BINOCULARITY OUTCOMES OF LASER ABLATION VERSUS ANTI-VEGF TREATMENTS IN RETINOPATHY OF PREMATURITY

by

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Abstract

Retinopathy of prematurity (ROP) is a leading cause of visual impairment in prematurely born children. Two treatment options for severe ROP utilize laser and/or anti-VEGF injections. We aim to determine the influence of treatment on binocularity outcomes.

This cross-sectional study prospectively measures binocularity using tests of fusion and stereopsis in children aged three to eight with a history of ROP treatment with either laser or anti-VEGF injections.

44 children were recruited: 23, anti-VEGF and 21, laser. No statistically significant difference in rates of binocularity was detected (67% laser vs 82% anti-VEGF). Laser-treated participants experienced a greater number of cumulative insults to binocularity than those in the anti-VEGF group (p=0.04).

Patients with a history of ROP treated with laser or anti-VEGF require long-term follow-up to address binocularity-disrupting factors. Further investigation with a larger sample size of visually mature subjects is needed to confirm these findings.
## List of Abbreviations Used

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AAO</td>
<td>American Academy of Ophthalmology</td>
</tr>
<tr>
<td>AAP</td>
<td>American Academy of Pediatrics</td>
</tr>
<tr>
<td>AP-ROP</td>
<td>Aggressive posterior retinopathy of prematurity</td>
</tr>
<tr>
<td>BEAT-ROP</td>
<td>Bevacizumab eliminates the angiogenic threat of retinopathy of prematurity study (see references)</td>
</tr>
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<td>BSV</td>
<td>Binocular single vision</td>
</tr>
<tr>
<td>BW</td>
<td>Birthweight</td>
</tr>
<tr>
<td>CRYO-ROP</td>
<td>Cryotherapy for retinopathy of prematurity (refers to studies by this group)</td>
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<tr>
<td>D</td>
<td>Diopters</td>
</tr>
<tr>
<td>ETDRS</td>
<td>Early Treatment Diabetic Retinopathy Study</td>
</tr>
<tr>
<td>ETROP</td>
<td>Early treatment for retinopathy of prematurity</td>
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<tr>
<td>GA</td>
<td>Gestational age</td>
</tr>
<tr>
<td>ICROP</td>
<td>International classification of retinopathy of prematurity</td>
</tr>
<tr>
<td>IOD</td>
<td>Interocular difference</td>
</tr>
<tr>
<td>IWK</td>
<td>Izaak Walton Killam Health Centre</td>
</tr>
<tr>
<td>logMAR</td>
<td>Logarithm of the minimum angle of resolution</td>
</tr>
<tr>
<td>NDVI</td>
<td>Neurodevelopmental impairment</td>
</tr>
<tr>
<td>OCT</td>
<td>Optical coherence tomography</td>
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<tr>
<td>PD</td>
<td>Prism diopters</td>
</tr>
<tr>
<td>ROP</td>
<td>Retinopathy of prematurity</td>
</tr>
<tr>
<td>SE</td>
<td>Spherical equivalent</td>
</tr>
<tr>
<td>SK</td>
<td>SickKids (refers to Hospital for Sick Children in Toronto)</td>
</tr>
<tr>
<td>TAC</td>
<td>Teller Acuity Cards</td>
</tr>
<tr>
<td>VA</td>
<td>Visual acuity</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
</tr>
<tr>
<td>+</td>
<td>Plus disease</td>
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</table>
Acknowledgements

First and foremost, I would like to acknowledge my wonderful supervisory committee: Dr. Johane Robitaille, Dr. Nasrin Tehrani, Dr. Kamiar Mireskandari, Maram Isaac, Heather Fennell-Al Sayed, Steve Van Iderstine, and Dr. Michael Vincer—thank you all so much for all your hard work and support. A special thank you to Dr. Nasrin Tehrani for the idea which initiated this project and for the opportunity to collaborate with the ophthalmology team at SickKids; to Dr. Johane Robitaille for taking me on as a master’s student and for being a great mentor to me throughout this process; to Dr. Kamiar Mireskandari for always forcing me to think deeper and more critically and so developing my skills as a researcher; to Maram Isaac for her incredible patience, kindness and encouragement; and to Heather Fennell-Al Sayed for fomenting my ability to consider issues from a clinical perspective. I have learned so much from you all and hope to continue doing so in future collaborations.

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*I will thank the Lord at all times. My lips will always praise him.*

- *Psalm 34:1* (NIRV)
CHAPTER 1: INTRODUCTION

1.1 Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is a condition that affects the developing retina in premature infants. The retina is the light-sensitive tissue at the back of the eye responsible for receiving incoming light signals and transferring them to the brain for interpretation via the optic nerve. This tissue including its blood vessels develops first at the posterior pole i.e. the area in the centre of the back surface of the eye around the optic nerve, and then grows outward reaching the most peripheral regions around 40 weeks gestation (Hartnett, 2017; Chan-Ling, Gock, & Stone, 1995).

The pathological changes of ROP evolve as a result of the incomplete development of retinal tissue (comprised of both neural and vascular cells/tissue) at the time of premature birth that is exposed to a deviation from the in utero environment (Smith, 2008). This can cause abnormal vascularization due to the relative hyperoxia followed by relative hypoxia disrupting normal vascular tissue growth despite continued development of the neuronal tissue in the avascular area (Hartnett, 2017; Hellström, Smith, & Dammann, 2013; Lynch, et al., 2017). The ensuing hypoxic environment in the avascular retina leads to the upregulation of vascular endothelial growth factor (VEGF) by peripheral retinal cells (Chan-Ling, Gock, & Stone, 1995; Hartnett, 2017; Young, Anthony, Pierce, Foley, & Smith, 1997). VEGF is a molecule that has been described as a mitogen (i.e. promoting mitosis) specific to endothelial cells in the walls of blood vessels (Ferrara, 1996; Smith L. E., 2004). It has been identified as the most potent endogenous agent related to the pathological angiogenesis seen in ROP, although other molecular factors such as insulin-like growth factor 1 are involved as well (Smith, 2008; Chen & Smith, 2007; Beharry, Valencia, Lazzaro, & Aranda, 2016; Tran, Cernichiaro-Espinosa, & Berrocal, 2018).

In a hypoxic state, the body is aiming to correct the lack of oxygenation by promoting the growth of vessels which, in normal conditions would supply oxygen via blood-flow to this region (Pierce, Foley, & Smith, 1996). However, because the blood vessels have stopped developing during the hyperoxic phase, the avascular area (i.e. the region of developing neuronal tissue ahead of the vascularized area) becomes hypoxic.
and the endothelial cells undergoing mitosis cannot progress normally into that area and crowd the border of the vascular-nonvascular retina (Hartnett, 2017). Over time, this crowding of blood vessels leads to the recognizable “neovascular ridge or edge” formation which is a hallmark of severe ROP that may cause blindness from dragging of retinal tissue towards the ridge during the scarring phase of the neovascular tissue. ROP is one of the leading causes of preventable childhood blindness in the developed world (Kim, et al., 2018). Furthermore, ROP also poses the threat of long-term ophthalmic morbidities the most prevalent of which are strabismus, high myopia and foveal hypoplasia (Pennefather, et al., 1999; Wheeler, et al., 2011; Gursoy, Bilgec, Erol, Basmak, & Colak, 2016).

As the name implies, ROP is associated with low gestational age (GA) which is one of the biggest risk factors that is associated with the development and degree of severity of ROP along with low birthweight (BW) (Hellström, Smith, & Dammann, 2013; Chen & Smith, 2007; Kim, et al., 2018). However, the exact minimum GA and BW under which children are deemed at-risk varies considerably from country to country where the most noticeable difference between populations is demarcated by the country’s income and access to high-quality neonatal care units (Wilson, Ells, & Fielder, 2017). Therefore, the screening protocol for ROP remains an evidence-based practice and guidelines differ internationally (Wilson, Ells, & Fielder, 2017). In Canada, the current guidelines indicate that any child born at GA 30\(\frac{6}{7}\) (30 weeks, 6 days) or sooner regardless of BW, and/or any child born with BW of 1250g or less requires screening (Jefferies, 2010; Jeffries, 2016). These guidelines also dictate that the neonatologist, at their discretion, could use the BW of 1500g or less as recommended by the American Academy of Pediatrics (AAP) and that it is appropriate to extend the BW guidelines to 2000g or less in babies with a complex clinical course (Jefferies, 2010; Fierson, 2013).

1.1.1 Diagnosis and Classification of ROP

Any infant meeting the screening criteria in accordance with the guidelines mentioned in the previous section is examined in a timely manner and ROP is diagnosed based on an indirect ophthalmoscopy examination performed by an ophthalmologist (Jordan, 2014). If ROP is detected, it is described by zone, stage, and presence of “plus
“disease” as indicated by the International Classification of Retinopathy of Prematurity (ICROP) guidelines, a system created through the collaboration of international experts to standardize the documentation of ROP (International Committee for the Classification of Retinopathy of Prematurity, 2005; The Committee for the Classification of Retinopathy of Prematurity, 1984; The International Committee for the Classification of the Late Stages of Retinopathy of Prematurity, 1987)

Zones indicate the area where the normally developed retinal tissue posteriorly meets the peripherally avascular retina. There are 3 zones (labelled I, II, and III); zone I is the most central while zone III is the most peripheral (Figure 1.1). The ICROP guidelines for zones are as follows:

- Zone I is a circle whose diameter is four times the distance between the center of optic disc and the macula and which has the optic disc at its center.
- Zone II extends centrifugally out from the border of Zone I to the nasal ora serrata.
- Zone III is the residual retinal crescent. It is the most peripheral and anterior portion of the retina temporally.
Figure 1.1. Classification of zones and extent of ROP.

Above are the zones and clock hours used to classify ROP relative to anatomical markers at the back of the eye. Adapted from Jefferies, 2016.
Stages describe the severity of the disease at the junction of the vascularized and avascular retina, (International Committee for the Classification of Retinopathy of Prematurity, 2005). There are 5 stages (labelled 1, 2, 3, 4 and 5) of which stage 1 is least severe and stage 5 is most severe and results in complete blindness. It is possible for one eye to have different concurrent stages therefore, by convention, the most severe stage is used to classify the retinopathy in each eye individually. Clinicians also use the term “stage 0” to indicate that there is a portion of immature retina but the pathological processes characterizing ROP, are not present; this description is not a part of the official ICROP classification guidelines (Lee T. , 2017). The criteria for assigning stages are as follows:

- **Stage 1** is characterized by a visible demarcation line between the vascular and avascular regions of the retina but no height or thickness to the ROP edge can be detected.
- **Stage 2** has grown in height and width forming an identifiable “ridge” however, the vasculature has not yet begun proliferating into the ridge or the vitreous.
- **Stage 3** is the point at which neovascularization begins creating a more voluminous expansion of the ridge from stage 2. Depending on the amount of fibrovascular tissue extending into the vitreous, Stage 3 can further be described as mild, moderate or severe.
- **Stage 4** is a partial or subtotal retinal detachment and can be subdivided to indicate whether the fovea has been compromised or spared:
  - **Stage 4a** is an extrafoveal retinal detachment.
  - **Stage 4b** is a retinal detachment involving the fovea.
- **Stage 5** is a total retinal detachment. When this occurs, funneling of the retina ensues which can also be described in a Stage 5 categorization specifying whether the anterior and posterior aspects of the funnel are opened or closed.

The extent of the disease quantifies the area of affected retina and is helpful in measuring progression of ROP between examinations but is not required for determining course of treatment—see Table 1.1 for details (Good, 2004). Describing the extent of the disease can be done using clock hours (Figure 1.1) as first indicated by the ICROP.
protocol which defines that, “3 o’clock is...nasal in the right eye and temporal in the left eye and 9 o’clock is...temporal in the right eye and nasal in the left eye,” (International Committee for the Classification of Retinopathy of Prematurity, 2005).

The final aspect of ROP reporting involves noting presence of “plus disease”, indicated by a “+” on documentation. The posterior vessels of the developed retina can become tortuous (arteries) and dilated or enlarged (veins) as a direct result of the pathological increased blood flow to the hypoxic peripheral retina and is therefore an indicator of severity and disease activity (International Committee for the Classification of Retinopathy of Prematurity, 2005; Lee T., 2017; Jordan, 2014). To diagnose plus disease, the physician must note significant vascular tortuosity and dilation compared to a standard photograph in two or more quadrants (International Committee for the Classification of Retinopathy of Prematurity, 2005). In addition, non-retinal signs of plus disease can include pupillary rigidity, increased dilation of iris vessels and vitreous haze (International Committee for the Classification of Retinopathy of Prematurity, 2005). The ICROP guidelines have also defined “pre-plus disease” as, “vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease but that demonstrate more arterial tortuosity and more venous dilation than normal,” (International Committee for the Classification of Retinopathy of Prematurity, 2005). Like extent of disease, noting presence of pre-plus disease helps clinicians monitor the progression of the ROP.

A sub-type of ROP called Aggressive Posterior ROP (AP-ROP) was added to the international classification in 2005 (International Committee for the Classification of Retinopathy of Prematurity, 2005). This type of ROP is characterized by its posterior location, rapid progression, presence of plus disease and the recognition that previously published standardized descriptions of ROP failed to adequately recognize the features and course of this severe form of ROP (International Committee for the Classification of Retinopathy of Prematurity, 2005). The importance of timely detection of AP-ROP is that it invariably and rapidly leads to retinal detachment if left untreated or caught late (Shapiro, Blair, & Gonzalez, 2017).

1.1.2 Treatment of ROP and Long-Term Outcomes
The first clue of an association between oxygen supplementation and ROP was described by Dr. T.L. Terry in 1942 (Terry, 1942). Since then, there has been a tremendous amount of research to understand the underlying pathophysiology and approaches to management including natural history, risk reduction, treatments for visually threatening ROP and long-term effects of treated and untreated ROP.

The initial rise of ROP correlated with the advances in medicine and technology allowing a higher survival rate in extremely premature babies, the population most at risk for developing ROP (Raghuveer & Bloom, 2011). In the 1950’s several reports emerged which examined the role of oxygen delivery to premature neonates; these reports concluded that elevated levels of oxygen were responsible for the pathology seen in ROP (Ashton, Ward, & Serpell, 1954; Patz, 1957; Quimson, 2015). It was later discovered that the true etiology behind ROP is much more complex and the pathology can be attributed to multiple risk factors and endogenous processes described in the previous sections.

The initial interventive protocol for treating ROP became popular in the late1980’s following the publication of the randomized, multicenter, prospective study presented by the Cryotherapy for Retinopathy of Prematurity Cooperative Group (CRYO-ROP). The treatment at the time consisted of cryotherapy applications using a freezing probe to ablate avascular retinal tissue anterior to the fibrovascular ridge (CRYO-ROP Group, 1988). The reasoning behind this therapy was the knowledge that destroying the peripheral hypoxic tissue driving the aberrant angiogenesis at the ROP edge would arrest the pathogenic proliferation of vessels and induce regression (Nissenkorn, Kremer, Ben-Sira, Cohen, & Garner, 1984). The CRYO-ROP group demonstrated that using cryotherapy as an intervention for ROP produced favorable results when compared to receiving no treatment (control group) (CRYO-ROP Group, 1988; Palmer, 1990).

Once the efficacy of retinal ablation in the treatment of ROP was established using the CRYO-ROP study protocol and with the advent of lasers in the treatment of retinal diseases, centers began to compare the outcomes of different methods of ablation, specifically laser vs cryotherapy. Many studies showed that visual acuity, refractive error and structural outcomes were superior in those treated with laser as opposed to cryotherapy (Knight-Nanan & O'Keefe, 1996; Ng, et al., 2002; Shalev, Farr, & Repka, 2001).
Laser ablation has since remained the “gold-standard” treatment using a protocol that favors treatment at earlier stages than was originally proposed by the CRYO-ROP studies. These new treatment criteria (Table 1.1) were established by the Early Treatment for Retinopathy of Prematurity Group (ETROP) that demonstrated successful prevention of retinal detachment in more than 90% of infants treated for Type 1 ROP with laser (Good, 2004; Quimson, 2015). Despite optimizing ROP treatment method and timing of intervention, some of the documented complications in those who were successfully treated include strabismus and high refractive error (Vanderveen D. K., et al., 2011; Geloneck, et al., 2014).
Table 1.1  Factors determining type classification of ROP as defined by the ETROP cooperative group. Adapted from Good, 2004.

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 2</th>
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<tr>
<td>- Zone I any stage with plus disease</td>
<td>- Zone I stage 1 or 2 without plus disease</td>
</tr>
<tr>
<td>- Zone I stage 3 without plus disease</td>
<td>- Zone II stage 3 without plus disease</td>
</tr>
<tr>
<td>- Zone II stage 2 or 3 with plus disease</td>
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Anti-VEGF agents have emerged in the last decade as an alternative treatment to laser ablation. Anti-VEGF agents are so named because they are ‘antibodies to VEGF’. These antibodies work by binding to the VEGF molecule, neutralizing its action to effectively stop the aberrant angiogenesis in stage 3 ROP and enabling the reversal of the disease (Ferarra, Hillan, Gerber, & Novotny, 2004). Anti-VEGF treatment is considered non-ablative and uses agents such as bevacizumab (Avastin™) and ranibizumab (Lucentis™) off-label. The Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity Group (BEAT-ROP) conducted a multicenter, prospective, randomized study to compare conventional laser ablation treatment to intravitreal injections of bevacizumab (Mintz-Hittner, Kennedy, & Chuang, 2011). This study found that bevacizumab had favorable results for stage 3+ and zone I disease when compared to laser ablation but that there was no difference between the two treatments for zone II disease (Mintz-Hittner, Kennedy, & Chuang, 2011). The main benefit cited for the use of this treatment is that it salvages the peripheral retina instead of destroying it like laser ablation and, although unproven, may permit “normal” vessel growth and possible retina function from the avascular area of retina during ROP phases (Mintz-Hittner, Kennedy, & Chuang, 2011; Quimson, 2015; Eldweik & Mantagos, 2016; Rivera, et al., 2011). The effects of anti-VEGF treatment are more rapid than those of laser and the intervention does not require the use of general anesthesia (Vanderveen, et al., 2017).

One of the controversial disadvantages of anti-VEGF treatment in ROP arose when it was discovered that bevacizumab is absorbed systemically with measurable drug levels and corresponding lowered VEGF levels in the bloodstream lasting weeks, meaning that it does not have a controlled and localized effect. The systemic risks attributable to the anti-VEGF treatment in the context of premature birth remains unknown (Quimson, 2015; Rivera, et al., 2011). There have been some investigations considering the effect of anti-VEGF agents administered intravitreally on neurodevelopment in ROP patients, but larger studies will be needed to clarify the risk (Chen, Schachar, & M, 2018; Martinez-Garcia, et al., 2017; Morin, et al., 2016; Lien, et al., 2016). Another problem with using this treatment is that dosage, type of anti-VEGF agent, retreatment criteria with more anti-VEGF agents and/or laser and long-term follow-up vary among institutions and physicians as there is currently insufficient
research to guide the development of a standardized treatment and follow-up protocol. (Rivera, et al., 2011; Eldweik & Mantagos, 2016). Studies are underway to refine these aspects of treatment. Finally, longer and significantly more intensive follow-up (including possible supplemental laser treatment) may be part of the treatment course for those treated with anti-VEGF agents as the long-term systemic and visual outcomes of anti-VEGF agents on ROP remain largely unknown (Mireskandari, Collins, & Tehrani, 2015; Isaac, Tehrani, & Mireskandari, 2016).

1.2 Binocularity

Binocular single vision (BSV), is the set of processes which allow the brain to integrate separate images seen by each eye into a composite image (Gregersen, 1985; Rowe, 2004; von Noorden & Campos, 2002). Though there is some debate on terminology, for the remainder of this text, the word “binocularity” (which some have argued simply describes the condition of having two eyes) will be used instead of BSV to represent the same idea i.e. the integration of two images seen by each eye into one.

The three levels of binocularity are: simultaneous perception, fusion and stereopsis (Rowe, 2004). With each of these processes, the brain can perceive and interpret an image normally only if the visual input is falling on corresponding retinal points (von Noorden & Campos, 2002). Corresponding retinal points, illustrated in Figure 1.2 are those that share a common visual direction and allow the viewer to localize visual stimuli in space relative to each other and to the viewer (von Noorden & Campos, 2002).
Figure 1.2. Representation of basic retinal correspondence.

The figure above illustrates how our brain interprets visual input coming from each eye and how these images are fused into one composite image in someone with normal binocularity. The cyclopean eye represents the visual perception of the composite image. The solid, coloured lines depict the light rays that physically transmit the image onto the retinae. The dashed lines represent the projections of those images the brain perceives in space. The pre-set retinomotor values (1 and -1 in this diagram), allow us to determine visual direction by correlating images falling on peripheral retinal points to objects in space that are peripheral to our central vision. Central vision comprises the images falling on our foveae (F) and are perceived as “straight ahead”. The horopter is the large circle encompassing all object points that fall on corresponding retinal areas relative to central fixation at a given fixation distance.
Historically, the requirements for developing binocularity have been debated with two main schools of thought emerging: that of “empiricism”, which theorized that binocularity was learned through visual experience, and that of “nativism”, which purported that binocularity was the consequence of the anatomy of the human visual system and therefore an intrinsic aspect of human physiology (von Noorden & Campos, 2002). Through many novel experiments in the 1960’s, ‘70’s and ‘80’s, however, we now know that the mechanism through which binocularity develops credits both theories of binocularity (Wiesel & Hubel, 1974; von Noorden & Middleditch, 1975; von Noorden, Crawford, & Levacy, 1983; Crawford & von Noorden, 1979; Hubel & Wiesel, 1970; Hubel & Wiesel, 1965). This means that though we need the basic neural building blocks and anatomical structures (such as forward-facing eyes which allow for central overlap of the visual fields) to promote the presence of binocularity, insults to the postnatal visual system have demonstrated that those neural connections can be disrupted suggesting that binocularity continues developing postnatally and normal binocularity is dependent on normal visual input during this period of development (von Noorden & Campos, 2002; Howard & Rogers, 1995; Deller, 1988)

1.2.1 Critical Periods

If the visual system does require normal stimulation as it continues developing, the next logical question is: for how long? How long does it take for binocularity to fully develop? At what point do the neural connections become concrete—or does the visual system remain plastic forever? It has been demonstrated that the visual system does have time frames of malleability during which it is most vulnerable to insults and when it is most likely to use adaptations to overcome these obstacles which the system cannot readily correct in order to function ‘normally’ (Banks, Aslin, & Letson, 1975). These time frames are called ‘critical periods’ and delineate, “the interval of time during which [an insult to the visual system] has irreversible effects,” which differ for the development of individual visual functions e.g. the critical period for stereopsis is not the same as the critical period for visual acuity (Howard & Rogers, 1995; Daw, 1998).

For the scope of this project, we are concerned with the critical period of binocularity. Early studies demonstrated that the critical period of binocularity was
between 1 and 3 years of age (most commonly agreed upon critical period was 24 months of age) based on the outcomes of early treatment of an insult (strabismus) to the binocular visual pathway (Banks, Aslin, & Letson, 1975; Deller, 1988; Ing, 1981). However, more recently, it has been shown that stereopsis (the highest grade of binocularity) has a peak critical period between 3 to 4 months of age but continued susceptibility until 4.6 years (Fawcett, Wang, & Birch, 2005).

Von Noorden lists several advantages to developing normal binocularity including better visuomotor function and better distinction of colour and form; furthermore, good binocularity or binocular potential is also a good indicator of maintenance of visual alignment post strabismus surgery (von Noorden & Campos, 2002; Arnoldi, 2009). Therefore, the critical periods become particularly important to the clinician when considering management of a patient and defining successful outcomes of treatment (Howard & Rogers, 1995). Simply put, the critical period is a time when insults to the visual system have the most profound effects, but it is also a time at which these effects can be reversed in order to optimize development (Daw, 1998; Howard & Rogers, 1995; von Noorden & Campos, 2002). To better illustrate this point, the next section will examine some common conditions which can interrupt the normal development of binocularity in the pediatric population during the critical period for binocularity.

1.2.2 Conditions that Interfere with Development of Binocularity

For binocularity to develop normally, the individual’s visual system must be comprised of two eyes with equal and normal vision; must be transmitting images to the brain via the two retinae which are similar in size, colour and brightness; and, must be visually aligned such that there is retinal correspondence between the two eyes (von Noorden & Campos, 2002). These conditions also assume that the brain can consistently and accurately interpret the images from both eyes i.e. presupposes no neurological insult along the pathway preventing that. Therefore, the conditions that most commonly interfere with the development of binocularity are ones which interrupt one of those four precursors. For the purposes of this study we will examine three conditions which interfere with the first three requirements of binocularity listed above.
Amblyopia

This condition has been historically described as low vision in one eye, which is where the term comes from: *ambly-* = dull, *ops* = sight, vision (von Noorden & Campos, 2002). Von Noorden also gives a very useful and, now, widely used clinical definition wherein he describes amblyopia as a “decrease of visual acuity in one eye when caused by abnormal binocular interaction or occurring in one or both eyes as a result of pattern visual deprivation during visual immaturity, for which no cause can be detected during the physical examination of the eye(s) and which in certain cases is reversible by therapeutic measures.” Since then, certain clinical guidelines have been developed to help identify individuals that may have amblyopia, such as the popular 10-optotype or 2-line interocular difference (IOD) on logMAR acuity testing charts proposed by the American Academy of Ophthalmology (AAO); however, amblyopia remains a diagnosis of exclusion (Kanonidou, 2011; American Academy of Ophthalmology, 2017).

Thanks to the investigations of scientists such as von Noorden, Hubel and Wiesel, we also know of the effect amblyogenic factors have on the striate cortex and lateral geniculate nucleus, important parts of the cortical visual system. Hubel and Wiesel’s experiment with visually immature kittens either by means of an induced strabismus or alternating monocular occlusion gave insight into how the neural cells of the striate cortex are affected by the visual information being transferred there from the optic nerves. The investigation led to the conclusion that ocular dominance columns within the striate cortex are organized by where the visual input is coming from, ranging from solely contralateral and monocular to solely ipsilateral and monocular, and that in the visual system of adult cats whose binocular development was not interrupted there were more “binocularly driven” cells (Hubel & Wiesel, 1965). Therefore, amblyopia, though described in terms of reduction in visual acuity, does have an important effect on how the integration of binocular signals occurs; indeed, amblyopia has been found to affect neural points all along the visual pathway--from retina to the visual cortex (Kanonidou, 2011; Barnes, Hess, Dumoulin, Achtman, & Pike, 2001). Another interesting point to note is that because amblyopia has such a profound effect on the development of neural binocularity, some of the causes of reduced binocularity below i.e. anisometropia and strabismus are also the biggest amblyogenic factors and because of this, the primary cause
of the pathology is usually used to classify the amblyopia e.g. anisometric and strabismic amblyopia respectively (Kanonidou, 2011). Another type of amblyopia arising from loss of visual form e.g. from a cataract or ptosis is called deprivation amblyopia. This type of amblyopia is typically resolved by first removing or correcting the obstacle to visual form and following with amblyopia treatment which may involve refractive correction, and/or occlusion of the non-amblyopic eye (Howard & Rogers, 1995).

**Anisometropia**

In most people, especially those born full term and with no underlying ophthalmic or in some cases systemic pathology, the eye initially begins hyperopic (farsighted) and undergoes a process called emmetropization which is a normalizing (via growth) of the ocular structures that allow it to focus the incoming light rays onto the retina (Flitcroft, 2014). An emmetropic eye can focus images directly and clearly onto the retina without the use of corrective lenses or refractive surgery. The opposite of emmetropia is ametropia—these eyes need corrective lenses to properly focus incoming light rays onto the retina and see clearly.

Anisometropia defines the condition in which the eyes have unequal refractive powers. A difference in refractive power results in a difference in the quality of the retinal image produced in terms of size, clarity and contrast (Hashemi, Khabazkhoob, Yekta, Mohammad, & Fotouhi, 2011). The differences between the retinal images in either eye cause abnormal binocular interaction and can lead to the development of suppression (Hashemi, Khabazkhoob, Yekta, Mohammad, & Fotouhi, 2011; Lee, Lee, & Lee, 2010). Due to the facilitation of suppression, anisometropia has also been associated with the development of amblyopia and strabismus (Hashemi, Khabazkhoob, Yekta, Mohammad, & Fotouhi, 2011; Lee, Lee, & Lee, 2010; Deng & Gwiazda, 2012; Jeon & Choi, 2017; Hu, et al., 2016).

Hashemi et al. documented that those with anisohypermetropia and aniso-astigmatism (anisometropia in which both eyes are hyperopic and anisometropia with the biggest difference in the cylinder measurement, respectively) had a high prevalence of amblyopia, however, other studies have shown that anisomyopia can also lead to amblyopia (Hashemi, Khabazkhoob, Yekta, Mohammad, & Fotouhi, 2011; Weakley, 1999). Regardless of the type of anisometropia however, the greater the anisometropia...
(i.e. the greater the difference in refractive power between the two eyes), the higher the prevalence of amblyopia (Lee, Lee, & Lee, 2010). Furthermore, amblyopia developing purely as a result of anisometropia often goes unnoticed, and therefore untreated, for longer periods of time as there is no obvious way to detect the condition physically (as is done in the case of strabismic amblyopia) and the patient is not always aware of the problem subjectively (Lee, Lee, & Lee, 2010).

Sudden onset anisometropia can affect even those individuals who developed normal binocularity and the results of this insult to the normally developed binocular interaction can be seen immediately as a decrease in stereoacuity significantly associated with the increase in anisometropia (Nabie, Andalib, Amir-Aslanzadeh, & Khojasteh, 2017; Hu, et al., 2016). Anisometropia can be a result of many structural differences between both eyes which include: anterior chamber depth, anterior and posterior lens curvature, lens thickness and axial length; of these, axial length seems to play the most important role in the development of anisometropia (Hashemi, Khabazkhoob, Yekta, Mohammad, & Fotouhi, 2011; Deng & Gwiazda, 2012; Hu, et al., 2016).

**Strabismus**

Strabismus is the misalignment of the visual axes caused by a physical misalignment of the eyes (Gunton, Wasserman, & Debenedictis, 2015). Strabismus occurs in 1 to 3% of the general population (Ticho, 2003; Gunton, Wasserman, & Debenedictis, 2015). A few syndromes exist in which paradoxical innervation of the extraocular muscles lead to congenital strabismus. However, not all instances of strabismus that is present from birth have such a clear cause. Though links have been made between increased incidence of strabismus and prematurity, the etiology of most forms of congenital strabismus remains elusive (Gunton, Wasserman, & Debenedictis, 2015; Burian, 1960; Schalij-Delfos, de Graaf, Treffers, Engel, & Cats, 2000).

A manifest strabismus describes a misalignment that is always present and is described as ‘-tropic’ or ‘heterotropic’. The misalignment can be further identified by its direction: an eye deviated inward is ‘eso-’, outward is ‘exo-’, upward is ‘hyper-’ and downward is ‘hypo-’. Therefore, a constant misalignment in which one of the eyes is deviated inwards is called an esotropia. Strabismus may also be controlled intermittently in some individuals. In the vast majority of the population, however, the tendency for the
eyes to deviate exists but is constantly controlled. Though outwardly these persons appear to have no strabismus, in ophthalmology this condition is called a ‘heterophoria’. Heterophoric individuals, maintain their alignment by fusion, therefore a heterophoria can only be uncovered when the eyes are dissociated (not allowed to fuse) (von Noorden & Campos, 2002). Due to this identifiable connection between fusion and alignment, von Noorden concludes, “Clearly, the fusion mechanism and its anomalies are involved in some manner in producing...heterotropias,” (von Noorden & Campos, 2002). However, the fusion-alignment balance is reciprocal; just as an issue with binocular vision can interrupt alignment, so can a misalignment caused by an external source disrupt fusion (Smith, et al., 2017).

To consider how strabismus affects binocularity, let us consider retinal correspondence again. In an orthotropic individual (one whose visual axes are aligned), the image being fixated by the person falls onto corresponding retinal points and the brain interprets it as one composite image even though it is being viewed by each eye individually from a slightly different angle. (von Noorden & Campos, 2002). What happens if one of the eyes is slightly, moderately or largely misaligned from the other? The brain’s default is to recognize the corresponding retinal points based on preset retinomotor values (see Figure 1.2). In the case of strabismus, the image is falling on non-corresponding retinal points e.g. fovea to nasal retina (as is the case in esotropia or “crossed eyes”). In the example above, the brain recognizes that usually something falling on the nasal retina must be temporal to that eye which results in the brain projecting a temporal image. However, at the same time the brain is doing this, it is also projecting the image of the centrally fixated eye. The two projections result in the brain perceiving two objects where there is only one. This is double vision, clinically termed diplopia. In young children, the brain and neural connections are still malleable so to prevent the confusion arising from diplopia, the brain sacrifices its binocular interaction and suppresses the input from the eye with the peripheral image as an adaptation (Howard & Rogers, 1995). The longer suppression persists, the higher the risk of developing amblyopia and the longer the brain goes without developing binocular interactions. In certain cases of small angle heterotropias, the brain may only suppress the central part of the image from the deviated eye. This adaptation is called a central suppression scotoma.
and allows the individual to suppress the double image while maintaining some peripheral fusion.

1.3 Purpose of Study

Both laser and anti-VEGF treatments result in overall equivalent favorable outcomes. (Isaac, Tehrani, & Mireskandari, 2016; Vanderveen, et al., 2017). Although laser ablation remains the gold standard due to outstanding uncertainties surrounding the effects of anti-VEGF treatment in this population, each patient’s condition and the extent of ROP is assessed individually as some may benefit from the advantages of using anti-VEGF agents. More information comparing the short-term and long-term outcomes of each treatment modality is needed to guide evidence-based implementation of best care practices in infants with severe ROP requiring treatment. In particular, there are no studies comparing binocularity outcomes in patients treated with laser as opposed to anti-VEGF agents.

The development of normal binocular vision is dependent on factors that may vary as a result of the different treatment effects. In addition to what is known about how each treatment modality affects the peripheral retina, studies have outlined that both laser and anti-VEGF treatments affect the central retina as well, specifically the fovea (Vogel, et al., 2018; Clark, et al., 2017; Stoica, et al., 2018). These peripheral and central effects may influence binocular development. This study aims to compare binocularity outcomes in children who were treated for ROP to help guide ophthalmologists, healthcare providers and parents in making informed decisions when faced with treatment options.

1.4 Hypothesis

We hypothesize that there will be a difference in binocularity outcomes between ROP patients treated with laser and anti-VEGF injections. Furthermore, we hypothesize that a difference in binocularity will be associated with differences in rates of strabismus, amblyopia and anisometropia.
CHAPTER 2: METHODOLOGY

2.1 Study design and recruitment

To assess the effects of treatment for ROP on binocularity, the target population included ROP patients who had received either laser ablation or anti-VEGF injections. The study is a cross-sectional observational study that recruited participants from either the IWK Health Centre in Halifax, Nova Scotia or SickKids in Toronto, Ontario. Participants in this study’s laser group were treated according to guidelines in the ETROP study while those in the anti-VEGF group received bevacizumab injections per guidelines from the BEAT-ROP study (Mintz-Hittner, Kennedy, & Chuang, 2011; Good, 2004). Furthermore, both Canadian centres mentioned above have similar guidelines for the identification and management of binocularity-disrupting events such as amblyopia, anisometropia and strabismus. All tests performed in this study are standard tests used in orthoptic evaluations. A single examiner masked to the treatment type performed all orthoptic evaluations in both recruitment centres. Data was obtained in a standardized fashion to enable comparisons between groups.

2.1.1 Inclusion and Exclusion Criteria

The following is a list of the inclusion criteria and justification for each point:

1. The participant must be between 3 and 8 years of age (inclusively) at the time of the examination. The minimum age limit was set to coincide with the end of the critical period for binocularity (see Section 1.2.1) while ensuring that participants were old enough to respond reliably to subjective testing (Fawcett, Wang, & Birch, 2005). Both recruitment centres began using anti-VEGF treatment around 50% of the time (using laser the other 50%) circa 2010. The upper age limit for the study was therefore 8 years of age.

2. The participant must have received only laser or anti-VEGF treatment for ROP to be included in either treatment group, or the condition must have regressed spontaneously without any treatment to be included in the control group.
3. The patient must have been followed-up at either the IWK Health Centre in Halifax, Nova Scotia or at SickKids Hospital in Toronto, Ontario.

4. If the patient had to be treated for recurrence of the disease, the same treatment modality must have been used.

5. Capacity to understand testing procedures and follow instructions in order to provide answers to subjective testing methods. The participant need not be verbal so long as their method of communication is consistent and reliable (pointing, communicating through a speech device or interpreter).

6. Sufficient gross motor skills to draw or point accurately and reliably (See #5).

The exclusion criteria and justifications for this study are the following:

1. Severe neurodevelopmental delay preventing the gross motor and cognitive skills necessary to respond to the subjective testing during the clinical evaluation. The response to subjective testing needed to be reliable as this is the main outcome measure.

2. Having received both laser and anti-VEGF treatment (either in the same eye or opposite eyes). If the participant received both treatments, it would not be possible to discern which treatment is causing the measurable effect.

3. Having received previous intraocular surgery for any reason other than ROP or any sequelae secondary to ROP. Intraocular surgery may affect the ocular structures needed to produce normal binocularity.

4. Having an allergy or sensitivity to cyclopentolate. This would preclude the standardized dilation of each participant.

2.1.2 Participant identification and recruitment

Screening for potential participants was facilitated through use of perinatal databases at both institutions. Using the inclusion (#1-4) and exclusion (#2-4) criteria, the treating ophthalmologists (one at the IWK and two at SK) and their research coordinators identified a list of eligible candidates for the study. Identified candidates were not
enrolled if their parents/guardians/treating ophthalmologist felt they did not meet inclusion criteria #5-6.

2.1.3 Ethical considerations

This study was conducted with consideration of the Good Clinical Practice guidelines presented by the International Conference on Harmonization and in compliance with the Research Ethics Board guidelines at both the IWK Health Centre in Halifax and SickKids in Toronto. Consent was obtained from each participant’s parent or legal guardian and verbal assent was obtained from participants whenever possible. Recruitment protocols differed slightly at both institutions—changes are outlined in Table 2.1.

The tests performed in this study were obtained by an orthoptist (masked examiner) at a regular follow-up interval for the participant and in accordance to standard of care practices at both institutions. All participants underwent the same protocol for the data collection and had the option of revoking their consent at any point during the examination.

Typically, patients in whom ROP regresses spontaneously (control group) with no further complications are discharged to primary eye care facilities. To recruit participants in this group, protocols differed slightly at both institutions—changes are outlined in Table 2.1.
Table 2.1 Differences between protocols at SickKids and IWK Health Centre.

<table>
<thead>
<tr>
<th>Protocol Item</th>
<th>SickKids</th>
<th>IWK Health Centre</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Introduction of study</strong></td>
<td>Done at time of appointment by ophthalmologist before examination by orthoptist</td>
<td>Done prior to scheduling appointment by ophthalmologist’s coordinator</td>
</tr>
<tr>
<td><strong>Recruiting controls</strong></td>
<td>Could only be recruited if they were being followed in the ophthalmology clinic at SickKids during the time of the study.</td>
<td>Could be recruited from community i.e. not necessarily followed at IWK.</td>
</tr>
<tr>
<td><strong>Compensation</strong></td>
<td>No compensation was given.</td>
<td>Compensation was given in the form of a $5 gift card to participants after the data was obtained.</td>
</tr>
<tr>
<td><strong>Dissemination of results</strong></td>
<td>No dissemination of results to individual participants after completion of the study.</td>
<td>Dissemination of results will be given to participants who indicated that they wish to receive this communication and will be provided in the way the participants indicated would be best for them (e.g. email, mail, etc.) after the study is completed.</td>
</tr>
</tbody>
</table>
2.2 Data Collection

2.2.1 Protocol

The families of the study candidates were contacted by a member of the research group. The participants in the treatment groups were scheduled as closely as possible to their regular follow-up times. The appointments of all participants included either a cycloplegic refraction with their treating ophthalmologist and an orthoptic assessment with the masked examiner; or only the orthoptic assessment, provided their most recent cycloplegic refraction had been done within one year.

Orthoptic examination

All participants that wore glasses were wearing their full cycloplegic correction at the time of sensory and VA testing as well as during quantification of strabismus. History questions listed in the research data collection sheet (Appendix A) were obtained either before starting testing, during testing or after testing depending on the attention/behaviour of the participant.

Before any of the sensory testing began, a quick assessment of alignment was done either through brief cover testing or by Hirschberg test which assesses alignment by detecting any displacement in corneal light reflexes. This was done to better interpret the results of sensory testing. Sensory testing was done next and was performed in order from least dissociative to most dissociative to preserve the control of any eye turn and obtain the best possible binocularity results. The Frisby Stereotest was obtained first, then Bagolini was performed; procedures for each are outlined below:

Frisby Stereotest: The participants were presented the thickest of the three plates at 30 cm (which relates to the most gross stereoacuity that this test can quantify) and asked to point to the 3-D target, which is a circle appearing to pop out of one of the four identical squares on the plate. If the participants correctly identified the target, the next plate was presented, and the trial was repeated. If the participants were able to correctly identify the target on the thinnest plate at 30 cm, then the plate was rotated out of view of the subjects and then presented again at 40 cm. This was repeated, moving back in increments of 10 cm until the participants correctly identified the target at 80 cm or until they could no longer find the target. If any participant made an incorrect guess, at any point during the procedure, the
plate was rotated out of view of the child and the same trial was repeated. If the subject would guess incorrectly 2-3 consecutive times, the testing would conclude and the last achieved stereoacuity was recorded; otherwise, the testing continued as outlined above.

Bagolini: This test required participants to look at a muscle light through a pair of striated lenses (placed either in trial frames or, in Halberg clips if the patient wore glasses) placed at 45° over one eye and 135° over the other eye. The participants would then either draw or describe what they see—in some cases, matching cards were used (see Appendix B). A normal response indicating the presence of binocularity would be seeing two lines of light forming an “X” with one small light (the muscle light) at the centre of the “X”. If participants were suppressing the image from one of their eyes, they would perceive only one slanted line, and if they had a central suppression scotoma (see Section 1.2.2) they would have seen an “X” with a corresponding “piece” missing (one of the arms of the “X” for example) for their scotoma location. Another possible response to this test is perceiving two lights and two lines which would indicate diplopia. However, the age group we tested would not likely exhibit this response, so this was not a “matching” option.

After sensory testing, strabismus was quantified using the alternate prism cover test while using the patient’s best correction in primary position only at near and distance. Vision was assessed using either ETDRS or Lea Symbols at near and distance for logMAR visual acuity. Even if the child improved with single optotype testing or pinhole testing, only the full chart testing acuity was recorded for each eye. This testing order was adhered to whenever possible. However, if the examiner determined there may have been better attention for one of the tests outside of this prescribed order, this was done, and those results were used.

To complete the orthoptic evaluation for the patient’s hospital chart, the examiner also obtained relevant history for the chart including any complaints/symptoms as well as general health, medication and allergies of the patient. The examiner also performed ocular motility testing and evaluated the patient’s pupils as well as recorded lensometry for those participants wearing glasses. If the examiner considered it important for the
diagnosis of the participants and for their future care, she may have also performed other tests including extra sensory testing; quantification of strabismus in various positions of gaze; quantification of strabismus with and without glasses; etc. At this time, age (in months and years) at time of assessment was recorded on the research data collection sheet. Finally, if the participant had not had a cycloplegic refraction within the year, pupils were dilated using cyclopentolate 1% and a refraction was done by their treating ophthalmologist. If the participant had obtained a cycloplegic refraction within the year, that refraction was obtained from retrospective chart review and used for analysis.

After the appointment, demographic data were obtained retrospectively from the participant’s chart including: gestational age at birth, birth weight, presence of any diagnosed/documented neurodevelopmental anomalies as well as date of treatment for participants that received treatment.

2.2.2 Justification for Testing Procedures

One masked examiner

A trained orthoptist was the single examiner who performed all orthoptic evaluations in both study centres following a standardized protocol and entered the data in a data collection form for analyses. The examiner was masked to the treatment group at the time of data collection and entry, but not during data analysis. The protocol was followed as much as possible but adjusted whenever necessary to enable each child to perform to the best of their abilities and optimize the amount of data collected (see Section 2.2.1).

Choosing the appropriate stereotest

The Frisby Stereotest was chosen to measure stereoacuity for the following reasons:

1. It provides no monocular cues therefore the examiner can be more certain that the individual truly has stereoacuity (Hahn, et al., 2010).
2. It does not require wearing glasses which may be uncomfortable/undesirable for younger participants/those that are easily distracted/put at alert.
3. A subjective answer can be obtained with most stereotests even with nonverbal patients by having them point to the answer that is “sticking out” or “3D”. In other stereotests such as Titmus, the targets that distinguish fine stereo are quite small
and require very precise pointing whereas fine stereo can be assessed on Frisby while the target image remains quite large, enabling participants who cannot point using only one finger to indicate the correct answer using their whole palm/hand.

Choosing the appropriate test for binocularity

Binocularity is the primary outcome measure in this study and careful consideration was given to find the most suitable test given the age range of the participants. As with the stereotest, precaution was taken to select the least dissociative test that could be performed with the most ease including in those participants who were nonverbal. The Bagolini test provided the best balance. One disadvantage of using Bagolini however, is that the participant does require relatively fine motor skills and cognitive abilities to describe/draw what they see. To address this, we designed an alternate response method for those participants who could understand the test but could not articulate/did not possess the motor skills necessary to draw: those participants were invited to “match” what they saw through the Bagolini lenses with one of 3 cards (depicting 3 possible responses seen on Bagolini) presented to them (see Appendix B).

Testing visual acuity

LogMAR acuity testing was obtained as it is the most standardized way of monitoring vision especially in a research context (Ferris, Kassoff, Bresnick, & Ian, 1982). Furthermore, logMAR ETDRS chart and the Lea Symbols are available for both literate and pre-literate individuals respectively. The results obtained from either chart are still comparable as the visual acuity is quantified in the same fashion. Furthermore, logMAR scores achieved with Lea Symbols in a pre-literate child are comparable to those of a literate child on ETDRS and both tests are equally efficient at accurately depicting a patient’s IOD (Mulla, 2007).

Cycloplegic refraction

Cycloplegic refraction is the most accurate method of determining the correct refractive power of the eye in this age group. Cycloplegics inhibit accommodation of the lens removing the variable results caused by the tendency of young eyes to compensate for their refractive errors by using their large accommodative amplitudes (Ganger, Bala, Kaur, Kaur, & Satpal, 2017).
2.3 Data Analysis

2.3.1 Definition of Categorical Outcomes for data analysis

For purposes of this study, the definitions that comprise each categorical outcome measure are outlined below:

Demographics: Neurodevelopmental Impairment

Presence of neurodevelopmental impairment (NDVI) was recorded after a chart review. The following conditions constituted NDVI for this study: presence of cerebral palsy, sensorineural or mixed hearing loss, any composite score < 85 on Bayley’s III and/or visual impairment (less than 20/70 VA in their better seeing eye wearing best correction).

Primary outcome: Binocularity

Presence of binocularity was interpreted from combined responses acquired from the Bagolini test and the Frisby stereotest. If the participant demonstrated fusion and/or quantifiable stereopsis that constituted presence of binocularity. Detection of a central suppression scotoma response was evaluated as peripheral fusion and therefore also counted as presence of binocularity. Conversely, no demonstrable stereopsis plus a suppression response on Bagolini (see Section 2.2.1) was recorded as absence of binocularity.

Secondary outcomes: level of binocularity

If the participant demonstrated presence of binocularity on the stereotest, they were evaluated as having “high grade” binocularity. If the participant demonstrated presence of binocularity only on Bagolini test, the response was recorded as “low grade” binocularity.

Secondary outcomes: events associated with disruption of binocularity (i.e. insults to binocularity)

Presence of anisometropia was identified if the participant had an IOD of 1.50 D or more in their spherical refractive error and/or 1.00 D or more in their cylindrical refractive error. Presence of amblyopia was identified if the participant had an IOD of two lines or more on distance best corrected visual acuity testing. Both definitions described above and used for this study were based on the most recent guidelines published by the AAO outlining the preferred practice patterns for managing anisometropia and amblyopia (American Academy of Ophthalmology, 2017; American
Academy of Ophthalmology, 2017). Though the values selected for this study to identify presence of anisometropia differ slightly from the AAO guidelines, our study had to maintain a consistent definition of anisometropia for all participants while the AAO guidelines are only applicable to anisometropes without strabismus (American Academy of Ophthalmology, 2017).

Strabismus was reported based on the control of the turn and recorded as either phoric, intermittent or manifest based on measures obtained in primary position at 1/3 m and 6 m. Participants were recorded as “phoric” only if they were phoric in both distances and as “manifest” if strabismus was manifest in both distances. Other combinations of control were labelled “intermittent”. These labels were used to analyze rates of binocularity-interrupting strabismus (i.e. manifest or intermittent) between groups. The analyses looking at rates of anisometropia, amblyopia and strabismus took into consideration only those events present at the time of the orthoptic assessment done for this study.

Separately, we also looked at presence of cumulative binocularity-interrupting events i.e. whether the participant had a previous diagnosis of amblyopia which had since been treated and had resolved, that individual still belonged to the binocularity disruption group. Insults to binocularity included any of the following events: previous or current diagnosis of amblyopia, anisometropia, intermittent or manifest strabismus either currently active or previously corrected by surgery.

2.3.2 Sample Size Calculations

The main outcome measure in this study was the presence or absence of binocularity in anti-VEGF and laser-treated ROP patients. We used the “Power Calculator for Binary Outcome Superiority Trial,” a web-based binary variable calculator to ascertain sample size. (Sealed Envelope Ltd., 2012).

To calculate sample size, the rate of binocularity in either treatment group is required. Because there is no published data on the binocularity values of either of these groups, we used the rates of strabismus reported in the literature. Based on these strabismus rates, the estimates of binocularity we used were 60% in the laser treated group and 92% in the anti-VEGF group. (Owen, et al., 2015; Vanderveen D. K., et al.,
We considered that manifest strabismus (rather than anisometropia or amblyopia) was the factor most likely to interrupt binocularity in this population. Since treated ROP patients are followed closely, amblyopia and anisometropia are identified and treated in a timely manner and the effect on disruption of binocularity is likely less than when these same binocularity disrupting events occur in the general population, as these do not manifest any symptoms in children and will therefore present later in clinic. The occurrence of strabismus in prematurely born children is well documented and is predicted to immediately disrupt binocularity with rare exception and was therefore considered a more predictable indicator of disruption to binocularity, our primary outcome measure.

Calculations determined that 25 participants are required per group to show a statistical significance between groups with 80% power and 95% confidence interval.

2.3.3 Comparability

To determine whether the treatment groups were comparable, we ran descriptive analyses and then tested for equality of means using an Independent Samples T-Test as well as a Chi-Square Test for the categorical data. The variables we evaluated for comparability were gestational age (in weeks), birthweight (in grams), age at time of assessment (in months) and presence of neurodevelopment impairment (NDVI). Since low gestational age and birthweight as well as presence of NDVI are all correlated to more severe perinatal morbidity—and consequently could affect binocularity outcomes—this analysis allowed us to detect potential biases that could affect the interpretation of our results. Furthermore, comparing age at time of assessment will allow us to determine whether one group was older than the other, as this may have given them more time to develop events that may have led to disruption of binocularity.

Gestational age, age at time of assessment and birthweight were numerical values and were analyzed with the Independent Samples T-Test. NDVI responses were analyzed using Chi-Square test.

2.3.4 Testing the Hypothesis
To test the hypothesis, a Chi-Square Test was used to detect a significant difference between the groups’ binocularity outcomes. Chi-Square Test was also used to identify significant differences between levels of binocularity as well as instances of amblyopia, anisometropia and strabismus between the groups.
CHAPTER 3: RESULTS

3.1 Participants

A total of 91 patients were identified who met the inclusion criteria, 36 at the IWK and 55 at SickKids. Of those, nine did not consent to participate (six from IWK and three from SickKids), six moved away (five from IWK and one from SickKids), and 22 were lost to follow-up (10 from IWK and 12 from SickKids). We consented the remaining 54 candidates however, had to exclude two from the IWK from analyses. One of the participants was excluded after a thorough chart review revealed that the individual had received both treatments, and the other was excluded after demonstrating extreme aversion to testing and unresponsiveness which the examiner (SM) deemed to be a lack of assent.

Initially, the sample size calculations only took into consideration the n required to compare the two treatment groups. Though eight controls were enrolled in the study and their data was collected, this number was too low to be included in the analysis and produce statistically significant results. Therefore, only the remaining 44 participants belonging to one of the two treatment groups were included in the analysis: 21 in the laser group (six from IWK and 15 from SK) and 23 in the anti-VEGF group (four from IWK and 19 from SK).

3.2 Summary of Results

The data for all 44 participants analyzed is summarized below in Table 3.1. Sections ‘Comparability’, ‘Cross-Sectional Outcomes of Binocularity’, and ‘Insults to Binocularity’ in the table below correspond with sections 3.3, 3.4 and 3.5 in this chapter, respectively. ‘Level of Binocularity’ can be found in section 3.4 of this chapter.
Table 3.1  Summary of results

<table>
<thead>
<tr>
<th>Comparability</th>
<th>Laser</th>
<th>Anti-VEGF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean gestational age (±SD) in weeks</td>
<td>25.5 (±2.0)</td>
<td>24.9 (±1.1)</td>
<td>0.16</td>
</tr>
<tr>
<td>Mean birthweight (±SD) in grams</td>
<td>770 (±203)</td>
<td>739 (±157)</td>
<td>0.21</td>
</tr>
<tr>
<td>Mean age at time of assessment (±SD) in months</td>
<td>83 (±16.5)</td>
<td>63 (±15.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of participants with neurodevelopmental impairment (%)</td>
<td>5 (24%)</td>
<td>7 (30%)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cross-Sectional Outcomes of Binocularity</th>
<th>Laser</th>
<th>Anti-VEGF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binocularity (%)</td>
<td>14 (67%)</td>
<td>19 (82%)</td>
<td>0.27*</td>
</tr>
<tr>
<td>No binocularity (%)</td>
<td>4 (19%)</td>
<td>2 (9%)</td>
<td></td>
</tr>
<tr>
<td>Unstable (%)</td>
<td>3 (14%)</td>
<td>2 (9%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level of Binocularity</th>
<th>Laser</th>
<th>Anti-VEGF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (%)</td>
<td>11 (79%)</td>
<td>17 (89%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Low (%)</td>
<td>3 (21%)</td>
<td>2 (11%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Insults to Binocularity</th>
<th>Laser</th>
<th>Anti-VEGF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amblyopia (%)</td>
<td>7 (33%)</td>
<td>5 (22%)</td>
<td>0.42*</td>
</tr>
<tr>
<td>Anisometropia (%)</td>
<td>12 (57%)</td>
<td>7 (30%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Binocularity-interrupting strabismus (%)</td>
<td>8 (38%)</td>
<td>7 (31%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Cumulative insults to binocularity (%)</td>
<td>17 (81%)</td>
<td>12 (52%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

All values in Cross-Sectional Outcomes of Binocularity, Level of Binocularity and Insults to Binocularity other than P-values represent the number of individual participants in the categories described. Gestational age, birthweight and age at time of assessment were all analyzed using Independent Samples T-Tests; all other analyses were done using Chi-Square tests.

SD = significant difference

* These groups included a small number of participants who did not comply with testing.

The Chi-Square Test and subsequent P-value in these group does not include the participants who did not comply.
3.3 Comparability

The gestational age (Figure 3.1), birthweight (Figure 3.2), age at time of assessment (Figure 3.3) and presence of any NDVI (Figure 3.4) were analysed to determine whether both groups were comparable. T-Tests for equality of means were performed for GA, BW and age at time of assessment; Chi-Square Testing was performed for presence of NDVI. The two treatment groups were comparable in terms of GA (P-value = 0.16), BW (P-value = 0.21) and presence of NDVI (P-value = 0.24) but the laser group was significantly older at the time of testing than the anti-VEGF group. The mean age at the time of assessment for the laser group was 83 (6.9 years) ± 16.5 months while the mean age of the anti-VEGF group was 63 (5.25 years) ±15.7 months, P-value <0.001.
Figure 3.1. Frequency chart of gestational age in treatment groups.

n = 23 for the anti-VEGF group; n = 21 for the laser group. Independent Samples T-test was used for analysis. P-value = 0.16. Mean Gestational Age (GA) ± standard deviation for anti-VEGF group = 24.9 ± 1.1 weeks; mean GA ± standard deviation for laser group = 25.5 ± 2.0 weeks.
Figure 3.2. Frequency chart of birthweight in treatment groups.

n = 23 for the anti-VEGF group; n = 21 for the laser group. Independent Samples T-test was used for analysis. P-value = 0.21. Mean Birthweight (BW) ± standard deviation for anti-VEGF group = 739 ± 157 g; mean BW ± standard deviation for laser group = 770 ± 203 g.
Figure 3.3. Frequency chart of age at time of assessment for treatment groups. n = 23 for the anti-VEGF group; n = 21 for the laser group. Independent Samples T-test was used. P-value < 0.001. Mean age ± standard deviation for anti-VEGF group = 63 ± 15.7 months; mean age ± standard deviation for laser group = 83 ± 16.5 months.
Figure 3.4. Presence of neurodevelopmental impairment.

n = 23 for the anti-VEGF group; n = 21 for the laser group. Chi-square test was used. P-value = 0.24.
NDVI = Neurodevelopmental Impairment
3.4 Cross-Sectional Outcomes of Binocularity

The presence of binocularity (Figure 3.5) and the level of binocularity (Figure 3.6) were analyzed with Chi-Square Tests to determine whether there was any significant difference between the rates of binocularity among the two groups. Although there was a trend towards a greater number of participants with presence of binocularity and higher grade of binocularity in the anti-VEGF group, rates of binocularity were not significantly different for presence of binocularity (P-value = 0.27) nor level of binocularity (P-value = 0.68). Only those participants demonstrating binocularity had the level of binocularity analyzed; this included a total of 33 participants, 14 in the laser group and 19 in the anti-VEGF group.
Figure 3.5. Rates of binocularity measured at the time of assessment.

n = 21 for the laser group; n = 23 for the anti-VEGF group. Chi-square test was used. P-value = 0.27. Participants in the “unable” group were those that did not comply with testing and were not used for this analysis.
Figure 3.6.  Levels of binocularity.

n = 14 for the laser group; n = 19 for the anti-VEGF group. Chi-square test was used. P-value = 0.68.
3.5 Insults to binocularity

The individual binocularity-disrupting events at the time of assessment as well as the cumulative rate of binocularity-disrupting events (events occurring up until the time of assessment) were compared using the Chi-Square test. The insults at the time of assessment included rates of amblyopia (Figure 3.7), anisometropia (Figure 3.8) and strabismus (Figure 3.9). Among all the individual binocularity-disrupting events, there was a trend for less insults in the anti-VEGF group. The difference between groups approached significance in the rate of anisometropia (P-value = 0.07) but was not significant for any of the insults (Amblyopia: P-value = 0.42, Strabismus: P-value = 0.59). There was a significant difference, however, in the rates of cumulative binocularity-disrupting events (P-value = 0.04) with the laser-treated group having accumulated more binocularity-disrupting events from time of treatment until time of assessment (Figure 3.10).
Figure 3.7.  Rate of amblyopia at time of assessment.

n = 21 for the laser group; n = 23 for the anti-VEGF group. Chi-square test was used. P-value = 0.42. Participants in the “unable” group were those that did not comply with testing and were not used in this analysis.
Figure 3.8. Rate of anisometropia at time of assessment.

n = 21 for the laser group; n = 23 for the anti-VEGF group. Chi-square test was used. P-value = 0.07. N.B. One participant in the laser group did not obtain their last cycloplegic refraction within one year of the assessment and could not be booked for an exam under anaesthesia (the most reliable method of obtaining refraction on this patient) during the time frame of the study. Therefore, there is a small chance that they could have developed anisometropia in that time, further increasing the rate of anisometropia seen in the laser group.
Figure 3.9. Rate of strabismus at time of assessment.

n = 21 for the laser group; n = 23 for the anti-VEGF group. Chi-square test was used. P-value = 0.59. Intermittent and manifest strabismus were considered binocularity-interrupting in this analysis. N.B. One participant in the laser group was classified as having a phoric deviation but a reliable measure was only obtained at near therefore it is possible that in the distance this participant is intermittent or manifest which would mean that the laser group has a potentially higher rate of binocularity-interrupting strabismus than reported.
Figure 3.10. Rate of cumulative binocularity-disrupting events.

n = 21 for the laser group; n = 23 for the anti-VEGF group. Chi-square test was used. P-value = 0.04 N.B. Two participants in the anti-VEGF group had no insults, however, both were unable to comply with standardized logMAR testing therefore presence of amblyopia could not be satisfactorily assessed. This could mean that the rate of insults in the anti-VEGF group is higher than what is reported here. One participant in the anti-VEGF group and one in the laser group both only had anisometropia as their insult and due to their lack of intermittent or manifest strabismus would not meet treatable anisometropia guidelines as determined by the American Academy of Ophthalmology (AAO) Preferred Practice Patterns for anisometropia 2017.
CHAPTER 4: DISCUSSION

Our study showed that in children aged 3-8 years, achievement of binocularity is not significantly impacted by the type of ROP treatment, laser or anti-VEGF agent, received in infancy. We did note a trend toward better binocularity outcomes (rates and level) and fewer individual insults to binocularity in the group treated with anti-VEGF agents. When the cumulative events disrupting binocularity were considered as a group, there was a significant difference in favour of anti-VEGF treatment. To our knowledge, this is the first study that looked at rates of binocularity in patients previously treated for ROP. Previous studies have reported on some of the binocularity-interrupting events considered in the present report; these are outlined below.

4.1 Binocularity and Events Leading to Disruption of Binocularity

Our study indicated a rate of binocularity of 67% in the laser-treated group and 82% in those treated with anti-VEGF in children aged 3 to 8 years. Among those with a positive binocular status, 79% had a high-grade binocular response in the laser group vs 89% in the anti-VEGF group. Although there is a trend towards better outcomes in those treated with anti-VEGF, these differences were not statistically significant.

This could be due in part to the small number of participants in each group and that our original power sample calculation was based on an estimate. If we recalculate the ‘n’ using the same binary variable calculator but inputting the rates of binocularity found in this study (rather than the estimates we used), we would need 129 participants in each group. Also, the laser group was slightly older at the time of assessment and may have contributed to the higher rates of cumulative events disrupting binocularity. Nevertheless, we do feel that this should have been partially offset by the fact that anti-VEGF is used more frequently than laser in the most severe cases that are more likely to develop complications in general. Following treatment for ROP, children are monitored closely to ensure the development of amblyopia, anisometropia and strabismus is identified and treated as early as possible. Timing of follow-up appointments and management for treated ROP patients are the same regardless of which treatment they received. This may explain the similar rates of binocularity between groups.
It is also important to note the relevance of the subjects who were not able to comply with binocularity testing. There were three participants in the laser group (14%) and two in the anti-VEGF group (9%) who were not compliant with subjective binocularity testing and were not used in the Chi-Square analysis. Had the non-compliant group been able to give a reliable response, the rates of binocularity in either group may have been meaningfully affected. For example, if the two subjects in the anti-VEGF group do have binocularity, the rate of binocularity in this group would be 91% (from 82%) widening the disparity between the two groups. This result would remain statistically significant if the three subjects in the laser group do not have binocularity. Conversely, if the 3 subjects in the laser group do have binocularity, the rate for the laser group increases from 67% to 81% effectively eliminating the difference in rates between the two groups. Therefore, given the relatively small sample size of the groups included in the analysis, the impact of the five non-compliant participants is important to consider when interpreting these results.

4.1.1 Rates of Amblyopia

Visual acuity (VA) has been an outcome of interest in many studies reporting the long-term and short-term effects of laser treatment for ROP. However, not many report rates of amblyopia in these populations (Ziylan, Öztürk, Yabaş-Kızıloğlu, & Çiftçi, 2014; Wu, et al., 2012; Sahni, Subhedar, & Clark, 2005; Axer-Siegel, et al., 2008; Mueller, et al., 2017). Furthermore, some studies evaluating visual acuity in the population of ROP patients requiring treatment used two separate treatments (either laser and anti-VEGF or laser and cryotherapy) in the same patient (one in each eye) in which case it would be difficult to attribute occurrence of amblyopia to one particular treatment. (O'Keefe, Murphy, O'Keefe, & Lanigan, 2016; Ng, et al., 2002). Our study reports rates of amblyopia in patients who received only one treatment modality for ROP: either laser or anti-VEGF. Therefore, our study can effectively compare rates of amblyopia between the two groups. Since binocularity requires that both eyes have equal and normal vision (see Section 1.2.2), we considered that amblyopia would be a bigger disruption to binocularity than bilaterally reduced VA and therefore a more relevant outcome for this study than VA alone.
The ETROP group reported rates of amblyopia which included either previous or current amblyopia (The Early Treatment for Retinopathy of Prematurity Cooperative Group, 2010). Since our study reported only cross-sectional rates of amblyopia, not cumulative rates like the ETROP group, the rates are not comparable. Mueller et al. did collect and report VA findings in ROP patients treated with bevacizumab or laser (Mueller, et al., 2017). However, their study included participants that were 12-15 months of age and the measure was of uncorrected VA using Teller Acuity Cards (TAC) (Mueller, et al., 2017). Though TAC are an appropriate method of measuring VA in that age group, it is a test dependant on preferential looking which requires the prolonged visual attention of the infant. Consequently, TAC testing can make it difficult to determine whether the child can no longer see the target to indicate that the endpoint is reached, or if they lose attention/become noncompliant, in which case the VA measure is nor reliable. Our study measured VA in an age range that was able to comply with logMAR acuity testing—a more reliable way of testing VA (see Section 2.2.2)—and reported rates of amblyopia as detected by a 0.2 logMAR IOD. Due to the differences in VA testing and age range of participants, our findings would not be comparable to those of Mueller et al.

Yang et al. reported on long-term visual outcomes of children treated for ROP with laser ablation. This report analyzed, among other outcomes, best corrected VA of 29 children at 7 years of age and found that the majority of eyes (65.5%) had better than 6/12 vision on Snellen with only 6.9% achieving an “unfavourable outcome” which they defined as 6/60 vision or worse in at least one eye (Yang, et al., 2010). The report did not comment extensively on amblyopia except to say that 2 out of 3 patients exhibiting unfavourable outcomes had amblyopic eyes (Yang, et al., 2010). However, Yang et al. did report the VA of both eyes for each subject, allowing us to extrapolate which subjects had amblyopia. Using the AAO guidelines that were the basis of our study’s definition of amblyopia, we determined that in the Yang et al. group, 11 out of 29 participants (37.9%) had amblyopia (Yang, et al., 2010). Although the rate of amblyopia found in the Yang et al. study is higher than the rate we measured in the laser group (33%), 10% of the participants in the laser group in our study were unable to comply with logMAR VA.
testing and the true rate of amblyopia may have been higher. Thus, we believe the rates of amblyopia in our study are comparable to those reported by Yang and colleagues.

4.1.2 Rates of Anisometropia

Refractive error is an outcome that has been studied more closely in this population both for anti-VEGF and laser-treated patients (Hwang, Hubbard, Hutchinson, & Lambert, 2015; Geloneck, et al., 2014; Mueller, et al., 2017; Wu, et al., 2012; Owen, et al., 2015; Harder, et al., 2013; Axer-Siegel, et al., 2008). Refractive error being one of the most frequently reported outcomes may be attributed in part to the fact that it is an objective measure that can be obtained even under anaesthesia if necessary. Rates of myopia (nearsightedness) and astigmatism in laser-treated vs. anti-VEGF-treated patients have been reported with some studies finding that these are both significantly higher in laser-treated patients (Geloneck, et al., 2014; Harder, et al., 2013). Though these are important findings related to long-term visual outcomes, a more relevant measure to disruption of binocularity would be presence of anisometropia (see Section 1.2.2).

Some studies have compared refractive error outcomes among different treatments but in contrast to our study, these used the fellow eye as control by treating with a different modality (Connolly, et al., 2002; O'Keefe, Murphy, O'Keefe, & Lanigan, 2016). Because presence of anisometropia is a measure that documents an interocular difference, the studies that use a separate treatment modality in each eye would not be able to attribute rates of anisometropia to either treatment.

Gunay et al. in 2015 reported and compared rates of anisometropia in 25 subjects treated with anti-VEGF therapy and 15 treated with laser ablation for AP-ROP at 2 years corrected age (Gunay, Celik, Gunay, Aktas, Karatekin, & Ovali, 2015). They defined anisometropia as spherical equivalent (SE) of more than 1.00D which is different from the definition of anisometropia used in this study (see Section 2.3.2). In their 2015 study, Gunay et al. found anisometropia rates of 66.7% the laser-treated group and 20% in the anti-VEGF group (Gunay, Celik, Gunay, Aktas, Karatekin, & Ovali, 2015). Our study found a slightly lower rate in the laser-treated group (57%) and a slightly higher rate in the anti-VEGF group (30%). Though Gunay and colleagues reported rates of anisometropia that were different from the rates in this study, this is not surprising as our
groups were not entirely comparable: the Gunay study evaluated subjects with a more severe form of ROP (AP-ROP). In 2016, using the same definition of anisometropia as in their 2015 study, Gunay et al. investigated a group of ROP patients (14 treated anti-VEGF injections and 28 with laser ablation) and found a rate of 46.2% anisometropia in the anti-VEGF group and 42.9% in the laser group (Gunay, et al., 2016). These reported values do not confirm our observed trend of a larger rate of anisometropia in our laser treated group. However, we cannot properly compare our findings with the 2016 findings from Gunay et al. as they do not specify the age group of their participants (Gunay, et al., 2016).

Three studies report anisometropia rates only in laser-treated patients and for each of these studies the rates are lower than what we measured in our laser group (57%). Yang and colleagues reported an anisometropia rate of 46.7% in 30 seven-year-old patients (Yang, et al., 2010). Yang et al. defined anisometropia as an IOD in refractive error of 1.50 D or more, and did not indicate if this was in the spherical or cylindrical refractive error or whether it was the difference in SE (Yang, et al., 2010).

Consequently, we cannot make a direct comparison between our findings and theirs. Gursoy et al. defined anisometropia as a SE of more than 1.00 D and found a rate of 48% in their group of 23 laser-ablated subjects at a mean follow-up of 20 months post-treatment (Gursoy, Basmak, Bilgin, Erol, & Colak, 2014). In addition to using a different definition of anisometropia than our study, Gursoy et al. also analyzed this outcome from participants in a younger age group. Studies have shown that in the first two years of life the eyes undergo significant and rapid changes in refractive error related to the growth of the eye but that these processes stabilize somewhat after that period (Morgan, Rose, & Ellwein, 2010; Mutti, et al., 2005; Mayer, Hansen, Moore, Kim, & Fulton, 2001). This suggests that it would be better to compare rates of anisometropia in subjects older than 2 years who are not subject to rapid changes in refractive error. Describing rates of anisometropia in a slightly older age group, as our study did, would provide a better picture of anisometropia that is likely to persist long-term.

Finally, a Turkish group, Ziyalan et al, looked at rates of anisometropia in a wider age range (3 to 12 years) similar to that in our study (3 to 8 years). They found an anisometropia rate of 43.1% in ROP patients treated with laser, however did not
adequately define what constituted ‘anisometropia’ for their analysis and therefore cannot be compared to our findings (Ziylan, Öztürk, Yabaş-Kızıloğlu, & Çiftçi, 2014).

4.1.3 Rates of Strabismus

Strabismus is a well-documented outcome in the population of laser-treated ROP. However, there is little data describing long-term effects in ROP patients treated with anti-VEGF therapy. In 2015, Owen et al. reported outcomes in a cohort of 27 infants who were treated with one of two concentrations of intravitreal bevacizumab in one or both eyes (Owen, Davidson, Trivedi, Shirer, Cheeseman, & Saunders, 2015). The age range at time of follow-up for these patients ranged from 3 months to 3.5 years and a “small angle” tropic deviation was found in only 2 of 27 subjects equating to a 7.4% rate of strabismus (Owen, Davidson, Trivedi, Shirer, Cheeseman, & Saunders, 2015). Gunay and colleagues compared strabismus rates (among other findings) in AP-ROP patients, 15 of whom received anti-VEGF therapy and 25 of whom received laser ablation (Gunay, Celik, Gunay, Aktas, Karatekin, & Ovali, 2015). This group, similarly to Owen and colleagues, found a strabismus rate of 8% in the anti-VEGF group; they also found a 40% strabismus rate in the laser group (Gunay, Celik, Gunay, Aktas, Karatekin, & Ovali, 2015).

For the purposes of our study, we considered both manifest and intermittent strabismus insults to binocularity as both cause suppression in visually immature subjects (see Section 1.2.2). Neither Owen et al. nor Gunay et al. describe whether only manifest strabismus was reported in their rates or if both manifest and intermittent strabismus were considered as in our study. The rates of manifest strabismus reported in the anti-VEGF group in our study (9%) closely approximate those reported by Gunay et al. and Owen et al., however, the age groups in the latter studies (2 years, and 3 months – 3.5 years, respectively) are not comparable to that used in our study. Further investigation on the long-term outcomes of anti-VEGF are necessary to confirm our results.

The remaining studies that evaluate strabismus are in patients who were treated with laser and did not compare to an anti-VEGF-treated group. In 2008, Axer-Siegel et al. reported on anatomical and refractive outcomes of laser-treated ROP patients in a retrospective analysis (Axer-Siegel, et al., 2008). Of the 73 subjects in whom ocular
alignment could be assessed, the group reported a strabismus rate of 28.8% which supports the rate of manifest strabismus reported by our study (29%) (Axer-Siegel, et al., 2008). However, Axer-Siegel et al. did not report the age at which these subjects were assessed, nor did they explain who was included in the strabismus group (Axer-Siegel, et al., 2008).

In their report of 30 seven-year-olds treated for ROP via laser ablation, Yang et al. found a strabismus rate of 30% (Yang, et al., 2010). Though their findings also support the rate of manifest strabismus reported in this study, subjects with strabismus in the Yang study were described as having either a symptomatic latent deviation, a manifest deviation or previous strabismus surgery which is not comparable to how we defined presence of strabismus in our group (Yang, et al., 2010).

In 2011, the ETROP group published the 6-year outcomes of strabismus in a group of 341 subjects all treated with laser ablation. At 6 years of age, they found that 42.2% of the laser-treated participants had strabismus though they did not define whether this included only manifest strabismus or both intermittent and manifest (Vanderveen D. K., et al., 2011). The figure reported by the ETROP group approximates our reported rates of manifest and intermittent strabismus, which, when combined, affects 38% of our laser-treated group. The ETROP study also indicates that the “cumulative prevalence of strabismus during the first 6 years was 59.4%...” (Vanderveen D. K., et al., 2011).

Though our study did not count previously treated strabismus in the laser group, our cohort included a wider age range which may account for the differences between these two figures.

Gursoy and colleagues described a cohort of 23 laser-treated ROP patients as having a strabismus rate of 43%; they defined strabismus as any tropic deviation larger than 10 PD at a mean follow-up of 20 months (Gursoy, Basmak, Bilgin, Erol, & Colak, 2014). Ziylan et al. found a strabismus rate of 41.1% in their cohort of 56 laser-treated ROP patients; they did not explicitly state the age group, nor a definition of what motility outcomes constituted strabismus for their study (Ziylan, Öztürk, Yabaş-Kızıloğlu, & Çiftçi, 2014). Neither study has a cohort comparable to ours in terms of age range (for the study which included a description of the subjects’ ages at time of assessment) though it could be said that Gursoy et al. identified binocularity-interrupting strabismus i.e. a
manifest deviation which lies outside of fusional range (larger than 10 PD). The discrepancy between Gursoy’s findings and those reported in our results section may be due to the different age range. With time, we could expect more children to develop strabismus in our cohort.

4.1.4 Rate of Cumulative Insults to Binocularity

Although at the time of the appointment, the individual insult rates were not significantly different between the two treatment groups, in keeping with the similarity between rates of binocularity, the laser group did have a significantly larger rate of insults throughout their lives until the time of recruitment. This could be explained by the fact that the participants belonging to the laser group were older on average and therefore had more time to develop and treat the insults that were not present at the time of the assessment. Therefore, this outcome should be measured again in a larger population when individuals are visually mature, within a narrower age range and following treatment of all events that would have led to disruption in binocularity. It would also help to compare the level of binocularity in those that do respond positively to confirm whether anti-VEGF treatment is associated with higher grades of binocularity.

Regardless of this limitation, the findings in our study underscores the necessity of continued close follow-up of all treated ROP patients regardless of which treatment they received and confirms that there is a considerable rate of treatable events that can lead to loss of binocularity in these patients. However, if detected and treated, a good proportion of patients can be expected to enjoy good binocularity in this group. This becomes important in long-term management of these patients as binocularity has been linked to better outcomes of success such as ocular alignment (Rowe, 2004).

4.2 Limitations

4.2.1 Small Sample Size

Due to the date when anti-VEGF agents became part of the treatment options for ROP, we had only a limited number of patients that fulfilled the study criteria and were still being followed-up at one of the two centres. Because this was a clinical study, participation was entirely at the discretion of the participants and their families/guardians.
in adherence to proper ethical considerations. In addition, ideally, we would have recruited more than the minimum number required to account for the fact that our sample size calculation was based on an estimate extrapolated from other studies looking at similar but not identical outcome measures.

The number of participants we enrolled ended up approaching but not reaching that required to detect a significant difference. Our study results now enable us to determine the sample size necessary to detect this difference: 258 if comparing both treatment groups (129 participants per group).

4.2.2 Two-Centre Study

As mentioned in section 4.2.1 above, the participants were screened at two centres in Canada. Both these centres employ similar treatment and follow-up practices for ROP patients and though they comply with current Canadian guidelines, we recognize that these practices do not necessarily represent treatment and follow-up patterns in all clinics internationally or even within Canada. Therefore, findings in the sample analyzed above may not be representative of all ROP patients. Further investigations should be conducted which compare the outcomes of binocularity and insults to binocularity in a larger population in Canada, North America and in international centres. This would facilitate recruitment of a higher number of participants to satisfy the sample size needed to demonstrate a meaningful result and would make the results more generalizable. Also, including more criteria such as more details on the neurodevelopment, ROP at time of treatment and structural outcomes that could include macular optical coherence tomography (OCT) would provide more information on the determinants of binocularity and levels of binocularity.

4.2.3 Age Range

As stated in the sample size limitation, the timing of the introduction of anti-VEGF treatment for ROP limited the age range of eligible participants. Many of the tests in this study, in particular those required to measure binocularity and vision, are subjective and a relative degree of comprehension and compliance is necessary. Unfortunately, for most patients under the age of 5 years, attention, comprehension and
reliable responses are not always obtainable which is why typically, in the management of a younger child, multiple assessments done on different days are often necessary to produce the most accurate assessment of the child’s condition. This lack of cooperation also precluded further testing such as the macular OCT to add insight with respect to possible structural abnormalities of the macula secondary to ROP and/or treatment. Finally, more children may have developed events that may lead to disruption in binocularity during visual development had they been recruited at an older age and a larger study could assess older children to account for both this limitation and that of cooperation due to age.

4.2.4 Control Group

We were interested in recruiting a group whose ROP had regressed spontaneously to control for ROP and prematurity as confounding factors to disruption of binocularity. We were only able to recruit 8 participants in this control group. Though we demonstrated that the two treatment groups were comparable in terms of severity of prematurity and risk factors associated with higher morbidity (low GA, BW and presence of NDVI), comparing to a control group in the same age range could be used to more reliably impart an effect of treatment on binocularity.

4.3 Future Indications

The results of our study indicate a trend toward better binocularity outcomes in patients who were treated for ROP using anti-VEGF agents as opposed to laser. This will require confirmation in a larger cohort recruited at an older age. It would be important to include a log-linear regression in future studies investigating more than one insult to binocularity and including more variables that could influence these outcomes. For example, recruiting an older age group could analyze differences between the two treatments in terms of the following outcomes: binocular potential on a synoptophore; quantification of high-level binocularity (i.e. stereopsis) achieved by these patients; physiologic abnormalities on the retina with macular OCT imaging; visual field testing; quality of life exploring the cost of monitoring and treating insults to binocularity long-term. Future investigations should include the ages when individual insults to binocularity
in each group were uncovered and treated (if treated at all). This could also uncover if there is a period in the ROP patient’s course when they are most susceptible to a binocularity-disrupting event and whether this affects the final binocularity rate and quality. Analysis of these outcomes would be highly informative when determining the burden of disease in these patients and whether one treatment offers less long-term morbidity.

4.4 Conclusion

Our study is the first to compare binocularity rates in the ROP population treated with laser and anti-VEGF. Although we did not detect a significant difference in binocularity between the two treatment groups, we have shown that in our cohort of patients aged 3 to 8 years, laser-treated patients experience a higher rate of insults to binocularity throughout their lives than the patients treated with anti-VEGF agents. Furthermore, we have demonstrated a trend towards developing worse binocularity outcomes in terms of rate and quality. Further studies will be needed to confirm our findings and provide a more detailed assessment of factors important in the development of binocularity. Binocularity has been attributed to better sensory (e.g. colour and form distinction) and motor (e.g. alignment of the eyes) long-term outcomes. Continued research in this area will contribute to the establishment of evidence-based protocols associated with best long-term maintenance of good visual outcomes in the ROP population.
REFERENCES


Mulla, S. (2007). A correlation between measurements obtained with LEA symbols visual acuity chart and the gold standard ETDRS VA chart for 3 to 7 years old normal children. ProQuest Dissertations and Theses.


years in participants of the Early Treatment for Retinopathy of Prematurity randomized trial. *Journal of AAPOS, 15*(6), 536-540.


APPENDIX A: DATA COLLECTION FORM

Data Collection Sheets

Participant ID:

Date refraction assessed (ddmmmyyyy):

Date consent obtained (ddmmmyyyy):

<table>
<thead>
<tr>
<th></th>
<th>Sphere (valid values from -30 to +30)</th>
<th>Cylinder (valid values from 0-20 in quarters)</th>
<th>Axis (valid values from 0-180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right eye</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left eye</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Date orthoptic assessed (ddmmmyyyy):

Diplopia:

→ present? (N=no diplopia, M=monocular, B=binocular) □
→ gaze (N=none, H=horizontal, V=vertical, O=oblique) □

Squinting:

→ which eye? (N=neither, R=right, L=left, B=both) □

Rubbing:

→ which eye? (N=neither, R=right, L=left, B=both) □

Eye turning:

→ which eye? (N=neither, R=right, L=left, B=both) □
→ is it? (N=not present, C=constant, I=intermittent) □

Data Collection Sheet Version 20-MAR 2018 Page 1 of 5
when is it noticed? (free field text, 4=n/a):

Blurry vision
  → Present? (N=no, Y=yes)

Photophobia
  → Present? (N=no, Y=yes)

Nystagmus
  → Present? (N=no, Y=yes)

Ocular management
  → current glasses? (N=no, Y=yes)
  → previous glasses? (N=no, Y=yes)
  → glasses stopped?
    (0=no, 1=0-12 mos ago, 2=12-24 mos ago, 3> 24 mos ago, 4=n/a)
  → current patching? (N=no, Y=yes)
  → previous patching? (N=no, Y=yes)
  → patching stopped?
    (0=no, 1=0-12 mos ago, 2=12-24 mos ago, 3> 24 mos ago, 4=n/a)
  → current other treatments? (N=no, Y=yes)

details (free field text, 4=n/a):
**VISUAL ACUITY (logmar scores)**

<table>
<thead>
<tr>
<th>Distance test (valid values from -0.3 to +50 but need to multiply by 10 so valid values actually -3 to +504 (code 501 if no better than recognizing hand mobility, 502 if no better than counting fingers, 503 if no better than light perception and 504 for no light perception))</th>
<th>right eye</th>
<th>left eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Near test (valid values from -0.3 to +50 but need to multiply by 10 so valid values actually -3 to +504 (code 501 if no better than recognizing hand mobility, 502 if no better than counting fingers, 503 if no better than light perception and 504 for no light perception))</td>
<td>right eye</td>
<td>left eye</td>
</tr>
</tbody>
</table>

### Frisky
- Plate thickness (circle result) → 0 1 2 3
- Distance held (circle result) → 30 40 50 60 70 80
- Stereo (valid values from 0 to 600)
- 4 Δ
  - (p=Positive, N=negative)
  - (1=base in, 2=base out, 4=n/a)
  - (R=right eye, L=Left eye, 4=n/a)

### WORTH 4 DOT
- Flashlight (1/3 m): (n=normal, A=abnormal)
- Wallbox (6 m): (n=normal, A=abnormal)

### Bagolini (ask patient to draw)
→ (n=normal, A=abnormal)
Date motility assessed (ddmmmyyyy):

<table>
<thead>
<tr>
<th></th>
<th>1/3 m (near)</th>
<th>6m (distance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(circle result)</td>
<td>P</td>
<td>I</td>
</tr>
<tr>
<td>APCT Horizontal (valid values -100 to +100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APCT Vertical (valid values -100 to +100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPCT Horizontal (valid values 0 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPCT Vertical (valid values 0 to 100)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gestational age (valid values from 0 to 40):

Date of treatment (ddmmmyyyy):

Birthweight (valid values from 0 to 2000):

Age at appointment (a yrs, b mos):

Neurodevelopmental impairment: cerebral palsy, sensorineural/mixed hearing loss, visual impairment, and developmental delay with any composite score <85 but better than severe neurodevelopmental disability? (N=no, Y=yes) □

Severe neurodevelopmental disability defined as presence of any of the following: cerebral palsy with a Gross Motor Function Classification Scale of 3, 4, or 5, 19 requirement for hearing aids or cochlear implants, bilateral visual impairment diagnosed by an ophthalmologist as presence of macular drag, traction or detachment, visual acuity of 20/70 or worse, or severe developmental delay with any composite score <70. (N=no, Y=yes) □
APPENDIX B: BAGOLINI TEST MATCHING CARDS
APPENDIX C: REB APPROVAL LETTER (IWK)

Approval – Delegated Review
September 27, 2017

Principal Investigator: Dr. Johane Robitaille
Co-Principal Investigator: Ms. Sonia Manuchian
Title: Binocularity Outcomes Following ROP Treatment
Project #: 1022647

On behalf of the IWK Research Ethics Board (IWK-REB) I have reviewed the documents included in this study. I am pleased to confirm the Board’s full approval for this research study, effective today.

Best wishes for a successful study.

Yours truly,

Adam Huber
Co-Chair, Research Ethics Board

This approval includes the following study documents:

<table>
<thead>
<tr>
<th>Document Name</th>
<th>Version Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol</td>
<td>2017/07/03</td>
</tr>
<tr>
<td>Information and Authorization Form</td>
<td>2017/09/08</td>
</tr>
<tr>
<td>Information and Assent Form</td>
<td>2017/09/08</td>
</tr>
<tr>
<td>Data Collection - Binocularity Trial</td>
<td>2017/06/26</td>
</tr>
</tbody>
</table>

The Board’s approval for this study will expire one year from the date of this letter (September 27, 2018). To ensure continuing approval, submit a Request for Continuing Review to the Board 2 - 4 weeks prior to the renewal date. If approval is not renewed prior to the anniversary date, the Board will close your file and you must cease all study activities immediately. To reactivate a study, you must submit a new Initial Submission (together with the usual fee, if applicable) to the IWK-REB and await notice of re-approval.

Please be sure to notify the Board of any of the following:
- Proposed changes to the initial submission (i.e. new or amended study documents)
- Additional information to be provided to study participants
- Material designed for advertisement or publication with a view to attracting participants
- Serious adverse events experienced by local participants
- Unanticipated problems involving risks to participants or others
- Sponsor-provided safety information
- Additional Compensation available to participants
• Upcoming audits/inspections by a sponsor or regulatory authority
• Closure of the study (within 90 days of the event)

Approved studies may be subject to internal audit. Should your research be selected for audit, the Board will advise you and indicate any other requests at that time.

**Important Instructions and Reminders**
Submit all correspondence to Ethics Manager Bev White or Ethics Coordinator, Joanne Street at the address listed at the top of this letter (do not send your response to the IWK-REB Chair or Co-Chair)

Be sure to reference the Board's assigned file number, 1022647* on all communications.

Highlight all changes on revised documents and remember to update version numbers and version dates, include a clean copy of all revised documents.

<table>
<thead>
<tr>
<th>Research Ethics Board Committee Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Victoria Apold</td>
</tr>
<tr>
<td>Tricia Beattie</td>
</tr>
<tr>
<td>Kimberly Brewer</td>
</tr>
<tr>
<td>Kelly Campana</td>
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<tr>
<td>Jill Chorney</td>
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<tr>
<td>Eleanor Fitzpatrick</td>
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<td>Isabelle French</td>
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<tr>
<td>Ron George</td>
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<tr>
<td>Kevin Gordon</td>
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<tr>
<td>Linda Hamilton</td>
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<tr>
<td>Adam Huber</td>
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<tr>
<td>Francois Tremblay</td>
</tr>
</tbody>
</table>

*REB members are not in attendance during review of their own proposed research involving human subjects or where there is conflict of interest with the proposed research.

This statement is in lieu of Health Canada’s Research Ethics Board Attestation: The Research Ethics Board for the IWK Health Centre operates in accordance with:
- Food and Drug Regulations, Division 5 "Drugs for Clinical Trials involving Human Subjects"
- The Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans - TCPS(2)
- International Conference on Harmonization - Good Clinical Practice Guidelines - ICH-GCP
- FWA #: FWA00005630 / IORG #: IORG0003102 / IRB00003719
APPENDIX D: CONSENT FORM (IWK)

Information and Authorization Form

Study Title: Binocularity Outcomes Following Retinopathy of Prematurity (ROP) Treatment

Investigator(s): Johane Robitaille, MDCM
Department of Surgery/Division Ophthalmology, IWK Health Centre
Dalhousie University Professor of Ophthalmology and Visual Sciences

Sonia Manuchian, BSc, OC(C)
Department of Orthoptics and Ophthalmology, IWK Health Centre.
Dalhousie University Student: Master of Science in Clinical Vision Science Candidate

Michael Vincer, MD
Department of Pediatrics/Division Neonatology, IWK Health Centre
Dalhousie University Associate Professor of Pediatrics

Alyssa Firlotte, MFSGN, BA
Department of Ophthalmology, IWK Health Centre
Research & Medical Administrative Assistant

Funding: Dr. R. Evatt & Rita Mathers Trainee Award in Ophthalmology & Visual Sciences and IWK Category A award

Introduction

Your child is being invited to take part in the research study named above. It is important that you and your child understand the purpose of the study, how it may affect your child, the risks and benefits of taking part and what you will be asked to do, before you decide if your child should take part. This information and authorization form is to help you decide if it is in your child’s best interest to take part in this study. Your child does not have to take part in this study. Taking part is entirely voluntary (your/their choice). If you have any questions that this form does not answer, the co-principal investigator (Sonia Manuchian) will be happy to give you further information.

Purpose of the Study

This study is going to measure how well a child’s eyes work together after having received either laser treatment or an injection of anti-VEGF medication for severe retinopathy of prematurity (ROP).

Problems of binocular single vision (3D vision) including misalignments of the eyes develop more often during the early childhood years in those with a history of premature birth. This is especially true for those who are the smallest at birth and who are also at greatest risk of ROP. There are currently two forms of treatment for severe ROP: we are interested in seeing if there is a difference in binocularity in children 3 to 8 years old that would tell us that one treatment can lead to better binocular outcomes. We also want to compare the same outcomes in a group of prematurely born children in the same age group who did not require treatment for ROP to see if the prematurity is more important than the need for treatment for ROP when measuring binocularity outcomes.

Study Design

Children ages 3 to 8 that have received treatment for ROP or were born prematurely but did not receive treatment (for the control group) will be invited to participate. This study will be performed together with
the Hospital for Sick Children in Toronto to recruit enough participants to complete the study. A maximum of 146 participants will be recruited from both centers, of which an approximate maximum of 50 participants will come from the IWK. We will be analyzing the results at the IWK Health Centre so no information will be sent to another location.

Potential IWK participants will be identified as part of their eye examination follow-up requirements following ROP treatment or, for those in the control group, from the perinatal databases. Once identified, the information and authorization form will be explained and signed if you and your child agree to participate. The co-principal investigator (Sonia Manuchian) will be the person who will verbally invite your child to participate in this study. You and your child will be given an opportunity to ask any questions concerning this study at this time.

Each participant will undergo a routine follow-up orthoptic examination. This will include standard questions about eye related problems and history and reading the strength of the glasses for those wearing glasses. Tests of binocular vision will be performed followed by vision testing at distance and near in each eye individually. Eye alignment will be completed using the standard prism cover tests at near (0.33m) and distance (6m) and eye movements will be tested. All questions and testing procedures are part of the standard of care for children with a history treatment for ROP. Although there are no specific guidelines for long-term follow-up of prematurely born children who do not require treatment, it is generally recommended that parents have their children examined by an eye specialist once a year because of the risk of misalignments in early childhood years.

**What Participation Involves**

Taking part in this study will involve a one-time assessment at the IWK Health Center that will approximate as much as possible the due date for your child’s regularly scheduled orthoptic follow-up appointment. It is possible that if all of the information is not possible to obtain in one visit, a second appointment may be needed (this would also happen in routine eye examinations). The time required to take part is estimated to be no longer than 90 minutes. The number of visits to the eye clinic will not change due to taking part in this study.

**Potential Harms**

There is the potential that someone finds out that your child is in this study that should not know. However, to avoid this all participant information will be kept locked and securely stored in the PI’s office. See below for confidentiality.

**Potential Benefits**

There is no guarantee that your child will personally experience any benefits from participating in this study. There is no intervention prescribed during this appointment other than what the child may receive at any standard follow-up appointment. The results will be forwarded to your child’s Ophthalmologist (eye doctor). However, the knowledge gained from this study may help us decide whether one treatment method results in better binocular vision. This information will provide us, and possibly others, with important information about the best approach to the treatment of severe ROP.

**Alternatives to the Study**

Before deciding to participate in this study, you should know your child does not have to take part in the study. If your child does not participate in the study, your child will receive the current standard of care, with regular Orthoptic follow-up examinations at your Orthoptists or Ophthalmologists recommended time.

**Withdrawal from Participation**

Participation in the study is entirely voluntary (yours and your child’s choice). You may decide not to enroll your child, or you may withdraw your child from the study at any time. This will not affect your child’s eye care at the IWK Health Centre in any way. If the study is changed in any way that could affect your decision to continue to have your child participate, you will be told about the changes and you may be asked to sign a new authorization form. If you decide to withdraw your child from the study, your child will be scheduled appropriately for their routine follow-up appointment.
Conflicts of Interest
The PI of this study is a Pediatric Ophthalmologist at the IWK Health Centre and the co-PI a Certified Orthoptist and an active part of the IWK Health Centre’s Eye Care Team. The co-PI is also a student and Masters of Science candidate in the joint IWK/Dalhousie University Clinical Vision Science program. This research is part of the requirements for graduation in the program.

Confidentiality
Any information that is learned about your child will be kept private. Research study staff will have access to the study records. The records may be shown to that of the Research Services of the IWK Health Centre and regulatory authorities to make sure the research is being done properly. If the results of the study are published in a medical journal it will not have any information that would identify your child. Study records will be stored in a locked area for 5 years past the age of majority as required by the IWK Research Ethics Board.

Costs and Reimbursement
There are no cost reimbursements in this study. We will offer a $5 gift certificate to Tim Horton for each participant.

Research Rights
Your signature on this form will show that you have understood, to your satisfaction, the information about the research study. By signing this document, you are not waiving any of your child’s legal rights, nor are you releasing the investigator(s), institution(s) and/or sponsor(s) from their legal and professional responsibilities.

If you have any questions at any time during or after the study about these legal rights or about research in general and you would like an independent opinion, you may contact the Research Office of the IWK Health Centre at 470-8765, Monday to Friday between 9 am to 5 pm.

Contact Person
The co-principal investigator (Sonia Manuchian) will be available to answer any questions or concerns that you have from Monday to Friday between 7:30 am to 4 pm at 470-8632 OR e-mail – Sonia.Manuchian@Dal.Ca.

Communication of Results
Research results will be available at the completion of the study. If you wish to have a copy of the results please print your address here:
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
Study title: Binocular Outcomes Following Retinopathy of Prematurity (ROP) Treatment

Participant ID: _______________ Participant INITIALS: _______________

Parental or Guardian Authorization - if participant living in the care of parent or guardian. I have read or had read to me this information and authorization form and have had the chance to ask questions which have been answered to my satisfaction before signing my name. I understand the nature of the study and I understand the potential risks of reactions. I understand that I have the right to withdraw my child from the study at any time without affecting my child’s care in any way. I have received a copy of the Information and Authorization Form for future reference. I freely agree to have my child participate in this research study.

Name of Participant (Print)______________________________
Parent/Guardian:______________________________                            ___________________________
Name of Parent/Guardian (Print)                                    Signature of Parent/Guardian

Date: ___________________ Time: _____________

STATEMENT BY PERSON PROVIDING INFORMATION ON STUDY
I have explained the nature and demands of the research study and judge that the Parent/Guardian named above understands the nature and demands of the study.

Name (Print): _____________________________Position: __________________________
Signature:_______________________________ Date: ________________ Time________

STATEMENT BY PERSON OBTAINING CONSENT
I have explained the nature and demands of the research study and judge that they understand that participation is voluntary and that they/their child may withdraw at any time from participating.

Name (Print): _____________________________Position: __________________________
Signature:_______________________________ Date: ________________ Time________

Other people present at time of signing:

Name (Print): _____________________________Position: __________________________
Signature:_______________________________ Date: ________________ Time________
APPENDIX E: ASSENT FORM (IWK)

Binocularity Outcomes Following Retinopathy of Prematurity (ROP) Treatment
Information for Children

Researcher: Sonia Manuchian, Orthoptist, IWK Eye Care Team

Why are we doing this study?
You were born prematurely meaning that you were born too early. That may have affected your eyes and you may have needed treatment when you were a baby. If so, you will have received one of two possible treatments. We are doing a study to find out if one treatment is better to make your eyes work together better. We also want to know if being born prematurely but without needing the eye treatment is enough to affect how well your eyes work together compared to other children who needed a treatment.

What will happen during this study?
You will have a normal eye appointment that you regularly have at an eye clinic. At these appointments the eye care professional will check how straight your eyes are, how well your eyes work together, and your vision. If your eyes are not straight, you will need to come back for another one and finish what you did not get to on the last visit. If you decide to be a part of this study, you will also be offered a gift card to Tim Hortons for $5.00.

Are there any good or bad things about this study?
Being in the study will not help your eyes. We hope that we will learn things in the study that will help us take better care of other children with same eye problem in the future.

Who will know about what I did in this study?
No one except the researchers will know you are taking part in this study unless you want to tell them. Your name, your study forms and your chart will only be seen by people involved in the study.

Do I have to be in this study?
You do not have to be in this study. Being in this study is totally up to you. If you don’t want to be in this study, tell us. It will not affect how your doctor will look after you if you decide not to be in the study. Even if you say yes now, you can change your mind later. Being in this study is totally up to you.

What if I have any questions?
You can ask questions about the study any time, now or later. You can talk to your parents about things in the study you don’t understand. You can also ask Sonia about the study. You can call or email her: Ms. Sonia Manuchian: 902-470-8632 or Sonia.Manuchian@Dal.Ca.

Version 2- September 8, 2017

Assent
Research Ethics Board (REB)
Study Approval Letter

2018-01-12

Nasrin Tahruni
Ophthalmology

REB number: 1000058540
Study Title: Assessing the binocularity outcomes of Retinopathy of Prematurity (ROP) patients treated with laser versus anti-VEGF therapy

Date of Approval: 2018-01-12
Expiry Date: 2019-01-12

Thank you for the application submitted on 2017-11-07. The above referenced study was reviewed through a delegated process (not by Full Board review). Any concerns arising from this review have been documented and resolved.

The REB voted to approve this study, and your participation as Principal Investigator, as it is found to comply with relevant research ethics guidelines, as well as the Ontario Personal Health Information Protection Act (PHIPA), 2004.

The Hospital for Sick Children Research Ethics Board hereby issues approval for the above named study. This approval is effective from 2018-01-12 to 2019-01-12. Continuation beyond that date will require further review of REB approval.

The following documents have been reviewed and are approved:

1. Protocol Version dated January 9, 2018 [Protocol Approved post Scientific Review (Jan 9 2018) eREB.docx (1.0)]
2. Parent Consent Form Version dated January 9, 2018 [Consent SickKids V2 (Jan 9 2018).docx (1.0)]
3. Assent Form Version dated January 9, 2018 [SickKids Assent V1 (Jan 9 2018) eREB.docx (1.0)]

During the course of this investigation, any significant deviations from the approved protocol and/or unanticipated developments or significant adverse events should immediately be brought to the attention of the REB.

Dr. E. Stephenson M.D., MSc, REB Chair
Arbella Manicant Emo, RN(EC), MS, NP Paeds REB Vice Chair;
Dr. Kathy Boutil, BSc, MSc, MD, FrCPC REB Vice Chair;
Rose Gaitano, RN, MSN REB Vice Chair

555 University Avenue, Toronto, ON M5G 1X8
Tel: (416) 813-8279 Fax: (416) 813-6515
The SickKids REB operates in compliance with the Tri-Council Policy Statement; ICH Guideline for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Devices Regulations of Health Canada. The approval and the views of the REB have been documented in writing. The REB has reviewed and approved the clinical trial protocol and informed consent form for the trial. All investigational drug trials at SickKids are conducted by qualified investigators.

Furthermore, members of the Research Ethics Board who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.
APPENDIX G: CONSENT FORM (SickKids)

SickKids
THE HOSPITAL FOR
SICK CHILDREN

Consent to Participate in a Research Study
Parent Consent Form

Title of Research Project:
Assessing the binocularity outcomes of Retinopathy of Prematurity (ROP) patients treated with laser versus anti-VEGF therapy

Principal Investigator:
Dr. Nasrin Tehrani 416-813-8919
Staff Ophthalmologist

Co-Investigators and Collaborators:
Staff Ophthalmologist: Kamilar Mireskandari 416-813-8375
Research graduate student: Sonia Manuchian 416-813-8919
Clinical research coordinator: Maram Isaac 416-813-7654 ext. 201402

Purpose of the Research:
We would like to invite or your child to take part in our research study.
We are studying an eye condition called retinopathy of prematurity (ROP). This condition can affect the eyes of some premature babies, especially if they are born very early or are very small. In this condition, blood vessels in the back of the eye develop abnormally. Children who are born early may have problems with how well their eyes work together. If the eyes do not work together, three-dimensional vision (3D vision) may not develop normally.

The standard or usual treatment for ROP at The Hospital for Sick Children (SickKids) is either laser therapy or a direct injection into the eye with a drug called bevacizumab (brand name Avastin). Some children have ROP but it is not bad enough to need treatment.

This study is going to measure how well children’s eyes work together after treatment with either laser or bevacizumab injection or no treatment by measuring their 3D vision. We will do this by doing an orthoptic assessment which includes the assessment of binocularity. We want to see which of those two treatments results in better 3D vision because of both eyes working together. This will also help us to understand if 3D vision is affected more by the treatment or by being born prematurely. We aim to enroll approximately (75) children in this study.
Your child is being invited to participate in this research study because he/she has the eye condition called retinopathy of prematurity (ROP).

**Description of the Research:**
If you consent for your child to be in this study, an orthoptic assessment will be done for research purposes. If all the testing needed for the orthoptic assessment is not completed in one appointment, you may be asked to return for one or two more appointments (until we have all the information) just as you would for your regular orthoptic check-ups. The amount of appointments you may attend will not exceed 3 visits. We will also review your child’s medical chart to use your child’s clinical eye check-ups and test results for research purposes. All personal health information collected about your child will be “de-identified” by replacing your child’s identifiable information (i.e. name) with a study number.

This study will be performed together with the IWK Health Centre in Halifax. De-identified research data will be sent to IWK Health Centre for analyses.

You and your child can ask any questions about this study at any time during the consent process or as you are participating.

**Potential Harms, risks, and or inconvenience or discomforts:**
We do not know of any harm that could come to your child as a result of taking part in this study.

There is an inconvenience time, orthoptic exam will take about 40 minutes.

**Potential Benefits:**

**To individual subjects:**
Your child will not have any direct benefits for participating in this study.

**To society:**
We hope that the information learned from this study can be used in the future to benefit other people with a similar disease and/or health condition.

**Confidentiality:**
We will respect your child’s privacy. No information about your child will be given to anyone or be published without your and or your child’s permission, unless the law requires us to do this.

The SickKids study staff (study investigators, coordinators, nurses and delegates) will collect personal health information about your child. This includes things learned from the study procedures described in this consent form and/or information from your child’s medical records. They will only collect the information they need for the study.

All personal health information or personal information collected about your child will be “de-
identified” by replacing your child’s identifiable information (i.e., name) with a “study number”. The SickKids study staff are in control of the study code key, which is needed to connect your child’s personal health information/personal information to your child. The link between the study number and your child’s identity will be safeguarded by the SickKids study staff and will not be available to the others. SickKids guidelines include the following:

- All information that identifies your child, both paper copy and electronic information, will be kept confidential and stored and locked in a secure place that only the study staff will be able to access.
- Electronic files will be stored securely on hospital or institutional networks or securely on any portable electronic devices.
- No information identifying your child will be allowed off site in any form without your and or your child’s consent. Examples include your child’s hospital or clinic charts, copies of any part of your child’s charts, or notes made from your child’s charts.

The study staff and the others listed above will keep the information they see or receive about your child confidential, to the extent permitted by applicable laws. Even though the risk of identifying you (or your child) from the study data is very small, it can never be completely eliminated.

Access to your child’s personal health information will take place under the supervision of the Study Doctor. You and or your child have the right to access, review and request changes to your child’s personal health information.

The following people may come to the hospital to look at your child’s personal health information to check that the information collected for the study is correct and to make sure the study followed the required laws and guidelines:

- Representatives of the SickKids Research Ethics Board and/or Research Quality and Risk Management team

De-identified study data will be sent to IWK Health Centre in Halifax for analysis.

The study staff will keep any personal health information about your child in a secure and confidential location for (7) years and then destroy it according to SickKids policy.

When the results of this study are published, your child’s identity will not be disclosed. You and or your child have the right to be informed of the results of this study once the entire study is complete.

**Reimbursement:**
You and your child will not be reimbursed for participating in this research study

**Participation:**
Participation in research is voluntary. If you choose to let your child take part in the study, you
can take your child out of the study at any time. The care your child gets at SickKids will not be affected in any way by whether he/she takes part in this study.

New information that we get while we are doing this study may affect your decision to take part in this study. If this happens, we will tell you about this information and we will ask you again if you still want to be in the study.

If your child becomes ill or is harmed because of study participation, we will treat your child for free. Your signing this consent form does not interfere with your legal rights in any way. The staff of the study, any people who gave money for the study, or the hospital are still responsible, legally and professionally, for what they do.

**Sponsorship:**
The sponsors of this study are Dr. Nasrin Tehrani and The Hospital for Sick Children.

**Conflict of Interest:**
The Principal Investigator, Dr. Nasrin Tehrani, and the other research team members have no conflict of interest to declare.

**Who can I call if I have questions about the study?**
If you (or your child) have any questions during the participation of this research study you (or your child) can contact the Study Doctor, Dr. Tehrani at 416-813-416-813-8919

**Research Ethics Board Contact information**
The study protocol and consent form have been reviewed by the SickKids Research Ethics Board (REB).

If you (or your child) have any questions regarding your (or your child’s) rights as a research participant, you (or your child) may contact the Office of the Research Ethics Board at 416-813-8279 during business hours.
Consent to Participate in a Research Study

Study Title: Assessing the binocularity outcomes of Retinopathy of Prematurity (ROP) patients treated with laser versus anti-VEGF therapy

By signing this research consent form, I understand and confirm that:

1. All of my questions about this study have been answered.
2. I understand the potential harms and benefits of having my child participating in this study.
3. I know what I could do instead of having my child take part in this study.
4. I understand that I have the right to refuse to take part in this study. I also have the right to withdraw my child from the study at any time.
5. My decision for my child to not take part in this study will not affect my child’s health care at SickKids.
6. I am free now, and in the future, to ask questions about this study.
7. I have been told that my child’s medical records will be kept private except as described to me.
8. I understand that no information about my child will be given to anyone or be published without first asking my permission.
9. I understand the information within this informed consent form

I consent to my child’s participation in this study.

________________________________________
Printed Name of Participant

________________________________________
Printed Name of Parent

________________________________________
Parent signature & date

________________________________________
Printed Name of person who obtained consent

________________________________________
Role of person obtaining consent

________________________________________
Signature & date

Parent Consent Form
Version date: January 9, 2018
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APPENDIX H: ASSENT FORM (SickKids)

Research Assent Form

Title of the Research Project:
Assessing the binocularity outcomes of Retinopathy of Prematurity (ROP) patients treated with laser versus anti-VEGF therapy

Principal Investigator:
Dr. Nasrin Tehrani
Staff Ophthalmologist
(416)-813-8919

Other Investigator(s):
Staff Ophthalmologist: Kamiar Mireskandari,
Research graduate student: Sonia Manuchian,
Clinical Research coordinator: Maram Isaac
(416)-813-8375
(416)-813-8919
(416)-813-7654 ex. 201402

Why Are We Doing This Study?
You were born prematurely meaning that you were born too early. That affected your eyes and you may have needed treatment when you were a baby. If you did need treatment, you will have received one of two possible treatments. We are doing a study to find out if one treatment is better to make your eyes work together better. If you did not need treatment, we also want to see how your eyes are working together.

What Will Happen During The Study?
You will have your normal eye appointments that you regularly have at an eye clinic. At these appointments, the eye care professional will check how straight your eyes are, how well your eyes work together, and your vision as they normally do. If you cannot finish all these things during one appointment, there is no problem--you can come back for another one and finish what you did not get to on the last visit.

Are there good things and bad things about the study?
Being in the study may not help your eyes. We hope that we will learn things in the study that will help us take better care of other children with same eye problem in the future.

Who will know that I did the study?
If we feel your health may be in danger, we may have to report your results to your doctor. Other than that, No one except the researchers will know you are taking part in this study unless you want to tell them. Your name, your study forms and your chart will only be seen by people involved in the study.
Can I decide if I want to be in the study?
Nobody will be angry or upset if you do not want to be in the study. We are talking to your parent/legal guardians about the study and you should talk to them about it too. If you don’t want to be in this study, tell us. Even if you say yes now, you can change your mind later. Being in this study is totally up to you.

Assent:

"I was present when ___________________________read this form and said that he or she agreed, or assented, to take part in this study."

Printed Name of person who obtained assent   Signature & Date