000 children under the age of 14 years, making it a leading ocular cause of childhood blindness and visual impairment in both Europe, the United States, and New Zealand. Cerebral midline structure abnormalities and associated pituitary axis hormone deficiencies are associated with optic nerve hypoplasia. There is currently no ophthalmic treatment for optic nerve hypoplasia, however, early detection and management of the associated systemic abnormalities may prevent growth and developmental delay in these children.
1.3.4 Retinopathy of prematurity

Retinopathy of prematurity (ROP) is a multifactorial, proliferative vascular disorder that affects the retinæ of preterm infants with low-birth weight. In 2010, an estimated 20,000 preterm infants worldwide were severely visually impaired or blind from ROP and a further 12,300 had some form of visual impairment. In New Zealand approximately 15/10,000 infants born at 31 weeks gestation or less are affected by ROP-related visual impairment. Incidence and severity of ROP increases with decreasing birth weight and gestational age. Retino-vascular immaturity in premature infants indicates possible ROP development, yet progression of ROP is dependent not only on development stage of the infant but also systemic and local factors. In New Zealand, children born less than 1250g, or those less than 31 weeks gestational age, undergo routine retinal screening examinations for ROP during their neonatal period due to their increased risk of developing visual threatening ROP. Many cases of ROP resolve spontaneously, but those which do not resolve may progress to full traction retinal detachment and complete blindness. Therefore, careful screening and monitoring of all at-risk infants is required to ensure timely detection of ROP that warrants treatment.
History of ROP

The history of ROP in terms of detection and treatment is linked closely to the development of neonatal intensive care units (NICUs). The survival rate of premature infants dramatically increased in industrialised countries in the 1940s and 1950s in parallel with improved neonatal care and use of unmonitored supplemental oxygen. This resulted in the ‘first epidemic’ of ROP due to unmonitored supplemental oxygen - a key risk factor for ROP development - infants affected had low mean birth weights of 1350-1370 grams. ROP was known at the time as retro-lental fibroplasia, and was observed as a membrane on the posterior surface of the lens obscuring the retina in premature infants, in fact this is a description of total retinal detachment due to ROP.

Improvements in neonatal intensive care in the 1960s and 1970s led to increased survival rates of lower gestational age and smaller birth weight infants. Despite the development of oxygen monitoring, a ‘second epidemic’ of ROP affecting the extremely premature and low birth weight infants occurred. This second epidemic is ongoing in developed countries, like New Zealand, with the affected infants having extremely low birth weight averages of 737 to 763g and average gestational age of 25.3 to 25.6 weeks (significantly lower than the first epidemic).

ROP rates are dependent on neonatal care and thus, are region and country dependent. Low income countries have the lowest occurrence of ROP due to high premature infant mortality rates. In comparison, ROP is only seen in very low birth weight or very low gestational age infants in industrialised countries, like New Zealand. The largest burden of ROP disease occurs in middle income countries, including India, Latin America, and Eastern Europe, where the ‘third epidemic’ is occurring due to improved premature infant survival rate. Middle income countries have high rates of preterm birth, highly variable neonatal care, and non-uniform ROP screening and treatment programs. The combination of these factors has resulted in a combination of characteristics of the first two epidemics, with a large demographic of infants affected and consequently an increased rate of visual impairment from ROP.
Management of ROP

The World Health Organization lists ROP as an avoidable cause of blindness in its Vision 2020: ‘The Right to Sight’ initiative, due to high efficacy treatment in the form of peripheral retinal ablation therapy.\textsuperscript{1, 38-41} Screening for ROP is recommended for all premature infants deemed to be at risk of developing the condition, as this allows timely detection and administration of treatment.\textsuperscript{1} Screening for ROP is discussed in depth in Chapter 2.

Treatment of ROP has evolved over the last two decades with the development of cryotherapy and then laser ablation therapy as treatment modalities. Cryotherapy was introduced in New Zealand in 1987, halving the rate of blindness from ROP.\textsuperscript{42} The CRYO-ROP study noted unfavourable anatomical outcomes occurred in 47\% of untreated eyes, whilst only 26\% of treated eyes.\textsuperscript{43} Laser ablation therapy has superseded cryotherapy as the preferred method of treatment in ROP. Laser can be applied more precisely resulting in less destruction of the retina, and is associated with less morbidity than cryotherapy.\textsuperscript{44} ‘The Early Treatment for Retinopathy of Prematurity’ (ETROP) study, published in 2004, revolutionised the treatment of ROP.\textsuperscript{45} ETROP indicated that treating ROP at an earlier stage than previously proposed resulted in improved outcomes.\textsuperscript{45} The ETROP protocol was implemented in New Zealand in 2005.\textsuperscript{31, 45} Treatment requiring ROP has since been re-defined by ETROP as Type 1 ROP.\textsuperscript{45} Thus, standard classification is needed to determine if Type 1 ROP is present, defined as any stage of ROP within zone I with plus disease, stage 3 ROP in zone I without plus disease, or stage 2-3 in zone II with plus disease.\textsuperscript{45, 46} Stage, zone, and plus disease are described below.

Classification of ROP

The International Classification of ROP (ICROP) determined a standard grading system of disease severity by grading the location of affected retina, the severity of ROP, and the level of abnormal vascular calibre and tortuosity.\textsuperscript{47, 48} Classification indicates that the more posterior and the larger the amount of retina involved in the disease, the more severe the ROP.\textsuperscript{47, 48}

To define the location of ROP the retina is divided into three distinct, concentric zones.\textsuperscript{47, 48} All three zones are centred on the optic disc as the retinal vascular development initiates at the disc and grows out towards the ora serrata (Figure 1-6).\textsuperscript{48} The most posterior zone is labelled zone I and has a radius
twice the distance of the optic nerve to the macula. Zone II extends the distance from the edge of zone I to the nasal ora serrata and tangentially around the retina. Zone III is the remaining temporal crescent of the retina.

Figure 1-6 – Retinopathy of prematurity zones I, II, and III. Image courtesy of the Auckland District Health Board – Newborn Services Clinical Guideline for Retinopathy of Prematurity.

The severity of ROP is denoted by the stage, which describes the state of the retinal vasculature at the immature vascular edge. There are five stages of ROP, illustrated in Figure 1-7. Stage 1 ROP is the presence of a white demarcation line between the posterior vascular and anterior avascular portions of the retina. Progression of ROP is indicated by a thickening and elevation of the demarcation line, this is stage 2 ROP. Stage 3 disease specifies the presence of extra-retinal tissue proliferation, appearing as a ragged, raised ridge. The sign of stage 4 and 5 ROP is detachment of the retina with stage 4 being any aspect of the retina detached, whether tractional or exudative, whilst stage 5 is complete retinal detachment.
Figure 1-7 – ROP stages. Stage 0 - no ROP, Stage 1 - demarcation line between vascular and avascular retina, Stage 2 - demarcation line thickening, Stage 3 - elevated ridge, Stage 4 - partial retinal detachment, Stage 5 - total retinal detachment.

Image courtesy of Dr Shuan Dai.

Figure 1-8 – Plus disease, venous dilatation and arteriole tortuosity.

Image courtesy of Dr Shuan Dai
The final aspect of ROP classification indicates the vascular incompetence of the immature retina, and is defined as retinal venous dilatation and arteriole tortuosity, known as plus disease (Figure 1-8). The 2005 ICROP revision introduced the classification of ‘pre-plus’ disease where retinal vessels are affected but not to the extent of full plus disease. Therefore, ROP can be classified as nil plus, pre-plus, or plus.

Aggressive posterior ROP (AP-ROP) is a separately defined classification of ROP. It is rapidly progressing and without treatment normally results in a full retinal detachment. AP-ROP tends to occur in zone I with extensive plus disease, a circumferential pattern of neovascularisation often with a circumferential vessel at the disease margin, and neovascularisation which tends to be flat.

ROP is a complex disease requiring regular screening and classification to carefully monitor for Type 1 ROP so treatment can be administered in a timely manner to prevent unnecessary visual impairment.

**ROP visual impairment**

A 22 year retrospective review of visual impairment due to ROP in New Zealand revealed that between 1991 and 2004 that 271.6/100,000 of live very preterm births suffered significant visual impairment. In the period of 2005 to 2012, this decreased to 146.1/100,000 with comparable mean gestational age and birth weight between the two periods. Changes in visual outcomes with no comparable difference in demographics of infants affected suggests improvement in detection and treatment, this difference coincides with New Zealand ophthalmologists adopting the ETROP guidelines.

A recent study based in the Blind Low Vision Education Network of New Zealand (BLENNZ), of a comprehensive national registry of children under the age of 21 with visual impairment of 6/18 or worse in the better eye, showed ROP was one of the three major causes of preventable childhood blindness (30.1% cortical visual impairment, 6.4% ROP and 3.6% non-accidental injuries). The long term visual outcomes of ROP with the advances in screening (discussed in Chapter 2) and treatment guidelines need to be investigated. Long term visual impairment has been reported to occur from prematurity alone and severe ROP is known to impact on vision if not treated. However, limited research has been completed in respect to the differences in visual outcome of children with treated ROP, self-resolving ROP, and prematurity alone. Prematurity alone is known to cause visual impairment that includes severe...
and high frequency of myopia, strabismus and astigmatism. \(^{42, 50, 51}\) Long term outcome differences in these groups of patients would impact on ophthalmological and optometric follow up.

### 1.4 Conclusion

Early detection of ocular pathologies that affect infants is essential to allow appropriate management of both the ophthalmic condition and any systemic associations to improve both visual and overall outcomes for the child. Hence, appropriate screening programs are needed to detect ocular conditions in neonates. The next chapter will describe screening and ophthalmic techniques for assessing the neonatal and paediatric eye, and subsequent chapters will describe the screening studies comprising a substantial component of this PhD research.
Chapter 2:

Ophthalmic evaluation techniques and screening protocols for neonates, infants and children
2.1 Introduction

Ophthalmological examination varies greatly between, neonates, infants, and children. In the neonatal stage, 0-28 days-old, only objective examination of ocular structures can be performed, as the child develops and grows, subjective assessments become possible. With continued visual and cognitive development children are able to interact with the examination process allowing a larger range of functional and structural assessments of the ocular system, including some subjective tests. However, objective testing remains the cornerstone of the paediatric ophthalmic examination.

Screening is an essential part of the neonatal health assessment to detect congenital abnormalities. In New Zealand there are currently two national screening programs in place for the newborn population, these are overseen by the National Screening Unit. The heel prick test for metabolic conditions, has a pick up rate of approximately 0.2%, whilst universal hearing screening detects hearing disorders in 0.1% of the population.52, 53 All other newborn assessments including the red reflex test for ocular conditions, are undertaken by the lead maternity carer of the neonate, which in New Zealand may be a midwife, general practitioner, or a private obstetrician.54 Specialist screening is also in place for unique populations, such as retinopathy of prematurity (ROP) screening in extremely premature and low birth weight infants.46

This chapter will outline the ophthalmological assessments and techniques utilised for assessment of participants in the studies described in this thesis.

2.2 Neonatal ophthalmic assessment

Newborn screening has been established for a number of conditions including hearing impairment and metabolic conditions.54 In New Zealand hearing and metabolic screening programs are nationwide with the remaining neonatal assessments, including the ocular examination by red reflex, being performed by the lead maternity carer.54 Screening programs are designed to detect treatable conditions, however, the identification of currently untreatable diseases may also produce benefits, including social and educational development.
2.2.1 Red reflex screening

New Zealand newborn eye screening guidelines dictate the use of the red reflex examination in the first 24-48 hours to detect ocular disorders, in particular congenital cataract. Red reflex testing is an essential part of the neonatal assessment in New Zealand with the examination technique and timeline outlined by the New Zealand Government in the Well Child/Tamaraki Ora Practitioners handbook. The red reflex test uses the light of an ophthalmoscope reflected off the neonatal fundus, with any impediment in the normally clear ocular structures resulting in an abnormal red reflex appearance. It has been designed as a simple, non-invasive, and easy to implement screening test, first described by Brückner in 1962.

A normal red reflex is defined as equal in colour and intensity, symmetric in both eyes, with no dark spots, opacities, or white reflexes. An abnormal red reflex can indicate sight threatening, life threatening, or systemically associated conditions such as congenital cataracts, retinoblastoma, or metabolic disorders. Early detection is crucial for timely treatment, in particular of congenital cataracts, which have an optimal surgical window of the first four to six weeks of life. Hence, screening guidelines in New Zealand recommend screening in the first week of life and at six weeks of age by the lead maternity carer, general practitioner, or paediatrician. These guidelines align with the American Academy of Pediatrics.

Early detection of congenital cataract is one of the crucial goals of red reflex screening, however, this is not always reliably achieved. In New Zealand, up to 20% of lead maternity carers do not perform the red reflex test as the national standard dictates. Many stated a lack of appropriate training or equipment as the key barrier to providing care. Therefore, without overcoming logistical and educational challenges vision impairing ocular opacities may still be missed.

Retinoblastoma detection is essential with a clear link of early detection to increased survival of children. However, red reflex of 37 paediatric eyes by an ophthalmologist failed to detect all 13 cases of retinoblastoma, even with a pharmacologically dilated pupil. Indicating that the red reflex test may not be a suitably stringent screening test for posterior ocular disorders of the infant. In New Zealand,
it is recommended that all infants with an abnormal red reflex, or a family history of ocular disorders, have a full ophthalmic examination.54, 56

2.2.2 Binocular indirect ophthalmoscopy

Binocular indirect ophthalmoscopy (BIO) is an indispensable tool for paediatric ocular examinations of the retina. It provides a stereoscopic view of the ocular fundus, with a field of view ranging from 35 to 65 degrees, depending on the condensing lens utilised.63, 64 The image viewed by the clinician is inverted and horizontally rotated as shown in Figure 2-1. BIO typically requires extensive training and a skilled clinician to be used effectively.

![Figure 2-1 - Binocular indirect ophthalmoscopy with a condensing lens illustrating the inverted and horizontally flipped image. Image courtesy of Fiona Tomlinson.](image)

BIO is the conventional gold standard technique for ROP screening. Dilation of the pupil is needed to obtain clear posterior views. Once dilation is achieved the infant is swaddled, a drop of topical
anaesthetic is instilled and a neonatal lid speculum is inserted.\textsuperscript{46} B/O causes an increase in blood pressure, both systolic and diastolic, and a decrease in oxygen saturation, indicating stress of the infant.\textsuperscript{65} Hence, examinations must be short but thorough to minimise risk to the infant.\textsuperscript{65}

2.2.3 Wide-field digital imaging

Wide-field digital imaging (WFDI) photographs ocular structures for clinical assessment. The RetCam (Clarity Medical Systems, Pleasanton, CA, United States of America) camera is able to capture a range of ophthalmic aspects, with anterior images captured with the camera held above the eye, whilst posterior images are captured via contact technique with a barrier of a viscous coupling fluid, such as Viscotears (Alcon, Fort Worth, TX, United States of America), for an example of a posterior ocular image captured with the RetCam, see Figure 2-2.

![RetCam Shuttle with D130 lens and wide-field digital retinal image captured with the RetCam Shuttle and D130 lens](image)

Figure 2-2 – RetCam Shuttle with D130 lens and wide-field digital retinal image captured with the RetCam Shuttle and D130 lens

There are various RetCam models available, in this thesis the RetCam III and RetCam Shuttle models were utilised (Clarity Medical Systems, Pleasanton, CA, USA). In this thesis research, a D130 lens was used on all RetCams, which can capture 130-degree WFDI of both anterior and posterior structures. Figure 2-2 illustrates the RetCam shuttle with a D130 lens on the hand-piece.

WFDI can be utilised for many paediatric ocular conditions. It can be used for documenting retinoblastoma to assess efficacy of treatment over time, as objective documentation in cases of
suspected non-accidental injuries, or for photographing anterior or posterior conditions to seek a second opinion. RetCam photography is a fast, cost-effective and accurate examination approach that has low impact on the infant and results in an objective record.\textsuperscript{36, 66-68} The introduction of the RetCam has opened the opportunity for telemedicine assessment of images, with ophthalmologists able to remotely assess images captured by trained allied health professionals.\textsuperscript{69, 70} RetCam WFDI can be successfully performed by specialist nurses, allowing ophthalmologists to analyse images at a remote site and at any time thereafter.\textsuperscript{71} The options of telemedicine using allied health professionals potentially increases access to ocular assessment. Telemedicine with WFDI was used in the studies described in Chapter 3 and Chapter 5.

2.2.4 Retinopathy of prematurity screening

Infants at risk of retinopathy of prematurity (ROP), a vasoproliferative disease affecting the immature retinae of premature infants, require regular screening to ensure timely detection of treatment warranted ROP (Type 1 ROP).\textsuperscript{36} ROP is described in detail in Chapter 1.

Appropriate, accurate and regular retinal examinations to detect the presence of treatable ROP have well-documented clinical benefits.\textsuperscript{70} Screening guidelines for ROP must be determined locally, due to regional variations in neonatal care and survival of extremely premature and low birth weight infants.\textsuperscript{35} In New Zealand national guidelines recommend all infants born less than 31 weeks gestational age, or weighing less than 1250 grams at birth are screened for ROP.\textsuperscript{46} Regional guidelines are derived from the national recommendations with the Auckland region of New Zealand guidelines stating all infants less than 30 weeks gestational age or less than 1250 grams require ROP screening.\textsuperscript{32, 46} Infants deemed to be at high risk due to a ‘tumultuous’ clinical course, as determined by their attending neonatologist, are also screened.\textsuperscript{46}

Screening is initiated between four to six weeks postnatally depending on the gestational age of the infant as detailed in Table 2-1. Initial screening ages are recorded as post-menstrual age (PMA), the gestational age plus time elapsed since birth. Timing of further screening is determined by the ophthalmologist based on the severity of ROP present ranging from one to three weeks, see Table 2-2.\textsuperscript{46}
The basis of follow up times align with the joint guidelines published by the American Academy of Pediatrics, as well as the New Zealand national guidelines.

Traditionally, ROP screening is performed by a paediatric ophthalmologist with BIO, however with recent technological advances in paediatric retinal imaging, WFDI has been incorporated as part of ROP screening programs in some countries including, the United States of America, India, and New Zealand. In Auckland, New Zealand, WFDI with the RetCam has been used exclusively for the entire ROP screening process, since 2006.

Table 2-1 - Post menstrual age (PMA) at first examination for infants at risk of retinopathy of prematurity based on gestational age at birth.

<table>
<thead>
<tr>
<th>GA at birth</th>
<th>PMA at first examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;26 weeks</td>
<td>30 weeks</td>
</tr>
<tr>
<td>26 weeks</td>
<td>31 weeks</td>
</tr>
<tr>
<td>27-28 weeks</td>
<td>32 weeks</td>
</tr>
<tr>
<td>29+ weeks</td>
<td>33 weeks</td>
</tr>
</tbody>
</table>

Table 2-2 - Examination follow up timing of infants at risk of retinopathy of prematurity based on severity of disease at previous examination.

<table>
<thead>
<tr>
<th>ROP grading at previous examination</th>
<th>Timing of subsequent examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zone I - Stage 1 or 2</td>
<td>1 week</td>
</tr>
<tr>
<td>Zone II - Stage 3</td>
<td></td>
</tr>
<tr>
<td>Zone I - Immature vessels or regressing ROP</td>
<td>1-2 weeks</td>
</tr>
<tr>
<td>Zone II - Stage 2</td>
<td></td>
</tr>
<tr>
<td>Zone II - Stage 1 or regressing ROP</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Zone II - Immature vessels</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>Zone III - Stage 1 or 2, or regressing ROP</td>
<td></td>
</tr>
</tbody>
</table>
Comparison of BIO and WFDI for ROP screening

The need for regular and accurate ROP screening to detect Type 1 ROP has been clearly established. However, a decreasing number of ophthalmologists are willing to perform this role. A survey of the American Academy of Ophthalmologists stated that 23% of Ophthalmologists currently screening for ROP planned on ceasing this activity. Reasons for discontinuation included low reimbursement, liability concerns, and complex logistic coordination. The use of WFDI of the retina to screen for ROP has been proposed as an alternative to BIO screening to increase access and overcome the increasing lack of trained professionals for screening purposes, Figure 2-3 illustrates the different screening techniques.

![Figure 2-3 – Retinopathy of prematurity screening illustrating binocular indirect ophthalmoscopy (left) and RetCam WFDI (right) techniques. Images courtesy of Dr Shuan Dai](image)

It is important that if WFDI is to be used for ROP screening, that it is equivalent or better at the detection of Type 1 ROP than BIO screening. A number of studies in a variety of locations have confirmed that WFDI has a high sensitivity for detecting Type 1 ROP. Comparison of techniques in New Zealand observed 100% sensitivity and 97.9% specificity in detection of treatment requiring ROP.
Telemedicine screening for ROP has also been determined as an accurate diagnostic tool with high inter- and intra-grader reliability.\textsuperscript{69}

The use of non-ophthalmologists for capturing ROP screening images has been shown to be a safe and effective alternative to BIO screening.\textsuperscript{78, 80} In a prospective comparison study of the time required by ophthalmologists to perform BIO versus telemedicine diagnosis of ROP, BIO took over four minutes per infant compared to under two minutes with telemedicine.\textsuperscript{67} The objective photographic record produced with WFDI is advantageous with utility in medical liability cases, second opinions, or comparing changes over time.\textsuperscript{36, 81} Nonetheless, current international guidelines generally state that BIO will remain the gold standard until further research can establish the benefits and precise role of WFDI and telemedicine in ROP care.\textsuperscript{70}

2.2.5 Universal newborn eye screening

The success of ROP WFDI and telemedicine has led to the suggestion of utilising the system for universal newborn eye screening for all newborn ocular abnormalities. A cohort of 3573 healthy full-term newborns in China received photographic screening.\textsuperscript{82} Abnormal ocular findings were documented in 871 cases, 769 of these cases were retinal haemorrhages.\textsuperscript{82} Other ocular abnormalities detected included congenital cataract, microphthalmos, retinal hamartoma, and optic nerve anomalies.\textsuperscript{82} A second study of healthy full-term newborns was conducted in India with 1021 infants, 48 infants had abnormal findings, 52\% of these being retinal haemorrhages.\textsuperscript{83} Early detection of ocular abnormalities may offer prompt management and appropriate treatment if needed. Further research is required to determine ocular abnormality rates and the potential impact on childhood visual morbidity.

2.3 Ophthalmic assessment of children

2.3.1 Introduction

Paediatric ophthalmic assessment differs from a standard adult ophthalmic examination. As children grow and develop, they learn to interact with the examination process, moving from the completely objective assessment of neonates, to giving some subjective responses. Although children are able to engage with the testing more than infants, they still do not have the same levels of concentration,
comprehension, and communication ability as adults. A plethora of tests are available to assess ophthalmic structure and function in children.

2.3.2 Visual acuity

Visual acuity is the most common assessment of visual function, and is defined as the ability of the eye to discriminate two stimuli as separate. Central vision is dictated by the fovea. The foveal function is allocated a large region of primary visual cortex, thus, the measurement of visual acuity indicates the function of the fovea, visual pathway, and related aspects of the visual cortex. Visual acuity is the most basic assessment of visual function. Vision matures rapidly, in the first few years of life as the visual pathway develops (as detailed in Chapter 1). Normal visual acuity for a newborn is approximately 1.5 logMAR (6/980) at one month of age, improving to 0.0 logMAR (6/6) by five years of age.  

![Figure 2-4 - Lea symbols matching card for paediatric visual acuity measurement](image)

Standard adult visual acuity charts require letter recognition and naming, a challenge for young children or children with developmental delay. Other challenges include sustained concentration, conceptual understanding of the test, and engagement with a distance target. Methods for assessment must
therefore be age and developmental stage appropriate. There are a large number of paediatric visual acuity tests with variations in the results achieved.\textsuperscript{86, 87} Formal visual acuity assessment begins with preferential-looking techniques, such as Cardiff or Teller cards, in pre-verbal or non-verbal children.\textsuperscript{2, 84} Lea Symbols (Figure 2-4) are an appropriate test for pre-school children with a success rate of 76\% at 3 years and 95\% at 4 years of age, and can be used in conjunction with a matching card.\textsuperscript{88} School aged children demonstrate good compliance with quantitative letter or picture based acuity-testing, with successful examination in the majority of cognitively normal 5 year olds.\textsuperscript{2} Once able, normally by the age of five, standard adult visual acuity charts such as the Snellen chart should be used, however, a matching card can be used if needed for confidence.

2.3.3 Binocular vision assessment

Binocular vision is established as early as three months of age, with alignment of the eyes, convergence, and sensory fusion all present.\textsuperscript{89} Stereopsis is the perception of relative depth due to the fusion of the two separate ocular images, which can be assessed through clinical tests.\textsuperscript{90} Coarse stereoacuity is established at four years of age, with fine detailed stereoacuity continuing to develop into the teenage years.\textsuperscript{90}

\textit{Cover test}

The cover test is used to detect a heterotropia or heterophoria, i.e. manifest or latent misalignments of the eyes.\textsuperscript{91} The unilateral cover test is performed by using an opaque cover paddle to cover each eye in turn, whilst the uncovered eye is observed for movement to determine the presence or absence of a heterotropia.\textsuperscript{91} To determine the magnitude of a heterotropia or a heterophoria the alternating cover test is used and in conjunction with neutralising prisms. The opaque cover is moved alternately between the eyes to break down fusion of the eyes thus, revealing the full magnitude of any eye misalignment.\textsuperscript{91}

\textit{Stereoacuity}

Stereoacuity measures the binocular vision function of a child by measuring the smallest detectable perception of depth. There are a variety of stereoacuity tests available for children some examples are the Titmus stereotest, Frisby stereotest, Random-dot E stereotest, and the TNO stereotest.\textsuperscript{92} The TNO stereotest was used in Chapter 4 of this thesis due to it being a cognitively easier test of stereoacuity.
for children, and having no monocular cues that could potentially confound results, in comparison to other stereotests for children. The TNO stereotest is an anaglyph random dot stereogram with two halves of the image presented separately to individual eyes with red and green dots, displayed in Figure 2-5. These dots, when viewed through red/green spectacles, are able to be fused in individuals with binocular vision to give the perception of a three-dimensional image. TNO stereotest is an effective tool for amblyopia monitoring, as well as detecting decreased stereoacuity in non-amblyopic eyes in children. Children achieving stereoacuity of 120 seconds of arc, or better, strongly indicates normal or correctable to normal vision. Time must be taken with children to ensure understanding of the test, and allow time for the 3D aspects of the test to ‘pop-out’, with reliability increasing with trained practitioners performing the test.

![Figure 2-5 – Red/green glasses and TNO anaglyph random dot stereogram](image)

### 2.3.4 Pupil assessment

The light reaction, constriction under a bright light, of the pupil is apparent at 31 to 32 weeks gestation, and not present in more premature infants. Standard pupil assessment involves evaluating the light response in each eye, then determining if a relative afferent pupillary defect is present with the swinging flash light test. Pupil assessment can be used to detect an optic nerve or severe retinal disorder, with a relative dilation of the affected eye seen when it is under direct light. A bright, ophthalmoscope light was used for pupil assessments in Chapter 4 of this thesis.
2.3.5 Slit lamp biomicroscopy

Slit lamp biomicroscopy enables stereoscopic and magnified examination of ocular tissues. The slit lamp consists of a parfocal microscope and illumination system, rotating around the same axis. The slit lamp biomicroscope produces a virtual, upright, and magnified image—allowing detailed assessment of the eye. Anterior structures of the eye can be viewed with diffuse illumination, which illuminates ocular features as a whole and allows detection of gross abnormalities. Direct focal illumination, achieved with an angled, narrow, slit beam, can be used to assess fine detail, and transparency of structures. The slit lamp can also be used in combination with a condensing lens, such as a 90D lens, to view the ocular fundus. In infants and younger children a hand-held slit lamp is necessary to accomplish anterior segment examination. Figure 2-6 illustrates the Topcon SL-D301 (Topcon Medical Systems, Oakland, New Jersey, United States) slit lamp biomicroscope used for the study reported in Chapter 4 of this thesis, as well as a hand-held slit lamp.

![Figure 2-6 – Topcon SL-D301 slit lamp biomicroscope (left) and hand-held slit lamp (right)]
2.3.6 Tonometry

Measuring the intra-ocular pressure is a necessary aspect of a standard eye examination, particularly in the management of glaucoma. The gold standard for intra-ocular pressure measurement is the Goldmann applanation tonometer.98 The Goldmann applanation tonometer can be challenging in the paediatric population due to the need for anaesthetic eye drops and extended cooperation to perform the technique.99 The iCare® TAO1i tonometer (Tiolat Oy, Helsinki, Finland) is a portable, rebound tonometer (Figure 2-7) which requires no anaesthesia.98 The iCare® produces rapid, accurate, and reproducible results in children, hence it was used for intraocular pressure measurements in Chapter 4 of this thesis.99

![Figure 2-7 - iCare rebound tonometer](image)

2.3.7 Cycloplegic autorefraction

The gold standard for paediatric refraction is cycloplegic retinoscopy.100 In addition to mydriasis, cycloplegia paralyses the ciliary muscle, preventing accommodation ensuring accurate refractive assessment.100 A combination of cyclopentolate 1.0% (Chauvin Pharmaceuticals Ltd, Kingston-Upon-Thames, United Kingdom) and tropicamide 1.0% (Chauvin Pharmaceuticals Ltd, Kingston-Upon-Thames, United Kingdom), were used to achieve cycloplegia in this thesis. Refraction occurs at least 30 minutes after drop instillation to ensure maximum cycloplegia.101 Autorefraction produces comparable spherical equivalent refraction results to retinoscopy, with the Topcon auto-kerato-refractometer KR-8100 being used, post-cycloplegia, in Chapter 4 of this thesis.102
2.3.8 Fundus imaging (Optos)

Viewing and assessing the peripheral retina is crucial to diagnose, monitor, and assess treatment plans. Traditional retinal cameras capture a 30- to 50-degree field of view, ultra-wide-field retinal imaging technology, such as the Optos P200C (Optos PLC, Dunfermline, United Kingdom) used in this thesis, can capture a field of view up to 200-degrees. The Optos non-contact system incorporates a confocal scanning laser ophthalmoscope and an ellipsoid mirror to scan the far retinal periphery. The image produced is false coloured with unrealistic rendering as only two laser wavelengths are used in the camera, compared to the true colour images of the direct contact RetCam. However, due to the ease of use, the Optos is suitable for viewing the peripheral retina in paediatric populations.

2.3.9 Visual field examination

Paediatric perimetry, examination of the visual field, falls into two main categories: automated static perimetry and manual kinetic perimetry. Manual kinetic perimetry involves visual stimuli being moved from beyond the field of view to the edge of visual perception in order to plot the boundary of the visual field. Automated static perimetry involves visual stimuli being presented at predetermined locations within a patient's visual field, to determine sensitivity within the field. Conventional visual field assessment in children has many challenges as it requires maintained central fixation, stable head posture, subjective responses, and can be time consuming.

Visual field assessments commonly used in paediatric practice include Goldmann perimetry and confrontation. The Goldmann perimeter is a manual kinetic perimeter, with stimuli varied in size and brightness to map the full extent and sensitivity of the visual field. The manual kinetic confrontation method was performed with an LED light on a stick (also known as a Bott confrontation wand), with the child's left eye occluded by an eye patch. Participants were instructed to maintain right eye fixation with the examiner's left eye and to inform the examiner when the light appeared and disappeared from view as it was traced along each of the 12 cardinal meridians.

Development of new paediatric perimetry options look at overcoming these known challenges, one example of this is the saccadic vector optokinetic perimeter (SVOP). The SVOP utilises infra-red eye tracking to overcome many limitations in paediatric perimetry (Figure 2-8). Infra-red eye tracking
assesses the direction of gaze in relation to the position of stimuli presented. This allows free movement of the head within 3D space and exploits the natural reflexive saccades to assess the visual field. Limited data are available on the utility of SVOP in paediatric populations, however, its potential to be used as an objective visual field screening device in children is of great interest. These visual field assessment techniques are compared in Chapter 6.

Figure 2-8 – Saccadic vector optokinetic perimeter screen with fixation target (star) and infra-red eye tracking (arrow).

2.4 Conclusion

Ophthalmic assessment of infants and children varies greatly from adults. The majority of tests are objective in nature. Increasingly subjective tests are introduced as a child develops and is able to interact in the examination process. Continuing development of paediatric assessment techniques is important to better detect and manage paediatric ocular disorders. Screening programs are a vital aspect of neonatal and paediatric eye care and require further research. The inter-related studies in this thesis evaluate current and potential assessment and screening techniques for identifying and managing paediatric ocular conditions in New Zealand.
Chapter 3:

Retrospective review of telemedicine screening for retinopathy of prematurity
3.1 Introduction

Retinopathy of prematurity (ROP) is a multifactorial, proliferative vascular disorder that affects the retinæ of preterm infants with extremely low-birth weight.\textsuperscript{12, 29} Annually 30,000 infants are affected by ROP related visual impairment worldwide.\textsuperscript{30} Visual loss due to ROP is considered avoidable by the World Health Organisation due to effective treatment options being available.\textsuperscript{1, 38, 45} Therefore screening of at-risk infants for ROP is essential to allow early detection of treatment requiring disease and thus prevent unnecessary visual loss.\textsuperscript{35}

The demographics of infants affected by ROP vary worldwide based on neonatal care and premature infant survival rates, thus, guidelines must be region specific.\textsuperscript{30, 35} In New Zealand, children born less than 1250g, or less than 30 weeks gestational age undergo routine retinal screening examination for ROP during their neonatal period.\textsuperscript{32}

Early treatment of retinopathy of prematurity (ETROP) guidelines have been implemented in New Zealand since 2005. ETROP indicates that all infants with ‘Type 1’ ROP must be treated within 48 hours. Type 1 ROP is defined as: any stage of ROP within zone I with ‘plus disease’, stage 3 ROP in zone I without plus, or stage 2-3 in zone II with plus disease.\textsuperscript{45, 46} Further details of ROP stage, zone, plus disease, and treatment are detailed in Chapter 2.

Binocular indirect ophthalmoscopy (BIO) has long been considered the gold standard for ROP screening.\textsuperscript{81} ROP screening with BIO is a technical skill that requires an experienced examiner of infants’ eyes. Rising premature birth rates along with improved survival of extremely premature and low birth weight infants,\textsuperscript{110, 111} is increasing the demand for ophthalmologists who perform ROP screening.\textsuperscript{36} Conversely, a survey from the American Academy of Ophthalmologists indicates a decrease in the number of ophthalmologists willing to undertake the responsibility of ROP screening, with 23\% of those currently screening planning on ceasing.\textsuperscript{75} Reasons for discontinuation included high medico-legal risk, complexity of patient scheduling logistics, low reimbursement rates and a lack of support.\textsuperscript{75, 76} This same trend is occurring in New Zealand, especially in greater Auckland where multiple neonatal units demand regular ROP screening service for infants at risk of developing vision threatening ROP. Current
screening practice is not sustainable within the existing framework for adequate ROP screening, thus new technology has been developed to combat this limitation.

The RetCam (Clarity Medical Systems, Pleasanton, California, United States of America) is a paediatric, ocular, wide-field digital imaging (WFDI) system. It provides a potential alternative screening tool for ROP that may overcome some of the challenges in ROP screening, and is increasingly being incorporated into ROP screening programmes. Efficacy of the RetCam WFDI for detecting treatment warranted ROP has been confirmed in both international and local studies. In comparison to conventional BIO, WFDI is a fast, cost-effective, and accurate examination approach with low systemic impact on the infant. Furthermore, WFDI provides objective documentation which is preferable to subjective BIO recordings if medico-legal issues arise.

RetCam WFDI can be successfully and safely performed by trained specialist nurses and medical photographers, allowing ophthalmologists to analyse images at a remote site and a later time. This concept of remote assessment of at-risk infants is known as ROP telemedicine, which may improve access to ROP screening, this is particularly important in the changing climate of ROP management.

The Auckland Regional Telemedicine ROP Network (ART-ROP), a real world WFDI telemedicine ROP screening network, has been implemented in the Auckland region since 2006. RetCam WFDI is used exclusively for ROP diagnosis, treatment decision making, and the decision to discharge infants from active ROP screening. This study aims to evaluate ART-ROP and its efficacy in the management of ROP in Auckland, New Zealand.

### 3.2 Materials and Methods:

#### 3.2.1 Study design

A retrospective chart and photo review of ART-ROP over a ten year period (2006-2015) was completed. This study was approved by the Health and Disability Ethics Committee (14/NTA/183). All research adhered to the tenets of the Declaration of Helsinki.
3.2.2 ART-ROP screening protocol

ART-ROP was established in 2006 across three neonatal intensive care units (NICU), one quaternary NICU and two secondary level NICUs, involving Auckland District Health Board (ADHB) and Waitemata District Health Board (WDHB). In 2010 Counties Manukau District Health Board (CMDHB) NICU joined ART-ROP.

The specific screening guidelines of ART-ROP were adhered to throughout the ten year review period. Screening occurs for all infants who meet the ROP screening criteria, that is, birth weight <1250 gram, or gestational age <30 weeks as identified via NICU database. Infants outside these limits, but deemed to be at high risk by their attending neonatologist, such as those with extended use of high-flow oxygen, were also be referred for screening. Initial ROP screening timing is between 4-6 weeks post birth, dependent on the infant’s gestational age at birth, these are outlined in Chapter 2.

Screening images were captured by a trained nurse specialist with the assistance of a medical photographer using the ‘RetCam 3’ or ‘RetCam shuttle’. Pupils were dilated with single use preservative free tropicamide 1.0% (Chauvin Pharmaceuticals Ltd, Kingston-Upon-Thames, United Kingdom) and preservative free phenylephrine 2.5% (Chauvin Pharmaceuticals Ltd, Kingston-Upon-Thames, United Kingdom), 30 to 60 minutes prior to screening. Topical anaesthesia with preservative free tetracaine 0.5% (Chauvin Pharmaceuticals Ltd, Kingston-Upon-Thames, United Kingdom), occurred immediately prior to eyelid speculum insertion and retinal photo capture. All procedures occurred in the NICU with close cardiac and respiratory monitoring. A minimum of three photos were captured of each eye: the posterior pole, nasal retina, and temporal retina. Captured images were stored as uncompressed and encrypted files on the secure ART-ROP network server. Images were then accessed from a secure, approved review computer by the consulting paediatric ophthalmologist for assessment and reporting. The resulting report along with appropriate images and management plan were uploaded to the infant’s electronic medical record.

Reporting of ROP disease by the paediatric ophthalmologist followed the International Classification of Retinopathy of Prematurity (ICROP) system. The ICROP system denotes the zone of the retina...
involved, the stage of ROP, and whether plus disease is present (further details of ROP classification can be found in Chapter 2).

Follow up ROP screening examinations observed the same protocol and ranged in timing from one to three weeks, based on ROP disease severity. Follow up screening schedule and treatment recommendations of the ophthalmologist were automatically sent to the appropriate NICUs via the existing hospital electronic medical record system. The follow up frequencies align with those published by the American Academy of Pediatrics.

Discharge of infants from active ROP screening occurred once retinal vascularisation was determined to have entered peripheral zone II or III, or when ROP had regressed. This normally occurs when the infant is 37 weeks postmenstrual age or older. The discharge decision was made exclusively based on reviewing of the WDFI images by the ophthalmologist, using telemedicine assessment. Three month outpatient clinical review for all infants in ART-ROP were scheduled upon the completion of ROP screening, due to the increased risk of myopia and strabismus. Infants who were transferred to other local hospitals, or deceased were not scheduled for follow up within the ART-ROP network.

3.2.3 Data collection

This retrospective study of the ART-ROP WFDI database covered mid-2006 to the end of 2015. Ophthalmic and medical records for each case were reviewed, this included demographic data, birth weight, gestational age, the presence or absence of any stage of ROP, out-patient clinic review outcomes, and total number of screenings. Demographic data included self-reported ethnicity which for infants is provided by their parents at birth. For those infants with ROP, the zone, stage, presence of plus disease, treatment, and follow up outcomes were collected for each screening session. Infants referred from or to NICUs outside of the ART-ROP network during their screening were included. However, it was noted if they did not receive all screening with ART-ROP, to allow separate analyses.

Children who meet criteria for ROP screening, regardless of final diagnosis, are referred to the Greenlane Paediatric Ophthalmology clinic for follow up at 3 to 6 months post ROP screening discharge according to ART-ROP protocols. Retrospective review of clinic attendance, reason for non-attendance as well as retinal and visual health were noted. The category ‘did not attend’ was recorded for those
patients who had appointments booked but did not attend multiple times. Reasons for non-attendance at these clinics were sought through review of files, hospital booking records and follow up of those children who were transferred out of the Auckland area.

3.2.4 Statistical analysis

Statistical analysis was completed using IBM SPSS software version 22 (Armonk, New York, United States of America). Normalcy of data was determined through calculation of skew and kurtosis along with subjective assessment of histogram distribution. Descriptive statistics for infant demographics and characteristics were calculated as mean ± standard deviation for parametric data. For nonparametric data median and interquartile range were determined. Differences between groups were calculated by Pearson Chi-squared test for categorical data, independent sample T-test for continuous data, and the Mann-Whitney U test for nonparametric variables. Four groups were compared; (A) infants receiving all screening in ART-ROP compared to those receiving partial screening, and (B) those infants who received ROP treatment compared to those who did not receive ROP treatment.

3.3 Results

A total of 1181 files of infants screened for retinopathy of prematurity in the ART-ROP network from 2006 to 2015 were reviewed. The number of infants screened per year increased over the decade, Figure 3-1, with a minimum of 65 infants and a maximum of 171 infants per annum.

![Figure 3-1 – Number of infants screened for retinopathy of prematurity by year from 2006 to 2015 in Auckland, New Zealand](image)
The retrospective ROP cohort comprised of 642 males (54.4%), 538 females (45.6%). Ethnicity was reported by the family for each infant, 39.0% of the cohort were identified as European (461/1181), whilst Māori comprised 23.9% (282/1181), Pacific Peoples 18.0% (213/1181), Asian 16.9% (200/1181) and other 2.1% (25/1181). The ethnicity composition of the cohort, when compared to the most recent ADHB maternity report (2015), indicated an over-representation of Māori and Pacific Peoples, whilst European, Asian and Other were under-represented in this cohort, Table 3-1. Although data were only compared to the most recent ethnicity report, trends in ethnicity of screened infants across the decade are stable indicating that the over- and under-representation observed of certain ethnicities can be applied to the cohort as a whole.

Table 3-1 – Comparison of ethnicity of infants (A) screened by ART-ROP from 2006-2015, (B) infants admitted to the NICUs within Auckland District Health Board (ADHB) in 2015, and (C) all preterm infants (<37 weeks gestational age) born in the ADHB in 2015

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>ART-ROP 2006-2015</th>
<th>Preterm NICU admission ADHB 2015</th>
<th>ADHB 2015 All newborns</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 1181</td>
<td>N = 449</td>
<td>N = 6933</td>
</tr>
<tr>
<td>European</td>
<td>461 39.0%</td>
<td>150 33.4%</td>
<td>3118 45.0%</td>
</tr>
<tr>
<td>Māori</td>
<td>282 23.9%</td>
<td>87 19.4%</td>
<td>469 6.8%</td>
</tr>
<tr>
<td>Pacific Peoples</td>
<td>213 18.0%</td>
<td>55 12.2%</td>
<td>805 11.6%</td>
</tr>
<tr>
<td>Asian*</td>
<td>200 16.9%</td>
<td>108 24.0%</td>
<td>2241 32.3%</td>
</tr>
<tr>
<td>Other+</td>
<td>25 2.1%</td>
<td>49 10.9%</td>
<td>300 4.3%</td>
</tr>
</tbody>
</table>

*Asian includes Indian, *Other includes all ethnicities that do not fit into the named categories

The birth weight of the ROP cohort ranged from 450 to 2140g with a mean of 1058.7g ± 288.5g. Gestational age ranged from 23 to 38 weeks with a mean of 27.6 ± 2.2 weeks.

The total number of screening sessions undertaken by ART-ROP was 4453. ROP screening sessions ranged from a single screening to 17 sessions with a positively skewed nonparametric distribution, with a median of 4 sessions per infant (interquartile range of 2 to 5 screenings). The number of ROP screenings an infant required was determined by the ROP severity.
3.3.1 ART-ROP exclusive screening

One of the four NICUs which comprise the ART-ROP network is the only quaternary NICU in the country, thus, it receives referrals from other NICUs around the country for infants who require higher level care. Part-screening between ART-ROP and the referring NICU occurred in 15.4% (182/1181) of cases, whilst the remaining 84.6% received all screening appointments within ART-ROP.

![Figure 3-2](Image)

Figure 3-2 – Decreasing percentage of infants who did not exclusively receive ROP screening with ART-ROP - the solid red line indicates when a fourth NICU, CMDHB joined the ART-ROP network.

The proportion of infants not receiving all ROP screening sessions with ART-ROP decreased over the period, $R^2 = 0.7866$, see Figure 3-2. CMDHB, was incorporated into ART-ROP in 2010, aligning with the decrease in infants transferred for ROP screening, indicated by the solid line on Figure 3-2. The characteristics of infants who received partial screening within ART-ROP varied from those who underwent full screening as detailed in Table 3-2. Individuals transferred for part of their screening had a significantly lower mean birth weight ($p < 0.001$), lower mean gestational age ($p < 0.001$), a different ethnic composition ($p < 0.001$), and fewer screening sessions per infant ($p < 0.001$).
Table 3-2 - Comparison of infant characteristics in individuals who have undergone full and partial ART-ROP screening

<table>
<thead>
<tr>
<th></th>
<th>ART-ROP partial screening</th>
<th>ART-ROP exclusive screening</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=182</td>
<td>N=999</td>
<td></td>
</tr>
<tr>
<td>n (%), mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.076</td>
</tr>
<tr>
<td>Male</td>
<td>110 (60.4%)</td>
<td>532 (53.3%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>72 (39.6%)</td>
<td>467 (46.7%)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>European</td>
<td>61 (33.5%)</td>
<td>400 (40.0%)</td>
<td></td>
</tr>
<tr>
<td>Māori</td>
<td>82 (45.1%)</td>
<td>200 (20.0%)</td>
<td></td>
</tr>
<tr>
<td>Pacific Peoples</td>
<td>22 (12.1%)</td>
<td>191 (19.1%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>14 (7.7%)</td>
<td>186 (18.6%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (1.6%)</td>
<td>22 (2.2%)</td>
<td></td>
</tr>
<tr>
<td>Birth weight grams</td>
<td>969 ± 226</td>
<td>1075 ± 296</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational age weeks</td>
<td>27.0 ± 2.0</td>
<td>27.8 ± 2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment</td>
<td>16 (8.8%)</td>
<td>60 (6.0%)</td>
<td>0.153</td>
</tr>
<tr>
<td>Total screenings</td>
<td>median [IQR]</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2 [1-2]</td>
<td>3 [3-5]</td>
<td></td>
</tr>
</tbody>
</table>

The severity of ROP is graded by stage, zone and the presence of plus disease, which determines the frequency and timing of subsequent ROP screening. The highest stage of ROP was determined for each infant, with decreasing average severity of ROP being observed each subsequent year (Figure 3-3). The proportion of infants with no ROP, Stage 0, increased throughout the time period.
3.3.2 Treatment

Seventy-six infants (6.4%) had ROP disease that required treatment. These infants had significantly lower mean birth weight and gestational age, and higher grading for ROP stage and plus disease as outlined in Table 3-3. No gender or ethnicity predilection was present (Table 3-3). Infants requiring treatment for ROP had significantly more screening sessions (p < 0.001). The proportion of ROP that required treatment has decreased over time since the ART-ROP network began, $R^2 = 0.9205$, detailed in Figure 3-4. Laser treatment was the primary treatment modality being used exclusively in 90.8% (69/76) of treatment-requiring infants. Avastin was introduced as a treatment option in 2009, seven infants received Avastin, four of whom had Avastin as adjunctive treatment to laser therapy.
Table 3-3 - Comparison of infant characteristics for individuals requiring treatment of ROP to those who did not require treatment

<table>
<thead>
<tr>
<th></th>
<th>Infants with ROP requiring treatment</th>
<th>Infants with no treatment required</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=76</td>
<td>N=1104</td>
<td></td>
</tr>
<tr>
<td>n (%), mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.769</td>
</tr>
<tr>
<td>Male</td>
<td>43 (56.0%)</td>
<td>599 (54.3%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>33 (44.0%)</td>
<td>505 (45.7%)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>0.230</td>
</tr>
<tr>
<td>European</td>
<td>24 (31.6%)</td>
<td>437 (39.6%)</td>
<td></td>
</tr>
<tr>
<td>Māori</td>
<td>17 (22.4%)</td>
<td>264 (23.9%)</td>
<td></td>
</tr>
<tr>
<td>Pacific Peoples</td>
<td>21 (27.6%)</td>
<td>192 (17.4%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>13 (17.1%)</td>
<td>187 (16.9%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.3%)</td>
<td>24 (2.2%)</td>
<td></td>
</tr>
<tr>
<td>BW (grams)</td>
<td>786 ± 191</td>
<td>1077 ± 285</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GA (weeks)</td>
<td>25.3 ± 1.7</td>
<td>27.8 ± 2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ROP stage</td>
<td>3</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median plus grading</td>
<td>Pre plus</td>
<td>No plus</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total screenings</td>
<td>median [IQR]</td>
<td>7 (4-9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 (2-4)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3-4 – ROP treatment rates in Auckland, New Zealand, 2006 to 2015, $R^2 = 0.9205$
3.3.3 Follow up

On completion of ROP screening, all infants are enrolled for a clinical follow up at three to six months post screening discharge. Follow up was attended by 61.1% (718/1181) of infants, 10.9% (128/1181) had multiple appointments scheduled which were not attended, while a further 14.7% (174/1181) were transferred to their local hospital for follow up care. Forty-seven infants deceased prior to their follow up appointment (4.0%). The remaining 114 infants (9.7%) were lost to follow up. Therefore, 76.0% (718/945) infants eligible for ART-ROP follow up attended, excluding infants who were transferred, or deceased.

Retinal examination findings at the last follow up were reported as normal in 98.9% (710/718) of the reviewed infants. The eight cases with abnormal retinal findings consisted of; six infants with persisting asymptomatic avascular retinal patches which were present at screening discharge, and two infants with known macula drag as result of previous laser treatment, both of these children maintain functional vision.

The Blind and Low Vision Education Network New Zealand (BLENNZ), a national registry of all children with vision worse than 6/18 in their best eye, provides educational and social support for children with visual impairment or blindness. No children screened by the ART-ROP network have been registered with BLENNZ for ROP-related visual loss over the reviewed time period.

3.4 Discussion

The ART-ROP network utilises WFDI and a telemedicine model exclusively, for ROP screening and represents a real-world ROP telemedicine screening programme. Telemedicine as a method for detecting treatment requiring ROP was acknowledged by the American Academy of Pediatrics in 2014, with digital fundus imaging being used in conjunction with, or to complement, conventional ROP screening in a number of international centres. The ART-ROP Network began in 2006 and, to the author’s knowledge, is the first ROP screening program to exclusively utilise WFDI with telemedicine for ROP detection and treatment. A retrospective review was undertaken of all 1181 patients who were screened via telemedicine from 2006 to 2015, inclusive. However, notably the well-established Karnataka Internet Assisted Diagnosis of ROP in India began in 2008 with a similar screening model.
The ART-ROP network showed a similar trend to the worldwide phenomena of increased numbers of infants requiring ROP screening, this is coupled with a decreasing number of ophthalmologists willing and able to screen for ROP. ART-ROP demonstrated an effective, alternative ROP screening method which not only provided accurate and timely ROP diagnosis but also decreased the time pressure on ophthalmologists in the work-flow conundrum. RetCam images for ART-ROP are captured by trained non-ophthalmologists with retinal image review by ophthalmologists to determine diagnosis, management, treatment of ROP and discharge of infants from screening of ROP. This method of utilising trained non-ophthalmologists to capture images is safe and effective with comparable results to ophthalmologist-captured images. The utilisation of non-ophthalmologists to capture images with a wide-field digital method for telemedicine can improve accessibility and delivery of ROP care whilst alleviating the challenge of ophthalmologist availability.

The ART-ROP network consists of four NICUs, across three DHBs, geographically spread throughout the Auckland metropolitan region, covering an ethnically and socio-economically diverse population. The quaternary NICU involved in ART-ROP is located in National Women's Hospital (NWH) which is known to have a higher rate of preterm birth than national New Zealand data, this might be anticipated due to the tertiary level care offered at NWH. Due to the high level of expertise and specialist treatment facilities available at NWH there are a high number of referrals of infants from outside and within the ART-ROP network to NWH NICU.

Infants who received only part of their screening through ART-ROP had significantly lower mean birth weight and gestational age, significantly different ethnic distribution and, significantly fewer screenings. These expected findings align with the demographic of infants who require transfer to quaternary level care. Interestingly, no significant difference in treatment rate was present between these two groups. This is likely due to the fact that babies with more complex medical needs remain in the quaternary Auckland NICU for a longer period from birth irrespective of their geographic residence location. The number of infants requiring transfer from CMDHB significantly decreased with the inclusion of CMDHB in the ART-ROP network. This has improved the service access and quality of ROP care.

Treatment requiring ROP was present in 6.4% of the cohort. Infants requiring treatment were extremely premature, mean gestational age of 25 weeks, and had an extremely low birth weight; mean birth
weight of 786 grams. These data are comparable to other developed countries with average birth weights reported as 737 to 763 grams and average gestational age of 25.3 to 25.6 weeks. The treatment rate of 6.4% coincides with rates throughout the Australian and New Zealand Neonatal Network. Other high income countries, such as the United States of America have a treatment rate of less than 4%. This notably lower treatment rate, may be due to the American Academy of Pediatrics screening criteria being more extensive, with 32 weeks gestational age, and 1500g birth weight. A higher prevalence of treatment-requiring disease is present in lower gestational age infants thus, a higher percentage of treatment-requiring ROP would be expected in this New Zealand cohort.

Annual ROP treatment rates reduced significantly across the ten-year period of the ART-ROP network. When NICU CMDHB was incorporated into the network in 2010 the decreasing rate was even more noticeable. The most recent treatment rate, in 2015, was approximately 2.5% of infants screened per year. This trend in treatment may be explained in part by the immediate comparison of sequential images that only WFDI provides, enabling more accurate assessment and documentation, thus ophthalmologists may feel more comfortable to observe rather than treat. In addition, a large number of the infants requiring ROP treatment before 2010 were transfers from the CMDHB NICU where binocular indirect ophthalmoscopy (BIO) screening was the standard of assessment. The subsequent incorporation of CMDHB into the ART-ROP network coincided with the more dramatic reduction in ROP treatment rate.

Treatment-requiring ROP did not vary in relation to the gender or ethnicity of the infant. Gender differences, with male predilection, and ethnic differences are known to occur in preterm birth rates with Māori infants at a higher-risk of preterm birth (Māori are the indigenous people of New Zealand). Māori ethnicity is thought to not be an individual risk factor per se but rather a reflection of the other risk factors for premature birth such as teenage pregnancy and maternal smoking. Such ethnic disparity was present, but over-represented in this review with Māori comprising 23.9% of infants screened, whilst Māori infants only comprise 10.8% of all premature infants (<37 weeks), and 6.8% of all births at NWH, 8.5% at WDHB, and 24.1% at CMDHB. It should be noted that ethnicity data of all births for NWH, WDHB, and CMDHB are reported at the maternal level (per birth), not the infant level with twins and triplets being included as a single birth (therefore although these data did
not reveal any differences in twin or triplet rate between ethnic groups, theoretically, since multiple births were classified under maternal ethnicity as a single birth, this could lead to under-reporting).

These data indicate an increasing proportion of infants of Māori ethnicity with extreme prematurity, indeed, Māori infants accounted for 22.4% of infants with ROP requiring treatment. However, Māori ethnicity as an individual factor does not appear to increase the risk of ROP which requires treatment, but rather these data indicate that the Māori population is over represented uniformly in rates of premature birth, rates of any stage of ROP, as well as Type 1 ROP which requires treatment. Therefore, more Māori infants are at risk of ROP due to their increased risk of premature birth.

Ophthalmology clinical review occurs for all premature infants screened for ROP due to the risk of ocular sequelae.\textsuperscript{114} On-going medical follow up is known to be challenging for this age cohort due to their need for a multitude of specialists input.\textsuperscript{123, 124} ART-ROP achieved an acceptable follow up rate of 76%. Reasons for being lost to follow up included: out of date contact information due to families moving locally or nationally, or a system failure in follow up organisation. This suggests that improved efforts are required to follow up, or appropriately refer, all at-risk infants in the future.

The rate of ROP-related sequelae in the infants with follow up was only 1.1% with the majority being asymptomatic avascular retinal patches, with no current visual impact. Two cases with macular drag did not have significant visual impairment and were diagnosed before their discharge from ROP screening. The low rate of ocular sequelae indicates the efficacy of the ART-ROP telemedicine screening method at detecting treatment-requiring ROP, and aligns with early data reports.\textsuperscript{113} No cases of severe ROP were missed by the ART-ROP Network screening protocol, with no child from this cohort being registered with BLENNZ for ROP-related vision loss.

The many benefits of WFDI with telemedicine for the evaluation of premature infants at risk of ROP have been noted previously.\textsuperscript{70, 74, 112} Our extensive data, of over a decade of the ART-ROP Network demonstrates the real world applicability, efficacy, and safety of WFDI telemedicine screening for ROP. A universal consensus for the standard of care for ROP screening is yet to be determined with the availability of the latest technology.\textsuperscript{70} However, there is an increasing body of evidence to support telemedicine WFDI for ROP screening as an alternative, and improved, ROP screening modality.
The limitations of our study include the retrospective nature of the study, and missing data on a significant number of infants that could potentially bias our conclusions. A prospective clinical review of all infants screened for ROP would be required for absolute certainty of the ART-ROP Network’s efficacy in the management of ROP. However, a small cohort of children were recruited for prospective follow up, and this study is detailed in Chapter 4.
Chapter 4:

Long term visual outcomes of children screened for retinopathy of prematurity with telemedicine in Auckland, New Zealand
4.1 Introduction

Retinopathy of prematurity (ROP) is a potentially blinding disease affecting very low birth weight (<1500g) and premature infants. Retinal screening of at-risk infants to detect Type 1 (treatment-requiring) ROP is essential. Effective ROP treatments are available with timely treatment maximising potential visual outcomes.\textsuperscript{1, 38, 125} The demand for ROP screening worldwide is escalating as a result of increased premature birth rates with simultaneous improvement in survival of these infants.\textsuperscript{126} Traditionally, ROP screening has been performed by an experienced ophthalmologist at the infant’s bedside using binocular indirect ophthalmoscopy. However, there are limitations with this screening method including: being labour intensive, time consuming for ophthalmologists, logistically challenging to coordinate screening times, and relying on subjective documentation with potential medico-legal implications.\textsuperscript{36, 66, 81} These factors have led to a reduction in the number of ophthalmologists willing to screen.\textsuperscript{36}

Wide-field digital imaging (WFDI) of the retina with remote grading via telemedicine has been studied as a viable option for ROP screening. Previous studies have shown the efficacy of WFDI at detecting referral warranted ROP (Type 1 or 2 ROP, which are further described in Chapter 2).\textsuperscript{36, 66, 74, 112} The use of WFDI may relieve workload pressures with non-ophthalmologists able to safely capture images for telemedicine assessment.\textsuperscript{78, 80} Interestingly, a real-world application of WFDI with telemedicine for ROP screening has been in place in Auckland, New Zealand since 2006, as the Auckland Regional Telemedicine ROP network (ART-ROP). ART-ROP uses wide-field digital images with telemedicine exclusively, to remotely diagnose, manage, and discharge infants from ROP screening. The ART-ROP network experience has already been reported in Chapter 3, showing its efficacy at detecting Type 1 ROP. The potential to improve access to timely ROP screening in the face of a decreasing workforce and increasing demand is essential to the future of ROP care.\textsuperscript{119} However, long term visual outcomes are needed to determine the robustness of telemedicine WFDI for ROP screening.

Decreased gestational age and low birth weight are known to be associated with an increased risk of ocular morbidity including: decreased visual acuity, myopia, strabismus, and amblyopia.\textsuperscript{42, 114, 127} Children with a history of any ROP are at additional risk of poor visual outcomes in the longer term.\textsuperscript{114}
Although WFDI is being increasingly used in the screening of ROP, and specifically in Auckland for more than a decade, unfortunately there are very little data in respect to longer term follow up of the children screened. Therefore, this prospective study was designed to assess the efficacy of ART-ROP by evaluating medium to long term ophthalmic structural and visual outcomes of children who were previously screened for ROP in our telemedicine system.

4.2 Subjects and Methods

4.2.1 Study design

A prospective observational study of ophthalmic outcomes of five to eight year old children who were previously screened for ROP by the ART-ROP Network. This study was approved by the Health and Disability Ethics Committee (14/NTA/183). All research adhered to the tenets of the Declaration of Helsinki.

4.2.2 Participants

Eligible children were identified via the established ART-ROP network database, which includes all infants born less than 30 weeks gestational age or birth weight less than 1250 grams or any infants deemed at-risk for developing ROP by the neonatal service. The telemedicine database was reviewed to identify children who had undergone screening for ROP and who would be at least five years of age, covering a three and half year period, thus potential participants were originally screened between May 2008 and October 2011. Children less than five years old at the time of this study were excluded due to their inability to reliably perform aspects of a comprehensive eye examination. Demographic and ROP data had already been obtained for all infants in the retrospective review of ROP screening with telemedicine, as reported in Chapter 3.

An invitation letter to participate was extended to the families of eligible infants by mail, and followed by a phone call. Children with a history of ophthalmic co-morbidities were excluded due to the potentially confounding long term ophthalmological outcomes. A total of three children, all with a history of non-accidental injury, were excluded.
4.2.3 Ophthalmological examination

All participants who attended the University of Auckland Eye Clinic for examination received a comprehensive paediatric ophthalmological examination, using methods outlined in Chapter 2. This included a full ocular and medical history, unaided distance vision, corrected visual acuity, cover test at distance and near, stereoacuity with the TNO, iCare tonometry for intra-ocular pressure (IOP) measurement, pupil assessment, slit lamp biomicroscopy, cycloplegic autorefraction with cyclopentolate 1.0% (Chauvin Pharmaceuticals Ltd, Kingston-Upon-Thames, United Kingdom) and tropicamide 1.0% (Chauvin Pharmaceuticals Ltd, Kingston-Upon-Thames, United Kingdom) to ensure full cycloplegia, and dilated fundus examination of the posterior pole. In addition dilated ultra-wide-field retinal images were captured of each eye with the Optos P200C (Optos, Dunfermline, United Kingdom). Image quality was evaluated at the time of capture and in cases of blinking, eyelashes encroaching on view, or unclear image, repeat images were captured. Ophthalmological evaluation techniques are described in detail in Chapter 2.

4.2.4 Statistical analysis

Statistical analysis was performed with IBM SPSS software version 22 (Armonk, New York, United States of America). A comparison of means was completed for both demographic and ROP associated characteristics to determine if the recruited cohort were representative of the population originally screened. Examination was undertaken for both eyes, however, only data from the right eyes of patients was used for analysis.

The cohort was divided into two groups based on ROP history, i.e. ROP or no ROP. The highest ROP stage recorded by the ART-ROP network was chosen for each individual for the purpose of this study, with any stage of ROP qualifying for the history of ROP group. ‘No ROP’ was defined as children who had no ROP (Stage 0) throughout the entire screening process. A one-way ANOVA was completed to further compare visual outcomes in ROP with three groups; no ROP, regressed ROP, and treated ROP.

Continuous data are reported as mean ± standard deviation. Comparison of means between groups was performed with a Pearson Chi-square test for categorical data and independent student t-test for continuous data.
4.3 Results:

A review of the ART-ROP network database determined 343 infants were screened for ROP between May 2008 and October 2011. A total of 314 children were eligible for participation. One hundred and twenty five potential participants were able to be contacted, 69 children attended the examination at the University of Auckland clinics. This was an attendance rate of 55.2% of potential participants contacted. Details of children's eligibility and recruitment are detailed in Figure 4-1.

Characteristics of children examined were compared to those who were eligible but did not participate, using Pearson chi-squared tests and independent student t-tests, (Table 4-1). No significant difference between groups was present for gender ($p=0.853$), birth weight ($p=0.595$), gestational age ($p=0.572$),
severity of ROP stage ($p=0.782$), or plus disease grading ($p=0.950$) as represented by the percentage of infants requiring treatment in both groups ($p=0.309$). Children who participated in this study had a history of more screening events of $4.1 \pm 2.3$ (mean $\pm$ SD), whilst those that did not participate had $3.4 \pm 1.9$ screenings ($p=0.011$), however this difference in number of screenings is not clinically significant.

The ethnicity composition of recruited children over-represented children of European ethnicity and under-represented Māori and Pacific Peoples. However, the severity of ROP as assessed by ROP stage, plus disease, and percentage requiring treatment, did not differ between recruited and the screened

### Table 4-1 - Characteristics of children in ART-ROP database from May 2008 to October 2011

<table>
<thead>
<tr>
<th></th>
<th>Children examined in the prospective ROP study</th>
<th>Remaining eligible children screened by ART-ROP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=69</td>
<td>N=245</td>
</tr>
<tr>
<td></td>
<td>n (%), mean ± SD</td>
<td>n (%), mean ± SD</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>38 (55.1%)</td>
<td>138 (56.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>31 (44.9%)</td>
<td>107 (43.7%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>50 (72.5%)</td>
<td>111 (45.3%)</td>
</tr>
<tr>
<td>Māori</td>
<td>6 (8.7%)</td>
<td>52 (21.2%)</td>
</tr>
<tr>
<td>Pacific Peoples</td>
<td>3 (4.3%)</td>
<td>39 (15.9%)</td>
</tr>
<tr>
<td>Asian</td>
<td>10 (14.5%)</td>
<td>38 (15.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0%)</td>
<td>5 (2.0%)</td>
</tr>
<tr>
<td>BW (grams)</td>
<td>1024 ± 288</td>
<td>1044 ± 266</td>
</tr>
<tr>
<td>GA (weeks)</td>
<td>27.5 ± 2.2</td>
<td>27.7 ± 2.2</td>
</tr>
<tr>
<td>Previous ROP treatment</td>
<td>7 (10.1%)</td>
<td>16 (6.5%)</td>
</tr>
<tr>
<td>Median ROP stage [IQR]</td>
<td>1 [0-2]</td>
<td>1 [0-2]</td>
</tr>
<tr>
<td>Median plus stage</td>
<td>Nil plus</td>
<td>Nil plus</td>
</tr>
</tbody>
</table>

$BW =$ birth weight  
$GA =$ gestational age
cohort (Table 4-1). Therefore, the recruited children can be considered a representative sample of all children screened by the ART-ROP network in terms of ROP severity, but not representative of the ethnicity of screened infants.

Sixty-nine children participated in this study. One child was removed from analysis due to their inability to complete a comprehensive eye examination due to global developmental delay, hydrocephalus, and cerebral palsy. Participating children had both eyes examined, with analysis confirming no significant difference between right and left eye results, hence, all further comparisons were performed using right eye data only, due to correlation between right and left eye observations in an individual.

Analysis was completed for the remaining 68 children with a mean age of 6.3 ± 0.9 years at time of examination and mean visual acuity of 0.05 ± 0.15 logMAR (Snellen equivalent of 6/6 part). Only one child had best corrected vision worse than 6/9, this was due to bilateral amblyopia for which he was under ophthalmological management. Four children had strabismus with no measurable stereoacuity, the mean stereoacuity of children without strabismus was 108 ± 91 seconds of arc. Cycloplegic autorefraction showed a range of spherical equivalents (measured in dioptre sphere, DS) from -2.00DS to +5.00DS with mean spherical equivalent of +1.35 ± 1.10DS. No significant amount of astigmatism was present for any child.

Forty-four children (63.8%) had a history of ROP with six of them having previous laser treatment for Type 1 ROP. The remaining 25 children had no history of ROP. A one-way ANOVA was performed to compare no ROP, regressed ROP, and treated ROP with no significant difference in distance visual acuity, stereoacuity, or cycloplegic autorefraction spherical equivalent. Further analysis was performed with groups divided into children with or without a history of ROP, demographics and characteristics of these children are detailed in Table 4-2. Children with a history of ROP had significantly younger gestational age ($\rho$<0.0005) and lower birth weight ($\rho$=0.001). Mean age at testing was higher for children with a history of ROP ($\rho$=0.007), however, this was not clinically significant. Visual and ocular structure outcomes indicated no missed ROP which in conjunction with no child from this cohort being registered with the Blind and Low Vision Education Network of New Zealand, a national registry of children with visual impairment, for ROP-related visual loss indicates that no ROP was missed by the ART-ROP network.
Comprehensive eye examinations indicated no significant difference between infants with, and without, a history of ROP in respect to: mean visual acuity ($p =0.596$), stereoacuity ($p =0.219$), cycloplegic autorefraction mean spherical equivalent ($p =0.472$), IOP ($p =0.180$), or optic cup to disc ratio ($p =0.818$). These results are highlighted in Table 4.2 with data indicating no significant difference in outcomes for ROP compared to prematurity without ROP.

Table 4.2 – Comparison of demographics and ophthalmic examination outcomes for infants with and without a history of ROP

<table>
<thead>
<tr>
<th>Demographics and Ophthalmic outcomes</th>
<th>Children with a history of ROP N=43 mean ± SD (n)</th>
<th>Children with no history of ROP N=25 mean ± SD (n)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at exam (years)</td>
<td>6.5 ± 0.8</td>
<td>5.9 ± 0.9</td>
<td>0.007</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>55.8%</td>
<td>52.0%</td>
<td>0.761</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>26.6 ± 1.9</td>
<td>29.1 ± 1.6</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>937 ± 237</td>
<td>1177 ± 311</td>
<td>0.001</td>
</tr>
<tr>
<td>Visual acuity (logMAR)</td>
<td>0.04 ± 0.15 (42)</td>
<td>0.07 ± 0.15 (24)</td>
<td>0.596</td>
</tr>
<tr>
<td>Stereoacuity (seconds of arc)</td>
<td>97 ± 83 (41)</td>
<td>127 ± 102 (23)</td>
<td>0.219</td>
</tr>
<tr>
<td>Mean sphere (DS)</td>
<td>+1.42 ± 1.12 (43)</td>
<td>+1.22 ± 1.06 (25)</td>
<td>0.472</td>
</tr>
<tr>
<td>Spectacles needed (%)</td>
<td>16.3% (7/43)</td>
<td>12% (3/25)</td>
<td>0.631</td>
</tr>
<tr>
<td>IOP (mmHg)</td>
<td>17 ± 4 (43)</td>
<td>18 ± 3 (25)</td>
<td>0.180</td>
</tr>
<tr>
<td>Right eye cup to disc ratio</td>
<td>0.33 ± 0.14 (40)</td>
<td>0.34 ± 0.14 (24)</td>
<td>0.818</td>
</tr>
</tbody>
</table>

Cycloplegic autorefraction results indicated spectacle correction was recommended for 10 children based on guidelines for preventing amblyopia by the ‘Paediatric Eye Disease Investigator Group’, with no difference between groups ($p =0.631$). These children were all referred for ophthalmic or optometric follow up including a full refraction. Myopia has been reported as a sequela of laser treatment, however this did not occur in this cohort with a mean spherical equivalent of +0.97DS for infants with laser treatment, this was not significantly different from infants with no history of treatment ($p =0.366$).
Optos images were captured for 68 of the participating children and analysed by a consultant paediatric ophthalmologist to assess the retina in particular for macula folds or drags, previous laser treatment, and peripheral retinal vascularisation. Peripheral avascular retinal patches were observed in four participants as illustrated in Figure 4-2 (Part A and B). All infants with avascular retinal patches had a history of ROP, with one child with avascular retina in the left eye having received right eye only laser treatment as an infant. Scars from previous laser treatment for Type 1 ROP were observed in six children, an example of these scars are illustrated in Figure 4-3.

Figure 4-2 – Avascular retinal patches (indicated by white arrows) in four children with a history of retinopathy of prematurity with a variation in size and appearance. All avascular patches were temporally located. Part A – Child 1, large bilateral avascular retinal patches. Child 2 had previous laser treatment in the right eye and avascular retina in the left eye.
Figure 4-2 – Part B - Child 3 had a large avascular retinal patch in the left eye, but poor image quality in the right eye. Child 4 had small bilateral avascular retinal patches.

Figure 4-3 – Optos images illustrating scars from previous laser treatment for ROP in a child with normal visual acuity and stereoacuity.
4.4 Discussion

The introduction of telemedicine with WFDI for ROP screening in the Auckland region has revolutionised the detection, and management of ROP. However, long term prospective outcomes of children under-going ROP screening with exclusive telemedicine WFDI have not been previously reported. There is also limited literature on differences in visual and structural outcomes of children who were deemed at-risk of ROP but did not develop it, compared to those who developed ROP which was subsequently treated or regressed. In this study comprehensive eye examinations were completed for 68 children aged 5 to 8 years old, previously screened for ROP with WFDI telemedicine due to their history of extreme prematurity and low birth weight. No new cases of ROP-related retinal change were detected, and no child was registered with BLENNZ due to visual impairment, indicating that these children were effectively screened by the ART-ROP network.

Ocular morbidity, including myopia, strabismus, and amblyopia, has been reported with increased prevalence in children with a history of prematurity and low birth weight. Determination of difference in outcomes of children with and without a history of ROP on top of these already known risks is important to inform appropriate follow up and management of these vulnerable infants. The mean visual acuity of all children assessed was 0.05 ± 0.15 logMAR (Snellen equivalent of 6/6 part), this is comparable to a large general population study of six year old children in Australia. Some literature has reported reduced visual acuity in infants with a history of low birth weight, however, our data do not support this although this is in the context of a relatively small sample size. It is important to note that children who did not participate may have potentially exhibited higher ocular morbidity rates.

Recruitment of eligible children for outcome measurements five to eight years following ROP screening is complicated due to family relocation, inability to contact patients, or parents unable to participate. Families being located out of town was a substantial issue in the current study due to one of the NICUs being a quaternary referral centre, with infants regularly referred from throughout New Zealand. Further difficulty in recruitment may be due to many reasons including but not limited to; the stress of an extra appointment when already caring for a disabled child, the perception that the child would be
unable to participate due to comorbidities such as developmental delay, hostility to healthcare profession in relation to their child’s disability, or other logistical issues such as transportation. The potential under-representation of ocular morbidities must be considered when evaluating these results, due to the conceivable but unintentional bias in recruitment.

This study indicated no significant differences between infants with and without a history of ROP in relation to: mean visual acuity, stereoacuity, mean spherical equivalent, IOP, cup to disc ratio, or the need for spectacles. The present research differs from a previous New Zealand report on children born in 1986 in which 64% of children born less than 1500 grams had some visual abnormality, and 100% of children with a history of stage 3 ROP having long term visual impact. Cryotherapy or laser treatments were not available in New Zealand for ROP treatment in 1986, hence, a higher percentage of ocular morbidity would be expected. Improvements in neonatal care, detection, and treatment of ROP, is reflected in the improved visual outcomes. The only noted difference in structural outcomes, other than the expected laser scars from known previous ROP treatment in six infants, were peripheral avascular retinal patches.

Avascular retinal patches were detected in the temporal retina of four children with a history of regressed ROP. Prior to this study, such findings have only been reported up to the age of 72 weeks post-menstrual age. However, the children in this study with avascular patches remain asymptomatic without treatment, however, longer term outcomes must be determined due to concerns that avascular retinal areas may potentially progress to retinal ischemia or detachment in the future. Though not applied in the current study, fluorescein angiography could reveal more information on the nature, extent, and blood vessel endings at the avascular edge, of these retinal patches.

Six children with previous laser treatment for ROP completed comprehensive eye examinations, with Optos images clearly showing large areas of previous laser treatment. Laser treatment for ROP has been associated with an increased risk of high myopia. None of the children with a history of laser treatment had a myopic refraction in this cohort, with a mean spherical equivalent of +0.97DS. However, these children should continue to be monitored for myopia due to their increased risk. Only a small number of children had ROP requiring laser treatment, thus these data may not be illustrative of the refractive outcomes noted in other larger studies.
Visual fields were not assessed in the current study due to the challenges involved in the young age group with potential comorbidities related to prematurity. However, previous research has indicated that even with treatment, there is minimal reduction in visual fields when compared to children not receiving treatment. Future research for longer-term outcomes should include visual field assessment, particularly of infants with laser treatment, or with avascular retinal patches.

The ethnic composition of the recruited cohort varied significantly from the infants screened by ART-ROP with an under-representation of Māori and Pacific Peoples. Further research is needed to determine if ethnicity impacts on long term visual and structural outcomes.

The present study endorses ART-ROP as an effective and safe screening program for ROP, with no cases of missed ROP being identified more than five years post-screening. This finding is supported by no children screened by the ART-ROP network in the time period reviewed being registered with the Blind and Low Vision Education Network New Zealand (BLENNZ), a national registry of all children with visual impairment of worse than 6/18 in their best eye, which provides educational and social support for children with visual impairment.

Furthermore, visual and structural outcomes of infants with and without a history of ROP were determined not to differ from one another, except for the presence of avascular retinal patches in children with a history of ROP. Future research is required into the implications and longer-term outcomes of avascular retinal patches with potential implications on follow up and management of infants with regressed ROP. Notwithstanding the difficulties in recruitment, as illustrated by the current study, longer-term and larger cohort studies are certainly required to confirm these promising observations of the ART-ROP screening network.
Chapter 5:

Universal Newborn Eye Screening
5.1 Introduction

Paediatric visual impairment has a lifelong impact on the social, economic and emotional status of any individual.\(^1\)\(^,\)\(^2\) Calculated ‘blind years’ from all causes of paediatric visual impairment is similar to the number resulting from adult cataract.\(^1\) A key aim of the World Health Organisation VISION 2020 is the prevention of childhood blindness worldwide.\(^1\) The causes of paediatric visual impairment and blindness are complex and varied with regional and national differences.\(^2\) Detection of the complex array of paediatric ocular disorders is essential for timely treatment, improved long term outcomes and decreasing ocular morbidity.

Currently several screening programs are in place to detect congenital abnormalities in the newborn population of New Zealand. The National Screening Unit in New Zealand oversees the two nationally-controlled newborn screening programmes. These screening programmes detect important conditions at rates of approximately 0.1% for metabolic conditions with the heel prick test and 0.1% for universal hearing screening.\(^52,\)\(^53\) All other newborn assessments including the red reflex test, are undertaken by the lead maternity carer of the neonate, which in New Zealand may be a midwife, general practitioner, or a private obstetrician.\(^54\) New Zealand newborn eye screening guidelines dictate the use of the red reflex examination in the first 24-48 hours to detect ocular disorders, in particular congenital cataract.\(^54,\)\(^55\)

Red reflex screening is the current standard screening test to identify paediatric ocular disorders during the newborn period.\(^56\) The ophthalmoscope transmits light through the optical pathway with any impediment to this light, such as congenital cataract, corneal opacities, iris abnormalities and retinal tumours, resulting in an abnormal red reflex.\(^56\) Although retinoblastoma and congenital cataracts can be detected via red reflex, often it is not reliably achieved.\(^61,\)\(^62\) A survey of screeners including midwives, paediatricians and general practitioners in New Zealand indicated that screening was regularly performed only 80-90% of the time, and that the majority of screeners would prefer further training.\(^55,\)\(^136\) Thus, potentially vision threatening disorders in newborn infants may be being missed.

Retinopathy of prematurity (ROP) is an ocular disease that affects premature and very low birth weight infants. Those who are deemed at risk of retinopathy of prematurity by local screening guidelines
undergo eye screening. ROP screening in Auckland, New Zealand is performed with wide-field digital images (WFDI) that are captured of the retina with the RetCam (Clarity Medical Systems, Pleasanton, CA, United States of America) paediatric ocular camera, these are then assessed via telemedicine by a consultant paediatric ophthalmologist. WFDI with telemedicine has been utilised as part of retinopathy of prematurity screening protocols in many centres worldwide.66, 74, 116 In the process of this there has been identification of many incidental findings of other ocular abnormalities.137 The use of WFDI for “Universal Newborn Eye Screening” (UNES) would aim to detect all congenital ocular abnormalities and thus prevent unnecessary visual impairment in the paediatric population. The concept of universal newborn eye screening has been explored in one study in China, reporting a prevalence for birth-related retinal haemorrhages of 21.52% and for other ocular abnormalities of 2.99%.82

Therefore our aims were: A) To identify the prevalence of ocular abnormalities, in particular retinal haemorrhages, using RetCam wide-field digital imaging eye examinations in a New Zealand newborn population. B) To identify any correlations between retinal haemorrhages and maternal, neonatal, and obstetric factors.

5.2 Subjects and Methods

5.2.1 Study design

Universal newborn eye screening was designed as a prospective cohort study, conducted within the Auckland District Health Board (ADHB) catchment area. Following fully informed consent, neonates were enrolled from ADHB birthing services between June 2015 and December 2016, inclusive. Screening occurred in one of two locations, ADHB National Women’s hospital and BirthCare, a primary maternal hospital. The region is ethnically and socio-economically diverse and by utilising both hospital level maternity wards and primary level birthing centre a range of neonates were accessed, with the goal of garnering a cohort representative of the region.117 The infants in the study represented those whose parents kindly consented to participation in the screening procedure.
5.2.2 Subjects and recruitment

Infants who already received WFDI as part of the established retinopathy of prematurity screening program, infants less than 30 weeks gestational age or less than 1251 grams birthweight, were excluded from this study. All other infants were invited to participate at the discretion of their parents and lead-maternity carers. Information brochures were inserted into every Tamariki Ora Well Child book, which is given to the guardian of each newborn on discharge from hospital. In addition recruiting took place at both the maternity ward and the local birthing centre. To determine the prevalence of ocular abnormalities in infants with 95% confidence, and absolute precision of 5%, a minimum sample size of 323 infants was estimated. This was based on the assumption of a rate of ocular abnormality of 30% or less, which aligns with current reported rates in the literature. Rates of ocular abnormalities other than retinal haemorrhages were too low to calculate power equations for individual conditions. Therefore, the goal recruitment number was 350 infants to account for cases of incomplete data, or study attrition rate.

Informed consent was sought from the families, with a full explanation of the screening procedure along with risk and benefits. This study was approved by the Health and Disability Ethics Committee (14/NTA/183). All research adhered to the tenets of the Declaration of Helsinki.

All infants were screened in maternity wards in the hospital or at community birth unit, with qualified midwives, paediatricians and nurses clinically observing them for adverse events. It was endeavoured to capture all images within 72 hours of birth, however, this was not always possible due to scheduling, infant or maternal health.

5.2.3 Photography protocol

Wide-angle images were obtained for all infants enrolled using the RetCam III or RetCam Shuttle (Clarity Medical Systems, Pleasanton, CA, United States of America) both using software v6.1. The screening team included the nurse specialist and medical photographer who regularly use the RetCam for ROP screening in Auckland. The nurse specialist and medical photographer had been trained by the consulting paediatric ophthalmologist on correct technique to capture appropriate, and focused images. Infants were swaddled and positioned during the screening by the third member of the screening team,
who had consented families and instilled eye drops, with parents welcome to help and support throughout if they so wished.

Participating infants had their eyes dilated with 1.0% tropicamide and 2.5% phenylephrine, 30-60 minutes prior to screening. Tetracaine 0.5% topical anaesthetic was instilled in each eye prior to RetCam imaging. A sterile speculum was used for each infant to allow adequate ocular exposure for anterior segment and retinal imaging. Viscotears Liquid Gel (Carbomer 2mg/g; Norvatis Pharmaceuticals UK Ltd., Camberley, UK) was placed on the RetCam lens (D130 lens) as coupling surface between the cornea and RetCam hand-piece lens. This photography protocol aligns with the current ROP RetCam screening protocol utilised within the ADHB, and similar to the recent study by Li et al.46, 82

Images captured were (A) an anterior image with iris and red reflex visible, (B) retinal images including posterior pole with macula and optic nerve, temporal and nasal peripheral retina. RetCam images were stored as uncompressed, encrypted MLX files on the secure ADHB ROP screening imaging server. The RetCam review station software version 4.1 allows stored images to be accessed, reviewed and reported on by the consulting paediatric ophthalmologist, from an approved computer in the hospital or remote access from an approved laptop. The resulting report of the infant’s ocular findings and appropriate images are uploaded to the participant’s electronic health record as a pdf document.

Infants with detected ocular abnormalities were contacted by phone to inform them of the results and follow up plan. Retinal haemorrhages were classified into all appropriate categories; macular haemorrhages were any haemorrhage within one disc diameter of the fovea, optic nerve haemorrhages were defined as any haemorrhage on or within one disc diameter of the optic nerve head, and extensive haemorrhages were classified when more than ten haemorrhages were present and they extended beyond the arcades. It was also noted if haemorrhages were white centred. Participants with retinal haemorrhages detected were re-screened six weeks after initial screening using wide field RetCam imaging to assess clearance of haemorrhages.139 Ocular abnormalities were recorded if they were deemed to have potential visual or systemic impact, with appropriate referral for ophthalmological follow up if needed.
5.2.4 Data collection

Further data points were collected from hospital records, including ethnicity, gestational age, age at screening, birth modality, if induction occurred, birth weight, infant length at birth, head circumference, maternal primiparity, and maternal height when available.

Maternal height was used as a surrogate for pelvic size, as pelvic dimensions are not routinely measured. Although maternal height is not considered a good indicator for pelvic adequacy it is known to strongly correlate to pelvic dimensions. Trial of labour is considered the best indicator of pelvic adequacy.

5.2.5 Outcomes

Outcome measures were (A) the ability to complete screening, (B) detection of ocular abnormalities; including retinal haemorrhages, (C) resolution of birth-related haemorrhages at follow up, and (D) adverse events of screening.

5.2.6 Statistical analysis

Statistical analysis was completed using IBM SPSS software version 22 (Armonk, New York, United States of America). Binomial logistic regression models were used to calculate odds ratio for birth-related retinal haemorrhages in relation to independent maternal, obstetric and, neonatal factors.

5.3 Results

5.3.1 Study population

Three hundred and fifty newborns were recruited for universal newborn eye screening. A full set of screening photos was unable to be obtained for four infants, thus these infants were removed from further analysis. Of the 346 infants analysed 51.3% were male (n=177), similar to the Auckland National Women’s Hospital most recent report, 51.6% male. Screening occurred within 72 hours of birth for 76.3% infants. The median age at screening was two days old, with an inter-quartile range of two to three days, and a range of zero to 36 days.
Self-reported ethnicity was categorised into European, Māori, Pacific Peoples, Asian, and other. The ethnic spread of the participants was comparable to that of the latest ADHB maternity report of maternal ethnicity, thus there was a good representation of the newborn population in the Auckland District Health Board region and these data are detailed in Table 5-1. It is noted that Pacific Peoples and Asian populations are slightly under-represented, whilst European ethnicity is slightly over-represented.

Table 5-1 - Ethnicity comparison of UNES participants to regional newborn data

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Infants enrolled in UNES</th>
<th>Regional newborn population data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 346</td>
<td>N = 6933</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>European</td>
<td>197 (56.9%)</td>
<td>3118 (45.0%)</td>
</tr>
<tr>
<td>Asian</td>
<td>88 (25.4%)</td>
<td>2241 (32.3%)</td>
</tr>
<tr>
<td>Māori</td>
<td>27 (7.8%)</td>
<td>469 (6.8%)</td>
</tr>
<tr>
<td>Pacific Peoples</td>
<td>22 (6.4%)</td>
<td>805 (11.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (3.5%)</td>
<td>300 (4.3%)</td>
</tr>
</tbody>
</table>

Over half of infants in UNES had vaginal delivery (n=182/346) with 23.6% of these (n=43/182) requiring instrumental intervention, 30 involving ventouse extraction. The remaining 165 infants being delivered by caesarean section, 47.4% were considered emergency caesareans. A minor over-representation of caesarean sections was present due to ease of recruitment due to on average longer hospital stays. This was in conjunction with an under-representation of spontaneous vaginal delivery was seen when compared to the ADHB maternity report, Table 5-2.

Table 5-2 - Delivery modality frequencies, comparison of UNES participants to regional newborn data

<table>
<thead>
<tr>
<th>Delivery modality</th>
<th>Infants enrolled in UNES</th>
<th>Regional newborn population data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 346</td>
<td>N = 6933</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Spontaneous vaginal delivery</td>
<td>139 (40.2%)</td>
<td>3594 (51.8%)</td>
</tr>
<tr>
<td>Instrumental vaginal delivery</td>
<td>43 (12.4%)</td>
<td>871 (12.6%)</td>
</tr>
<tr>
<td>Caesarean delivery</td>
<td>164 (47.4%)</td>
<td>2468 (35.6%)</td>
</tr>
</tbody>
</table>
The mean gestational age of enrolled infants was 38.8 weeks ± 1.7 weeks, ranging from 31 to 42 weeks gestation. Birth weights had a large range from 1270g to 4690g with a mean of 3284 ± 558g. Newborn size measurements: mean head circumference was 34.6 ± 1.7cm, and mean length was 50.5 ± 2.6cm, ranging from 39 to 58cm. Maternal height was able to be recorded for 327 of 346 infants, with a mean of 165 ± 7cm (range 148 to 187cm).

5.3.2 Retinal haemorrhages

The prevalence of retinal haemorrhages at birth was 14.5% (50/346) in this study. Thirty-five of the fifty cases (70%) of haemorrhages were bilateral with unilateral haemorrhages being equally distributed between the right and left eye, nine and seven, respectively. Haemorrhages were further described as macular, optic nerve, extensive, and/or white-centred, examples in Figure 5-1.

![Figure 5-1 - Wide-field digital images of retinal haemorrhages of infants in UNES. A) isolated optic nerve haemorrhages, B) extensive haemorrhages involving the optic nerve and macula, and C) extensive, white-centred haemorrhages involving the optic nerve, macular, and extending beyond the arcades.](image)

Any haemorrhage within the peri-macular region were classified as macula involving, this occurred in 31% (31/100) of eyes. Eight infants had bilateral macula involving haemorrhages. Optic nerve haemorrhages were classified as any haemorrhage adjacent to, or directly involving the optic nerve. Optic nerve haemorrhages were common, being reported in 50% (50/100) of participant eyes. Extensive haemorrhages, extending beyond the arcades, were identified in 67% (67/100) of eyes while white-centred haemorrhages were observed in 53 eyes. A single infant had pre-retinal haemorrhages noted in this study, the largest is displayed in Figure 5-2A. Types of haemorrhages were comparable between right and left eyes as detailed in Table 5-3.
Table 5-3 – Comparison of haemorrhage type between right and left eyes

<table>
<thead>
<tr>
<th>Haemorrhage Type</th>
<th>Right eye n (%)</th>
<th>Left eye n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral</td>
<td>9 (18%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Macular</td>
<td>13 (26%)</td>
<td>17 (34%)</td>
</tr>
<tr>
<td>Optic nerve</td>
<td>23 (46%)</td>
<td>27 (54%)</td>
</tr>
<tr>
<td>Extensive – beyond arcades</td>
<td>34 (68%)</td>
<td>33 (66%)</td>
</tr>
<tr>
<td>White-centred</td>
<td>25 (50%)</td>
<td>28 (56%)</td>
</tr>
</tbody>
</table>

* Percentages may add to more than 100% as classification of haemorrhage type are non-exclusive groupings

A comparison of infant characteristics between those with and without retinal haemorrhages was undertaken, see Table 5-4. Chi squared tests revealed a significant difference in characteristics of infants when grouped by the presence or absences of haemorrhages, in respect to: delivery modality, induction, and whether screening took place within 72 hours of birth. Demographic aspects such as ethnicity and gender were no significantly different between these groups. Anthropomorphic features of infants and mothers were considered for their potential impact on the risk of retinal haemorrhage occurrence with no significant differences noted. Infants with haemorrhages had an increased gestational age relative to those without ($p=0.049$), however, this difference was not clinically significant, infants with haemorrhages had a median gestational age of 39.0 weeks (inter-quartile range of 37.9 to 40.0), compared to 39.4 weeks (38.3 to 40.3) in the no haemorrhage category.
A logistic regression was performed to establish the effects of delivery modality and screening before or after 72 hours of age on the likelihood that participants would have retinal haemorrhages. Although induction was significantly associated with the presence or absence of haemorrhages it is closely linked to delivery modality and therefore, only delivery modality was included in the binomial logistic

### Table 5-4 - Birth prevalence of retinal haemorrhages by baseline characteristics in UNES

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RH absent N = 296</th>
<th>RH present N = 50</th>
<th>p-value</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>155 (52.5%)</td>
<td>2 (44.0%)</td>
<td>0.264</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>141 (47.5%)</td>
<td>28 (56.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Early Screening</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;72 hours</td>
<td>218 (73.7%)</td>
<td>45 (90.0%)</td>
<td>0.014</td>
<td>1.0</td>
</tr>
<tr>
<td>≥72 hours</td>
<td>78 (26.4%)</td>
<td>5 (10.0%)</td>
<td>0.36</td>
<td>(0.13-0.98)</td>
</tr>
<tr>
<td><strong>Delivery modality</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>162 (54.7%)</td>
<td>2 (4.0%)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>SVD</td>
<td>104 (35.1%)</td>
<td>35 (70.0%)</td>
<td>26.3</td>
<td>(6.18-111.91)</td>
</tr>
<tr>
<td>IVD</td>
<td>30 (10.1%)</td>
<td>13 (26.0%)</td>
<td>33.61</td>
<td>(7.18-157.26)</td>
</tr>
<tr>
<td><strong>Birth weight (grams)</strong></td>
<td>3272 ± 575</td>
<td>3353 ± 449</td>
<td>0.345</td>
<td></td>
</tr>
<tr>
<td><strong>Head circumference (cm)</strong></td>
<td>34.6 ± 1.8</td>
<td>34.4 ± 1.3</td>
<td>0.457</td>
<td></td>
</tr>
<tr>
<td><strong>Birth length (cm)</strong></td>
<td>50.5 ± 2.8</td>
<td>50.9 ± 1.8</td>
<td>0.228</td>
<td></td>
</tr>
<tr>
<td><strong>Maternal height (cm)</strong></td>
<td>164.9 ± 7.1</td>
<td>164.5 ± 7.0</td>
<td>0.760</td>
<td></td>
</tr>
<tr>
<td><strong>Gestational age (weeks)</strong></td>
<td>Median [IQR]</td>
<td>39.0 [37.9-40.0]</td>
<td>39.4 [38.3-40.3]</td>
<td>0.049</td>
</tr>
</tbody>
</table>

RH = retinal haemorrhage, reported at the participant level (i.e. a haemorrhage in either eye, or in both eyes, classifies that infant into the retinal haemorrhage present group)  
SD = standard deviation  
CS = caesarean section  
SVD = spontaneous vaginal delivery  
IVD = instrumental vaginal delivery  
IQR = inter-quartile range  
p-values reported to three decimal places  
*Gestational age is not normally distributed, therefore, results are presented as median [IQR] rather than mean ± SD
regression model. The model demonstrated a significant increase in the odds of retinal haemorrhages in both normal vaginal delivery (OR, 26.30; 95% CI, 6.18−111.91; p <0.0005) and instrumental vaginal delivery (OR, 33.61; 95% CI, 7.18−157.26; p <0.0005) than infants delivered by caesarean section. Early screening, within 72 hours of birth increased the odds of retinal haemorrhages being present (p =0.046). The baseline characteristics for infants with and without retinal haemorrhages are outlined in Table 5-4.

5.3.3 Retinal haemorrhage resolution

Follow up was attended by 66% (33/50) of infants with retinal haemorrhages. Follow up was not attended for a number of reasons including; families not attending scheduled appointments, families unable to schedule an appointment that was suitable for their six week old infant, families not responding to multiple attempts to contact, or families choosing to not have a follow up appointment.

Figure 5-2 – Initial haemorrhage presentation for two infants with non-resolving haemorrhages; Infant 1 extensive haemorrhages: a) left eye with pre-retinal haemorrhage, b) right eye; Infant 2 extensive haemorrhages c) left eye, b) right eye.
Follow up screening occurred at a median of 50 ± 14 days, with an inter-quartile range of 43 to 59 days. At follow up screening 94.0% of retinal haemorrhage cases had complete resolution. However, two infants had persisting haemorrhages, both of which were born via ventouse delivery with extensive haemorrhages at initial presentation as shown in Figure 5-2, one imaged within 72 hours and one after 72 hours.

5.3.4 Other ocular abnormalities

Ocular abnormalities with potential visual, or systemic impact not including retinal haemorrhages were detected in five infants (1.4%), see Figure 5-3. This included one case of congenital cataract (Figure 5-3A), two cases of suspected optic nerve hypoplasia (Figure 5-3B), a suspected choroidal haemangioma (Figure 5-3C), and one case of congenital hypertrophy of the retinal pigment epithelium (CHRPE, Figure 5-3D).

Figure 5-3 – Ocular abnormalities detected during UNES; (A) congenital cataract, (B) optic nerve hypoplasia, (C) choroidal haemangioma, and (D) inferior CHRPE.
5.3.5 Adverse events

No episodes of allergic reaction, significant bradycardia, or corneal abrasions were identified at or after screening. In addition, there were no reports of adverse events to the screening team, throughout the period that screening was being undertaken.

5.4 Discussion

This study presents the results of a prospective universal newborn eye screening program of 350 newborn infants in Auckland. Three hundred and forty-six newborn infants completed screening with full photo sets captured and subsequently assessed by a paediatric ophthalmologist.

An ocular abnormality was detected in 54 infants. UNES detected retinal haemorrhages in 14.5% of participants and other ocular abnormalities in 1.4% of those screened. The screened cohort was comparable in terms of ethnicity, gender, mother’s parity and delivery modality to the population of newborn infants at the National Women’s Hospital in Auckland.¹¹⁷

Ocular abnormality screening at birth has been in place in the form of the “red reflex test” in many developed countries.⁵⁴ ⁵⁶ However, the rate of ocular abnormality rate is significantly higher in our study than red reflex screening. The red reflex test is designed to check for certain visual axis obscuring diseases whilst, full photographic imaging of the eye is able to assess major structures of the eye, hence, a higher rate of abnormality would have been expected. However, to further assess the difference between current screening practices and UNES much larger population studies are needed, due to the relatively uncommon incidence of the ocular conditions screening is designed to detect.

Detected ocular abnormalities, excluding retinal haemorrhages were a case of congenital cataract, a posterior pole choroidal haemangioma, a CHRPE and two cases of suspected optic nerve hypoplasia. Some of these ocular disorders are treatable from an ophthalmic perspective, whilst others are not. Although vision may not be improved or restored in some of the ocular abnormalities detected by UNES, such as optic nerve hypoplasia, early detection may still be beneficial for the infant development and family with possible impacts on educational and systemic health outcomes.
Small optic nerves, as in suspected cases of optic nerve hypoplasia, are unable to be detected via red reflex screening, yet were detected by UNES. Early detection of optic nerve hypoplasia is important as it can be associated with cerebral midline malformation resulting in hormonal deficits.\textsuperscript{145} Hormonal monitoring and replacement in optic nerve hypoplasia is essential to ensure proper global development of these infants, with early diagnosis key to improving outcomes.\textsuperscript{145}

The prevalence of ocular abnormalities (excluding retinal haemorrhages) identified by universal newborn eye screening has previously been reported in two large studies, with a range of 2.25-2.99\%.\textsuperscript{82, 83} This reported prevalence (≤3\%) comes from Asia, and differs from our reported UNES data, yet regional differences are to be expected due to geographic differences in paediatric ocular conditions. Systemically associated uveitis were noted in both reported cohorts but no cases of ocular inflammation were noted in UNES, aligning with known regional variations.\textsuperscript{82, 83} Due to the small number of each type of congenital abnormality or ocular disease in the newborn, large studies are required to determine regional detection rates, and thus prevalence of ocular abnormality as a whole.

A large number of retinal haemorrhages were detected by UNES screening. In addition to determining the prevalence of retinal haemorrhages; description of retinal haemorrhage appearance and factors including; neonatal, obstetric and maternal were assessed. Retinal haemorrhages detected by the UNES program ranged greatly in appearance from a single haemorrhage to extensive, peripheral, white-centred haemorrhages. The range and type of haemorrhages reported in this study align with that reported in the literature of other recent studies.\textsuperscript{82, 83, 139, 146, 147} Haemorrhage presentation was most commonly bilateral (70\%), with 16 cases of unilateral haemorrhages. In contrast, other studies have noted an increased prevalence of left eye haemorrhages, but no laterality difference was noted in this study.\textsuperscript{146}

Neonatal, obstetric and maternal factors were assessed. Interestingly, maternal height, parity, infant birth weight, infant length at birth, head circumference, and ethnicity had no significant association with presence of retinal haemorrhages. Some studies report primiparity to be associated with birth-related retinal haemorrhages, whilst others find no correlation.\textsuperscript{146, 148} In relation to the detection of retinal haemorrhages factors that were significant included: delivery modality, age at screening and gestational age.
The most significant variable in relation to prevalence of retinal haemorrhage was clearly delivery modality. When compared to caesarean section, logistic regression identified a 26.30 times increase in the odds of retinal haemorrhage in infants born by normal vaginal delivery and a 33.61 times increase with instrumental vaginal delivery. Previous reports have queried foetal head compression and thus, compression of the globe, as a factor in the development of birth-related retinal haemorrhages. If such compression of the globe was the sole or principle factor in retinal haemorrhage formation, then one might expect a link between maternal size relative to infant head circumference, weight or length. However, no such relationship was noted in this study, or in other prospective studies of birth-related retinal haemorrhages. Increased rate and persistence of retinal haemorrhages with ventouse delivery has been previously noted, with intracranial pressure changes from the vacuum suction being attributed as a possible causative factor. The suction force of the vacuum extraction, has been hypothesised to cause an increase in intra-cranial pressure affecting central ophthalmic venous and arterial flow with retinal bleeding eventuating. The hypothesis that intra-cranial pressure changes are a key component in the aetiology of birth-related retinal haemorrhages, may explain in part why caesarean sections appear to be protective against retinal haemorrhages.

Early screening, within 72 hours, as defined by Egge et al, increased the odds of detection of retinal haemorrhage. Other studies also report a significant difference in the rate of retinal haemorrhages with early screening, and a variation in prevalence based on initial age of screening, possibly indicating a rapid resolution rate of birth related retinal haemorrhages. Haemorrhage resolution is of great importance due to the potential impact on visual development, or the possibility to distinguish birth-related from non-accidental injury (Shaken Baby Syndrome) retinal haemorrhages. The rate of resolution has been widely discussed with a large review of the literature determining that 97% of retinal haemorrhages cleared by six weeks of age. The current study had a median follow up time of just over six weeks with 94% of haemorrhages resolving in that timeframe, however, two cases had incomplete resolution of haemorrhages at that follow up. These two infants had dense, confluent haemorrhages at initial presentation, and both were born via ventouse delivery, they will continue to be monitored by ophthalmology for long term sequelae. Therefore, ventouse delivery is not only linked to an increased rate of haemorrhage, but also increased length of haemorrhage duration. Indeed,
retinal haemorrhage was actually detected in 11 of the 30 (36.7%) ventouse deliveries in this study. Other factors may influence the rates reported, such as distribution of delivery modality in individual studies, examiner experience, and the mode of examination.\textsuperscript{147}

Unfortunately, the long term impact of retinal haemorrhages in newborn, particularly macular and long-standing haemorrhages, is currently unknown. Obscuring the visual axis during the critical period is known to cause deprivation amblyopia,\textsuperscript{2} which could occur with long-standing haemorrhages, such haemorrhages could also result in subtle changes in local retinal architecture that subsequently may affect function. This may explain some cases of ‘idiopathic’ amblyopia, which typically at the time of detection of the amblyopia, would have no ophthalmological findings as haemorrhages would be long-resolved. Substantial, prospective longitudinal data are required to appraise such hypotheses.

Birth-related retinal haemorrhages, may also give an insight into associated changes in the central nervous system, particularly the brain. Hypothesised increased intra-cranial pressure forming retinal haemorrhages would be expected to not only affect the eye, but also impact the brain. Prospective assessment of subdural haemorrhage rates has seen a range of rates reported from 8.1\% to 46\% in asymptomatic infants.\textsuperscript{149, 150} There is also a noted variation in presentation rates based on delivery modality, with instrumental delivery being associated with the highest rates.\textsuperscript{149, 150} These asymptomatic subdural haemorrhages also have a similar healing course to birth related retinal haemorrhages, with birth-related intra-cranial haemorrhages resolving by four weeks of age.\textsuperscript{149, 150} The clinical significance of birth-related subdural haemorrhages is yet to be clinically established. It could be postulated that those infants with retinal haemorrhages may also experience subdural haemorrhages, further research into intra-cranial pressure changes and the link between subdural and retinal haemorrhages in newborn infants would be of considerable interest, with future clinical significance of such bleeding, and healing to be determined.

The possibility of significant pressure changes through the birthing process being contributory to the development of retinal haemorrhages might indicate that pelvic size is of importance to understanding this complication. A limitation of the current study in this regard is that pelvic size is not routinely measured and thus could not be assessed, with maternal height being used as a surrogate measurement. Maternal height was collected from the prenatal assessment form routinely used in
Auckland, however, height was not always recorded or in some cases mothers did not present for prenatal care. Mothers were asked to report their own height, which was used if no other height report was present, thus may not be accurate. Further research into maternal size, in particular pelvic outlet dimensions in comparison to neonatal size and head circumference, could give more insight into the relationship, if any, in respect to the development of retinal haemorrhages.

This prospective, screening study indicates the applicability of UNES to successfully detect ocular abnormalities at birth. Introducing a large screening program would result in a large increase of workload for ophthalmology. If screening is implemented before 72 hours post-birth it would allow detection of more birth-related retinal haemorrhages. Screening teams would need to be appropriately trained and rostered to cover all newborn infants, this would be logistically challenging but has been achieved for other nation-wide screening programs such as universal newborn hearing screening. Detection rates for ocular abnormalities were significantly higher than other national screening programmes currently in place in New Zealand. Early detection of neonatal ocular conditions is known to improve long term outcomes and thus, be beneficial and ultimately cost-effective.
Chapter 6:

Clinical applicability of Saccadic Vector Optokinetic Perimetry in normal-sighted and visually impaired children
6.1 Introduction

Visual field defects can occur in children due to visual pathway tumours, paediatric glaucoma, retinal dystrophies and cerebral visual impairment. Perimetry, the assessment of visual fields is therefore a key diagnostic and monitoring tool in paediatric ophthalmology.

Technological advances in perimetry have occurred with increasing understanding of the visual field, both in normal situations and abnormal cases due to ophthalmic or neurological conditions. A number of perimetry techniques are currently available for detecting ophthalmic and neurological conditions, however, these may be challenging for children to perform. The Humphrey Visual Field Analyser (HVFA), an automated static perimeter, is considered the gold standard for adult perimetry. However, children struggle with automated static perimetry due to long periods of sustained concentration, the ability to maintain central fixation, a fixed head position, and subjective responses.

The Swedish Interactive Thresholding Algorithm (SITA) was designed and introduced with the goal of minimising HFVA assessment time in children. Whilst SITA was able to half the testing time for HFVA in a cohort of six to eighteen year olds, time taken was still on average greater than six minutes per eye, and the challenges of head positioning and central fixation maintenance persist in children. Length of test in combination with short concentration spans in children causes reduced applicability and reproducibility of paediatric visual field assessment with HFVA. These barriers to performance are highlighted in younger children and individuals with neuro-disability, however, the need for visual field results and visual information is high for such groups.

Children with both visual impairment and cognitive impairment require visual field assessment to assess and monitor their condition as they grow and develop. Cerebral visual impairment (CVI) is the most common cause of severe childhood visual impairment in New Zealand at approximately 30% of severe childhood visual impairment, with similar rates as the United States of America. Currently, standard objective visual acuity and visual field tests are not available for children with CVI given the associated cognitive delay. Available subjective tests are not accurate, or not appropriate. It is also known that CVI incidence is on the rise due to an increased survival rate of premature and complex medical need.
A visual field screening that is appropriate for children with CVI, would be clinically beneficial. The screening or testing procedure would need to overcome the aforementioned challenges, including head positioning, requirement of subjective responses, and sustained concentration.

The Goldmann perimeter, the current clinical gold-standard for paediatric patients, utilises a projected light that is manually controlled in position, luminance and area by an experienced clinician. As previously noted in earlier chapters, the light can be displayed in a kinetic manner moving from beyond the edge of peripheral vision into view, or alternatively, but less frequently, in a static manner by switching the light on and off once positioned. The examiner observes the patient through the eyepiece to ensure central fixation is maintained, and for children to also note when the child first notices the peripheral stimuli, normally by a saccade to the stimulus.

The Goldmann maps the visual field through varying the luminance and area of the stimulus size to produce isopters and thus map the island of vision. However, it is often used in a simple screening method in children to determine the extent of the visual field, due to the innate difficulties of perimetric testing in children. Lakowski and Aspinall in 1969 determined the youngest age for accurate perimetric testing with the Goldmann perimeter was six years of age and specifically it “was only achieved in one child of six who was above average intelligence”, however, more recent studies have indicated that Goldmann testing can be achieved with patience and perseverance in children as young as four. The challenges of sustained concentration, central fixation, are present with the Goldmann, however, the manual nature of the Goldmann does allow the experienced examiner to engage with the child to attempt to overcome these issues by observing loss of concentration, searching manoeuvres or fatigue in the child and giving rest breaks as necessary. Unfortunately, the Goldmann perimeter is no longer being produced, limiting supplies, thus further developments in paediatric visual field assessments are necessary.

Visual fields can also be assessed by means of confrontation, a manual kinetic perimetry technique, which involves a flashing light on a confrontation wand. It is currently used as a screening test as it is faster to perform than Goldmann perimeter, but less accurate. Challenges with confrontation mirror some of those seen with Goldmann, particularly the understanding of the concept to see while maintaining constant head posture, otherwise referred as ‘to see without looking’. This, in alignment
with the subjective and interpretative nature creates opportunity for a more accurate and reliable means of screening the visual field.

As has been highlighted with all these methods the concept of seeing without looking for perimetric assessment is challenging. Peripheral stimuli result in a reflexive saccadic response which is more difficult for children to suppress than adults, thus maintaining central fixation requires more exertion for children. 165, 166

There have been many attempts to address the challenges of perimetry in children using moving fixation targets, preferential looking and other techniques. 165, 167-169 The Saccadic Vector Optokinetic Perimeter (SVOP) (i2Eye Diagnostics Ltd., Edinburgh, United Kingdom), Figure 6-1, is an automated static perimeter that is specifically designed for children and individuals with neuro-disabilities. 170 SVOP assesses the central 30° of visual field using infra-red eye-tracking thus allowing: the child’s head to be unrestricted, avoidance of a single fixation point and objective rather than subjective responses. 109, 170

It is comprised of a personal computer, secondary display monitor, and the infra-red eye-tracking device as shown in Figure 6-1. 109 SVOP software interprets eye responses within 3D space from the eye-tracking device and correlates it to the display monitor to determine if stimuli have been ‘seen’. 109 SVOP accuracy, when compared to the gold standard HVFA, was determined to have a sensitivity of 73% and specificity of 90%, in a small pilot study. 109 SVOP is a supra-threshold, objective, perimeter with the goal of detecting and characterising the size of areas of sensitivity loss in the visual field.

Visual field testing in children is challenging but an objective, screening assessment may theoretically be possible using SVOP. However, more data on accuracy and applicability of SVOP is certainly required to confirm its usability in the intended population. Therefore, this study was designed to address two main aims: A) to compare SVOP, to both Goldmann perimetry and confrontation in normal-sighted children, and B) to determine the clinical applicability of SVOP in both normal-sighted and visually impaired children.
6.2 Subjects and Methods

6.2.1 Participant recruitment and assessment

Paediatric participants were recruited into two unique cohorts; normal-sighted, children with no known vision affecting conditions and visual acuity of 6/7.5 or better (<0.1 logMAR), and visually impaired, children with a known visual deficit significant enough to allow enrolment in Blind and Low Vision Education Network New Zealand (BLENNZ). Enrolment criteria for BLENNZ is visual acuity of 6/18 (≥0.5 logMAR) or worse in the better eye or a visual field less than 10 degrees or other significant reduction of visual field.

Locations for recruitment were the University of Auckland for the normal-sighted cohort and the BLENNZ national assessment clinic for the visually impaired cohort. Ethics approval for this study was granted by the New Zealand Health and Disability Ethics Committee (14/NTA/183) and complies with the Declaration of Helsinki.

Normal-sighted cohort

Children in the normal-sighted cohort were aged between four and fourteen years of age, and were assessed by all three visual field assessments of Goldmann perimetry, confrontation and SVOP. Visual
acuity was confirmed with a standard Snellen distance chart, with children excluded from participating if their binocular or right monocular visual acuity was worse than 6/7.5 (≤0.1 logMAR).

The three visual field assessment techniques were performed on the right eye of each child with the left eye appropriately occluded. All tests were performed with high contrast targets to detect significant visual field losses, whilst minimising length of assessment. The order of visual field assessment technique (SVOP, Goldmann perimetry and confrontation method), were randomised to prevent subject fatigue confounding their performance. Children were given a short rest between each type of visual field assessment. The visual field results and test length were recorded.

**Visually impaired cohort**

The SVOP is used in the BLENNZ National Assessment Service clinics when clinically indicated. Families of paediatric patients who had undergone SVOP examination were offered the opportunity for the results to be retrospectively analysed as part of the study. The families who were interested received a participant information sheet and consent form. Prior to the SVOP being used clinically at BLENNZ verbal assent is obtained from parents/guardians and children, where possible. Only individuals who wanted their information to be anonymously used in the study were included.

All the children with known visual impairment had an ophthalmological and optometric assessment as part of the BLENNZ National Assessment Service clinic. This included all appropriate tests for the diagnosis and management of the child’s visual and related medical needs. The children at BLENNZ have a range of cognitive abilities and ages, thus a range of visual acuity charts were used as deemed appropriate for the child’s age and developmental ability, further details on the range of visual acuity charts can be found in Chapter 2. All children who attempted SVOP were able to be included in the study, whether or not they were able to complete the assessment. Due to the large range of visual and cognitive abilities in the visually impaired cohort, comparative assessments were not feasible for the majority. Review of previous ophthalmic notes provided HVFA in one child, with comparison of test data discussed in relation to this case (*vide infra*).
**Goldmann perimetry**

Goldmann perimetry is a well-known technique for visual field assessment, with stimuli kinetically presented from the periphery, whilst central fixation is maintained. Participants were positioned in the Goldmann perimeter with their chin and forehead against the appropriate rests (Figure 6-2), and an eye patch covering the left eye. The participant was instructed to focus on the central fixation point. Fixation was observed through the examiner’s eye-piece, this allows appropriate instruction and encouragement to be given throughout the testing procedure. Stimuli were moved slowly from the periphery along twelve evenly distributed meridians with children asked to verbally identify when it was first noticed. The stimulus was then continued along the meridian to the central point, and then reversed until the child reported it had disappeared from view. Participants were also instructed to alert the examiner if the stimulus disappeared from view at any other time point to detect central scotomas. Goldmann III (4mm²) with maximum brightness was the stimulus used, to align with the SVOP stimuli.

![Figure 6-2 – Goldmann perimeter (A) patient side, and (B) examiner side](image)

**Confrontation method**

Manual kinetic confrontation was performed with an LED light on a stick, also known as a Bott confrontation wand. The child’s left eye was occluded by an eye patch throughout this procedure.
Participants were instructed to fixate on the examiner’s left eye and to inform the examiner when the light appeared and disappeared from view as it was traced along each of the 12 cardinal meridians.

**Saccadic vector optokinetic perimetry**

Children were seated 50-70cm from SVOP with the left eye occluded, and instructed to observe anything that appeared on the screen. Test stimulus size was pre-set at Goldmann III equivalent for children in the normal-sighted cohort. Larger test stimuli were selected for children with severe visual impairments based on their acuity. SVOP was set to a 14 point test, stimulus intensity of 14 dB, and stimulus duration of 200 milliseconds, these settings were chosen to correspond to be the equivalent of the standard settings of the Goldmann perimeter. For children in the visually impaired cohort the 14 point visual field assessment was undertaken, when possible. In cases where 14 point testing was too challenging then a smaller number of test-points were chosen, either a 12 or 4 point test. If an accurate result was achieved in the 14 point then further testing was carried out with a 40 point test. Only one child performed a 16 point test. In 19 cases binocular assessment was performed if the child was unable to cope with monocular occlusion for the duration of the assessment.

### 6.2.2 Statistical analysis

Analysis of data were completed with IBM SPSS software version 22 (Armonk, New York, United States of America). Descriptive statistics were calculated for the characteristics of both cohorts with results presented as mean ± standard deviation unless otherwise stated. Comparison of cohort characteristics was completed using Pearson Chi-squared tests and independent t-tests.

To compare visual field assessment techniques in the normal-sighted cohort visual field results were divided into one of the two categories, normal or abnormal. A normal test result was the ability to complete the visual field assessment with a full visual field. The abnormal score category incorporated both those children unable to complete the visual field assessment as well as children with visual field losses, this was due to abnormal visual field results in visually normal children being considered false positive results. The categories were determined based on the understanding that children with normal vision should have a full visual field and be able to complete an appropriate visual field test. McNemar’s test of agreement was used to determine comparability of test results in those children able to attempt.
all three tests. The McNemar test determines differences between dichotomous dependent variables, such as two visual field assessments in the same subject.\textsuperscript{173}

For comparison of visual field results in the visually impaired cohort there were limited data with variability in results, hence, qualitative comparison of the results was completed by a paediatric ophthalmologist.

6.3 Results

6.3.1 Characteristics of cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal-sighted cohort</th>
<th>Visually impaired cohort</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 26</td>
<td>N = 35</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mean ± SD, n (%)</td>
<td>mean ± SD, n (%)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.395</td>
</tr>
<tr>
<td>Male</td>
<td>12 (46%)</td>
<td>20 (57.1%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14 (54%)</td>
<td>15 (42.9%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>9.2 ± 3.0</td>
<td>9.8 ± 4.4</td>
<td>0.519</td>
</tr>
<tr>
<td>Visual acuity (logMAR)</td>
<td>-0.12 ± 0.8</td>
<td>0.82 ± 0.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SVOP completed</td>
<td>21 (88.5%)</td>
<td>26 (74.3%)</td>
<td>0.168</td>
</tr>
<tr>
<td>Time (seconds)</td>
<td>51.3 ± 19.6</td>
<td>169.5 ± 135.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Twenty-six normal-sighted children, 46% male, ranging from 4 to 14 years of age, with a mean visual acuity of \(-0.12 \pm 0.08 \) logMAR (equivalent to Snellen acuity of 6/4.5), attempted SVOP, Goldmann perimetry and confrontation methods (Table 6-1). Three children were unable to complete the SVOP calibration, and therefore could not attempt the visual field assessment. These three children were excluded from further analysis.

Thirty-five visually impaired children attempted the SVOP assessment, 20 males and 15 females, with an average age of 9.9 years (range of 3 to 19 years). Visual acuity of these children ranged from 0.2 to 1.8 logMAR (6/9.5 to worse than 6/360 Snellen acuity equivalent), with an average of 0.8 ± 0.4 logMAR (mean ± standard deviation), cohort details are highlighted in Table 6-1. Of the 35
children 7 had nystagmus associated with their ocular diagnosis, however, there was no significant statistical difference between those with and without nystagmus in relation to age or visual acuity.

![Figure 6-3](image)

**Figure 6-3** – SVOP results showing inconsistent findings and poor calibration results for three children with oculocutaneous albinism and nystagmus. Calibration results are displayed with circle fixation targets in up to nine positions of gaze, with lines indicating fixation pattern of the individual.

### 6.3.2 Normal-sighted cohort

Comparison of the three visual field assessments was undertaken for the 23 children able to attempt the SVOP assessment. Full visual field results were subsequently recorded for 91% (n=21) of children on SVOP, 87% (n=20) on the Goldmann perimeter and 100% (n=23) with the confrontation field method. The McNemar’s test of agreement determined that there was no statistically significant difference in results between the three visual field assessments. With comparison of results showing good agreement between each pair of tests: SVOP vs Goldmann perimetry (p=1.00), SVOP vs confrontation method (p=0.50) and Goldmann perimetry vs confrontation method (p=0.25).

Further analysis of children with normal vision was undertaken with three separate groups; normal visual field result, abnormal visual field result, and unable to complete SVOP. No significant differences were present between these groups in relation to the age of participants (p=0.30), visual acuity (p=0.91), or the ability to complete either the Goldmann or confrontation visual field methods.

The average time to complete SVOP, by those children able to attempt all three visual field assessments was 50.9 ± 19.9 seconds, Goldmann 205.8 ± 32.4 seconds, and confrontation 72.6 ± 21.5 seconds.
SVOP was significantly faster to perform than Goldmann (p<0.001) and confrontation (p=0.003). Average calibration time for the SVOP was 65.7 ± 38.5 seconds. In 60.9% of children, the blind spot was identified during the SVOP visual field assessment.

6.3.3 Visually impaired cohort

Completion of at least one SVOP visual field, was achieved by 27 out of the 35 visually impaired children. Of the 27 able to perform SVOP, 19 completed a binocular visual field assessment, whilst the remaining 8 managed a monocular assessment, with only right eye data being used for analysis. There was no statistically significant difference in age, visual acuity, or the presence of nystagmus between those who could and could not complete the SVOP visual field assessment. However, children with nystagmus had inconsistent visual field results due to poor calibration, as illustrated in Figure 6-3.

Fifteen children (55.6%) completed a 14 point SVOP test, 4 required more detailed clinical assessments, as concluded by the consultant ophthalmologist, of either 16 (n=1) or 40 (n=3) point tests. Eight children were unable to complete the 14 point test but were able to complete less detailed assessments of 12 test-points (n=3) and 4 test-points (n=5).

The average time to complete SVOP was 161.1 ± 113.0 seconds with a range of 30.1 to 363.1 seconds. There was no statistically significant difference in time between binocular (n=19) and monocular assessments (n=8) (p= 0.095), or in time between SVOP assessment types (number of points) with p=0.94.

A twelve year old female with an ophthalmic diagnosis of bilateral optic nerve atrophy with a history of craniopharyngioma was the only child in the visually impaired cohort who had previously been able to complete a reliable HVFA. The central 24-2 SITA-standard threshold test she completed was referred to BLENNZ, revealing a significant total reduction of fields along with a left junctional scotoma. The SVOP screening examination completed at BLENNZ, revealed a similar visual field loss. The extensive visual field loss revealed by HVFA and SVOP can be appreciated in Figure 6-4. A significant time difference was observed between the HVFA testing (right 493 seconds, left 549 seconds), and the SVOP screening (right eye 117 seconds, left eye 56 seconds). The significantly faster time to complete SVOP,
along with the comparable visual field result, indicates the feasibility of SVOP being used as a screening method for visual field assessment.

Figure 6-4 – Visual field results showing complete bilateral left hemianopia with a right inferior quadrantanopia of the right eye, for HVFA (A) and SVOP (B)

6.4 Discussion

Visual field assessment in children is challenging, with key issues including maintaining centralised fixation, suppressing reflexive saccades, and supplying subjective responses. These challenges are present for both the Goldmann perimeter and confrontation methods which are the primary clinical paediatric techniques currently. The SVOP was designed to overcome these challenges by utilising
infra-red eye tracking, allowing free movement of the child’s head within 3D space whilst utilising the child’s natural reflexive saccades to determine if stimuli are seen. The 3D visual field mapping is important for children with neuro-disabilities and complex needs as it allows access to those who have poor mobility, short concentration, or the inability to comprehend traditional visual field testing techniques which require ‘seeing without looking’.

In the current study the clinical applicability of SVOP was assessed for both normal-sighted and visually impaired children. Normal-sighted children also completed comparative Goldmann perimetry and confrontation fields to determine the relative efficacy of SVOP to these commonly used paediatric visual field assessment techniques.

The clinical applicability of SVOP was assessed in 26 normal-sighted children, mean visual acuity 6/4.5, and 35 visually impaired children, mean visual acuity 6/38. No significant difference in age or gender was present between the two groups. Of the 26 children in the normal-sighted cohort, only 3 were unable to complete calibration on the SVOP and, thus, did not progress to visual field assessment. A further two children demonstrated only moderately reliable calibration on the SVOP and recorded multiple random visual field point defects, which are unexpected in normal-sighted children. Therefore, although they completed the SVOP visual field assessment they were classified as abnormal results. Such calibration errors can occur in children with deep set eyes, long eyelashes or eyelids covering part of the pupil as these features interfere with the infra-red eye tracking, as was noted in this cohort. Further developments in infra-red eye tracking and the SVOP software may be necessary to overcome current calibration issues, for this sub-group. Excluding calibration challenges, all children were able to complete SVOP indicating its potential in the target age group of 4 to 14 years old.

Children in the normal-sighted cohort also attempted Goldmann perimetry and confrontation visual field assessments, both of which require central fixation. Maintaining central fixation requires children to suppress reflexive, eccentric, re-fixation saccades which may produce an error rate of 50% in children aged 5-8 years old. Three children (four to six years old) who did not achieve full visual field results on the Goldmann perimeter struggled with the maintenance of central fixation and duration of the test resulting in incomplete test results. Nonetheless, the number able to complete Goldmann perimetry was comparable to a study of feasibility and reliability in 154 children, which noted fatigue...
affected 8.4% of children during Goldmann perimetry visual field assessment, but only affecting those under 9 years of age. This highlights the problems with reliability of Goldmann perimetry in younger children. Due to the challenges of Goldmann and confrontation visual field assessment in children, these tests have typically been performed by individuals with significant training and experience in performing the tests appropriately and interpreting the subjective responses. In contrast, SVOP assessments can be administered by a lay-person with interpretation completed by an eye health professional.

The length of visual field testing is another important factor, as fatigue from sustained concentration reduces the reliability of visual field results, particularly in those aged less than 8 years old. In the current study, SVOP required significantly less time than either the confrontation method or Goldmann perimetry, with Goldmann perimetry taking four times longer on average. However, the time needed for calibration was not included in the SVOP test time. Though notably, nor was the time taken for explanation prior to assessment with either the Goldmann perimetry or confrontation method, as these times were perceived to be approximately similar (approximately one minute) in relation to the three techniques. SVOP has been designed to require no/minimal explanation to the child performing the test as it relies on reflexive saccadic responses to presented stimuli. In practice, the speed of SVOP may potentially be beneficial for prolonged engagement of younger children.

A limitation of SVOP is that it relies on testing an individual’s blind spot at a pre-determined point, 15 degrees temporally and 1.5 degrees below the horizontal midline. Sixty-one percent of normal-sighted children had their blind spot correctly identified in this study. However, the physiological blind spot varies between individuals and in some cases the test point may not directly correspond to the individual child’s blind spot. Our observations are similar to the only previous study of SVOP in normal-sighted children, where blind spots were not accurately mapped in one of four children.

SVOP results from the normal-sighted cohort indicated good agreement with the completion rates of both the Goldmann perimeter and confrontation methods. SVOP has been previously compared to HVFA with 99.1% and 99.2% agreement in normal children and adult subjects respectively, furthermore, 89.8% agreement was identified in adults with visual field losses. However, the study included only 10 children – four normal-sighted and six with visual field defects. Those children with visual field
The larger sample size of normal-sighted children in the current study provides further baseline data for SVOP as well as showing its feasibility for clinical use.

Feasibility of the clinical application of the SVOP in children with visual impairment (with or without complex needs) is important to determine as this is a niche of visual field assessment that is under-serviced by currently available techniques. Of the 35 visually impaired children who attempted SVOP, 27 were able to complete it. Our data indicates that testability was limited in the full test protocol of 40-points, but improved with reduced plots such as the 14-point used in our study, this aligns with the only other publication of SVOP in children with neuro-disabilities and visual field defects.176 Tailor et al were able to compare SVOP results to Goldmann perimetry in children with no neuro-disability with known visual field defects, indicating good agreement.176 As visual field assessment was clinically determined direct comparisons were often not completed, or were unable to be completed due to the child’s co-morbidities. However, the case report in this study comparing SVOP to HVFA in a cognitively able 12 year old, indicates good agreement.

A specific issue for children with visual impairment is nystagmus, which can occur in conjunction with a number of paediatric ocular disorders including optic nerve hypoplasia, optic nerve atrophy, and oculocutaneous albinism.177 SVOP relies on fixation stability to determine whether or not stimuli have been ‘seen’ yet nystagmus results in fixation instability for the majority of patients.178 These results replicate the findings of Tailor et al on the incompatibility of SVOP with nystagmus.176 Development of eye tracking devices that can detect and correct for nystagmus would be hugely beneficial.

The current study highlights the high accessibility of SVOP. Although, SVOP has limitations as already discussed it is deemed useful to fill a gap in currently available visual field assessment techniques for children, particularly for children with neuro-disabilities, complex needs, or very young children. SVOP is most appropriately used as a screening technique or a functional assessment tool for children, as it does not measure threshold sensitivity across the field, but rather gives a global impression of the field. Therefore, it is an appropriate clinical option for assessing visual fields in those who are unable to do
more standard tests due to it being fast, easy to administer, and with the child not being required to maintain a stationary head posture or suppress reflexive saccades.

The main strength of this study is that it is the largest study to date of the clinical applicability of SVOP in normal-sighted children, as well as assessing the utility of SVOP in visually impaired children of all cognitive abilities. As the study was an assessment of the usability of SVOP in a normal paediatric population a full eye examination was not undertaken, and comparative visual field techniques were not possible in many of the children with visual impairment. Therefore, further research is needed to garner a full understanding of the accuracy of SVOP in a range conditions affecting the visual fields. However, the ability to functionally assess visual fields in children, who previously were often unable to perform any formal visual field testing, is an exciting step forward for paediatric visual field assessment.
Chapter 7:

Visual loss and vitamin A deficiency in the developed world – a case report
7.1 Introduction

As mentioned in Chapter 1, Vitamin A deficiency is a major cause of avoidable childhood blindness and visual impairment in developing nations. Lack of vitamin A is also associated with increased childhood morbidity and mortality. Treatment is simple and inexpensive with either supplementation or increased dietary intake of vitamin A. In developed nations vitamin A deficiency is extremely uncommon hence, vitamin A associated visual morbidities including; night blindness, conjunctival xerosis and, Bitot spots, are rare. However, in certain cases, extremely restricted diets, malnutrition, or liver abnormalities can result in vitamin A deficiency. The following case, assessed by the author during these PhD studies was published in The Lancet in 2015, and describes visual impairment from vitamin A deficiency due to severe diet restrictions in New Zealand.

7.2 Case Report

Published in the Lancet, January 2015.

A 16-year-old white boy presented to the Blind Low Vision Education Network of New Zealand (BLENNZ) clinic in November, 2014, with a two year history of progressive vision loss in both eyes, recurrent systemic infections, and recurrent mononeuropathy.

He had initially been seen at another clinic in mid-2012 with an uncorrected visual acuity of 6/6 right eye and 6/18 left eye, which showed no improvement with refraction. He had been found to have bilateral optic nerve pallor, which was worse on the left than the right and mild eye dryness bilaterally.

Over the same time as his vision had deteriorated, he had had increased susceptibility to infection and recurrent abscesses, including a perineal abscess that had needed drainage, olecranon osteomyelitis, and urinary tract infections. Over the next 2 years he had also had recurrent, bilateral, time-separated, Bell’s palsies, which had partly responded to prednisone but had not resolved entirely. Magnetic resonance imaging (MRI) later that year showed possible bilateral enhancement of the affected facial nerves, but no other abnormalities.

Investigations including genetic testing for Leber’s hereditary optic neuropathy, multiple brain and visual pathway MRI, lumbar punctures, infectious serological tests, thyroid function, antiganglioside
autoantibodies, and catecholamine concentrations, were within normal limits. The presumed diagnosis was idiopathic optic neuropathy and he had been given ocular lubrication treatment for his dry eye disease.

When examined at the BLENNZ clinic in 2014 for further assessment and registration for access to special educational assistance, the child was evidently unwell and lethargic. Visual acuity was reduced to hand movements at one metre. Slit lamp biomicroscope examination showed severe bilateral xerosis conjunctivae (abnormal drying and conjunctival thickening), Figure 7-1A, mild punctate corneal epithelial staining, and bilateral optic nerve atrophy, Figure 7-1B. The corneal and conjunctival appearance along with recurrent infections raised the possibility of vitamin A deficiency. On further questioning the patient reported anaphylaxis to peanuts and allergy to dairy products, the onset of which had led to an anxiety-driven diet of solely white bread and French fries.

The patient was admitted for treatment of severe urinary tract infection and further investigation of probable vitamin deficiencies. Blood tests for serum vitamins showed severe vitamin A deficiency (0.1µmol/L; normal range 0.9 - 2.5µmol/L), and low vitamin D, E, B12, and iron. He was started on vitamins A, B, and E and other micronutrient supplements, and referred to a dietician for dietary support and a child and adolescent psychologist for anxiety related to his diet.

At follow up in March, 2015, 4 months after starting treatment, he looked well and had improved visual acuity (6/60 bilaterally) and resolution of his xerosis conjunctivae (Figure 7-1C). He had had no more systemic infections and his facial nerve palsies had completely resolved.

Vitamin A is essential in the maintenance of epithelial function, most notably in the mucous membranes of the conjunctivae and urinary and respiratory tracts. Vitamin A deficiency include recurrent infections of the skin, genitourinary tract, and upper respiratory tracts.\textsuperscript{181, 182} Bilateral facial nerve palsies in vitamin A deficiency have been reported only in conjunction with cystic fibrosis,\textsuperscript{182} but cystic fibrosis was excluded in our patient.

Several case reports describe severe vitamin A deficiency from multiple allergy dietary restrictions causing xerosis conjunctivae.\textsuperscript{184} Other micronutrient deficiencies such as B12, D, and E, often present concurrently with vitamin A deficiency in allergy-restricted diets,\textsuperscript{185} as in our patient, and deficiency of
vitamin B12 has previously been associated with optic neuropathy leading to visual loss.\textsuperscript{184} Vision and ocular surface abnormalities can be treated successfully if nutritional deficiencies are treated early.\textsuperscript{182} Normal visual function is dependent on good nutrition, and low concentrations of essential micronutrients such as vitamins A, B12, E, C, cobalamin, biotin, iron, and zinc have all been associated with visual problems.\textsuperscript{182}

This case highlights the severity of extreme dietary restrictions on ophthalmic and systemic health. Visual loss due to vitamin A deficiency is mainly seen in low-income countries as the result of malnutrition. Because of its rarity in developed countries, vitamin A deficiency is often overlooked as a potential cause for visual loss, as in our case. Unfortunately, in this case, delayed diagnosis resulted in visual loss that was entirely preventable. Increasing prevalence of food allergies, irritable bowel syndrome, anorexia, and self-imposed diet restrictions might contribute to an increase of vitamin A deficiency in developed countries.
Figure 7-1 – 16 year old Caucasian male with vitamin A deficiency (A) bilateral, grey, thickened and keratinised conjunctiva (xerosis conjunctivae), (B) Optic disc atrophy (C) Resolution of xerosis conjunctivae following treatment with vitamin A and other supplementation
Chapter 8:

Conclusions
8.1 Introduction

Paediatric visual impairment and blindness impacts individuals, families, and society with high emotional, social, and economic costs.\textsuperscript{1} Eliminating preventable and treatable paediatric visual disorders is of high priority for the World Health Organization’s \textit{VISION 2020 – The Right to Sight} programme.\textsuperscript{186} The causes of paediatric visual impairment are numerous and vary between regions.\textsuperscript{15} However, regardless of the cause of visual impairment, it has emotional and economic impact on the individual, family and wider community.\textsuperscript{1} Early detection of paediatric ocular disorders through accurate screening and assessment techniques, can improve the long term visual outcomes for affected children.

The inter-related research studies that constitute this thesis evaluated current and potential assessment and screening techniques to identify and manage paediatric ocular conditions and potentially improve long term outcomes. Each project has already been presented and discussed in detail in the context of the current literature in relevant preceding chapters. However, in this concluding chapter I hope to bring together the key conclusions that can be drawn from my work in terms of new knowledge, practical applications and future avenues of research.

8.2 The Auckland Regional Telemedicine Retinopathy of Prematurity screening network (Chapter 3 and 4)

8.2.1 Retrospective review of telemedicine screening for retinopathy of prematurity (Chapter 3)

A key avoidable cause of paediatric visual impairment in \textit{VISION 2020 – The Right to Sight} is retinopathy of prematurity (ROP) which affects the retinae of premature and very low birth weight infants.\textsuperscript{12, 29} Timely detection through ROP screening programs prevents unnecessary visual loss due to the availability of highly effective treatments.\textsuperscript{1, 45} As previously noted, traditionally such screening was completed by skilled ophthalmologists using binocular indirect ophthalmoscopy (BIO). The introduction of wide-field digital imaging (WFDI) as an adjunct to BIO has many potential benefits including, objective documentation, utilising non-ophthalmologists, telemedicine review of images by
ophthalmologists, the ability to seek second opinions, and the development of teaching libraries. In principle, these benefits all aim to increase access and efficacy of ROP screening.

The Auckland Regional Telemedicine Retinopathy of Prematurity Network (ART-ROP), has exclusively used wide-field digital imaging (WFDI) to screen for retinopathy of prematurity (ROP) since 2006. To assess the efficacy of a local telemedicine approach to ROP a retrospective clinical note review of 1181 patients who were screened by ART-ROP between 2006 and 2015 was completed.

**Objective**

- To determine the efficacy of the ART-ROP network screening program

**Conclusions**

- The number of infants requiring ROP screening has significantly increased since the inception of ART-ROP in 2006
- A significant annual increase in the number of infants receiving full screening in the ART-ROP network was identified
- Infants receiving only partial ART-ROP screening were of significantly lower birth weight and gestational age
- The severity of ROP significantly decreased across the ten year period
- The rate of ROP treatment also significantly decreased over the ten year period of ART-ROP
- Significantly lower mean birth weight and gestational age was observed in infants who required treatment for ROP
- Both male infants and Māori infants were over-represented in ART-ROP due to their individual over-representation in premature birth rates, however, no additional risk of developing ROP, or treatment was observed for either characteristic
- No ROP was missed by the ART-ROP screening method as determined by three month follow up
- ART-ROP model is an effective and reliable potential alternative to binocular indirect ophthalmoscopy for ROP screening

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8.2.2 Long term visual outcomes of children screened for retinopathy of prematurity with telemedicine in Auckland, New Zealand (Chapter 4)

The objective of ART-ROP is to improve visual outcomes of premature infants through timely detection and treatment of ROP. In addition to the potential visual impact of ROP, children with a history of premature birth have an increased risk of other ocular morbidity.\textsuperscript{114, 127}

Therefore to assess long term outcomes post-screening, 68 children aged 5 to 8 years old were prospectively recruited from the ART-ROP network database for a comprehensive eye examination.

**Objectives**

- To determine long term outcomes of children screened for ROP with ART-ROP network
- To determine any differences in structural, or visual outcome between those children who developed ROP and those who did not, based on their screening results from ART-ROP

**Conclusions**

- Children recruited did not differ significantly from the eligible ART-ROP screened population in terms of gender, ROP severity, birth weight or gestational age
- No new ROP-related retinal changes were detected
- Children with a history of ROP had significantly lower mean birth weight and gestational age than those with no ROP
- No significant differences in visual outcomes were detected between children with and without a history of ROP
- Significant structural differences were observed between children with and without a history of ROP, including the presence of laser scars in children with a history of treatment. Asymptomatic avascular retinal patches were also observed in four children, all of whom had a history of ROP which had regressed but had not received treatment
- Long term outcomes of ART-ROP indicate the efficacy of the current ROP screening program, with positive visual outcomes, and no new ocular pathology, whether or not the child developed ROP
8.2.3 Future directions for the ART-ROP network

Access to ROP screening is a known challenge worldwide, and is of particular concern in middle income countries with highest burden of disease. The ART-ROP network has confirmed the safety and efficacy of WFDI and telemedicine screening for ROP screening, which if implemented appropriately can lead to improved access for infants at risk for ROP, such as had been achieved with the ‘Karnataka Internet assisted Diagnosis of ROP’ in India.\(^{116}\)

Due to the objective records created in the ART-ROP system, prospective studies of differences in ROP rates, including severity and treatment, can be undertaken and correlated with changes in neonatal care in order to better understand the multifactorial disease of ROP. This is of particular interest with the introduction of new treatments such as anti-vascular endothelial growth factors.\(^ {137}\)

Larger studies of long term outcomes of children who were at-risk of ROP as infants are needed to further validate our observations in the current study.

An outcome of particular interest identified in the current study was identification of asymptomatic avascular retinal patches in children with regressed ROP. These have only previously been reported up to 72 weeks post-menstrual age where they were prophylactically treated with laser.\(^ {132}\) The presence of avascular patches in older children with no current symptoms, queries whether such treatment is necessary. Thus, further research into the long term risks, if any, of avascular retinal patches would help to determine if prophylactic laser treatment is necessary or whether untreated persisting avascular areas may create ocular risk over time.

ROP screening continues to be an exciting area where new screening methods and treatments are evolving. Further research to develop the most efficient screening programs for individual regions is urgently needed to prevent the ongoing risk of visual impairment from ROP worldwide.

8.3 Universal Newborn Eye Screening (Chapter 5)

For infants not screened for ROP the current ocular screening standard of the red reflex test is not consistently administered,\(^ {136}\) and has poor sensitivity for posterior ocular disorders in newborns.\(^ {188}\) WFDI is an effective ocular screening tool for detection of ROP among premature infants. Therefore,
this prospective study explored a universal newborn eye screening (UNES) program with WFDI as an alternative newborn screening strategy in full term infants. A cohort of 346 infants underwent UNES.

**Objectives**

- To identify in a prospective manner the prevalence of ocular abnormalities, in particular retinal haemorrhages, using RetCam wide-field digital imaging eye examinations in a New Zealand newborn population.
- To identify any correlations between newborn retinal haemorrhages and maternal, neonatal, and obstetric factors.

**Conclusions**

- Ocular abnormalities had a significant prevalence of 15.6% of the infants screened in UNES
- Retinal haemorrhages were the most common ocular abnormality - observed in 14.5% of infants
- Other ocular abnormalities observed included: congenital cataract, optic nerve hypoplasia, and other retinal lesions
- No significant difference in gender or ethnicity was present between infants with and without retinal haemorrhages
- Earlier screening after birth was significantly associated with the presence of retinal haemorrhages
- Infants with spontaneous vaginal delivery had a significantly higher rate of retinal haemorrhage than infants delivered by caesarean section, with an odds ratio of 26.30 for normal vaginal delivery and 33.61 for instrumental vaginal delivery
- Resolution of retinal haemorrhages occurred in 94% of infants at six-week follow up
- Ventouse delivery was associated with haemorrhages not resolving by six-week follow up in two infants
- No significant difference in anthropomorphic measurements of infants or mothers were observed for infants with retinal haemorrhages compared to those without retinal haemorrhages
- UNES successfully detects ocular abnormalities (at a relatively high rate) in newborn infants and therefore could be part of a potential future New Zealand newborn screening program
Future directions

Early detection of neonatal ocular conditions is known to improve long term outcomes. This prospective study of UNES with WFDI indicates it can successfully be used as a screening program for ocular abnormalities at birth. Larger studies would need to be conducted to determine specific rates of individual conditions due to the rarity of many neonatal ocular conditions. Currently UNES could be clinically implemented for infants with abnormal red reflex, family history of paediatric ocular conditions, or if their parents or lead-maternity carer are concerned. To determine the true benefit of UNES a large comparison study of UNES to the red reflex test should be undertaken in conjunction with an economic evaluation.

Retinal haemorrhages were the most common ocular abnormality detected in UNES and further research is required to ascertain causative factors and potential impact. The key association with retinal haemorrhages was vaginal delivery, but evaluation of factors such as pelvic size, length of the stages of labour, and contraction variables could further elucidate the mechanism of retinal haemorrhages in certain infants. The long term impact of retinal haemorrhages is currently unknown, however normal visual development requires clear input in the early weeks of life. Retinal haemorrhages obscuring the visual axis, particularly those which are long-standing, may potentially cause visual impact, thus, long term follow up of infants with retinal haemorrhages would be beneficial to understand this pathology further.

8.4 Clinical applicability of Saccadic Vector Optokinetic Perimetry in normal-sighted and visually impaired children (Chapter 6)

Visual fields are an important assessment and management tool of paediatric ocular disorders including congenital glaucoma, visual pathway tumours, retinal dystrophies, and cerebral visual impairment. Visual field assessments have many challenges, particularly for young children and those with neuro-disabilities. Goldmann perimetry is the current clinical gold standard visual field assessment for children with the confrontation method being commonly used as a screening technique. However, both
techniques require prolonged fixation, suppression of reflexive saccades, and subjective responses.\textsuperscript{107, 164} The saccadic vector optokinetic perimeter (SVOP) was developed to overcome these challenges by using infra-red eye tracking which determines the child’s relative eye and head position in 3-D space whilst utilising the natural reflexive saccadic response to evaluate if visual stimuli are seen.\textsuperscript{109} Infra-red eye tracking techniques are valuable for children with poor mobility, short concentration, or the inability to comprehend ‘seeing without looking’ as is required for most traditional visual field tests.

Unfortunately, SVOP has undergone limited research of its applicability in children with and without visual impairment. To further assess this technique children were recruited in two groups; 35 children with visual impairment attempted SVOP, and 26 normal-sighted children were examined with SVOP, Goldmann and confrontation techniques.

\textit{Objectives}

- To determine the clinical applicability of SVOP in both normal-sighted and visually impaired children
- To compare the clinical applicability of SVOP, to both Goldmann perimetry and confrontation assessment in normal-sighted children

\textit{Conclusions}

- SVOP was able to be completed for 88.5\% of normal-sighted children and 74.3\% of visually impaired children, with no significant difference in completion between the two cohorts
- Excluding calibration challenges, due to deep set eyes or long eyelashes, all children with normal vision were able to complete SVOP
- SVOP was significantly faster in children with normal vision compared to children with visual impairment of comparable age
- Unreliable calibration and variable SVOP visual field results were observed in children who had nystagmus associated with their visual impairment
- No significant difference in ability to complete SVOP, Goldmann, and confrontation assessment was noted in normal-sighted children
• SVOP was determined to be a significantly faster visual field test than Goldmann and confrontation methods in normal-sighted children
• SVOP is a potential screening tool for visual fields in children who are unable to perform standard techniques due to neuro-disabilities, complex needs, or mobility issues

**Future directions**

SVOP addresses many of the barriers to assessing paediatric visual fields by utilising infra-red eye tracking, as indicated by its clinical applicability in both normal-sighted and visually impaired children. However, the literature on the accuracy of SVOP is still limited with larger studies of SVOP accuracy still required in cases with known visual field defects, in both adults and cognitively able children. Currently, SVOP can be considered a relatively quick technique that can potentially be used to assess the functional visual fields in children and cognitively impaired individuals who are unable to complete any other visual field assessment.

Further development of SVOP to address eye-tracking issues for children with deep-set eyes or long eyelashes, would increase the applicability of SVOP. Importantly improvements to allow children with nystagmus to accurately complete SVOP would be of great benefit as nystagmus is a common occurrence in children with visual impairment, the target population for SVOP. However, our ability to functionally assess visual fields in a large number of visually impaired children, who previously were unable to perform any formal visual field testing, indicates the potential clinical applicability and role for SVOP in the future.

### 8.5 Final conclusions

Paediatric visual impairment has various causes, ranging from congenital structural abnormalities to acquired causes from nutritional deficiencies. Early detection, accurate assessment, and timely treatment are all needed to maximise potential visual and systemic outcomes for infants and children. WFDI with telemedicine for ROP screening is an effective and safe alternative to BIO screening, with current long term outcomes indicating no ROP is missed by this method. This successful ROP screening model can also be utilised for all newborns through UNES. UNES successfully detected visually and systemically significant ocular conditions including congenital cataract, optic nerve hypoplasia, and
birth-related retinal haemorrhages. Ocular assessment in children is challenging and continual development of techniques is needed. The SVOP system improves access to functional visual field screening for children with visual impairment or neuro-disabilities that prevent them from completing other traditional visual field assessments.

The field of paediatric visual impairment is vast and of great importance. Improved screening and assessment techniques for infants, both premature and full-term, and children is an important step towards eliminating the unnecessary burden of visual impairment and blindness from preventable and treatable conditions. I hope the inter-related research studies contained in this PhD thesis help contribute, in some small way, to improved assessment and care of newborn and paediatric patients.
Appendix One:

Related publications and presentations
Related publications

Simkin SK, Tuck K, Garrett J, Dai S.
Vitamin A deficiency – an unexpected cause of visual loss.

Related presentations and posters

Presentations

Simkin SK, Misra SL, Battin MR, McGhee CNJ, Dai S.
Universal Newborn Eye Screening with RetCam wide-field digital imaging.
[Best Scientific Presentation]

Simkin SK, Misra SL, Han JV, McGhee CNJ, Dai S.
Auckland Regional Telemedicine Retinopathy of Prematurity Network: the ten year Auckland experience.

Simkin SK, Misra SL, Battin MR, McGhee CNJ, Dai S.
Universal Newborn Eye Screening.
[Invited lecture]

Simkin SK, Misra SL, Battin MR, McGhee CNJ, Dai S
Retinal haemorrhages in infants: Report from a prospective study.
[Invited lecture]

Simkin SK, Misra SL, Battin MR, McGhee CNJ, Dai S
Neonatal and infant eye screening in Auckland, New Zealand.
Calvin Ring Prize Evening. Auckland, April 2017
[Invited lecture]

Simkin SK, Misra SL, Battin MR, McGhee CNJ, Dai S
Universal Newborn Eye Screening.
[Best Paper Runner Up]

Simkin SK
Visual impairment in the children of Aotearoa.
[Invited lecture]

Simkin SK
A person's a person no matter how small – assessment of paediatric patients in primary care Optometry.
Specsavers Dispensing Day. Auckland, April 2016.
[Invited lecture]

Simkin SK, Misra SL, McGhee CNJ, Dai S.
The real world experience of Auckland regional telemedicine retinopathy of prematurity network.

Simkin SK, Misra SL, McGhee CNJ, Dai S.
ART-ROP: A Real World Telemedicine Screening for Retinopathy of Prematurity.

Simkin SK, Tuck K, Garrett J, Dai S.
Opening our eyes to Vitamin A Deficiency.

Simkin SK, Misra SL, McGhee CNJ, Dai S.
Objective visual field information is revealed by SVOP in visually and cognitively impaired children.
Asia Pacific Academy of Ophthalmology Congress. Guangzhou, April 2015.

Simkin SK
Visual Impairment in the children of Aotearoa.
Specsavers Dispensing Day. Auckland, April 2015.
[Invited lecture]

Simkin SK, Misra SL, McGhee CNJ, Dai S.
SVOP reveals objective visual field information in visually impaired children.

Simkin SK, Misra SL, McGhee CNJ, Dai S.
SVOP reveals objective visual field information in visually impaired children.
NZAO Annual Conference. Auckland, October 2014.

Posters

Simkin SK, Tuck K, Garrett J, Dai S.
Vitamin A Deficiency in the Developed World.

Simkin SK, Misra SL, McGhee CNJ, Dai S.
Saccadic Vector Optokinetic Perimetry visual field testing in moderate to severely visually impaired children.
Vitamin A deficiency—an unexpected cause of visual loss

Samantha K’Simi, Katie Tuck, John Garrett, Shaun Dui

A 16-year-old white boy presented to the Blind Low Vision Education Network of New Zealand (BLENNZ) clinic in November, 2014, with a 2-year history of progressive vision loss in both eyes, recurrent systemic infections, and recurrent mononeuropathy.

He had initially been seen at another clinic in mid 2012 with an uncorrected visual acuity of 6/6 right eye and 6/18 left eye, which showed no improvement with refraction. He had been found to have bilateral optic nerve pallor, which was worse on the left than the right, and mild eye dryness bilaterally. Over the same time as his vision had deteriorated, he had had increased susceptibility to infection and recurrent abscesses, including a perimplant abscess that had needed drainage, osteomyelitis of sternum, and urinary tract infections. Over the next 2 years he had also had recurrent, bilateral, time-separated, Bell’s palsies, which had partly responded to prednisone but had not resolved entirely. MRI late that year showed possible bilateral enhancement of the affected facial nerves, but no other abnormalities.

Investigations including genetic testing for Leber’s hereditary optic neuropathy, multiple brain and visual pathway MRI, lumbar punctures, infectious serological tests, thyroid function, anti-angiotensin II antibodies, and cataract lamellar concentrations, were within normal limits. The presumed diagnosis was idiopathic optic neuropathy and he had been given ocular lubrication treatment for his dry eye disease.

When examined at the BLENNZ clinic in 2014 for further assessment and registration for access to special educational assistance, the child was evidently unwell and lethargic. Visual acuity was reduced to hand movements at 1 m. Slit-lamp biomicroscope examination showed severe bilateral xerotic conjunctivae (abnormal drying and conjunctival thickening) (figure), mild punctate corneal epithelial staining, and bilateral optic nerve atrophy. The corneal and conjunctival appearance along with recurrent infections raised the possibility of vitamin A deficiency. On further questioning the patient reported anosmia to peanuts and allergy to dairy products, the onset of which had led to an anxiety-driven diet of solely white bread and French fries.

The patient was admitted for treatment of severe urinary tract infection and further investigation of probable vitamin deficiencies. Blood tests for serum vitamins showed severe vitamin A deficiency (0.1 μmol/L; normal range 0.9–2.5 μmol/L), and low vitamin D, E, B12, and iron. He was started on vitamins A, D, E and other micronutrient supplements, and referred to a dietitian for dietary support and a child and adolescent psychologist for anxiety related to his diet.

At follow-up in March, 2015, 4 months after starting treatment, he looked well and had improved visual acuity (6/60 bilaterally) and resolution of his xerotic conjunctivae (figure). He had had no more systemic infections and his facial nerve palsies had completely resolved.

Vitamin A is essential in the maintenance of epithelial function, most notably in the mucous membrane of the conjunctiva and urinary and respiratory tracts. Vitamin A deficiency typically causes xerotic conjunctivae, fissured cheeks, and gradual visual loss. Systemic symptoms of vitamin A deficiency include recurrent infections of the skin, genitourinary tract, and upper respiratory tracts. Bilateral facial nerve palsies in vitamin A deficiency have been reported only in conjunction with cystic fibrosis, but cystic fibrosis was excluded in our patient.

Several case reports describe severe vitamin A deficiency from multiple allergy dietary restrictions causing xerotic conjunctivae. Other micronutrient deficiencies such as B12, D, and E often present concurrently with vitamin A deficiency in allergy-restricted diets; as in our patient, and deficiency of vitamin B12 has previously been associated with optic neuropathy leading to visual loss. Vision and ocular surface abnormalities can be treated successfully if nutritional deficiencies are treated early. Normal visual function is dependent on good nutrition, and low concentrations of essential micronutrients such as vitamins A, B12, E, and C, cobalamin, biotin, iron, and zinc have all been associated with visual problems.

This case highlights the severity of extreme dietary restrictions on ophthalmic and systemic health. Visual loss due to vitamin A deficiency is mainly seen in low-income countries as the result of malnutrition. Because of its rarity in developed countries, vitamin A deficiency...
is often overlooked as a potential cause for visual loss, as in our case. Unfortunately, in this case, delayed diagnosis resulted in visual loss that was entirely preventable. Increasing prevalence of food allergies, irritable bowel syndrome, anorexia, and self-imposed diet restrictions might contribute to an increase of vitamin A deficiency in developed countries.

Contributors
All authors contributed to patient care and writing of the report. Written consent to publication was obtained.

Reference
Appendix Two:

Participant information sheets and consent forms
Participant Information Sheet

Study title: Neonatal and Infant Eye Screening in New Zealand – Prospective Study of Retinopathy of Prematurity Long Term Outcomes

Locality: Auckland

Ethics committee
ref.:

Lead investigator: Dr Shuan Dai

Contact phone number: 0272488883

Your child is invited to take part in a study on long term outcomes of Retinopathy of Prematurity in New Zealand, whether or not your child takes part is your choice. If you don’t want your child to take part, you don’t have to give a reason, and it won’t affect the care your child receives. If you do want your child to take part now, but change your mind later, you can pull your child out of the study at any time.

This Participant Information Sheet will help you decide if you’d like your child to take part. It sets out why we are doing the study, what your child’s participation would involve, what the benefits and risks to your child might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not your child will participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree for your child to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 5 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

What is the purpose of the study?

The purpose of this study is to see if digital wide field retinal photo screening, using RetCam, in premature infants at risk of the eye disease, retinopathy of prematurity (ROP) is accurate and to see the long-term results of using this technique. The RetCam has been in use in Auckland for premature babies who are at risk of ROP since 2005 but more consistently since 2007. ROP happens at the back of the eye. A retrospective review will be carried out for all infants screened for ROP in Auckland to see how accurate the RetCam is for detecting ROP. We are asking some of the children who had the screening during their newborn period to have a full eye exam to help understand what happens to the vision of these children as they get older. This information will help to figure out correct follow up times and any risks factors for those children who get ROP.
A child’s vision is very important in the normal development process with it having effects on both social and school life. We want to help every child have the best chance for normal vision by understanding long term outcomes of ROP better. The study is part of a PhD being run through the Department of Ophthalmology, Faculty of Medical and Health Sciences, the University of Auckland.

WHAT WILL MY CHILD’S PARTICIPATION IN THE STUDY INVOLVE?

Participation in this study will involve a comprehensive eye test for your child. This will include some questions about their eyes, vision measured on the eye chart, visual field, pupil dilation and other standard eye tests. This is a one off eye test of about 1 hour. The SVOP machine is a new visual field machine for measuring the peripheral vision in children, this will be used along with the standard machine (Goldmann visual field machine) to measure the visual field of children with previous ROP.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

As the eye exams are being done by trained professionals your child will benefit from an eye health check which can detect early eye problems. Eye drops are safely used in a normal eye exam, however, they can very occasionally have side effects. Trained professionals will be putting in the drops and testing your child. It is normal for the eye drops to cause slight stinging of the eye, when put in and make vision blurry for the rest of the day. This will be explained again on the day of the eye test.

If there are any abnormal findings during the eye exam then the correct care, referral or follow up will be arranged.

WHO PAYS FOR THE STUDY?

Your child’s participation in this study will not result in any cost to you.

WHAT IF SOMETHING GOES WRONG?

If your child were injured in this study, which is extremely unlikely, your child would be eligible for compensation from ACC just as one would be if one were injured in an accident at work or at home. We will lodge a claim with ACC on your child’s behalf, which may take some time to assess. If the claim is accepted, you will receive funding to assist in your child’s recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won’t affect your cover.

WHAT ARE MY RIGHTS?

Participation in this study is completely voluntary. You are free to decline your child’s participation or to withdraw your child from the research at any time. Your decision to participate or decline participation in this study will have no effect on the medical treatment your child receives now or in the future.
As a participant your child has the right to access any information collected about him/her during the study period. Participants will be kept informed of any new knowledge during the study that may impact on their health.

**WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?**

Information collected about your child in this study will be kept in a de-identified manner securely in the Department of Ophthalmology in a locked file cabinet and a password protected hard-drive. This is to ensure privacy and confidentiality of the participant. It will be retained for possible future use in a de-identified manner. Ms Samantha Watkins, PhD student will be responsible for the secure storage and, when needed, destruction of this data. For those participants who request a copy of the study findings upon completion these will be sent via the email address filled out below.

**WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?**

If you have any questions, concerns or complaints about the study at any stage, you can contact:

**Primary Contact:**
Ms Samantha Watkins (BOptom Hons), PhD Student  
The Department of Ophthalmology  
The University of Auckland  
Ph: 021 082 69814 or (09) 373 7599 ext 86471  
Email: samantha.watkins@auckland.ac.nz

**Principal Investigator:**
Dr Shuan Dai, Consultant Paediatric Ophthalmologist, Co-ordinating Investigator  
Telephone number: 027 248883  
Email: shuandai@me.com

If you want to talk to someone who isn’t involved with the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050  
Fax: 0800 2 SUPPORT (0800 2787 7678)  
Email: advocacy@hdc.org.nz

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS  
Email: hdecs@moh.govt.nzik
**Consent Form**

**Please tick to indicate you consent to the following**

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<tr>
<th>Description</th>
<th>Yes □</th>
<th>No □</th>
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<tr>
<td>I have read, or have had read to me, and I understand the Participant Information Sheet.</td>
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<td>I have been given sufficient time to consider whether or not to participate in this study.</td>
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<td>I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study.</td>
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<td>I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.</td>
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<td>I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.</td>
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<tr>
<td>I consent to the research staff collecting and processing my information, including information about my health.</td>
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<td>If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.</td>
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<tr>
<td>I consent to my GP or current provider being informed about my participation in the study and of any significant abnormal results obtained during the study.</td>
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<td>I understand that the eye drops, tropicamide 1% and cyclopentolate 1%, will be used to dilate the pupil for part of the full eye examination by a trained professional.</td>
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I agree to an approved auditor appointed by the New Zealand Health and Disability Ethics Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.  

Yes ☐  No ☐

I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.  

Yes ☐  No ☐

I understand the compensation provisions in case of injury during the study.  

Yes ☐  No ☐

I know who to contact if I have any questions about the study in general.  

Yes ☐  No ☐

I understand my responsibilities as a study participant.  

Yes ☐  No ☐

I wish to receive a summary of the results from the study.  

Yes ☐  No ☐

**Declaration by participant:**
I hereby consent to take part in this study.

Parent/Caregiver’s name: 

Signature: 

Participant’s Name: 

Date: 

Email: 

Phone: 

**Declaration by member of research team:**
I have given a verbal explanation of the research project to the participant, and have answered the participant’s questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher’s name: 

Signature: 

Date: 

Lay study title: 
Page 5 of 5
Participant Information Sheet

Study title: Neonatal and Infant Eye Screening in New Zealand
- Universal Newborn Eye Screening

Locality: Auckland
Ethics committee ref.: 

Lead investigator: Dr Shuan Dai
Contact phone number: 0272488883

Your child is invited to take part in a study on Universal Newborn Eye Screening, whether or not your child takes part is your choice. If you don’t want your child to take part, you don’t have to give a reason, and it won’t affect the care your child receives. If you do want your child to take part now, but change your mind later, you can pull your child out of the study at any time.

This Participant Information Sheet will help you decide if you’d like your child to take part. It sets out why we are doing the study, what your child’s participation would involve for your child, what the benefits and risks to your child might be, and what would happen after the study ends. We will go through this information with you and answer any questions you, as the parent/guardian may have. You do not have to decide today whether or not your child will participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree for your child to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 5 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to see if digital wide field retinal photo screening, using Retcam, in newborns is accurate for screening. Finding eye problems earlier in children means earlier treatment is available. With the use of a specialist digital camera, the RetCam, infant’s eyes will be screened to see if there are any retinal haemorrhages or congenital abnormalities. The RetCam takes images that the ophthalmologist (eye doctor) then looks at to see if everything is healthy or not. The number of problems found will help to decide if this screening method is useful for all newborns, like the current hearing test all newborns have. The RetCam is already in use for premature babies who are at risk of an eye disease called retinopathy of prematurity, ROP. A child’s vision is very important in the normal development process with it having effects on both social and school life. We want to help every child have the best chance for normal vision by looking at their eyes as early as possible.

The study is part of a PhD being run through the Department of Ophthalmology, Faculty of Medical and Health Sciences, the University of Auckland.
WHAT WILL MY CHILD’S PARTICIPATION IN THE STUDY INVOLVE?

The RetCam test needs eye drops to be put into each eye of your child. The first drops will be put in half an hour before the test, they are 1.0% tropicamide and 2.5% phenylephrine that causes the pupil (the black part of the eye) to get larger so a better picture of the back of the eye can be taken. The second drop 0.5% amethocaine, will be put in immediately before the test begins to numb your child’s eye and make it comfortable for your baby. A speculum will be used to hold your child’s eyelids open. A gel is put on the end of the RetCam to protect your child’s eye as photos are taken. Taking the photos will take about 5 minutes for both eyes. The test will be done within 72 hours of your child’s birth. A second set of photos will be taken at 6 weeks for those children in whom retinal haemorrhages are found. Each test will take 35 minutes with the first 30 minutes being time for the drops to work.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

As the eye exams are being done by trained professionals your child will benefit from an eye health check which may detect eye problems early, if present. Eye drops are safely used in a normal eye exam, however, they can very occasionally have side effects. Trained professionals will be putting in the drops and testing your child. It is normal for the eye drops to cause slight stinging of the eye, when put in and make vision blurry for the rest of the day. This will be explained again on the day of the eye test.

If there are any abnormal findings during the eye exam then the correct care, referral or follow up will be arranged.

WHO PAYS FOR THE STUDY?

Your child’s participation in this study will not result in any cost to you.

A grant from the Save Sight Society is funding parts of this project.

WHAT IF SOMETHING GOES WRONG?

If your child were injured in this study, which is extremely unlikely, your child would be eligible for compensation from ACC just as one would be if one were injured in an accident at work or at home. We will lodge a claim with ACC on your child’s behalf, which may take some time to assess. If the claim is accepted, you will receive funding to assist in your child’s recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won’t affect your cover.

WHAT ARE MY RIGHTS?

Participation in this study is completely voluntary. You are free to decline your child’s participation or to withdraw your child from the research at any time. Your decision to participate or decline participation in this study will have no effect on the medical treatment your child receives now or in the future.

As a participant your child has the right to access any information collected about him/her during the study period. Participants will be kept informed of any new knowledge during the study that may impact on their health.
What happens after the study or if I change my mind?

Information collected about your child in this study will be kept in a de-identified manner securely in the Department of Ophthalmology in a locked file cabinet and a password protected hard-drive. This is to ensure privacy and confidentiality of the participant. It will be retained for possible future use in a de-identified manner.

Ms Samantha Watkins will be responsible for the secure storage and, when needed, destruction of this data.

For those participants who request a copy of the study findings upon completion these will be sent via the email address filled out below.

Who do I contact for more information or if I have concerns?

If you have any questions, concerns or complaints about the study at any stage, you can contact:

Primary Contact:
Ms Samantha Watkins (BOptom Hons), PhD Student
The Department of Ophthalmology
The University of Auckland
Ph: 021 082 69814 or (09) 373 7599 ext 86471
Email: samantha.watkins@auckland.ac.nz

Principal Investigator:
Dr Shuan Dai, Consultant Paediatric Ophthalmologist, Co-ordinating Investigator
Telephone number: 027 248883
Email: shuandai@me.com

If you want to talk to someone who isn’t involved with the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS
Email: hdecs@moh.govt.nz

If you require Māori cultural support talk to your whānau in the first instance. Alternatively you may contact the administrator for He Kamaka Waiora (Māori Health Team) by telephoning 09 486 8324 ext 2324

If you have any questions or complaints about the study you may contact the Auckland and Waitematā District Health Boards Māori Research Committee or Māori Research Advisor by telephoning 09 4868920 ext 3204
Please tick to indicate you consent to the following

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<td>I consent to my GP or current provider being informed about my participation in the study and of any significant abnormal results obtained during the study.</td>
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<td>I understand that the eye drops 1.0% tropicamide, 2.5% phenylephrine and 0.5% amethocaine will be administered to my child by a trained professional and that they have a very small risk of side effects.</td>
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<td>I agree to an approved auditor appointed by the New Zealand Health and Disability Ethics Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.</td>
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that no material, which could identify me personally, will be used in any reports on this study.

I understand the compensation provisions in case of injury during the study.  
Yes ☐  No ☐

I know who to contact if I have any questions about the study in general.  
Yes ☐  No ☐

I understand my responsibilities as a study participant.  
Yes ☐  No ☐

I wish to receive a summary of the results from the study.  
Yes ☐  No ☐

Declaration by participant:
I hereby consent to take part in this study.

Participant’s name: ___________________________  Mother’s Height: ___________________________

Signature: ___________________________  Date: ___________________________

Email: ___________________________  Phone: ___________________________

Declaration by member of research team:
I have given a verbal explanation of the research project to the participant, and have answered the participant’s questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher’s name: ___________________________

Signature: ___________________________  Date: ___________________________
Participant Information Sheet

Study title: SVOP - the clinical applicability of an objective visual field measurement in children

Locality: Auckland

Ethics committee ref.

Lead investigator: Dr Shuan Dai

Contact phone number: (09) 373 7599 ext 86471 (Samantha Watkins)

Your child is invited to take part in a study on visual field testing in children which is part of Ms Samantha Watkins’ PhD, whether or not your child takes part is your choice. If you don’t want your child to take part, you don’t have to give a reason, and it won’t affect the care your child receives. If you do want your child to take part now, but change your mind later, you can pull your child out of the study at any time.

This Participant Information Sheet will help you decide if you’d like your child to take part. It sets out why we are doing the study, what your child’s participation would involve, what the benefits and risks to your child might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not your child will participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree for your child to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 5 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

What is the purpose of the study?

This study is looking at how we test the side vision or visual field in children. A person’s visual field is the total area that they can see when looking at a point. It is important to test the visual field in children because it can help diagnose eye and brain disorders.

Visual fields in children are normally tested using the Goldmann visual field machine or by the confrontation method. However, a new machine has been developed, the SVOP, that is thought to be easier for the child to use, quicker to perform and accurate. Unlike the Goldmann visual field machine and confrontation, SVOP has the advantage of not needing the child to keep their eyes and head still or give any response to the examiner. This study aims to find out if SVOP is an accurate and effective way of testing visual fields in children. Your child has been chosen to participate in this study because they are between 4 and 14 years of age and they have no current eye problems.
**WHAT WILL MY CHILD’S PARTICIPATION IN THE STUDY INVOLVE?**

If you choose for your child to take part, they will have their distance vision tested and then three visual field tests: SVOP, Goldmann visual field machine and confrontation. SVOP will involve your child sitting 50-70 cm away from a computer screen in a faintly lit room.

The Goldmann visual field machine will involve your child being seated in front of it with their head placed on the chin rest. They will be required to keep their head still and focus their eyes on the centre of the bowl. They will then be presented with light which will be moved around the bowl. They will be required to tell the examiner when they see or do not see the light.

Confrontation will involve your child being examined by an optometrist, who will move a small light in front of your child. Once again, your child will be required to tell the examiner when they see or do not see the light.

The total amount of time involved for the three visual field tests will be approximately half an hour. This can be completed in one session. The study will be completed by the end of February 2015.

**WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?**

Your child’s participation in this study involves the completion of three visual field assessments, which are used to detect visual field defects. All tests are non-invasive and have no foreseen risks to your child. If you have any concerns at any stage, please discuss this with your health care provider.

**WHO PAYS FOR THE STUDY?**

Your child’s participation in this study will not result in any cost to you.

**WHAT IF SOMETHING GOES WRONG?**

If your child is found to have a visual field defect we will explain the finding to you and your child and refer them to an ophthalmologist or optometrist.

If your child were injured in this study, which is extremely unlikely, your child would be eligible for compensation from ACC just as one would be if one were injured in an accident at work or at home. We will lodge a claim with ACC on your child’s behalf, which may take some time to assess. If the claim is accepted, you will receive funding to assist in your child’s recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won’t affect your cover.

**WHAT ARE MY RIGHTS?**

Participation in this study is completely voluntary. You are free to decline your child’s participation or to withdraw your child from the research at any time. Your decision to participate or decline participation in this study will have no effect on the medical treatment your child receives now or in the future.

As a participant your child has the right to access any information collected about him/her during the study period. Participants will be kept informed of any new knowledge during the study that may impact on their health.
WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?

Information collected about your child in this study will be kept in a de-identified manner securely in the Department of Ophthalmology in a locked file cabinet and a password protected hard-drive. This is to ensure privacy and confidentiality of the participant. It will be retained for possible future use in a de-identified manner.
Ms Samantha Watkins, PhD student will be responsible for the secure storage and, when needed, destruction of this data.
For those participants who request a copy of the study findings upon completion these will be sent via the email address filled out below.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns or complaints about the study at any stage, you can contact:

Ms Samantha Watkins (BOptom Hons), PhD Student
The Department of Ophthalmology
The University of Auckland
Ph: 021 082 69814 or (09) 373 7599 ext 86471
Email: samantha.watkins@auckland.ac.nz

If you want to talk to someone who isn’t involved with the study, you can contact an independent health and disability advocate on:

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Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS
Email: hdecs@moh.govt.nz

There are no interpreters available for this study.

If you require Māori cultural support talk to your whānau in the first instance. Alternatively you may contact the administrator for He Kamaka Whaora (Māori Health Team) by telephoning 09 486 8324 ext 2324

If you have any questions or complaints about the study you may contact the Auckland and Waitematā District Health Boards Māori Research Committee or Māori Research Advisor by telephoning 09 4868920 ext 3204
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Declaration by participant:
I hereby consent to take part in this study.

Participant’s name:

________________________________________________________________________________
Signature:                                                                 Signature:
________________________________________________________________________________
Email:                                                                  Phone:

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant’s questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher’s name:

________________________________________________________________________________
Signature:                                                                 Date:
Consent Form for BLENNZ
Saccadic Vector Optokinetic Perimeter (SVOP)

Dear parent/guardian,

The Blind and Low Vision Education Network NZ (BLENNZ) is a unique organization that assess and supports young people who are blind, deafblind or have low vision in Aotearoa.

Measuring the peripheral vision (visual field) in children is known to be challenging. The SVOP machine is a newly developed visual field machine. It is a non-invasive objective test of peripheral vision designed specifically for children and those with complex needs. We are wanting to assess the effectiveness and utility of the SVOP machine in children with and without visual impairment. SVOP will be used as part of your child's normal assessment exam where clinically indicated, it will be performed by a qualified optometrist or ophthalmologist.

If you do not want your child to be included you do not have to give a reason and doing so will not affect the care your child receives from BLENNZ. Please feel free to ask any questions or discuss this with other people such as family, whānau or friends, before making a decision.

By signing this form you consent to the use of your child’s information in an unidentifiable manner for research at BLENNZ. I understand that my child will not be able to be identified in any way in this research and that further consent would need to be sought for the use of any information that would make my child identifiable.

I hereby give consent as legal parent/guardian

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<tr>
<td>Parent/Guardian's name:</td>
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References


