Predictors of Recurrence After the Surgical Correction of Exodeviation

by

Dominique Salh

Submitted in partial fulfilment of the requirements
for the degree of Master of Science

at

Dalhousie University
Halifax, Nova Scotia
April 2019

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List of Abbreviations

AAO: American Academy of Ophthalmology

AC/A: Accommodative Convergence/ Accommodation ratio

APCT: Alternate Prism Cover Test

BVA: Binocular Visual acuity

DVD: Dissociated Vertical Deviation

ETDRS: Early Treatment Diabetic Retinopathy Study

IV: Independent Variable

IWK: Izaak Walton Killam Health Care Centre Eye Clinic

IXT: Intermittent Exotropia

LH: Lea Hyvarinen

m: Meters

NPC: Near Point of Convergence

pd: prims diopters

PMO: Prolonged Monocular Occlusion

R&R: Recession and Resection Procedure

STD DEV: Standard Deviation

TPF: Tenacious Proximal Fusion

VA: Visual Acuity

XT: Exotropia

ACKNOWLEDGEMENTS

The preparation for, and process of performing this study would not have been possible without the support of my two supervisors, Leah Walsh and Erik Hahn. Without you both I know I would not be the person I am today, nor the clinician I am still becoming. You have instilled a special kind of confidence in me over the last handful of years that will serve me well in my career and personal life. They say it takes a village, or in my case, an entire pediatric ophthalmology department. Thank you to each of the CVS instructors, ophthalmologists, technologists, administrative staff, my co-students, and every other person who was involved in my journey. It is with incredible gratitude that I am able to complete this next phase of my education.

Leah Walsh, I wish every clinician in the world could have your passion, your drive, and your enthusiasm. I wish every orthoptic student in the country could be given the chance to absorb the wealth of knowledge that you have accumulated over your career. It has truly been my greatest pleasure learning from you. I remember being in first year and knowing that you would be the clinician I would model myself after. Your skill and dedication have far exceeded any of the expectations I could have had for a clinical instructor, and I feel so lucky. Thank you for investing in me, taking your time with me, and lastly, for believing in me. You have such a gift. Thank you for everything.

Erik Hahn, I will absolutely never ever forget you. You believed in me before I believed in myself. I hope you know how much I value your support, your opinion, and your leadership. You have taught me much more about life and carrying on, than about the bending of light rays as they pass from regions of dense mediums, and so on. I catch myself striving to make you proud on a regular basis. Thank you for all the good you have given me, and for all of your remarkable contributions to the Clinical Vision Science program.

Kailee Algee, although I would have loved to have you on my examining committee, I am so glad you were able to take this time investing in your growing family. You have given me more opportunity, support and inspiration than I can acknowledge in a short paragraph. It is your work that inspired and directed my research. This dissertation would not be complete without the inclusion of your name here. I am forever grateful to you.

Abstract

Exodeviations have been defined as outward misalignments of the eyes that may be characterized by periods of control and binocular single vision. While patients are commonly diagnosed with this condition, the treatment outcomes for exodeviations remain inconsistent. One of the most common treatment options pursued is surgery. The variability in testing of stereopsis, deviation size and refractive error between subjects preoperatively may result in poor surgical outcomes in this patient population. This study seeks to determine how many surgically corrected subjects with exodeviations have favourable outcomes; or if there are measurable predictors for unsuccessful surgical outcomes on orthoptic examination, either pre or post-operatively; or whether there is a relationship between the personalization of recommended surgical doses and surgical outcomes. Following this retrospective chart review, a success rate of 43% was determined. Successful surgical intervention was associated with Duane's classification, angle of deviation, visual acuity in the left eye, and follow up period.

1.0 Chapter 1 Introduction

1.1 Background

Strabismus is an ocular misalignment, where one or either eye deviates inward, outward, or vertically, respective to the fellow eye (von Noorden & Campos, 2002; Wright 2003). Exodeviations are outward eye turns that can present at any age and affect about 1% of children under the age of 11 in western populations (Govindan, Mohney, Diehl & Burke, 2005). The etiology of this condition remains inconclusive. Potential causes have been linked to mechanical, anatomical or innervational abnormalities, or any combination of these (Wright, 2003). Others have postulated that accommodative convergence imbalances may also have a role in the cause (Cooper and Meadow, 1993; Kushner 1998b). Symptoms of exodeviations include one or either eye deviating outward some or all of the time; double vision; headaches; light sensitivity; closing or winking of one or either eye; neck pain; or reduced vision in one eye. (Santiago, Kushner, & Rosenbaum, 1999).

1.2 Etiology

The cause of exodeviations has yet to be definitively described but most cases of childhood strabismus are thought to be idiopathic in nature (Wright, 2003). Various theories including mechanical, anatomical and/or innervational imbalances have been suggested (Wright, 2003). Genetics has been thought to play a role in the cause of some cases of infantile exotropia (Engle, 2007). Duane (1897), stated that exodeviations are a result of an imbalance of innervation, which interferes with the reciprocal relationship existing between active divergence and convergence. However, the idea that exodeviations are mostly a result of hypertonic divergence was called into question by Bielschowsky. According to him, Duane's theory failed to consider the anatomical and mechanical anomalies that lead to an abnormal position of rest,

characterizing exodeviations (von Noorden & Campos, 2002). Considering that individuals with exodeviations also have reduced fusional ability, Worth (1929) suggested that deficient fusion faculty also played a role in the etiology of exotropia, especially the more severe and symptomatic forms of this condition. Cooper and Meadow (1993) speculated that accommodative convergence anomalies may play a role in the presentation of exotropia, and Kushner (1988) investigated this phenomenon as well. Kushner discovered a link between high accommodative convergence to accommodation ratios (AC/A) and a subcategory of patients with high (AC/A) exotropia. The AC/A ratio is the relationship between the amount of convergence elicited among both eyes, based on how much the crystalline lens accommodates to focus a near image (von Noorden & Campos, 2002). When the AC/A ratio is high, there is increased convergence associated with a given amount of accommodation (von Noorden & Campos, 2002). Knapp (1953) and Jampolsky (1954) stated that patients with controlled exodeviations have developed bitemporal, bilateral, hemiretinal suppression mechanism, which permits the eyes to deviate outward. It was postulated that this mechanism facilitates a lack of diplopia associated with the manifest period of intermittent deviations (Knapp, 1953; Jampolsky 1954). Pratt Johnson, Tilson & Pop (1983) found evidence of a hemiretinal trigger mechanism that operates in exodeviations leading to suppression in patients with exodeviations.

Uncorrected refractive error has been implicated in the etiology of exodeviations for over 100 years (Donders, 1899; Jampolsky, Flom, Weymouth & Moster, 1955; von Noorden & Campos, 2002;). This relationship is due to the effect of accommodative convergence on the alignment of the eyes. In conjunction with Worth's theory of fusion faculty, uncorrected anisometropia has also been suggested as a cause of exotropia (Jampolsky et al., 1955). Anisometropia can be a barrier to fusion (von Noorden & Campos, 2002). When images from

the two eyes are not fused, the eyes are less stimulated to maintain their alignment. In patients with uncorrected bilateral myopia, less accommodation is required to clear a blurry image at near, as compared to in individuals who have negligible refractive error, or are emmetropic (von Noorden & Campos, 2002). When less accommodation is required, there is reduced convergence effort which can result in the development of an exodeviation. Patients with significant hyperopia may not have a clear image at near or distance fixation, thus the effects of accommodative effort on alignment in this population can be significant (Donders, 1899; von Noorden & Campos, 2002).

1.3 Classification

Strabismus, including exodeviations are diagnosed in part, based on a subject's control of their deviation, for which 3 grades of control exist. Manifest exotropias are outward eye turns, where a deviating eye is misaligned constantly. Exophorias are outward eye turns that are always controlled by the subject, becoming manifest under monocular occlusion. Therefore, the patient's eyes appear straight all of the time, despite there being a controlled, latent deviation. Thirdly, intermittent exotropia (IXT) describes a deviation that is controlled some of the time, but becomes manifest during periods of fatigue, illness, cognitive inattention, or after the use of some pharmacological agents (Govindan et al., 2005). The diagnosis of IXT represents between 50-90% of congenital cases of outward deviations (Mahoney & Huffaker, 2003; Wright 2003). This type of deviation typically presents around age 5, but can be very well controlled until later in life. In IXT, the deviating eye may be more noticeable when a subject looks into the distance compared to when viewing up close (Hatt & Gnanaraj, 2013; Kushner, 1998a). It is possible for an exophoria or intermittent exotropia to decompensate into a manifest exotropia over time,

when there is a decrease in control over the deviation (AAO, 2012; Kushner 1998; von Noorden & Campos, 2002).

Exodeviations are also classified according to deviation size characteristics. These categories are determined by comparing the difference in the degree of deviation when the individual focuses at 0.33m, with the degree deviation when focussed at 6m. Using Duane's classification system (1897), if the deviation is the same at both distances, or is within 15 prism diopters (pd) of each other, it is classified as basic type. If the deviation is greater than 15 pd at near compared to distance, this is termed convergence insufficiency/weakness type. In true divergence excess type, the deviation is 15 or more pd at distance than at near. When the deviation at near is re-measured at 0.33 m after prolonged occlusion, or with +3.00D lenses, the deviation at near remains 15 pd or more smaller than the distance deviation in true divergence excess type. Finally, the fourth type of Duane's classification of exotropia considered by this study is pseudo or simulated divergence excess type exodeviation. Unlike true divergence excess type exodeviation, the deviation at near will increase in size with the use of prolonged occlusion or with +3.00D lenses at near, to being within 15 pd of the distance deviation. If a deviation was measured the same angle at both near and distance, it is categorized as basic type. Orthophoric subjects at both near and distance post-operatively are also considered basic type. Despite that Duane's classification system uses a difference of 15 pd between fixation distances to determine subtype, a difference of 10 pd is routinely used clinically (Kushner, 1988). A study by Kushner (1988) acknowledged that Burian had also used a 10 pd near/difference classification criteria in his previous research. For the purposes of this research , the term Duane's classification will represent a 10 pd difference in all categories.

1.4 Factors Permitting Deviation Control

Exophoria and intermittent exotropia are two of the control grades which describe a deviation that is not manifested all of the time. Several different mechanisms have been suggested to play a role in the ability to control a deviation (Superstein, Dean, Holmes, Chandler, Cotter, Mohney, & Birch 2017). The mechanisms used to control a deviation may alter the presentation of the strabismus before treatment, and therefore testing prior to surgery is a priority (Superstein et al., 2017)

In true divergence excess exodeviations there is a smaller angle of deviation to overcome while focussing at near, and control of the deviation may be better. In pseudo-divergence excess type, there may be improved control at near, despite a larger deviation that is revealed through disruption of fusion or accommodative convergence. Reduced deviation size at near may be due to tenacious proximal fusion (TPF) or high AC/A ratio (Kushner 1988; Kushner & Morton 1998; Wright 2003). Tenacious proximal fusion is thought to be a vergence after-effect mechanism that is active at near, and prevents the intermittent exotropia from manifesting at close fixation distances (Kushner & Morton, 1983). The tenacious proximal mechanism dissipates slowly, and requires at least an hour of monocular occlusion to counter its effects according to the results of previous studies (Kushner & Morton, 1983). Burian & Franceschetti (1970) concluded that a period of 30-45 minutes would be adequate for binocular dissociation. Currently, at the discretion of the clinician, a period of 30-60 minutes is now routinely used (Wright, 2003).

Maddox (1893) was amongst the first to develop a classification of inward vergence movements of the eyes; voluntary convergence, accommodative convergence, tonic convergence, proximal convergence, and finally fusional convergence. According to von Noorden & Campos (2002), voluntary convergence is unique, as it is one of the only vergence

movements that can be elicited without an external stimulus. Jampolsky denied the existence of voluntary convergence, suggesting that it is an outcome of someone willingly converging their eyes (Jampolsky, 1970). Accommodative convergence is the amount of convergence elicited with a given amount of accommodation (von Noorden & Campos, 2002). Tonic convergence describes the convergence tonus of the extraocular muscles that acts to overcome the naturally divergent tendency of the eyes (von Noorden & Campos, 2002). Proximal convergence is detected most frequently during the synoptophore exam, when the instrument creates an awareness of near, regardless of a target image positioned at optical infinity (von Noorden & Campos, 2002). Lastly, fusional convergence is the inward vergence mechanism which acts to clear blurred images, and overcome retinal disparity (Maddox, 1893; Von Noorden & Campos 2002).

Convergence mechanisms play a role in enabling individuals to control an intermittent or exophoric deviation through motor fusion: the ability of the eyes to align themselves so that corresponding points of both retinas permit the fusing of binocular images (von Noorden & Campos, 2002). When alignment is orthophoric, a patient should achieve simultaneous perception, fusion, and/or stereopsis. However, a patient will be less likely to achieve higher grades of binocularity if there are other barriers to fusion present (Wright, 2003). When a patient achieves a higher grade of binocularity, they may be more likely to keep their eyes aligned (Wright, 2003). However, not all patients will achieve sensory fusion in the presence of motor fusion (Wright, 2003)

Pediatric patients with minimal hyperopic refractive error and an exodeviation are seldom prescribed their full cycloplegic refractive correction, as long as there is normal accommodative ability present (Chung, Kim, Kim & Lee, 2011; Wright, 2003). These patients use

accommodation instead of spectacles to overcome their minimal refractive error to maintain a clear image. The convergence response which occurs with the accommodation elicited may also play a role in the control of hyperopic patients with controlled exodeviations (Chung et al., 2011. Not all clinicians consider the absence of minimal hyperopic refractive correction to be a form of minus lens therapy, despite this, patients are using their accommodative ability to form a clear image (Chung et al., 2011).

1.5 Clinical Presentation and Symptoms

The management, or need for surgical intervention on patients with exodeviations relies heavily on the presentation and symptoms of each individual patient (Kushner 2008; Santiago et al., 1999). The nature of signs and symptoms of exodeviation relies heavily on two variables; age and control. Visually immature patients under the age of approximately 7 years can be asymptomatic due to cortical suppression of the image from the deviating eye (Santiago et al., 1999). After visual immaturity, a visually mature patient with a recent-onset or decompensating controlled strabismus would likely experience diplopia in the presence of a manifest deviation (Santiago et al., 1999). Diplopia can be debilitating and challenging to ignore, often warranting management through surgical intervention, prism correction or other non-surgical treatment modalities (Kushner, 2008).

It is important to recognize that not all visually immature patients who demonstrate suppression of a second image in the presence of a manifest deviation will be asymptomatic. The benefits an individual experiences through binocularity, such as binocular depth perception, may provide enough visual enhancement to motivate individuals to control their deviation (Kushner, 2008; Santiago et al., 1999). Unfortunately, the controlling of a deviation is a likely cause for symptoms associated with strabismus of any kind. Frontal headaches that are exacerbated by

periods of visual attention, and relieved by visual breaks may be a symptom of controlled deviations (Santiago et al., 1999). Blurred vision can be a result of young patients using excessive accommodation in attempts to control their deviation (Walsh, La Roche & Tremblay, 2000). Asthenopia or "eye strain" has also been shown to be bothersome to children in a study by Hatt et al. (2016), where children reported "eyes feeling tired" as one of the most common symptoms associated with their eye condition. This study also reported that experiencing problems with the eyes in the sun (eg. photophobia) and eye rubbing, similar to monocular closure, were other commonly reported symptoms. Less reported symptoms were difficulty focusing the eyes, double vision and eyes hurting (Hatt et al., 2016).

Another study by Hatt et al. (2008) used an open-ended question methodology to determine symptoms of IXT. The most significant symptoms experienced by children were worries about the eyes, social problems such as receiving negative comments about the eyes, and being troubled by blurry vision. Although head postures are less likely to be reported with a typical exodeviation, it was noted that some patients will hold their head in a certain position to reduce the size of the deviation, or exert better control over the deviation (Hatt et al., 2008). This is most likely associated with an incomitant deviation (Hatt et al., 2008). An example of an incomitance is when a patient has pattern strabismus associated with their deviation. For example, with a V-pattern exodeviation, a patient may hold their chin up to better control the deviation that is smaller in downgaze. "A" and "V" Pattern strabismus is not uncommon with exodeviations, due to the occurrence of oblique muscle dysfunction in these patients (Lee et al., 2017) . Comitant deviations are those that measure similarly in all central and peripheral gazes.

Children with exodeviations have minimal refractive error on average (Ekdawi, Nusz, Diehl, & Mohney, 2008; Superstein et al., 2017). Hyperopia and myopia are common, but one large scale study reported an average refractive error of less than 1 diopter of myopia in both eyes in their sample of over 1000 patients with exodeviation (Yang, Chen, Shen, Kang, Deng, Lin & Yan, 2016). Although this study did not report on hyperopia; astigmatism, amblyopia, anisometropia, suppression, and diplopia were common clinical findings (Yang et al., 2016). When assessing all grades of exodeviation control the unequal prevalence between genders has been poorly represented (Rowe, Noonan, Freeman, & Debell, (2007). Rowe suggested that there is an equal distribution of exodeviations between the sexes.

1.6 Clinical Assessment

As previously stated, patients with exodeviation often present with varying levels of control over their deviation, and this is one indicator for the need for therapeutic intervention (Kushner, 2008; Santiago et al., 1999; Wright, 2003). Routinely, patients with controlled or intermittently controlled deviations, exophoria and intermittent exotropia respectively, will undergo a number of clinical tests on routine examination. These tests are largely aimed at quantifying a patient's control of their deviation (Algee, Walsh & Hahn; Accepted for publication 2019).

The evaluation of the patient's convergence ability is one set of clinical tools utilized in the assessment of deviation control. Overall, there are 5 convergence mechanisms that are known to support the control of exodeviations. These include voluntary, fusional, accommodative, proximal, and tonic convergence (Maddox, 1893; von Noorden & Campos 2002; Worth, 1929; Wright, 2003). Voluntary convergence is the measurement of volitional convergence. It is elicited without an external stimulus (von Noorden & Campos, 2002). Fusional convergence is

stimulated by disparate retinal images reaching both eyes, and is used to align the images reaching corresponding retinal points on each retina (Wright, 2003). It can be suspended through the occlusion of an eye (Burian & Franeschetti, 1970; Kushner, 1983; Wright, 2003). Fusional convergence can be measured using horizontal prisms, increasing the strength of the prism until the patient is no longer able to converge their eyes while maintaining a clear object of regard (Wright, 2003). Tonic convergence speaks to the amount of tonus in both medial rectus muscles that acts to counterbalance the natural tendency for the eyes to drift outward (von Noorden & Campos, 2002). It is not routinely measured in the clinical setting. Finally, accommodative convergence is the amount of convergence elicited for a given amount of accommodation, as previously stated (von Noorden & Campos, 2002). Clinically, this type of convergence is represented as a ratio of accommodative convergence in pd to accommodation in diopters, also called the AC/A ratio. However, the measurement of binocular visual acuity (BVA), to be discussed later, also relies on accommodative convergence (von Noorden & Campos, 2002; Walsh et al, 2000; Wright, 2003). There have been many different methods described for the assessment of the AC/A ratio (Kushner, 1999; von Noorden & Campos, 2002).

The four procedures for calculating AC/A ratio based on clinical outcomes are the gradient method, heterophoria method, fixation disparity method, and haploscopic method. The gradient method is widely used clinically, and relies on lenses to manipulate the amount of accommodation that is stimulated. This method can be accomplished using convex or concave lenses (Wright, 2003). Normal values fall between 3 and 5 (von Noorden & Campos, 2002). The heterophoria method relies on changes in fixation distance to manipulate the amount of accommodation that is evoked (von Noorden & Campos, 2002; Wright, 2003). This calculation also considers a patient's interpupillary distance, with normative values equalling one half of the

patient's pupillary distance (von Noorden & Campos, 2002; Wright, 2003). The fixation disparity and haploscopic methods have been described, but are not used routinely in clinic because they rely on variable procedures or lab-controlled environments (von Noorden & Campos, 2002; Wright, 2003).

An additional clinical test for detecting the use of accommodative convergence to control a deviation is examining binocular visual acuity (BVA) (Walsh et al., 2000). As a patient reads across and down a distance Snellen chart with both eyes open, the examiner may observe an eye deviate as the patient attempts to read smaller optotypes. As the patient continues reading using accommodative control to maintain alignment, they will need to reduce their accommodation to clear the smaller image (Walsh et al., 2000). The patient subsequently loses the co-occurring convergence activity, allowing an eye to diverge (Walsh et al., 2000). A patient who uses accommodative convergence to control their deviation will have a worse binocular visual acuity than someone who does not (Walsh et al., 2000). In cases where accommodative convergence is not used to control the deviation, the patient will often read as far down as their best monocular visual acuity, without losing their alignment (Walsh et al, 2000).

In contrast to accommodative convergence, fusional convergence is the conjugate movement of both eyes to maintain corresponding images on fellow retinal points (von Noorden & Campos, 2002). Clinically we can evaluate this as a function of motor fusion, vergences, or amplitudes. In testing horizontal vergences, a horizontal prism is placed over one eye to displace the image falling on the retina of that eye. In convergence amplitudes, the eye with the base-out prism over it will have to deviate inwards in order to fuse images reaching corresponding elements of each retina. Normal convergence amplitudes vary depending on the theorist and fixation distance. At near, a convergence amplitude less than 20 pd would be considered low,

and at distance, less than 12 pd would be considered reduced (Parks, 1976). A patient with reduced motor fusion may be more symptomatic or become manifest more often, as they have less convergence amplitudes in reserve to maintain their alignment (Wright, 2003). The point where the patient is no longer able to maintain a clear, single image is called the blur point (Wright, 2003). This is differentiated from the break point, where the patient is no longer able to fuse the images and becomes diplopic (Wright, 2003). The strength of prism at which the patient is able to regain fusion is called the recovery point (Wright, 2003). The convergence amplitudes of patients with controlled deviations, such as intermittent exotropia or exophoria are often monitored, as convergence fusional reserves can be reduced from normal values. The idea being that while a patient is controlling a deviation using convergence amplitudes, there is less convergence in reserve for the patient. For example: A patient with an exophoria of 25 pd and base out amplitude break point of 15 would therefore have a total convergence ability of 40 pd. Most of that convergence ability, 25 pd, is no longer in reserve, but is actively used to control the exodeviation.

When fusion is not maintained, there is less stimulus to keep the two eyes aligned (von Noorden & Campos, 2002). When the visual acuity is reduced in one or both eyes, there is less incentive to maintain control, thus the eye(s) may drift (Kushner, 2008). A patient with a central suppression scotoma, or reduced fusional or stereoscopic perception, may experience decreased control, because these binocular functions indicate how well the two eyes work together (Superstein et al., 2017). Microtropia or monofixation syndrome following surgery has been reported in the literature (Baker & Davies, 1979; Kushner, 2009). It is characterized by a small central suppression scotoma and reduced stereoacuity. Kushner (2009) stated that the presence of monofixation post-operatively is likely due to the presence of monofixation pre-operatively.

"Monofixational exotropia" manifests a small angle deviation, and should be considered as a unique clinical entity according to Kushner (2009).

Deviation size is another important factor to consider when attempting to establish how symptomatic a patient may be, and to determine the impact of the deviation on binocular function (Santiago et al., 1999; Superstein et al., 2017). The larger a deviation, the more effort that individual has to make in order to keep their eyes aligned. Measurements achieved using +3.00D lenses at 0.33m, or using a targets further than 6m away, have been shown to reveal the largest angle in the exodeviation population (Algee et al., 2019; Kushner 1988; Kushner, 1998). A deviation size larger than fusion range is considered to have surgical relevance (Wright, 2003). Multiple methods have been described for measurement of the largest strabismic angle, but there is a lack of replicated, conclusive evidence suggesting which method is most effective (Kushner 1998a, Algee et al., 2019).

1.7 Treatment of Exodeviation

The natural history of surgically untreated IXT remains obscure. The limited knowledge on this topic has been gained primarily through retrospective studies. Early evidence on the progressive nature of this disorder was reported by von Noorden & Campos (2002,). In his research, Fifty-one untreated IXT patients, ranging in age from 5 to 10 years, were followed for an average of 3.5 years. Progression of the exodeviation occurred in 75% of the study population, no change in 9%, and 16% elicited some improvement in control. Despite his earlier findings, von Noorden does emphasizes that all exodeviations are not progressive in nature. A more recent study by Romanchuk KG, Dotchin SA, and Zurevinsky J (2006), reported that the majority (58%) of untreated IXT cases remain stable, 23% had more than a 10 pd increase in the angle, and 19% had a reduction in the size of the exodeviation. This study was a retrospective

chart review on 109 untreated IXT patients with a minimum of a five year follow up. The inconsistencies in the reported stability of this disorder result in further lack of clarity on the timing of intervention.

Many treatment modalities exist for the management of exodeviations. The appropriate therapeutic plan for each individual patient is based heavily on their symptoms, clinical presentation, and whether or not control of the deviation deteriorates. (Santiago et al., 1999; Wright, 2003). Depending on symptomatology and the size of the deviation, surgical intervention may be the suggested course of management (Rosenbaum & Stathacopoulos, 1992; Santiago et al., 1999; Wright, 2003).

1.8 Surgical Correction of Exodeviation

Strabismus surgeons have been encouraged to plan surgery according to their patient's largest measured angle of deviation (Burian & Franceschetti, 1970; Kushner, 1998b; Wright, 2003). Kushner suggested that successful surgeries for exodeviations target the largest measured angle of deviation. The most accurate clinical test for determining the largest deviation in these patients is debatable (Algee et al.,2019; Kim & Hwang, 2005; Kushner, 1998).

There are a number of different surgical procedures that a surgeon may choose in the treatment of exodeviation. Burian & Spivey (1964) recommended different procedures based on the near /distance disparity. A Basic type of Exotropia was suggested to be treated with a unilateral recess/resect procedure. A similar surgical approach was also recommended by Kushner (1998b). Surgeons may opt to perform surgery on one eye, or both eyes . They may choose to alter 1, 2, 3 or 4 horizontal extra-ocular muscles. This decision is made depending on a number of factors including, but not limited to: the size of the deviation, the presence of amblyopia or an ocular fixation preference, as well as whether or not there is an associated

pattern characterizing the strabismus (AAO, 2012; Wright, Ning & Strube, 2015). While surgeons vary in the surgical procedure they will use to target an angle of exodeviation, the degree of surgical correction is also inconsistent in the literature. (AAO, 2012). It is standard for surgeons to tailor their surgical dosages based on experience. Surgeons may choose to augment or titrate the amount of surgery that is recommended by the American Academy of Ophthalmology (AAO), with the intention of arriving at a better surgical result (AAO, 2012). The AAO is not the only source of surgical doses for surgical exodeviation correction, and other tables are available to practicing strabismus surgeons (Wright et al., 2015). In an attempt to reduce the re-operative rate, some authors have suggested augmentation of the original surgical doses (Lee, Kim, & Thacker, 2007; Yuksel, Spiritus & Vandekannoitte, 1998). The majority of the patients in these studies had been classified as basic type exodeviation. Kim, Yang and Hwang (2017), in a more recent study, did a comparison analysis of the surgical outcomes of patients whose surgical plan was based on the "original" dosage tables versus the augmented dosage tables. The augmentation surgical dose was defined an additional 1.0-1.5mm of bilateral lateral rectus recession. Patients in the "original" group had a reported recurrence rate of 49%, compared to a 37% recurrence in the augmented group.

Variable post-operative outcomes have been associated with IXT (Ekdawi et al., 2008; Gezer, Sezen, Nasri & Gozum, N, 2004; Yang et al., 2016; Zou, Casafina, Whiteman & Jain, 2017). This may be due to individual differences in accommodative, refractive, or binocularity outcomes (Ekdawi et al., 2008; Gezer et al., 2004; Yang et al., 2016; Zou et al., 2017). It is possible that several clinical factors could be contributory to unsuccessful surgical outcomes and post-operative drift towards a patient's initial angle of deviation. Some examples of these variables include past refractive or amblyopia management, age at the time of surgery, the

surgical procedure performed, binocularity, visual acuity, or control of the deviation (Ekdawi et al., 2008; Gezer et al., 2004; Yang et al., 2016; Zou et al., 2017).

There is a lack of standardization for defining successful surgical outcomes in this population. A good surgical candidate is one who experiences adverse signs or symptoms associated with their diagnosis, such as reduced control, decreased stereopsis, headaches, asthenopia or light sensitivity (Rosenbaum & Stathacopoulos, 1992). Retrospective studies have used post-operative alignment to quantitate surgical success rates (Ekdawi et al., 2008; Yang et al., 2016; Zou et al., 2017). The surgical management of patients with an exodeviation has been associated with high recurrence and subsequent reoperation rates, which is expensive and may have negative implications for younger patients (Ekdawi et al., 2008; Satterfield, 1993). This includes career limitations and poorer psychosocial outcomes in children with strabismus (Chua, 2004; Satterfield, 1993). There is a pressing need to investigate the outcomes of these patients prior to, and following surgery (Holmes, Hatt & Leske, 2014). Ideally, this information will be valuable in determining prognosis, and surgical planning, for future patients diagnosed with an exodeviation.

As previously stated, there are many surgical procedures that a surgeon may employ in the treatment of an exodeviation (AAO, 2012; Wright et al., 2015). The two most common procedures for the treatment of exotropia are bilateral lateral rectus recessions, or the recession of the lateral rectus and the resection of the medial rectus (R&R) in one eye. In a R&R procedure, the eye that deviates most frequently is usually the eye that is operated on (AAO, 2012). Kushner (1988) made recommendations on surgical procedure based upon the Duane's classification type of the exodeviation. Kushner (1988) suggested that a patient with simulated divergence excess type exodeviation would respond equally as well to a R&R procedure as they

would a bilateral lateral rectus recession procedure. He also proposed that basic type exodeviations responded better to R&R procedures than bilateral ones (Kushner, 1988). Other surgeons have suggested the use of bilateral lateral rectus recession technique for a true divergence excess deviation (AAO, 2012; Wright et al., 2015). According to the AAO (Table 2) surgical dosages provided for bilateral lateral rectus recession create small to moderate overcorrection in the early post-op stages (AAO, 2012).

It is common for surgeons to perform transpositions to collapse pattern strabismus, inferior oblique weakening procedures to address severe oblique dysfunction, and slants minimize near distance disparities (AAO, 2012; Wright et al., 2015). In a transposition procedure, horizontal muscles are reattached at a predetermined location either upward or downward depending on the pattern of strabismus being corrected (AAO, 2012). In slant procedures, the insertion of the muscle is attached on a vertical slant (AAO, 2012). The American Academy includes tables of proposed surgical procedures, including the amount of millimeters a muscle should be moved, according the size of the deviation (AAO, 2012). These tables were distributed by the authors of the text, who also practice strabismus surgery.

Exodeviation Size (pd)	LR Recess
Approximately 15 pd	7-8mm

Table 1. AAO Surgical Table for Single Muscle Surgery (AAO, 2012)

Exodeviation Size (pd)	LR Recess OU	**OR**	MR Resect OU
15 diopters	4		3
20 diopters	5		4
25 diopters	6		5
30 diopters	7		6
40 diopters	8		6

Table 2. AAO Surgical Table for Symmetrical Two Muscle Surgery (AAO, 2012)

Exodeviation Size (pd)	LR Recession	**AND**	MR Resection
15 diopters	4		3
20 diopters	5		4
25 diopters	6		5
30 diopters	7		6
40 diopters	8		6
50 diopters	9		7
60 diopters	10		8
70 diopters	10		9
80 diopters	10		10

Table 3. AAO Surgical Table for Asymmetrical Two Muscle Surgery (AAO, 2012)

Exodeviation Size (pd)	LR Recess OU	AND	MR Resect
50-75 diopters	7-7.5		9-9.5
75 diopters	8 + mm		4

Table 4. AAO Surgical Table for Three Muscle Surgery (AAO, 2012)

1.9 Non-Surgical Treatment Methods

Symptom severity and the degree of control over an intermittent deviation are important factors to consider when determining the appropriate management for individuals with exodeviations (PEDIG, 2016; Wright, 2003). A patient whose deviating eye often becomes manifest may be more inclined to require strabismus surgery than a patient who is mostly orthotropic (Kushner, 1998b). Aside from surgery, other treatment options include the use of base in prisms, convergence and fusion exercises, and antisuppression therapy (Cassin, 1995).

It is important to consider a patient's refractive error during the treatment of strabismus (Hatt & Gnanaraj, 2013; PEDIG, 2016; Rowe, Noonan & DeBell, 2007). If the patient requires lenses to improve their visual acuity, or to treat amblyopia, refractive correction is the first step of treatment (PEDIG, 2016; Wright, 2003). Patients with amblyopia may require further treatment to improve the vision in their amblyopic eye, such as occlusion therapy or pharmacological penalization (PEDIG, 2016). In certain cases, the correction of myopic refractive error can also improve the alignment in patients with exodeviations. Myopic correction is beneficial because of the stimulation of accommodative convergence mechanisms (PEDIG, 2016; Rowe et al., 2007). Overminus lens therapy is one treatment option for patients with controllable exodeviation. This involves prescribing additional myopic corrective power, or in the case of prescribing a hyperopic patient, less than their total plus prescription, determined by

cycloplegic refraction (PEDIG, 2016; Rowe et al). The amount of accommodation required to see clearly through the lens increases, with subsequent convergence of the eyes. A patient with exodeviation may then have better alignment of the eyes. The deviation should measure smaller in size when the overminus lenses are in place due to the accommodative convergence of the eyes (Rowe et al., 2007).

Refractive correction of controlled exodeviation with over-minus lenses may not always be the best treatment option (Wright, 2003). Some patients with controlled exodeviation require the prescription of their full hyperopic correction to improve their visual acuity and potential symptoms of asthenopia (Chung, Kim & Lee, 2010). With full correction, the patient should perceive clearer images in both eyes, and may be more motivated to use their two eyes together (Chung, Kim & Lee, 2010). A clinical standard for the refractive correction of intermittent exotropia prior to strabismus surgery has not yet been established, as there is no empirical data suggesting that such a change would have an effect on ocular alignment, and subsequently, post-operative outcomes (Algee et al., 2019). The surgical outcomes of under-corrected refractive error have not yet been empirically documented, and may or may not be associated with recurrence of exodeviation. This highlights the importance to compare refractive error with refractive correction of patients undergoing strabismus surgery for exodeviations.

A final method of management for exodeviation is observation. Typically, patients undergoing observation management are either asymptomatic or decline other methods of treatment (PEDIG, 2016; Wright, 2003). The outcomes of a lack of treatment, or observational management may be considered through the study of the natural history exodeviation. A study by Romanchuk et al. (2006) published the natural history of untreated patients with intermittent exotropia. They reported a mean of 6/12 visual acuity in the amblyopic eye, and 88 seconds of

arc among patients aged 5-25 years. While visual acuity and stereopsis scores were "good" according to the authors, long term stability of the distance deviation was variable (Romanchuk et al., 2006). A study by Mohney, Cotter, Chandler, Holmes, Wallace, Yamada & Wu (2019) complimented the findings of Romanchuk et al. (2006), describing stable measures of stereopsis, control and angle of deviation after three years of follow-up on untreated intermittent exodeviation.

The tendency for surgically corrected exodeviations to recur has been established throughout the literature (Ekdawi et al., 2008; Gezer et al., 2004; Yang et al., 2016; Zou et al., 2017). Surgically corrected patients with exodeviations have a tendency to show a regression towards their preoperative deviation of angle (Ekdawi et al., 2008; Gezer et al., 2004; Yang et al., 2016; Zou et al., 2017). Successful long term outcomes for exodeviations have been shown to follow surgery for the largest deviation measured preoperatively, leaving the patient slightly overcorrected immediately post-operation (Kushner, 1998; Oh & Hwang, 2009). Measures of surgical success in the exodeviation population vary from +/- 10 pd of orthotropia. For the purposes of this study, regression or a lack of surgical success was considered an angle of deviation greater than 10 pd from orthotropia, or the need for re-operation (Gezer et al., 2004; Zou et al, 2017).

2.0 Chapter 2 Literature Review

The outcomes of exodeviation surgery have been addressed by various researchers. Previous studies have been particularly interested in clinical variables determined peri-operatively and their relationship with surgical success, as well the prevalence of successful surgical outcomes (Baker, 2008; Gezer et al., 2004; Yang et al., 2016; Zou et al., 2017). Surgical success for exodeviation is reported as being variable, with minimal consistency between studies that consider clinical outcomes that correlate with successful surgical results (Gezer et al., 2004; Oh & Hwang, 2005; Yang et al., 2016; Zou et al., 2017). Success of exodeviation surgery in the literature has ranged from 39.4% and 78 % (Gezer et al., 2004; Yang et al., 2016; Zou et al., 2017).

Zou et al. (2017), retrospectively reviewed the charts of 82 British patients that underwent uni-ocular recess-resect surgery for exodeviation. The objective of the study by Zou et al. (2017) was to identify preoperative factors that correlate with surgical success for IXT. This study used a univariate binomial regression to report odds ratios of preoperative variables for successful surgical outcome within a predictive model. Success of surgery was defined within the range of less than 10 pd of exotropia, or 5 pd of esotropia. In a repeated analysis success was also defined as within 10 diopters of exotropia or esotropia. Using the latter criteria, Zou et al, (2017) found an overall surgical success rate of 58.5% in patients followed for a minimum of 3 months post-operatively. Of the clinical variables under study, a smaller preoperative angle of deviation at near or distance correlated with success. In 60 of these patients, higher myopia also correlated with success. Age at surgery, stereopsis, motor fusion, visual acuity and Duane's classification type revealed statistically insignificant relationships with surgical success. The authors also presented statistically significant odds ratios for 3 variables: preoperative deviation

at near (0.33m), distance (6m) and amount of myopia. Patients with smaller deviation sizes preoperatively were 4 times more likely to have successful surgeries, according to statistically significant odds ratios.

An initial limitation of the study by Zou et al. (2017) is that only patients diagnosed with IXT were considered. This limits the generalizability of the findings, excluding other control grades of exodeviations, such as exotropia and exophoria. Moreover, the predictive model used to determine the effect of multiple variables on the success of surgery may limit the applicability of the study. A binomial logistic regression using multiple independent variables within one equation could have been used to determine which variables significantly contribute to a successful outcome (Stoltzfus, 2011). Zou (2017) instead developed a model using a multivariate logistic regression. A multivariate logistic regression is the appropriate model to apply when there are more than 2 possible outcomes of the dependent variable (Clarke, Dunn & Mickey, 1987). In the Zou (2017) study, the only two outcome variables were success or lack of success after surgical intervention. The authors also did not consider pseudo-divergence excess type intermittent exotropia, a common subcategory of exodeviation throughout pediatric ophthalmology practices (Wright, 2003). It is not known if these patients were incorrectly categorized as another subcategory, or left out of this analysis. Further, Zou et al. (2017) only considered patients who underwent unilateral recess-resect surgery, but included 10 patients with true divergence excess type intermittent exotropia. A common procedure recommended for patients within this subcategory of exodeviation is a bilateral procedure, affecting the lateral rectus muscles in both eyes (AAO, 2012). The findings by Zou et al. (2017) may be limited to the outcomes of patients who undergo the same recess-resect surgical procedures. The authors did not discuss their decision to include true divergence excess type patients, but not pseudo-

divergence excess type patients undergoing monocular procedures. Therefore, the clinical relevance of these outcomes may be limited.

One main finding of the study by Zou et al. (2017) was that higher levels of myopic refractive error is predictive towards successful surgical outcome (OR = 0.75, $p = 0.005$), where 95% confidence intervals were not reported. The methodology of this study explained that refractive errors were determined by subjective retinoscopy, or cycloplegic refraction "where possible". The author's stated all patients were taken out of their over-minus lens therapy prior to pre-operative measurements and surgery, however it is challenging to know how many of these patients' true myopic refractive error was known without cycloplegic refractions on all patients. There is a tendency for young individuals with accommodative reserves to prefer more minus power on subjective refraction (Cassin, 1995). Therefore, the average strength of myopic refractive error in this study is confounded by inaccurate refraction techniques, calling in to question the potential clinical applications of these results.

Although patients had to be seen at least 3 months post-operatively, the researchers do not report the maximum length of time that patients were followed (Zou et al., 2017). For example, if patient records were only considered up to one year following surgery, the findings of this study cannot necessarily be related to long-term outcomes. Conversely, if patients were followed for a significant length of time after operation, some descriptive analysis describing that period could be useful for the interpretation of the statistical outcomes.

Deeper consideration to the statistics applied in the study by Zou reveal some inaccuracies. The statistical significance of any variable within a regression model can change depending upon the number and nature of the other variables contributing to the model (Clarke et al., 1987). The validity of the study by Zou et al. (2017) would have been strengthened if the

authors had reported which variables were non-significant . The variables contributing to any regression model include all of the independent variables involved in the analysis. Regression models will not always incorporate all relevant information, depending on the need to achieve statistical significance in one or more predictor variables (Stoltzfus, 2011).

Strengths of the study by Zou et al (2017) include a specific population of interest, clearly defined statistical methods, and clear inclusion and exclusion criteria. Despite the fact that regression analyses usually require more than 84 subjects to achieve significance, the authors describe compelling findings, which have been shown in part by earlier researchers (Clarke et al., 1987; Gezer et al., 2004).

In 2004, Gezer et al., investigated to determine the factors associated with favourable and less favourable outcomes in strabismus surgery for the treatment of exotropia. The case files of 225 patients from a Turkish hospital were retrospectively reviewed. Of this data set, 40% of subjects had intermittent exotropia, and 60% had manifest exotropia. Clinical variables assessed included age of onset, patient age at surgery, interval between surgery and onset, preoperative deviation, refractive error, control of deviation, degree of anisometropia, visual acuity, presence of amblyopia, presence of a pattern, amount of surgery performed, classification of exotropia, and presence of binocular single vision preoperatively. The outcome indicated 49% of patients had a successful surgical outcome after the first surgery, and 55% had a successful outcome following 2 surgeries. Success was defined as alignment within 10 pd of orthotropia in either direction. This study found preoperative deviation and refractive error to be the only significant variables associated with surgical success. No other variables reached significance.

Patients included in the study by Gezer et al. (2004) had undergone treatment over a span of 23 years. Between the years of 1975 to 1998. However, the authors failed to disclose how

variables such as clinician experience, surgical precision and approach, and pre-operative management could vary widely within such a significant period of time. Additionally, the authors' reference two separate dependent variables within the study; response to surgery and surgical outcome. Surgical outcome was defined as successful if the most recent deviation was within 10 pd of orthotropia. Response to surgery was described as change in deviation divided by the amount of surgery performed. While surgical outcome is a categorical or binary outcome, response to surgery is a scale variable. It was unclear which dependent variable was analyzed within which statistical analyses. These analyses were also not linked to clearly defined hypothesis. This made it challenging to establish what analysis was implied by each result presented. The authors used a binary outcome variable within a linear regression model, which may not have been the appropriate test for all analyses. A binary logistic regression may have been more appropriate for any success analyses, due to the categorical nature of the dependent variable (Clarke et al., 1987). However, if a scale variable such as surgical response in pd was being analyzed as the dependent variable, a linear regression would be adequate. It is unclear when and how each test was applied (Clarke et al., 1987).

This study by Gezer at al. (2004) has a large sample size, including the charts from 225 patients. The authors excluded patients with reoperations in order to maintain the homogeneity of the sample, and included patients who had been followed postoperatively, between 1 and 15 years. The authors also provide statistics on reoperation incidences, in addition to independent variable outcomes. This provides a more comprehensive set of results for clinicians. The findings of the study by Gezer et al. (2004) were contrasted the findings of Zou et al., (2017), which was published 13 years later. Gezer et al. (2004) found that greater myopic refractive error was associated with less favourable surgical outcomes, but Zou et al. (2017) found more myopic

refractive error to be more associated with success. However, the methodology for the determination of refractive error in the study by Gezer et al. (2004) was far more consistent. The contrast in these findings regarding the role of myopic refractive error on surgical outcomes suggests a need for further research.

Using a much larger sample size of 1228 patients, Yang et al. (2016) assessed the clinical characteristics and surgical outcomes of patients with intermittent exotropia in south China. The researchers also performed an analysis of risk factors associated with surgical failure. The authors did not identify a main hypothesis associated with their research, but followed an alternative approach to define success outcomes by adding binocular sensory status as a measure of assessing surgical outcome. In order to be considered a surgical success, patients had to have a post-operative alignment less than 8 pd of exotropia, or 6 pd of esotropia. Patients were also required to have normal stereopsis scores, which the researchers defined as 60 seconds of arc or less using "random dot stereograms" or "Titmus stereograms" (Yang et al., 2016). The criteria for success had to be met at a 6 month follow up assessment or later. The researchers found a 35.6% success rate when the criteria included both sensory and motor stipulations. However, when classifying surgical successes based on motor outcomes alone, they found a success rate of 80.5%. The only variable associated with poor outcome in the multivariate risk analysis performed by this research group was loss of stereoacuity pre-operatively.

The study by Yang et al. (2016) complimented the finding of previous researchers (Jang, Park & Lee, 2012; Yang, Man, Tian, Zhou, Kong, Meng, Gao & Ning, 2014), by suggesting that surgical success should include an index of binocularity post-operatively. The use of random dot stereograms and the Titmus stereopsis test interchangeably challenges the test re-test reliability of this study. Furthermore, it is possible that patients would find one test more simple than the

other. For example, the Titmus test has been criticized for the provision of monocular clues to correct answers, enabling patients to achieve a falsely high score of stereopsis (Cooper & Warshowsky, 1977; Hahn, Comstock, Durling, MacCarron, Mulla, James & La Roche, 2010). Further, the researchers failed to describe how they determined a stereopsis score of 60 seconds of arc to be normal. Nor did they outline how they might account for differences in a stereopsis score of 60 on a randot test versus the Titmus test, depending on which randot test was used. Yang et al. (2016) used a narrow range of post-operative deviation to determine success. While the patients were closer to orthotropia, the advantages of this new criteria for success are limited. First, it is more difficult to compare the findings of other studies to those of this study, as the outcome measure was different. Secondly, despite the fact that successful patients in this study were closer to orthotropia using the 8 pd exo to 6 pd eso range, compared to the traditional 10 and 10 pd range of exotropia to esotropia, this criteria may be of limited clinical relevance. The criteria by Yang et al. (2016) still falls within normal fusion range, leaving the potential for a post-operative microtropia in successful outcomes (Kushner, 2009).

The long-term surgical success rate in IXT patients was investigated by Pineles, Ela-Dalma, Zansky and Rosenbaum (2010) over a 28 year period. Only patients with a minimum of a 10 year follow up were included for data analysis. One hundred and ninety seven patients met their inclusion criteria. Fifty of those returning for a follow up motor and sensory assessment. In this investigation, the fusional status was analysed and reported separately to define surgical success. The authors concluded that an "excellent" motor status was achieved in the majority (64%) of this population. The authors did acknowledge that over the 10 year time frame, 60% of patients did require at least one re-operation. Twenty four (80%) of the re-operations was for a residual IXT.

Ekdawi et al. (2008) had previously used a score of 60 seconds of arc in the analysis of successful surgical outcomes. Their study focused on a risk analysis for subsequent re-operations after initial treatment for intermittent exotropia. However, they did not use the stereopsis score as a criteria for success. Instead, they showed that 45% of patients had a score of better than 60 seconds of arc after their initial surgery, where 55% had been shown to be within 9 pd of orthotropia. The results of this study showed that the Kaplan-Meier rate of developing a misalignment greater than or equal to 10 pd was 54% within the first 5 years of follow up, 76% by 10 years of follow up, and 86% by 15 years of follow up. The purpose of this study was more focused on determining risk for reoperation than providing a detailed description of surgical success rates and associated clinical variables. The findings by Ekdawi et al. (2008) suggest that the success of initial surgery for exodeviation is limited, considering the majority of patients required re-operation within 15 years of treatment.

A survival analysis performed by Oh and Hwang (2005) in Korea reviewed 350 patients to determine what factors might affect the outcomes of exotropia. The authors considered peri-operative patient characteristics including refractive error, angle of deviation and stereopsis, in addition to surgical procedure performed and early post-operative alignment as potential risk factors. The researchers determined that the estimated median time from surgery to recurrence was 48.3 months in the patients who underwent surgical treatment for their deviation. The mean time to recurrence was not reported, which may be due to extreme outliers within the dataset. Early postoperative overcorrection was the only predictor of a successful long-term outcome after surgery to correct exotropia, where the median recurrence time was reported to be 48.3 months. “Early” post-operative overcorrection was defined in this study as being greater than 5 pd of esotropia or esophoria. These findings suggest that surgeons should aim to slightly

overcorrect their patients being treated for exotropia, in order to achieve favourable long-term outcomes.

This retrospective study by Oh and Hwang (2005) included patients who were managed by one primary surgeon over a 5 year period. The authors clearly define their management and assessment techniques, and describe their results in a clear and accessible manner. The authors' contribution to the literature reinforces the predetermined notion that the response to exotropia surgery is variable, and predicting how an individual will respond based on pre-operative patient characteristics will be challenging. In conclusion, they determine a post-operative characteristic of small over-correction to be the only variable associated with success.

Eighty percent of the subjects in the study by Oh & Hwang (2005) was composed of basic type subcategorized patients, according to Duane's classification system. This suggests that the other subcategories may not be as accurately represented by the findings of this study. A study by Bae, Lee, Rhiu, Lee, Choi, Paik & Choi (2018) described a significant post-operative shift towards basic type subcategorization in an analysis of Duane's classification comparing both pre- and post-operative classifications. That is, 96.2% of pre-operative basic type deviations maintained their subtype post-operatively. However, only 18.2% and 11.1% of pseudo-divergence excess and convergence insufficiency type deviations respectively, maintained their classification post-operatively. This trend was significant at each of the 1 month, 3 month and 6 months follow up assessments following surgical treatment for intermittent exotropia.

Superstein et al. (2017) proposed to determine the relationship between stereoacuity, control of exotropia and angle of deviation in children with intermittent exotropia. The authors suggested that if strong relationships could be shown to exist, certain variables may be used as surrogates for each other. This large scale sub-study assessed the outcomes of 652 patients being

prospectively evaluated. Poorer control of a deviation was weakly associated with poorer distance stereoacuity and larger angle of deviation at distance. Also, worsened near stereoacuity was weakly associated with worsened near angle of deviation. Deviation angle and distance stereopsis were not associated with each other. The authors concluded that the results remain unclear and that the diagnosis, management and pathogenesis remain ambiguous. They suggest analyzing these variables independently as researchers continue to study and manage intermittent exotropia.

The study by Superstein et al., (2017) included a very large sample size of 652 participants on a single measure of stereopsis at near or at distance, across multiple North American centres. This was a particular strength because many retrospective studies do not have the luxury of analyzing stereopsis scores from just a single test. While there are many available tests of stereopsis, which differ in the type of stereoacuity being tested, the use of a variety of tests can be a challenging confounder to control for. Superstein et al., (2017) was a sub-study from a larger Pediatric Eye Disease Investigator Group (PEDIG) study, where stereopsis testing was controlled (Donahue et al., 2019). Although many clinicians performed these assessments, all were trained specifically for PEDIG associated clinical testing (Donahue et al., 2019). Unfortunately this study performed more statistical analyses than were described within the purpose or hypotheses sections. This methodology subjects the findings of Superstein et al. (2017) to the risk of a type I error, or chance of rejecting the null hypothesis when the null hypothesis is true. The authors did adjust their p value to <0.01, however, the article is challenging to interpret where most of the clinically significant results did not have associated hypotheses or background information.

The clinical applications of the study by Superstein et al., (2017) were in contrast to the two previously discussed studies. Instead of analyzing predictors of success, this study tried to increase the efficiency of future studies, by suggesting that certain variables could stand in place of each other if strong correlation values were found. This could potentially increase the flexibility of clinical data during the analysis of variables related to the control of exodeviations. This is of particular usefulness because there are many assessments for control of an exodeviation, many of which are not performed pre-operatively due to time constraints. In instances of retrospective analysis where all outcomes of control are analyzed, certain variables acting as surrogates for one another could prevent methodological concerns such as missing data. However, the outcomes of the study by Superstein et al., (2017) suggest there is an ongoing need to collect data for each control variable, independently.

Kushner (1998) suggested that the surgical management of patients with exotropia should target the largest deviation measured in order to achieve the best surgical outcome. His study of 166 patients revealed that a measurement determined after one hour of monocular occlusion produced the largest angle pre-operatively. Eighty-two percent of the patients whose deviations increased after prolonged monocular occlusion had successful surgical outcomes, between 10 pd of exodeviation and 5 pd of esodeviation. This is compared to a 62.5% success rate in the control group, whose surgery was planned according to the deviation measured using a 6m target. This study was prospectively designed with both randomization and a control group. Although the writing in this publication can make the comprehension of the results challenging, all outcomes of statistical significance were summarized concisely. The Kushner study provides enough detail to ensure replicability of his methodology by future researchers.

Kushner's findings were contrasted by the findings of a study by Algee et al. (accepted for publication 2019) which determined that the largest deviation was revealed by the +3.00D measurement at 0.33 m, or by a measurement taken at greater than 20ft. The measurement at greater than 20ft did not differ significantly from a measurement after prolonged monocular occlusion at greater than 20 ft. The authors acknowledge that these findings do not align with the findings by Kushner's study. The study, again designed prospectively, used experienced clinicians within a controlled environment. The Algee study provides a guide for which pre-operative measurements could be considered by surgeons aiming for successful outcomes, and researchers assessing pre-operative predictors of success.

Overall, the differences in post-operative success and clinical variables associated with surgical outcome reveals a lack of consistency between the studies that were included in this literature review. As it stands, no research of this nature have been performed in Atlantic Canada on a large scale. The study of surgically treated patients diagnosed with exodeviation in Atlantic Canada would benefit both patients and physicians in terms of patient management and education, as well as guiding future prospective analyses.

2.1 Study Objectives and Hypotheses

The disadvantages of an exodeviation are numerous when considering the many advantages of having aligned eyes. Some benefits of binocular single vision are increased job opportunities and reduced likelihood for the development of amblyopia (Hatt et al., 2016). Orthotropic patients with two straight eyes will fixate with both foveae at the same time, exhibiting bifoveal fixation (Hatt, et al., 2016; von Noorden & Campos, 2002). This is the use of two eyes together to promote the simultaneous perception of two incoming images, the fusion of those images as one, and fine stereopsis (von Noorden & Campos, 2002). Bifoveal fixation on

the object of regard does not occur in the presence of manifest strabismus or during the manifest phase of an intermittent deviation. Binocular single vision is a component of some driver's license requirements, and eligibility for certain careers with higher visual demands (Hatt, Leske, Liebermann & Holmes, 2016). Additionally, patients with intermittently controlled exotropia experience a variety of symptoms not limited to eye rubbing, eyes fatigue, problems with their eyes in the sun, diplopia, trouble focusing, asthenopia and headaches (Hatt et al., 2016).

This study seeks to investigate the following research questions. What is the rate of success and failure for patients with exodeviation following surgical treatment? Secondly, is there a relationship between success rate and clinical outcomes measured pre-operatively? Finally, is there an association between the personalization of doses for the surgical correction of exodeviation and success rate of surgery?

The null hypotheses predict that there will be no measurable differences in angle of deviation, stereopsis, refractive error, acuity, and control measures between successful and unsuccessful subjects preoperatively. Also, that the degree of personalization of surgical doses for surgical correction of exodeviations will be independent of surgical outcome.

3.0 Chapter 3 Methodology

3.1 Study Design

This retrospective cohort study was performed between July 2018 to January 2019 in Halifax, Nova Scotia at the Izaak Walton Killam Health Care Centre, Eye Clinic (IWK). Ethical approval was obtained from the Research Ethics Board for the use of ophthalmology and orthoptic reports from pre-operative assessments and most recent follow up assessments following strabismus surgery. An effort to minimize the need to access multiple charts per subject was enforced due to ethical considerations. Adult and child subjects in this study were operated on by an IWK-employed pediatric ophthalmologist for the surgical correction of an exodeviation from October 2011 until August 2018. Follow up examinations were considered until November 2018.

3.2 Rationale for Methods

A retrospective chart review was chosen for the design of this study in order to maximize the eligible number of subjects. Eligible subjects were screened according to the inclusion and exclusion criteria, in an effort to minimize confounding variables within the study. Using a retrospective design, researchers experienced less challenges associated with subject enrollment and attrition. A retrospective clinical study design, also increases the likelihood that enough subjects would be enrolled to adequately power the study. Additionally, this design captures the profiles of patients who have received long term follow up. In a prospective design, many patients are followed for approximately one year post-operatively. Therefore, success in these studies is often determined around the one year follow-up period, regardless of how the patient's alignment changes after the one year mark.

A retrospective chart review may provide rationale for future prospective studies to take place. For example, if a significant number of unsuccessfully treated patients in this study were found to have under-corrected hyperopic refractive error, the retrospective review may offer the rationale for further investigation into this treatment paradigm. This study could potentially provide a foundation of knowledge surrounding the existing patients, at this clinical institution. Information regarding the distribution of exodeviation at the IWK may be an additional benefit of this research. With this knowledge, departmental committees and ethical research boards could have sufficient evidence to justify the need for prospective studies, which potentially could alter existing treatment paradigms.

3.3 Study Population

All patients followed by an IWK pediatric ophthalmologist between the dates of October 2011 and November 2018 were considered in this study. The IWK is located in Halifax, Nova Scotia, Canada and services the provinces of Nova Scotia, New Brunswick, Prince Edward Island, and Newfoundland and Labrador. An administrative assistant to the chief of ophthalmology filed a billing code search for patients diagnosed with various diagnoses pertaining to any exodeviation or consecutive esodeviations, to create a master list of potential subjects. The master list of known patients surgically treated for exodeviation was screened by the principal investigator. Those patients with potential for being included in this study were screened more thoroughly for consistency using the predesigned inclusion and exclusion criteria. Patients were not contacted before being included in the study under the approval of the IWK Research Ethics Board. Adequate measures were taken into place throughout the subject enrollment and data collection phases to ensure patient confidentiality was maintained.

The billing code search revealed 956 patient names coded for the diagnosis of exodeviation, with an additional 964 patients names associated with an esodeviations. Esodeviation codes were then searched in order to capture as many patients with consecutive esodeviations as possible. This secondary coding search was conducted as an additional check to ensure these patients met all of this study's inclusion criteria. Of the originally coded 964 patients, 36 were included in the study. From the group of patients with exodeviations, 132 patients from the list were included following the screening process. Sixteen patients were brought to the attention of the principal investigator directly by orthoptists who had evaluated these patients during a regularly scheduled follow up assessment. Eight of those patients met the inclusion criteria thus were included in this sample. A total of 176 subjects, between the ages of 1-75 years, entered in the study. All included patients were immediately scored for their post-operative status as being either successful (within 10 pd of orthotropia), over-corrected unsuccessful(>10 pd of esodeviation), or undercorrected unsuccessful (>10 pd of exodeviation).

3.4 Predicted Sample Size

For the statistical comparison of successful and unsuccessful groups, a power analysis was performed, with the assistance of the IWK consulting scientist (PhD Health Psychology), using G power statistical calculation software. Following this consultation, this study aimed to recruit a minimum of 130 participant random sample in order to detect a medium effect size, with power = 0.80 and $p = 0.05$. From the master list of eligible patients, sixty-five subjects were randomly sampled from each of the successful and unsuccessful groups for comparison. This was achieved using an online data randomization tool that considers the total n value from each subgroup and the number of subjects to be sampled. Each subject within each group was assigned a numerical value, corresponding to the numbers that could be distributed by the

randomization tool. From the eligible 176 subjects, 130 were selected using the randomization tool, due to ethical concerns associated with excess patient data collection that has no statistical value.

3.5 Inclusion Criteria

To determine patient inclusion or exclusion, patients were assessed individually using medical records for confirmation of diagnosis, history of initial surgery for exodeviation, and surgical outcome at the most recent IWK visit, and cogence with pre-determined inclusion and exclusion criteria. Inclusion criteria required the presence of a pre-operative exodeviation at near or at distance fixation, with a minimum 10 pd deviation at distance in all patients. Basic type, simulated divergence excess, true divergence excess, and convergence insufficiency type exodeviations were included in this research. Basic, simulated divergence excess, true divergence excess, and convergence insufficiency type exodeviations were included. Patients with post-operative diagnoses of consecutive esotropia were also considered in this study, provided that their pre-operative deviation characteristics met the criteria described. Juvenile patients were required to have undergone cycloplegic refraction using 1% cyclopentolate, within 1 year before the operation date. All included patients had normal fundus exams. Although this study welcomed patients of all ages, patients had to have reliable, monocular LogMAR visual acuity recorded prior to their operation.

3.6 Exclusion Criteria

This study excluded those without a pre-operative diagnosis of exodeviation. Any patients with poor cooperation on the day of the pre-operative exam, per the clinician's notes on the chart, were not included. This study excluded the individuals with neurological or mechanical abnormalities, dissociated vertical deviation strabismus, or manifest and/or latent

nystagmus, in order to minimize confounding variables to outcome measures. Subjects who had previous strabismus surgeries for which pre-operative orthoptic assessments could not be accessed through the IWK Meditech system or Iron Mountain chart storage system were also excluded in this research. Study participants were not included if they have had prior refractive, intra-ocular, or orbital surgery.

3.7 Data Collection

All patients meeting the inclusion criteria formed a large sample to determine an overall percentage of surgical success in exodeviations at the IWK. After determining success outcomes, 130 subjects from either the unsuccessful and successful groups were randomly sampled. Patients with over-corrections greater than 10 pd of esodeviation were not included in the random sampling. Further, some patients who were corrected to more than 10 pd of esotropia fall into a unique category of high AC/A ratio. Further, this population did not reach statistical power to warrant inclusion in the random sampling.

During the data collection process, the investigator recorded information pertaining to which surgeon performed the surgery, patient age at surgery, details regarding the nature of the surgical procedure, the outcomes of the pre-operative orthoptic assessments, as well as the post-operative alignment and age at surgery. Outcomes of clinical exams from pre- and post-operative visits were recorded. Pre-operative outcomes were measurements taken no more than one week before the surgical date, and post-operative outcomes were from assessments no less than 8 weeks after the operation date.

3.8 Clinical Measures

3.8.1 Deviation size

Deviation size was recorded according to the outcomes of the alternate prism cover test (APCT), using an accommodative target. In cases of severe amblyopia in the deviating eye, Krimsky or modified Krimsky measurements were considered acceptable (Cassin, 1995). Traditionally the APCT starts with the cover-test, to determine the presence of a tropic deviation (Cassin, 1995). It is followed by a cover-uncover test to reveal a phoric deviation (Cassin, 1995). Finally, the cross cover test is used in conjunction with the prism bars to reveal the total size of the deviation (Cassin, 1995). Increasing strengths of prism are held over the non-fixating eye until neutralization is determined. The expected method for performing the APCT at the IWK is a slow and deliberate cross-cover test to ensure dissociation of the ocular alignment. The examiner should have demonstrated an overcorrection, one prism strength beyond the neutralizing prism, to verify the neutralization point of the deviation (Cassin, 1995). Additionally, patients are encouraged to fixate on the smallest accommodative target they can see. Measurements are either taken once at the pre-operative assessment, by a Canadian Orthoptic Council certified orthoptist, or taken first by a student, and confirmed by the supervising orthoptist. When comparing near and distance angles for classification purposes, a 10 pd difference was considered rather than 15 (Parks, 1975; Duane, 1897; Parks, 1975).

3.8.2 Stereoacuity Testing

Stereoacuity was tested with the Adult Vectographic Projector Slide 9100, Stereo Optical Company Inc., Chicago, IL, at distance (6m), yielding stereoscopic perception scores from nil or 60-240 seconds of arc. The Original Randot Stereotest, or Original Stereo Fly Test (Titmus) Stereo Optical, Chicago IL, USA were used at near (0.40 m). An alternative near test for younger

patients was the Frisby Natural Stereo Test, Clement Clarke Ltd, Harlow, UK, or Lang Stereotest, Lang, Switzerland. The near tests reveal stereoscopic perception ranging between nil and 20-3000 seconds of arc.

3.8.3 Horizontal Fusional Amplitudes

Horizontal motor fusional amplitudes, binocular visual acuity, near point of convergence, AC/A ratio, pupillary status were assessed using standard protocol (Cassin, 1995). Finally, accommodative ability was monitored via dynamic retinoscopy. Due to the retrospective nature of this study, no clinical assessment tools were required by the investigators.

3.8.4 Visual Acuity

Both of the Early Treatment Diabetic Retinopathy Study (ETDRS), and Lea Hyvarinen (LH) Symbols, (using the CSV-1000, Vector Vision, OH, USA) charts were used for the measurement of visual acuity in this study. For the younger patients, either verbal naming of indicated letter or matching shapes to a handheld card during acuity testing was acceptable. The Sloan Letter Near Card ® (Catalog number: 72500), Good-lite Co. Elgin, IL, USA, Precision Vision, IL, USA, or (LH) Symbols near card were used for near visual acuity. Visual acuity was scored according to the logMAR score corresponding to the acuity of each eye.

3.8.5 Refractive Error

Refractive error in this study was determined within one year prior to surgical date and was performed using 1% cyclopentolate. One or 2 drops were administered to both eyes 40 minutes before a refraction, performed by an experienced pediatric ophthalmologist. None of the patients in this study received or required cycloplegic refractions with other agents (e.g. atropine, mydfrin, mydriacyl).

3.8.6 Control Scale

Control of the exodeviation was assessed by the orthoptist, and was rated as either poor, fair, good or excellent. This clinical outcome was then translated to a numerical scale for purposes of data analysis. One denoted a manifest deviation, and a deviation described as having "poor control" was translated to a score of 2. "Fair control" was translated to a score 3. "Good control" denoted a score of 4. A score of 5 denoted a deviation with "excellent control" within the statistical analysis. This control scale was designed to assign categorical values to predetermined control ratings for statistical analysis.

3.9 Surgical Procedure

Surgical procedure was determined by reviewing the post-operative chart for each subject in the study, and confirming the procedure on the chart with the procedure on the operative report from the operating room. Zero subjects in this study showed discrepancies between procedures reported on both reports. The investigator looked at 9 separate variables pertaining to the operation of subjects, listed in Table 5.

Variables were not limited to amount of surgery performed on any of the 4 horizontal recti muscles, total number of muscles operated on, date of the surgery, the surgeon who performed the procedure, or the presence or absence of co-occurring slant or transposition procedures. The type of procedure was noted and categorized according to number. A bilateral lateral rectus procedure was given a value of 1, R&R a 2, and so on (see Table 11). If there were no co-occurring slant or transpositions performed, the subject was assigned a score of 1. A score of 2 would indicate that one or both of those procedures had occurred. Finally, in order to address whether or not a relationship existed between the success of the surgery, and personalization of surgical procedures, the investigator compared surgical values. First, the

amount of surgery performed on each horizontal recti muscle was recorded. An example of a lateral rectus (LRc) recess and medial rectus resect (MRs) procedure for a target angle of 35 pd on the right eye is shown Table 5. A score of 1 underneath the variables of transpositions or slants indicated the absence of these procedures.

Study ID #	Surgeon Number	Date of Surgery	Surgical Procedure	# of muscles operated	LRc 1 (mm)	LRc 2 (mm)	MRs 1 (mm)	MRs 2 (mm)	Target angle per MD	Transp-ositions	Slants
3041	3	Aug 12 2013	2	2	7.5	0	5.5	0	35	1	1

Table 5. Example of Data Entry for 35 Prism Diopter Exodeviation

An additional analysis was performed to indicate by how many millimetres the performed procedure differed from the Academy's recommended amount for a given procedure, and a given target angle. If a surgeon recessed the lateral recti muscles 1 mm more or less than was recommended by the AAO (2012) for the established target angle, a score of +1 or -1 was assigned respectively. A 2 mm difference was scored +/- 2 depending on whether or not the surgeon performed more or less than the recommended amount, and so on. A total of less than 1 mm difference was deemed negligible. If the subject had undergone co-occurring slant or transposition procedures, they were excluded from this analysis. The target angle for a given surgery was determined using the preoperative assessment where possible, or by corresponding performed doses to physician surgical tables shown in Table 6 and 7.

Exodeviation Size (pd)	LR Recession	**AND**	MR Resection
15 diopters	4		3
20 diopters	4		4
25 diopters	6		4.5
30 diopters	6.5		5
35 diopters	7.5		5.5
40 diopters	8		6
50 diopters	9		6
60 diopters	10		6
70 diopters	10		7
80 diopters	12		9

Table 6. IWK Surgical Table (Two of Five Surgeons) Asymmetrical Two Muscle Surgery

Exodeviation Size (pd)	LR Recess OU	**OR**	MR Resect OU
15 diopters	4.5		3
20 diopters	5.5		4
25 diopters	6		4.5
30 diopters	7		5
35 diopters	8		5.5
40 diopters	9		6
50 diopters	10		Not indicated by physician

Table 7. IWK Surgical Table (Two of Five Surgeons) Symmetrical Two Muscle Surgery

3.10 Comparing Performed Procedures with Recommended Procedures

First, each patient's pre-operative clinic report was screened in order to determine the surgical plan, including the target angle of the strabismus surgery to be performed. This value was recorded as the target angle. Then the quantity of surgery performed on each muscle was recorded and compared to the aforementioned target angle on the surgeon's surgical table, if available. A deviation with a target angle of 40 pd, that underwent surgery number/category 2, would theoretically have received 8 mm of lateral rectus recess surgery and 6mm of medial rectus resection surgery according to Table 5. If a target angle was not included in the pre-operative report by the physician, or there was no surgical table available for the surgeon treating the subject, that subject was excluded from the analysis. The cumulative amount of surgery performed over one or both eyes, was then compared to the millimetres of surgery recommended by the AAO (2012). If the surgeon performed greater than a total of 1 mm more or less surgery than what was recommended by the academy, the subject was scored a value of +/-1. If the surgeon performed greater than 2mm more or less than the recommended amount of surgery, the subject received a score of +/- 2, and so on.

3.11 Defining Success

Success was defined in this study as any deviation that did not exceed 10 pd in either direction at near or distance fixation. If a deviation was greater than 10 pd at either near or distance fixation distances for post-op measurements of the deviation, the outcome would be categorized as unsuccessful. This post-operative deviation was taken at the most recent follow up exam at the time of data collection, with a range of 8- 344 weeks post-operatively. This criterion

was chosen to compensate for the variable times of immediate post-operative follow up, ranging from 1 week to 6 months, of patients included in this study.

3.12 Statistical Analysis

The outcomes of 176 patients were analyzed using percentage scores to determine the number of patients who met the criteria for having successful, unsuccessful undercorrected or unsuccessful overcorrected post-operative outcomes. Sixty-five of the subjects were then sampled from either the successful or unsuccessful undercorrected group, for a total of 130 subjects. The 9 patients who were overcorrected more than 10 pd were not included in further analysis, due a lack of statistical power. Descriptive statistics were run on each of the 130 sampled patients, from either of the successful or unsuccessful undercorrected groups. This included mean and measures of central tendency, standard deviation and measures of variance, as well as percentage and ratio outcomes. Non-parametric analyses such as the Fischer's exact test, chi-square test, and binary logistic regression were run for both groups to accommodate the non-normative distribution of the data.

A Fischer's Exact Test analysis was used to evaluate potential relationships between Duane's classification pre-operatively versus post-operatively, across all 130 subjects. This analysis was used for its appropriateness with non-parametric data, and the comparison of categorical variables, where the assumptions of chi-squared analysis had been violated. The Fischer's Exact Test is a test of independence and does not show the direction of an association. The Cramer's V statistic was also considered in order to determine an associated effect size statistic. This statistic is used in lieu of the Phi statistic, when there are more than 2 subtypes within each category of variables. The Phi statistic is the alternative effect size statistic that is chosen when an analysis considers 2 binary, nominal variables.

To compare means of pre-operative variables between patients with successful and unsuccessful surgical outcomes, a factorial logistic regression was performed. This analysis was chosen due to the binary, categorical nature of the outcome variable; success versus lack of success. This study also collected a total of 48 pre-operative variables, composed of both nominal and scale data. The factorial logistic regression reliably considers the relationships of multiple independent variables against the outcome variable when the assumptions of the analysis are not violated, and when the model is neither under- nor overloaded. In order to determine which variables should be run in the final logistic regression analysis, each categorical variable underwent either a chi squared analysis, or Fischer's exact test. The Fischer's exact test would be used in cases where SPSS statistical software indicated that the data distribution violated the assumptions of the chi squared test. An appropriately applied chi-squared test assumed an expected cell count of less than or equal to 20%. Independent variables that were continuous in nature were run individually in a univariate logistic regression for association. In order to prevent overloading the model, only those variables which demonstrated a statistically significant independent correlation with the outcome variable prior to the regression were included in the final analysis.

Finally, descriptive statistics were used to describe the surgical procedures performed, as well as the amount of surgery performed for a given exodeviation size or subtype. The chi square test is a test of independence, which suggests that the two variables are independent from each other when the p value is less than 0.05. It is often used to compare 2 categorical variables, or as in this analysis, a nominal variable with an ordinal variable. The success outcome was the nominal value, and the surgical variability rank was the ordinal variable. The chi-square analysis was used to determine whether success was related to the surgical variability rank. The surgical

variability rank was determined by comparing amount of surgery performed, with the amount of surgery recommended by the AAO for a given deviation size.

3.13 Management and Ethical Considerations

Upon acceptance from the research ethics board, study documents were protected. Password protected software was used for the storage of all data files. Personal names were not recorded in the data collection process. Each patient was assigned a study number, and a password-protected master file associating each study number with a corresponding IWK identification number was documented. The study number was used to represent all clinical findings associated with each patient in the study database. Upon completion of the study and publication of the findings, the database will be destroyed.

Potential harms facing the participants of this study include the risk of someone discovering a patient was used as a subject in the study, who should not know. To prevent this, all data was recorded onto encrypted electronic files that contain only the unique study number assigned to each subject upon enrollment. One master copy linking a subject's hospital health number to their study number was created, and this copy was safely locked on an password protected Universal Serial Bus (USB) device, locked in the office of the principal investigator. Identifying information such health number had to be collected in order to keep track of which subjects had been enrolled in the study. Age was a variable of interest in this study as it has been related to deviation control (Santiago et al., 1999; Wright, 2003). Subject age was included in the collected data despite being a potentially identifying variable. The potential harms to individuals from this retrospective study are otherwise unremarkable.

Potential benefits of this study include contributing to the overall knowledge gained by the scientific community, for a better understanding of the clinical findings and surgical

outcomes of exotropia. The individual benefits of being involved in a retrospective study are limited.

3.14 Expenses

Costs associated with this study were limited to the electronic and labour requirements of this study. The principal investigator performed the study with the assistance of the supervisor, advisory committee and IWK statistician, so there was no need to compensate additional research assistants. There were no participants or treatment paradigms in this retrospective design, so there were no additional associated costs for compensation or treatments. Finally, a computer supporting Excel and SPSS software as well as password protected software had previously been obtained by the principal investigator prior to this study, so there were no further technologic demands requiring financial support.

4.0 CHAPTER 4 RESULTS

A total of 176 patients were enrolled. Of these patients, 91 patients were found to be unsuccessful, with exodeviations of greater than 10 pd at either near or distance at their most recent follow up. Seventy-six patients were within 10 pd of orthotropia, ranging from equal to or less than 10 pd of esodeviation, to equal to or less than 10 pd of exodeviation. These 76 patients were considered to be the successful group. Finally, 9 patients were overcorrected with esodeviations exceeding 10 pd at near or distance post-operatively. Some of these patients required further surgery or alternative treatment, for example, bifocal lenses. Overall, this information suggests a success rate of 43%, a 52% recurrence rate, and a 5% overcorrection rate for the surgical correction of exodeviations. The overcorrected patients were disregarded from further analysis, due to a lack of power in this patient group. Sixty-five randomly sampled patients from both of the success and the recurrence groups made up the final sample of 130 patients, as per the power calculation. Of the 130 randomly selected subjects, 21 subjects had manifest exotropia, 107 patients had intermittent exotropia, and 2 patients had exophoria preoperatively.

4.1 Descriptive Statistics

Descriptive characteristics were analyzed according to outcome groups, where categorization between success and unsuccessful determines what group each subject was analyzed with. Subjects who did not show a post-operative deviation greater than 10 pd, termed successful outcomes, had a mean age of onset of 4 and a half years (Table 8), with a median age of 2 years. However, age at the time of surgery was closer to 15 years (median 8 years). In this group, 9 patients had manifest exotropia, 54 had intermittent exotropia, and 2 had exophoria pre-

operatively. There was an almost equal distribution between sexes, with 34 females and 31 males. The average preoperative deviation was 21 pd at near, and 24 pd at 6m. Visual acuity at near and distance was on average approximately 6/7.5, or 0.1 logMAR in both eyes. There was on average, a 5 optotype interocular difference in visual acuity between eyes at distance. Mean near stereopsis was 146 seconds of arc. Less than a diopter of spherical or cylindrical refractive error was revealed on average in either eye. Post-operatively, there was a mean follow-up period of 84 weeks, and a deviation of 4 pd on average, at both near and distance. Pre-operatively, there were 49 basic type exodeviations, 13 pseudo-divergence excess types, 1 true divergence excess, and 2 convergence insufficiency types in the successful group.

Subjects who did have post-operative exodeviation greater than 10 pd, termed unsuccessful outcomes, had a mean age of onset of almost 6 years (Table 8). Age at the time of surgery was approximately 11 years. In this group, 12 patients had exotropia, 53 patients had intermittent exotropia, and no patients had exophoria pre-operatively. The sex distribution was identical to the successful group, with 34 females and 31 males. The preoperative deviation was 31 pd at near, and 31 pd at 6m. Visual acuity at near and distance was on average approximately 6/7.5, or 0.1 logMAR in both eyes. There was on average almost a 4 optotype interocular difference in visual acuity between eyes at distance. Mean near stereopsis was 215 seconds of arc. Less than a diopter of spherical refractive error was revealed on average in either eye. The right eye had less than 1 diopter of cylindrical refractive error, and the left eye had a mean of almost 1.5 pd of cylindrical refractive error Post-operatively, there was a mean follow-up period of 111 weeks, and an average postoperative deviation of 19 pd at near and 18 pd at distance. Pre-operatively, there were 34 basic type exodeviations, 17 pseudo-divergence excess

types, 2 true divergence excess, and 12 convergence insufficiency types in the unsuccessful group.

VARIABLE OF INTEREST	SUCCESS MEAN (PREOP)	SUCCESS STD DEV (PREOP)	UNSUCCESS MEAN (PREOP)	UNSUCCESS STD DEV (PREOP)
AGE OF ONSET	4.54 Median: 2 Range:0-63	9.27	5.72 Median: 2 Range:0-73	14.11
AGE AT SURGERY	14.98 Median: 8 Range:1-67	15.85	11.59 Median: 6 Range:1-75	15.22
SEX (FEMALE/MALE)	34/31		34/31	
PREOPERATIVE ANGLE OF EXODEVIATION (PD) @ 0.33M	21.31 Range: 6-63	11.44	31.92 Range: 4 - 183	26.67
PREOPERATIVE ANGLE OF EXODEVIATION (PD) @ 6M	24.46 Range: 10-58	8.8	32.25 Range: 10-141	17.88
ANGLE OF EXODEVIATION (PD) WITH +3.00 LENSES AT 0.33M	33.48	11.04	40.10	13.85

VARIABLE OF INTEREST	SUCCESS MEAN (PREOP)	SUCCESS STD DEV (PREOP)	UNSUCCESS MEAN (PREOP)	UNSUCCESS STD DEV (PREOP)
VERTICAL DEVIATION PRESENT	N = 32		N = 34	
STEREOPSIS SCORE AT NEAR (SECONDS OF ARC)	146 Median: 40	385.05	215.20 Median: 40	628.85
VISUAL ACUITY RE (LOGMAR)	0.12	0.13	0.13	0.16
VISUAL ACUITY LE (LOGMAR)	0.09	0.13	0.14	0.13
VISUAL ACUITY RE NEAR (LOGMAR)	0.10	0.13	0.11	0.16
VISUAL ACUITY LE NEAR (LOGMAR)	0.08	0.12	11.59	15.22
CYCLOPLEGIC REFRACTION				
RE Sphere	0.41	1.63	0.33	2.03
RE Cylinder	0.38	0.57	0.40	0.62
LE Sphere	0.28	1.41	0.24	1.99
LE Cylinder	0.31	1.41	1.45	7.52
INTEROCULAR DIFFERENCE IN	5.32	9.60	3.77	6.40

VARIABLE OF INTEREST	SUCCESS MEAN (PREOP)	SUCCESS STD DEV (PREOP)	UNSUCCESS MEAN (PREOP)	UNSUCCESS STD DEV (PREOP)
CORRECT OPTOTYPES ON VA TESTING				
LENGTH OF FOLLOW UP (WEEKS)	84.15 Median: 62 Range: 8-344	72.62	111.35 Median: 100 Range: 10-339	77.18
POSTOPERATIVE ANGLE OF EXODEVIATION (PD) @ 0.33M	4.26	7.72	19.70	11.67
POSTOPERATIVE ANGLE OF EXODEVIATION (PD) @ 6M	4.21	5.63	18.78	7.91
DUANE'S CLASSIFICATION				
BASIC TYPE	N = 49		N = 34	
PSEUDO-DIV EXCESS	N = 13		N = 17	
TRUE DIV EXCESS	N = 1		N = 2	
CONV INSUFFICIENCY	N = 2		N = 12	

Table 8. Demographics of patients with successful and unsuccessful outcomes

Table 9 shows that from the 130 subject sample preoperatively, 83 were basic type, 30 were pseudo-divergence excess type, 3 were true divergence excess type, and 14 were convergence insufficiency type. Post-operatively, 104 were basic type, 15 were pseudo-divergence excess type, 1 was true divergence excess type, and 10 were convergence insufficiency type. The fractions shown in brackets within each classification subtype represents the distribution of the group between either the successful or unsuccessful groups. That is, there were 83 exodeviations who classified as basic type deviations preoperatively. Of these subjects, 34 would recur after surgery, and 49 would have successful surgical outcomes. Seventeen pseudo-divergence excess pre-operative deviations would have successful surgical outcomes, and 13 would have unsuccessful, or recurring outcomes. Two of the 3 total true divergence excess exodeviations has successful post-operative outcomes, where 1 was unsuccessful. Twelve of 14 convergence insufficiency type patients recurred after surgery.

	PRE-OP (n) /130 (recurred/success)	**% of Total Subjects Pre-op**	**POST-OP (n) /130** (recurred/success)	**% of Total Subjects Post-op**
Basic	83 **(34/49)**	63.8	104 **(41/63)**	80
Pseudo-divergence excess	30 **(17/13)**	23.1	15 **(13/2)**	11.5
True divergence excess	3 **(2/1)**	2.3	1 **(1/0)**	0.8
Convergence insufficiency	14 **(12/2)**	10.8	10 **(10/0)**	7.7

Table 9. Duane's Classification distribution before and after surgery

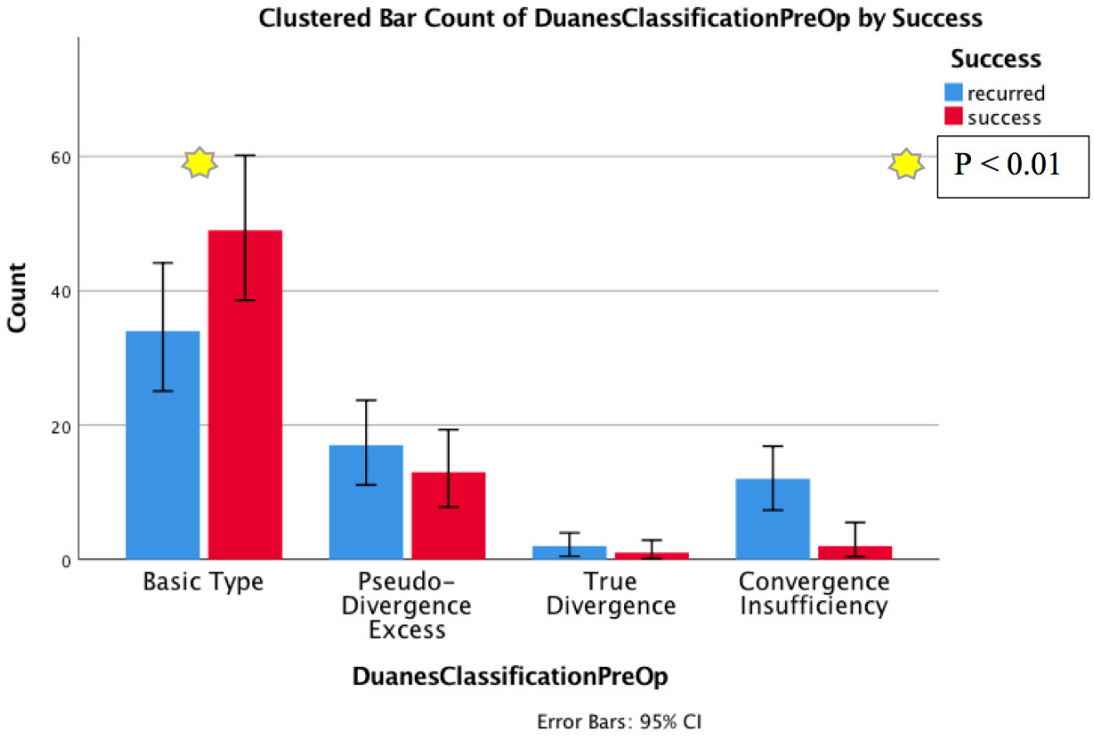

Figure 1. The Frequency of Duane's Classification Subgroups Pre-operatively

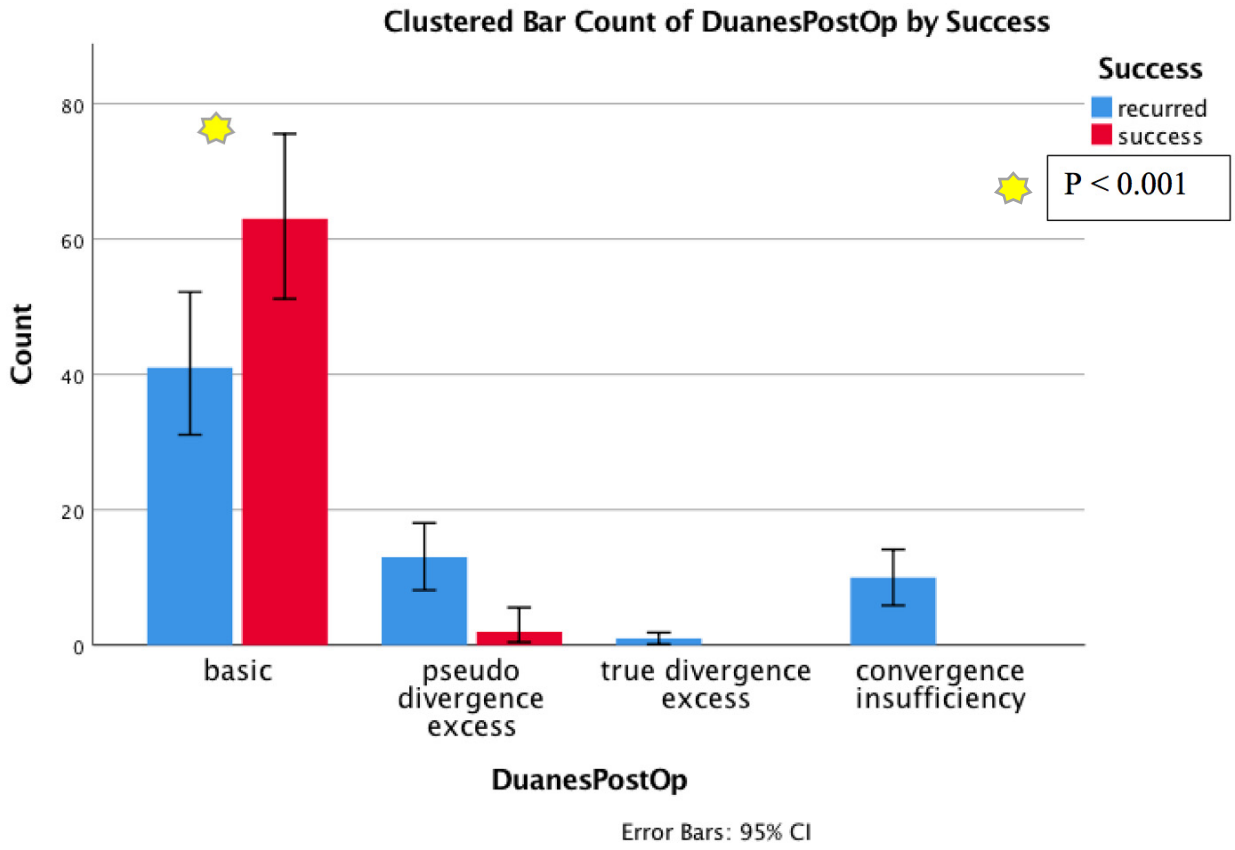

Figure 2. The Frequency of Duane's Classification Subgroups Post-Operatively

Sixty-three of the basic type exodeviations at post-op were from the success group, and 41 were from the unsuccessful group. From the 15 total pseudo-divergence excess group, 13 were categorized as the unsuccessful, and 2 were successful. The 1 true divergence excess patient at post-operation had an unsuccessful surgery. And none of the post-operative convergence insufficiency types were represented in the success group. Post-operatively, 63 of the total 65 sampled patients had basic type exodeviations.

A Fischer's Exact Test of independence comparing the variables of Duane's classification pre- and post-operatively was performed. The test was significant at the $p < 0.01$ level, with a chi-squared value of 32.20, suggesting that the post-operative Duane's classification

outcome is not independent from the pre-operative classification. Cramer's V was equal to 0.328, suggesting a medium effect size. We can assume the post-operative nature of the deviation significantly relies on the pre-operative nature of the deviation. The frequency of each sub-classification is shown pre-operatively and post-operatively in Figure 1 and Figure 2, respectively.

4.2 Relationships Between Preoperative Variables and Success

Table 10 displays the relationships determined by the appropriate correlational or association statistic for each peri-operative variable when compared to surgical outcome. A total of 7 pre-operative variables (Table 10) were significantly associated with surgical outcome, suggesting that the null hypothesis could be rejected. The statistically significant pre-operative variables within independent analysis were applied to the binary logistic regression for a predictive model. The independent variables included were Post Op Near Angle, Post Op Distance Angle, Duane's Post Op, Duane's Pre Op, Near Pre Op Angle, Distance Pre Op Angle, Target Angle, Distance Angle VS Target, +3.00D Deviation Pre Op, LE Acuity, and Follow up. In this predictive analysis, none of the independent variables were significant at the $p < 0.05$ level by themselves. Therefore, neither odds ratios nor relative risk were considered.

Variable	Association statistic	Significance value (*p*)	n Value
Post Op Near Angle	31.585	< .001*	130
Post Op Distance Angle	37.944	< .001*	130
Duane's Post Op • **Cramer's V**	25.015 .427	< .001* < .001 *	130
Duane's Pre Op • **Cramer's V**	10.936 .287	.007* 0.010*	130
Near PreOp Angle	7.751	.005*	130
Distance PreOp Angle	9.447	.002*	130
Target Angle	7.107	.008*	110
Distance Angle VS Target angle (Difference)	1.473	.225	110
+3.00 Deviation Pre Op	7.383	.007*	119
ACA Ratio (using +3.00D measurement)	0.394	.530	119
-2.00D Deviation Pre Op	0.030	.863	66
Greater Than 6m	1.927	.165	63
Surgery Date	3.494	.062	130
Age Surgery	.974	.324	130
Stereopsis Near	.548	.459	129
Fusion Near	3.863	.383	128

Variable	Correlation statistic (with success)	Significance value (*p*)	n Value
BVA Near	2.985	.848	92
Convergence Near	2.439	.118	126
Control Score Near	5.246	.271	112
Stereopsis Distance	1.017	.301	121
Fusion Distance	2.319	.748	112
Convergence Distance	1.682	.195	126
BVA Distance	0.040	.842	79
Control Score Distance	3.203	.524	111
Control Subtype Pre Op	2.072	.391	130
Dis VA RE	0.073	.787	130
Dis VA LE	3.946	.047*	130
Amount Amblyopia	1.023	.312	130
Cyclo RE Sphere	0.268	.527	102
Cyclo RE Cylinder	2.388	.122	102
Cyclo LE Sphere	0.084	.772	102
Cyclo LE Cylinder	3.276	.070	102
Cyclo VS Lensometry (difference)	5.518	.129	102
NPC	0.036	.849	119
Anisometropia	.428	.513	130

Variable	Correlation statistic (with success)	Significance value (*p*)	n Value
Uncorrected Hyperopia	5.518	.129	124
Surgical Procedure	16.890	.203	130
Weeks of Follow Up	4.039	.044*	130

Table 10. The Association Between Clinical Variables and Success

The regression model was refit to consider peri-operative variables of statistical and clinical significance collectively, with an emphasis on the inclusion of variables with no missing data. Therefore, all 130 cases were considered for each variable in the second logistic regression. Independent variables included within the model were Duane's classification pre-operatively, post-op deviation at near, post-op deviation at distance, and pre-op angle at near as well as weeks of follow up. The Duane's classifications were broken down into subcategories, independently contributing to the model, where basic type was the indicator or reference variable in the regression, due to its high occurrence rate.

The post-operative near and distance ($p < 0.05$) deviations were two of the three variables which maintained significance within the model. Additionally, Duane's classification pre-operatively was significant (Wald $\chi2 = 8.957$ $p = 0.035$), particularly the basic type subcategory (Wald $\chi2 = 5.199$, OR $= 0.121$, $p = 0.023$) was significant. Pre-operative deviations and follow up periods were non-significant within the predictive model. The final regression model was determined to account for 59-78 % of successful surgical outcomes, according to the Cox & Snell and Nagelkerke R Square statistics, respectively. The predictive model would be correct

93.8% of the time. The *p* value for Duane's Basic Type was 0.023 and Exp(B), or (OR = 0.121, *p* = 0.023) with 95% C I [0.020, 0.743]. The confidence interval did not contain the null value of 1 within its range, and the Wald statistic was significant at $p<0.05$. Therefore, this odd's ratio was considered significant.

4.3 Details Regarding Surgical Outcomes

Out of a total of 130 surgical procedures analyzed, the median date for surgical procedure was the 27th of August 2015, with a range between June 21, 2011 and August 14, 2018. Only 7 surgeries were performed before 2013, before electronic medical records. This subject information was acquired by ordering paper charts from Iron Mountain chart storage in Halifax. There was a total of 5 surgeons whose management and operations were considered by this study. Surgeon 1 performed 76 (58.5%) of the operations analyzed, and surgeon 2 performed 13 (10%) operations. Surgeon 3 performed 30 (23.1%) surgeries, surgeon 4 performed 5 (3.8%) operations, and surgeon 5 performed 6 surgeries (4.6%). Four subjects underwent inferior oblique weakening procedures in tandem with their horizontal muscle surgery, and 5 subjects underwent surgery of one muscle, unilateral lateral rectus recession. All 121 other subjects underwent surgery of 2 muscles. Six patients had slant procedures and 22 patients had transposition procedures coinciding with their horizontal muscle surgery. There were 16 different procedures performed across all patients.

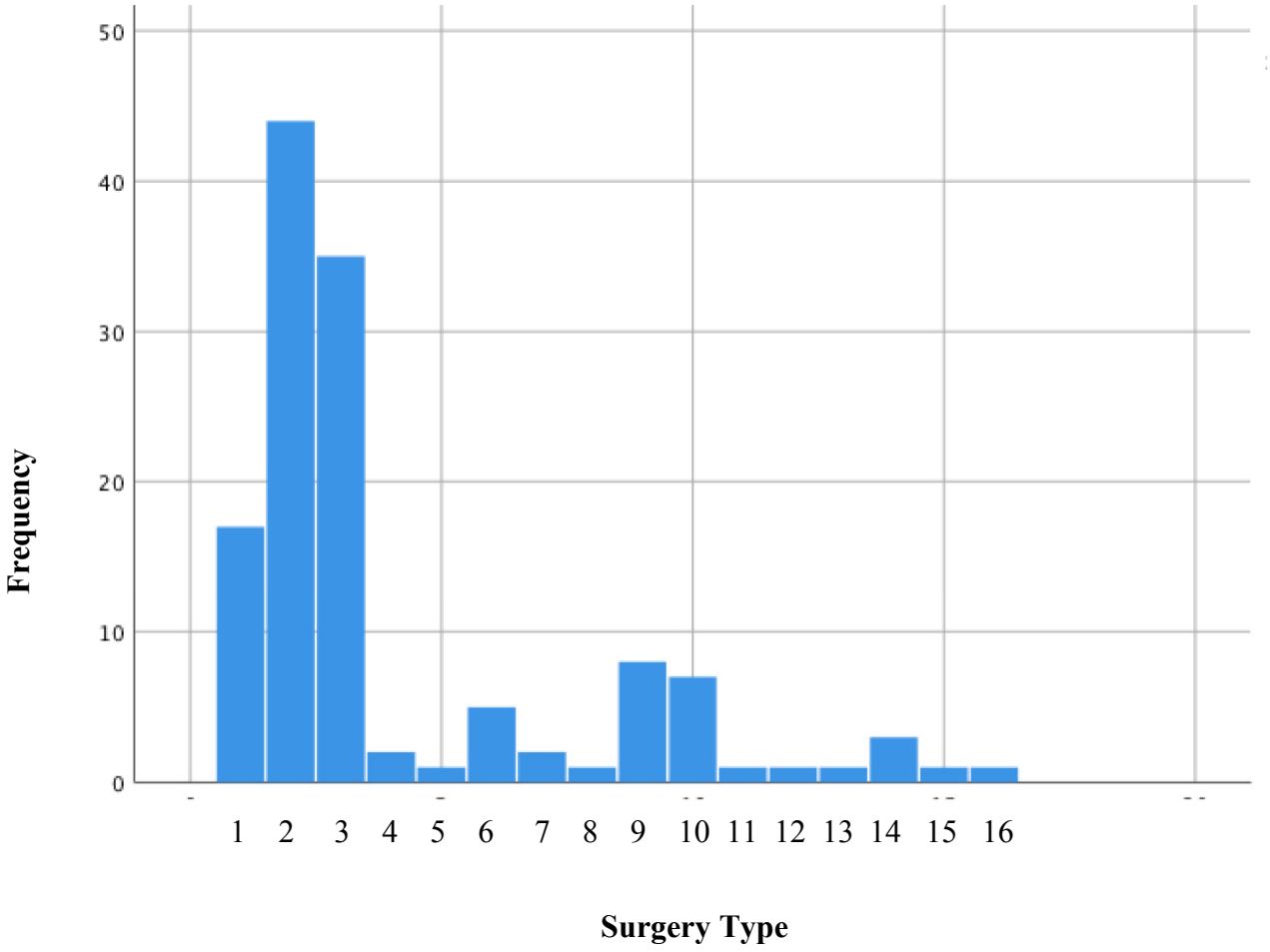

Figure 3. The Frequency of Surgical Procedure Categories

Category Number	Procedure Description	N (/130)	Success	Unsuccess	Mean Follow up (weeks)
1	Bilateral lateral rectus recessions	17	9	8	98.8
2	Lateral rectus recession and medial rectus resection (R&R)	44	24	20	101.6
Category Number	**Procedure Description**	**N (/130)**	**Success**	**Recurrence**	**Mean Follow up (weeks)**
3	Lateral rectus recession and medial rectus tuck	35	12	23	104.5
4	Lateral rectus recession and medial rectus resection with transpositions and slants	2	2	0	28
5	Lateral rectus recession and medial rectus tuck with transpositions	1	0	1	8
6	Unilateral lateral rectus recession	5	2	3	96.8
7	Lateral rectus recession and medial rectus resection with slants	2	1	1	23.5

Category Number	Procedure Description	N (/130)	Success	Unsuccess	Mean Follow up (weeks)
8	Bilateral medial rectus resections with transpositions	1	0	1	23
9	Lateral rectus recession and medial rectus resection with transpositions	8	5	3	80.4
10	Bilateral lateral rectus recessions with transpositions	7	5	2	110.9
11	Bilateral lateral rectus recessions with slants	1	1	0	148
12	Bilateral medial rectus tucks	1	0	1	131
13	Lateral rectus recession with medial rectus tuck and bilateral inferior oblique myectomies	1	0	1	140
14	Bilateral lateral rectus recessions and bilateral inferior oblique myectomy	3	3	0	58.7
15	Bilateral medial rectus resections	1	1	0	201
16	Lateral rectus recession and medial rectus tuck with slants	1	0	1	70

Table 11. Procedure Categories and Distribution with Follow Up Times

Figure 3 displays the distribution of surgeries performed on the patients to correct a total of 130 exodeviations of contrasting size, classification subtype, control, and associated symptoms. The figure uses surgery types categorized by numbers from 1 to 16, with the frequency of each shown by bar height. A detailed description of all 16 surgeries is found in Table 11. In addition to procedural descriptions, the table also shows how many subjects received each type of surgery, and whether the patients were categorized within the successful or unsuccessful groups. Lastly, the mean follow up time for subjects within each surgical subtype is given. The surgical procedures varied based upon the number of muscles involved, whether surgery was performed on one eye or both eyes, whether or not slants or transpositions were also performed. Procedures also differed in terms of what kind of strengthening or weakening procedure was performed during surgery, for example, whether there was a medial rectus tuck or resection. The most common procedure was the unilateral recess and resect procedure, category number 2, which 44 subjects underwent. Thirty-five patients received the second most common procedure was the lateral rectus recession and medial rectus tuck. The third most common procedure were bilateral lateral rectus recessions, with 17 subjects. There were 7 procedures that were only performed once on 7 separate patients. Five of these procedures were unsuccessful.

A chi-square analysis comparing the variables of success and degree (score) of surgical personalization determined that both variables are independent of each other ($X^2 = 9.45$, $p = 0.272$). Surgical success was not dependent upon how far a surgical procedure deviated from the recommendations of the AAO, nor was it associated with surgical outcome (Table 8). As the outcome of the chi square analysis was non-significant, the Cramer's V effect size statistic was not considered. These outcomes suggest that the null hypothesis cannot be rejected.

5.0 Chapter 5 Discussion

5.1 Summary of Results and Clinical Significance

Overall, surgical correction in this sample revealed a success rate of 43%, a 52% unsuccess rate, and a 5% overcorrection rate. A successful surgical outcome was statistically associated with 10 independent variables when analyzed independently against surgical outcome, including 7 pre-operative variables. Pre-operative near angle (Wald $\chi 2= 7.751$, $p = 0.005$), pre-operative distance angle (Wald $\chi 2= 9.447$, $p = 0.002$), surgical target angle (Wald $\chi 2= 7.107$, $p = 0.008$), and+3.00 D deviation (Wald $\chi 2= 7.383$, $p = 0.007$). In all four cases, a smaller deviation was related to success. Stronger LogMAR left eye visual acuity (Wald $\chi 2= 3.946$, $p = 0.047$), Duane's classification pre-operatively ($\chi 2= 8.923$, $p = 0.030$), as well as weeks of follow up (Wald $\chi 2= 4.039$, $p = 0.002$) were also associated with success. However, a longer follow up period was related to lack of success, rather than success (Table 8). All three post-operative findings, including near deviation, distance deviation, and Duane's classification were related to surgical success outcome (Wald $\chi 2= 31.585$, $p < 0.001$, Wald $\chi 2= 37.944$, $p < 0.001$, $\chi 2= 9.579$, $p < 0.001$) when run independently from the final regression model. However, this finding is largely intuitive. In order to be categorized as a surgical success, the deviation had to be within 10 pd of orthotropia. In consideration of the other variables of significance, there may be a limited role for pre-operative clinical characteristics such as smaller deviation size at either fixation distance, and better visual acuity particularly of the left eye when considering post-operative outcomes for a patient undergoing exodeviation surgery.

The first logistic model included all independently correlated independent variables (IV). In this model no variables were found to be statistically predictive of success. The second model reported included 7 variables, of which Duane's pre-operative classification was the only significant pre-operative characteristic (Wald $\chi 2 = 5.199$, $p = 0.023$, OR = 0.121, 95% CI 0.020 – 0.743). The odd's ratio suggests that basic type deviations are more likely than any other Duane's sub-classification to be successful. Paraphrased, the odds of a successful outcome are higher for a patient with a basic type deviation. This finding, although statistically significant, may be of little clinical significance due to the use of limited independent variables, a relatively small sample size for a predictive model, and the high occurrence of basic type deviation compared to other categories.

5.2 Comparing Results to Previous Studies

Our findings are consistent with previous studies suggesting approximately a 50% success rate. Despite that our success rate was on the lower end of the spectrum of success outcomes in the existing literature, our follow up period was longer than most studies. Had previous studies incorporated longer follow up periods or more stringent criteria and assessment methods for successful outcome, the outcome reported by other studies may have been more comparable to the present outcomes.

Regarding associations between pre-operative characteristics and surgical outcomes, it is difficult to draw comparisons between this study and previous ones. The present study differed from others in terms of statistical analyses performed, for example, by using regressions instead of risk factors. Another limiting agent is the frequent use of incorrect statistics in previous studies, where linear or multivariate regressions were performed in lieu of binary logistic regressions. Due to an abundance of missing data for variables of interest, such as deviation at

greater than 6 metres, deviation with -2.00 D lenses, and BVA at near and distance, it is difficult to determine whether a lack of significance associated with these variables is due to a non-existent association, a lack of statistical power, or otherwise. Comparisons between the present study and others are also limited by population of interest, with respect to age range and control of the exodeviation. With that said, some findings of this study have mirrored those of previous researchers. These similarities are drawn in the context of replicated findings from retrospective designs employing association statics, therefore, causation cannot be implied.

The findings by Zou et al. (2017) were similar to the findings of this study. They found pre-operative near and distance angles to be significant in a logistic regression including multiple other variables, such as higher myopic refractive error, which was also statistically significant in their study. These authors concluded that preoperative angle of deviation and refractive error were predictive of surgical success, due to the significance reached in a predictive model. By contrast, only preoperative angle at near and distance were associated with surgical success when assessed independently for association within a logistic regression analysis. In the present study these variables were non-significant when incorporated into the final predictive model that included all statistically related variables. Therefore, we cannot say that preoperative angle is predictive of surgical success in this sample. We can say that preoperative angle is associated with success, however. Refractive error, myopic or otherwise, did not achieve significance during independent analysis, and were not included in the final regression model.

The study in 2004 by Gezer et al. included 40% of patients with IXT and 60% of patients with manifest exotropia. This study also had a success rate of 49%, comparable to 43% found in the present study. Similar to the study by Zou et al., (2017), Gezer et al., (2004) also found pre-operative angle of deviation and refractive error to be associated with surgical success. The

authors had run a regression analysis, similar to Zou et al. (2017), however, only concluded that the variables of preoperative deviation and refractive error were associated rather than predictive. The present study was able to confirm the association between deviation size and surgical outcome that was concluded by Gezer et al (2004). Again, the relationship with refractive error was not reproduced in the present study. This could be due to the fact that eastern Asian populations have more myopic refractive error on average than North American populations (Zou et al., 2017).

Yang et al. (2016) reported that of all clinical characteristics, loss of stereoacuity pre-operatively was the only variable to be associated with poor surgical outcome in a risk analysis. The present study was unable to confirm this association, as stereoacuity did not achieve significance in the independent logistic regression analysis against surgical outcome for either of near or distance stereoacuity. Further, this study did not perform association statistics through a risk analysis statistic. One consideration differentiating the outcomes of these studies is the type of analysis that was run. Another is the methods by which stereopsis measures were acquired. Where Yang et al. (2016) used only two tests of stereopsis, the present study used four. This degree of variability in assessment procedures may have led to reduced reliability surrounding the stereoacuity variable, potentially leading to a type II error, where the null hypothesis cannot be rejected despite the null hypothesis being false. The role of stereopsis when considering surgical outcome for exodeviation surgery remains unclear. The outcomes of the risk analysis by Oh and Hwang (2005) can be compared to the present study using similar limitations to those previously described. Oh and Hwang determined stereopsis, refractive error and angle of deviation preoperatively to all be risk factors for unsuccessful surgical outcomes. The comparison between our findings is limited, due to the differences between risk analysis and

predictive model methodologies. Additionally, the role of refractive error could be confounded by different populations under study.

Using the chi-square analysis, the present study complimented the findings by Bae et al. (2018), suggesting a statistically significant post-operative shift towards the basic type Duane's sub-classification. That is there are less patients with convergence insufficiency type, pseudo- and true divergence excess type sub-classifications post-operatively than existed pre-operatively. This could be due to a number of difference variables, such as what muscles are targeted in surgical correction of exodeviations, or how different muscles targeted in surgery are more effective at different fixation distances. Overall, this trend has been shown to be significant in two different populations, perhaps warranting a prospectively designed study for further investigation into these outcomes.

5.3 Limitations

As with any retrospective cohort study, all variables were assessed and reported before the study was proposed. Therefore, procedures for determining measurement outcomes may not be as accurate or precise as they would be with a prospective design. Additionally, multiple examiners and surgeons would have been used, performing unstandardized testing methods for the purposes of this study. Naturally, two different clinicians who have potentially been trained at different centres may have varied approaches to assessments, impressions, and management plans. In a prospectively designed study, the examination would be administered a step-wise fashion, by clinicians certified by comparable governing bodies prior to patient recruitment. Clearly defined testing procedures would outline exactly how each assessment should be performed, an approximate time estimate for each assessment step, and how the clinician should determine and report their findings. Clinicians involved in this study would be blinded to the

nature of the patient's deviation prior to their assessments, as well as the type of the surgical intervention associated with a patient. Finally, the study would be limited to 2 – 3 orthoptists for the performance of assessments, to maximize the inter-rater reliability of test variables. By incorporating more than one orthoptist, the generalizability and external validity of the study is strengthened.

Unfortunately, this study did not reveal an abundance of clinically relevant significant outcomes from the original predictive model. This was likely due to a conservative sample size used for a regression analysis, as well as a significant amount of missing data. Despite that inclusion criteria for this study required a full orthoptic examination at least 7 days prior to surgery, this study analyzed exodeviation characteristics that are not routinely performed across all clinicians. This is not an uncommon outcome of retrospectively acquired clinical data. In fact, often times this information can be made beneficial to clinicians, by highlighting variabilities within or across clinics.

Another limitation of the design of this study is that it did not compare immediate post-operative outcome with long-term follow-up outcomes. Instead, the only orthoptic assessment considered post-operatively was the most recent follow up assessment. This is partly due to variability in the timing of early post-op assessments. Therefore, no relationship could be determined between immediate post-operative deviation and long term success. Some studies have showed that surgeons should aim for a small esodeviation post-operatively to achieve overall success over a long period of time (Oh & Hwang, 2005). We did not collect enough data in order to compare our outcomes to the findings of previous authors. If a similar study were to be performed using a prospective design, patients would be seen shortly after their surgery, or

post-treatment in order to capture the postoperative deviation. The patient would then be followed annually for long-term outcome assessments.

This study included patients who were managed by up to 5 different surgeons, with an unequal distribution of patients being treated by each physician. Surgeons in this study varied greatly amongst each other in years of experience practicing pediatric ophthalmology. Two of the surgeons had completed fellowships under the direction of the other 3 surgeons considered in this study. One of the surgeons with more years of experience had completed his training in the UK, versus others who were trained in North America. Further, surgeons all have unique approaches to strabismus surgery, and differ in how they perform the same type of procedure. Any two surgeons may even differ in their suturing technique which could possibly lead to contrasting surgical outcomes for the same intended procedure. These five surgeons performed the surgeries individually and managed these patients pre-operatively at their own discretion. This includes refractive and amblyopia treatment, as well as the determination of the surgical target angle, pre-operatively. In an ideally designed prospective study, participating surgeons would be comparable to one another in years of experience, and there would be a standardized guide for management of surgical patients, pre-operatively. In particular, refractive treatment for patients with minimal hyperopia, or for those undergoing over-minus lens therapy would be standardized before the collection of pre-operative alternate prism cover test measurements.

An additional limitation to this study is the lack of standardization to the order of testing. This is considered a potential limitation as there are multiple outcomes for deviation control considered by this study, such as stereopsis, BVA, convergence amplitudes, NPC and control scale rating. Standardized testing order is particularly advantageous when considering control

outcomes because control is a phenomenon that can easily deteriorate with prolonged testing, or occlusion. After significant testing control may be quite poor, as represented by low control ratings, poor BVA, and severely reduced or absent stereopsis. Conversely, if vergences are performed before stereopsis, the patient may reach their break point and dissociate their control. By the time stereopsis is to be determined, the patient may demonstrate a negative stereopsis outcome, regardless of the fact that they have the ability to perceive stereopsis in their day-to-day life. If these tests of control are performed at the beginning of a patient exam, with the examiner avoiding monocular occlusion beforehand, a patient with fragile control may demonstrate better outcomes, as they will be less fatigued at this stage. Where the assessment of relationships between peri-operative variables and success was one of the objectives of this study, a lack of control surrounding these variables may have diluted potentially significant outcomes in a retrospective review.

The follow up period in this study for determining successful outcome of surgery is at least 8 weeks post-op, with a mean follow up equal to longer than 1.5 years (median = 40 weeks, range 8-344 weeks). The findings of this study may not truly represent success for exodeviation surgery post-operatively, as a longer follow up period would be ideal in cases where subjects had only been followed for 8 weeks. A total of 5 patients in this study were followed for only 8 weeks, and 16 of the total 130 were followed for 12 weeks or less. Traditionally, many studies consider success to be within 10 pd of orthotropia after 3 months from the time of surgery, or after one year. At 8 weeks, the patient may not have been be fully healed, and could deviate further outward if followed for a longer period. The concern would be that patients who are only followed for 8 weeks would be considered successful and discharged from physician care. This could leave the potential for these subjects to deviate into a larger deviation at a later time period,

potentially not captured within this study. In summary, it is important to acknowledge that follow up period is an important threat to the construct validity of the dependent variable in this study. Statistically, 11 out of 15 patients who were followed up at 12 weeks or less were categorized in the success group. However, there was no significant relationship between follow up period and surgical success on Chi-Squared analysis. This study considered patients with a minimum follow up of 8 weeks as that is standard practice within the clinic for some physicians, especially in adult cases.

This study set a liberal standard for successful surgical outcome, where the post-operative deviation could be no larger than 10 pd than orthotropia. However, one must consider how an individual could have an esodeviation of 9 pd at near and an exodeviation of 10 pd at distance, and still be considered a success. One patient in this study was found to have a small consecutive esodeviation of 4 pd at near and 6 pd at distance, and experienced diplopia post-operatively. However, this patient was still categorized as a successful surgical outcome. The patient was satisfactorily managed with prisms and did not require additional surgery. The standards of success used in this study have been used to define success in similar studies previously, however it is important to consider that success in research may not always be translatable to clinical success.

While this study focused on horizontal outward deviations, patients with small vertical deviations were also considered in this study. However, patients with unresolved vertical deviations, whose horizontal deviations were consistent with the parameters of a successful horizontal surgery were still classified as successful. Clinical intuition alone tells us that a patient with a large residual vertical deviation would have a difficult time attaining/maintaining fusion,

regardless of the nature of the horizontal deviation component. These patients often require multiple surgeries. Ideally, a future study would consider the outcome of surgery for both the horizontal and vertical deviation post-operatively, when determining surgical outcome. Previous researchers did not discuss how they handled post-operative vertical deviations when categorizing patients as successful or unsuccessful, so it is difficult to relate this as a potential flaw in methodology to previous studies.

This study attempted to identify a relationship between surgical dose individualization by surgeons, and a tendency to move away from standardized surgical doses provided by the AAO. However, because strabismus surgeons are encouraged to create surgical tables of their own, and each surgeon has a slightly different technique, suture, or procedure, this was a challenging analysis to perform. Additionally, this relationship has not been previously analyzed in the literature to the knowledge of the principal investigator rendering advanced statistical analysis challenging to perform. With the assistance of a clinical consulting scientist (PhD Health Psychology), it was decided to allow this aspect of the analysis to remain exploratory in nature, purely running tests of independence. The results of the chi-square analysis showed that success and surgical individualization were not statistically dependent each other. That is, the success of a surgical procedure for exodeviation was not found to be dependent upon the degree of personalization by the surgeon for surgical dosage.

5.4 Future Directions

The findings of this research could certainly inform future, prospective studies. One such study would be to recruit patients with exodeviations prior to receiving their surgical treatment. This study would apply a predetermined, controlled pre-operative assessment to reduce the

frequency of missing data and variability in testing administration. These patients would then be followed for at least 5 years to determine successful versus unsuccessful outcomes. Patients could be followed at least annually during the post-treatment period to determine duration until recurrence, and post-operative clinical characteristics associated with recurrence of an exodeviation greater than 10 pd.

If this study were to be repeated including a retrospective design, it would be interesting to ensure enough data were collected for each control subtype; exotropia, IXT, and exophoria, in order to confidently extrapolate findings to each subgroup. Within the patient groups with IXT and exophoria, investigators should include stereopsis scores from only one stereoacuity test. This could potentially rule out confounds of different testing mechanisms for a lack of relationship between stereoacuity and surgical outcome within this population.

While this study assessed the characteristics of patients with successful post-operative alignment and recurrent exodeviations, it did not adequately describe the characteristics of those patients who received surgical overcorrections. A future study might follow these patients long term, considering how many require bifocal therapy associated with high AC/A ratio, additional surgical treatment or eventually realigned to within fusion range after surgery. Of particular interest would be the assessment of patients with small overcorrections within success range (<10 pd), and the likelihood of eventual recurrence in this group compared to those with small post-operative exodeviations.

Approximately 80% of the patients who were excluded from this study could not be included due to comorbid dissociated vertical deviation (DVD). The relatively high rate of DVD throughout the screening process was so significant, that the principal investigator had to expand the enrollment process to include patient sign-up sheets throughout the pediatric ophthalmology

clinic associated with this study. DVD is traditionally thought to be a less common clinical finding and is most often associated with infantile strabismus. It would be particularly interesting to contact these excluded patients for follow up, to determine the etiology of their strabismus. Further, to confirm the accurate diagnosis of DVD in these patients, as opposed to a similar outcome such as unilateral or alternating hyperdeviations.

Lastly, a survival analysis following the period until likely regression toward pre-operative deviation could be useful analysis, requiring follow up of the patients included in this study over a period of at least 10-15 years. This information could be useful in the post-operative counselling, follow-up and discharge procedures by surgeons.

5.0 Conclusions

The findings of this study compliment the suggestions of previous research groups, suggesting that the outcome of exodeviation surgery is highly variable and unpredictable. Further, our findings further complicate the existing body of research regarding predictor variables associated with successful exodeviation surgery. However, this research focused on the outcomes of all exodeviations instead of intermittent exotropia exclusively. Therefore, comparisons between this study and others should consider this significant difference in populations of interest. Having a smaller deviation at either near or distance preoperatively has been shown to be associated with successful surgical outcomes in many separate studies, including the present study. The findings of this research highlight a potential role for Duane's classification into the existing body of literature, as potentially being both associated and predictive of successful outcome.

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Appendix A: Glossary

Accommodative convergence: the amount of convergence elicited for a given amount of accommodation

BVA: Binocular Visual Avuity

Cycloplegic correction: The prescription for refractive error that is based solely upon anatomic features of the eye, excluding accommodative variables. Performed with cycloplegic agents which dilate the pupil and prevent accommodation through the ciliary body.

Fusional convergence: Convergence stimulated by disparate retinal images from both eyes.

Intermittent Exotropia (IXT): An outward eye turn that is intermittently controlled, characterized by periods of straight eyes and binocular single vision.

Overminus lens therapy: The prescription of more minus power in refractive correction to assist in the management of patients with intermittent exotropia

Orthotropia: The achievement of straight eyes and binocular vision, even in the presence of a controlled or intermittently controlled deviation.

Prolonged monocular occlusion (PMO): Analogous to the 45-minute patch test. The ongoing dissociation of incoming images to both eyes achieved with a patch left in place for an extended time.

R&R: Recess and resect surgical procedure

Stereopsis: Three dimensional vision

Titmus: Stereo Optical Fly Test

Appendix B: IWK Research Ethics Board Approval

IWK Health Centre
Research

5850/5980 University Avenue
PO Box 9700, Halifax
Nova Scotia B3K 6R8
Canada
tel: 902.470.8888
www.iwk.nshealth.ca

Approval – Delegated Review
September 26, 2018

Principal Investigator: Ms. Dominique Salh
Supervisor: Leah Walsh/Erik Hahn
Title: Predictors of Recurrence After the Surgical Correction of Exotropia
Project #:1023790

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,

Co-Chair, Research Ethics Board

This approval includes the following study documents:

Document Name	Version Date
Protocol	8/13/2018
Data Collection Form	8/13/2018

The Board's approval for this study will expire one year from the date of this letter (June 26, 2019). 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 experience 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 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, 1023790 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.

Research Ethics Board Committee Members		
Victoria	Allen	Obstetrics and Gynecology (Clinical Researcher)
Carol	Digout	APPHON
Tricia	Beattie	Pediatric Psychology
Kimberly	Brewer	BIOTIC
Christine	Cassidy	Nursing (Clinical Researcher)
Eleanor	Fitzpatrick	Nursing (Clinical Researcher), Co-Chair
Isabelle	French	Legal Representative
Ron	George	Women's Anaesthesia (Clinical Researcher)
Kevin	Gordon	Pediatric Neurology (Clinical Researcher)
Crystal	Himmelman	Privacy Officer
Adam	Huber	Pediatric Rheumatology (Clinical Researcher), Co-Chair
Greg	Muzika	Lay Representative
Francois	Tremblay	Pediatric Ophthalmology
Robin	Whyte	Executive Chair

* REB members are not in attendance during the review of their own proposed research involving human subjects or where there is a 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 C: Data Collection Example & Variables of Interest

Variable		**Variable**	
Study ID number		NPC	
Age of Onset		BVA Nr	
Sex		BVA Dist	
Nr Preop Angle		Nr Control	
Dist Preop Angle		Dis Control	
+3.00 D Deviation		Cyclo RE Sph	
AC/A ratio		Cyclo LE Sph	
Duane's Classification Preop		Cyclo RE Cyl	
Vertical Deviation (y/n)		Cyclo LE Cyl	
-2.00D Deviation		Lens RE Sph	
>6m Deviation		Lens LE Sph	
Fusion Near		Lens RE Cyl	
Fusion Distance		Lens LE Cyl	
Stereo Near		Cyclo Vs Lens Strength	
Stereo Dist		Surgeon	
Control Subtype		Surgery Date	
Synoptophore Stereo		Weeks of Follow Up	
Nr Convergence		Number of Muscles Operated On	
Dist Convergence		LRcAmount1	
Central Suppression Scotoma		LRcAmount2	
Dist VA RE		MRsAmount1	
Dist VA LE		MRsAmount2	
Nr VA RE		Target Angle	
Nr VA LE		Versus Academy Surgery	
Test of VA Dist		Slants	
Test of VA Nr		Transpositions	
Age at Surgery		Pattern	
Anisometropia		Postop Near Deviation	
Amount Amblyopia		Postop Distance Deviation	
Patching History		Duane's Classification Postop	
Orthoptic History		Success (Y/N)	

Minus Lens History			

Appendix D: Patient Age Frequencies

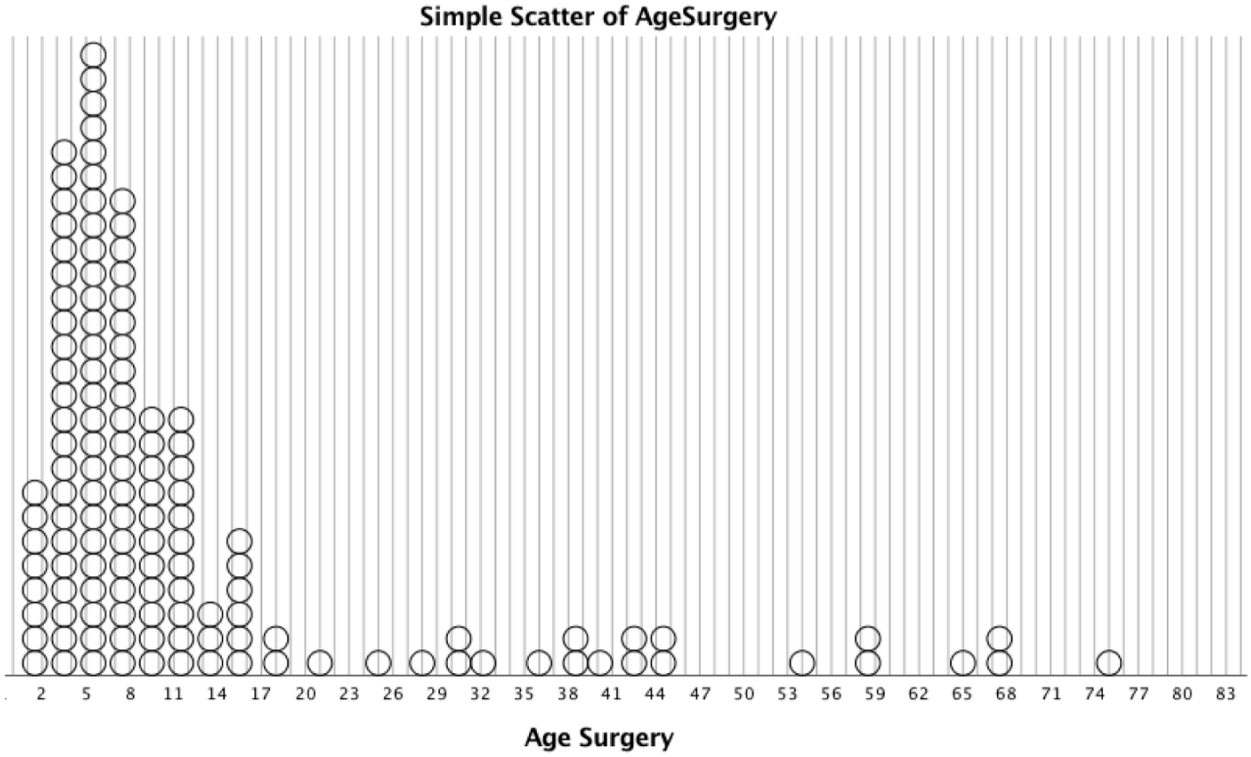

Figure 4. Simple Scatterplot Showing the Frequency of Different Ages of Subjects Undergoing Surgery