PREDICTION OF RETINOPATHY OF PREMATURITY USING THE WINROP SCREENING ALGORITHM IN A SOUTH AFRICAN POPULATION

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree

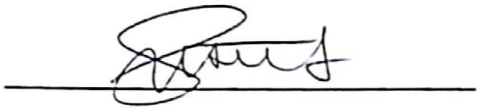
of

Master of Medicine in the branch of Paediatrics

Johannesburg, May 2018

DECLARATION

I, Samantha Jane Kesting declare that the research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



25th day of April, 2018.

I, certify that the study contained in this thesis has the approval of the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg. The ethics clearance number is M151123.

25th day of April, 2018.

DEDICATION

In memory of my loving grandmother

Bubbles Waldeck

1923 – 2016.

PRESENTATIONS

1. **SAPA & SAAPS Congress Durban**

   1 September 2016

   Poster Presentation

2. **University of the Witwatersrand Paediatric Research Day Johannesburg**

   26 November 2016

   Poster Presentation

3. **USANA Congress Johannesburg**

   15 – 17 September 2017

   Poster Presentation

ABSTRACT

TITLE: PREDICTION OF RETINOPATHY USING THE WINROP SCREENING ALGORITHM IN A SOUTH AFRICAN POPULATION

Introduction

WINROP (Weight, IGF-1, Neonatal Retinopathy of Prematurity) is an online screening algorithm with sensitivities of 84.7 – 100% for severe ROP in other countries. The aim of this study is to test the efficacy of WINROP as a screening tool in a South African population.

Methods

This retrospective record review included infants born between 1 January 2013 and 1 December 2014 who underwent ROP screening. Gestational age, date of birth, weekly weights and final ophthalmology screening results were entered into WINROP. The outcomes of ophthalmology clinical examinations were compared to alarms triggered on the system. Sensitivity and specificity, positive predictive and negative predictive values, the mean time of alarm and average weight gain per week were calculated. Results were compared between patients with complete and missing weekly weights.

Results

Two hundred and twenty infants were included with a mean gestational age of 29.1 weeks (SD 1.8 weeks), and a mean birth weight of 1115.5g (SD 201.0 grams). Infants with complete weights totalled 193 patients with a mean gestational age of 29.1 weeks (SD 1.8 weeks) and a mean birth weight of 1115.8g (SD 201.2 grams), with no statistical difference between groups. The rates for all stages/severity of ROP were 5.9% and 2.3% for severe ROP. Weekly weight gain ranged between 4.6 to 83.8g/kg per week. WINROP triggered a high risk alarm in 70.5% of infants at a mean of 30.7 weeks gestational age. The sensitivity for severe ROP was 100%, but 76.9% for ROP in all infants and 83.3% in the complete weight group. The specificity was low for both severe and all ROP at 30.2% (complete weights 26.6%) and 30.0% (complete weights 26.5%) respectively.

Conclusion

Our rates of ROP are low. Rates of severe ROP have been found to be lower in African populations. The high number of alarms with a low negative predictive value, would reduce the number of screens by 29.5%. The alarms were triggered before scheduled screening, possibly helpful in planning discharges and follow up visits. The poor growth rates postnatally may have resulted in the increased alarms. This may be due to lower levels of IGF-1 and absolute weight gain postnatally in black infants. Screening algorithms relying on growth and IGF-1 levels are race dependent, which needs to be considered in future algorithms for African populations.

ACKNOWLEDGMENTS

I would like to thank my supervisor Dr F Nakwa for her assistance and guidance, not only with this research, but also in her inspiring me to continually strive for the best care for my patients possible despite the many challenges we face.

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LIST OF ABREVIATIONS

CGA	Corrected Gestational Age
DEBM	Donor Expressed Breast Milk
ETROP	The Early Treatment for Retinopathy of Prematurity Study
EBM	Expressed Breast Milk
HIE	Hypoxic Ischaemic Encephalopathy
HIV	Human Immunodeficiency Virus
IGF-1	Insulin-like Growth Factor – 1
IMR	Infant Mortality Rate
LMIC	Lower Middle Income Countries
NPV	Negative Predictive Value
NMR	Neonatal Mortality Rate
PPV	Positive Predictive Value
ROP	Retinopathy of prematurity
SD	Standard Deviation
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organisation
WINROP	Weight, IGF-1, Neonatal Retinopathy of Prematurity

PREFACE

Retinopathy of prematurity (ROP) is an important cause of childhood blindness. There are many obstacles to screening for this complication in a developing country including large numbers of premature infants, stretched neonatal care resources and inadequate numbers of trained ophthalmology specialists. In addition, many infants are discharged prior to their screening examinations, and often lost to follow up. After reading about the WINROP (Weight, IGF-1, Neonatal Retinopathy of Prematurity) algorithm, I questioned if this screening tool would be useful in planning ROP screening by prioritising those infants at high risk of ROP in our setting at Chris Hani Baragwanath Academic Hospital. No studies have been done on an African population, and so I felt it would be important to investigate WINROP's efficacy in predicting ROP at Chris Hani Baragwanath Academic Hospital.

CHAPTER 1

1. INTRODUCTION

1.1 Background

Retinopathy of prematurity (ROP) has been found to be the third leading cause of avoidable blindness worldwide and forms part of the World Health Organisation (WHO) Vision 2020 Targets[1]. In South Africa, it has been shown to be responsible for 10.6% of cases of childhood blindness[2].

Terry initially described the most severe form of retinopathy of prematurity as retrolental fibroplasia in the 1940's[3]. This first epidemic of ROP followed the injudicious use of supplemental oxygen in the 1940's and 1950's[4]. The second epidemic developed in the 1960's with the increased survival of extreme low birth weight infants in developed countries[5]. Currently a third epidemic is taking place in developing countries. It is in these settings where the neonatal intensive care is still evolving, oxygen therapy is often liberally used and inadequately monitored[5].

1.2 Epidemiology

Globally the incidence of ROP varies greatly, correlating with Infant Mortality Rates (IMR's) and the socioeconomic state of countries. Low and lower middle income countries (LMIC), often with a high IMR greater than 60 per 1000 live births, do not have sufficient neonatal intensive care facilities and so preterm infants often do not survive to develop ROP. Countries with IMR's of less than 9 per 1000 live births are usually high income countries that can offer premature infants neonatal intensive care and thus good chances of survival and appropriate treatment of ROP. The intermediate group with IMR's of 9 – 60 per 1000 live births is a high risk group for ROP as many of these middle income countries have improved survival of premature infants but suboptimal oxygen therapy, ROP screening and treatment[5].

A systematic review grouped studies done between 2000 and 2010 into categories based on their neonatal mortality rates (NMR). This was done in order to estimate the quality of newborn care and the proportion of neonatal units with an ROP programme. Data was inadequate with regards to the coverage of screening for ROP in all settings and estimates were made based on expert opinion. Screening was assumed to be close to universal in countries with NMR below 5, 40% in countries with a NMR between 5 and 15, and 20% in countries with a NMR greater than 15. It was found that in countries with a NMR less than 5 per 1000 live births, 21.89% of survivors developed any stage of ROP. In

countries with a NMR greater or equal to 5 per 1000 live births, 36.5% of neonates would develop ROP of any severity[6].

The United States of America, United Kingdom and Canada all reported severe ROP as defined by the ETROP study, in infants with mean gestational ages of less than 26 weeks, and mean birth weights of less than 800g. Severe ROP is found in larger, more mature infants in moderately and poorly developed countries in comparison. Argentina, Lithuania, Chile, Cuba, Brazil, Columbia, Peru, Ecuador, Vietnam and India showed mean gestational ages of 26.3 – 33.5 weeks and mean birth weights of 903g – 1527g to be associated with severe ROP[7].

There is little data regarding ROP in Africa outside South Africa. Data from schools for the blind in Uganda, Kenya, Eritrea, Malawi and Ethiopia showed that none of the pupils were blind secondary to ROP, and in Nigeria it was reported as the cause in only 0.5%[7].

In South African studies done at Groote Schuur Hospital and Tygerberg Hospital in the Western Cape, ROP of any severity was found in 19.2%[8] and 33.4%[9] of infants respectively. In Gauteng, Kalafong Hospital showed any ROP in 24.5%[10] and Chris Hani Baragwanath Academic Hospital 16.3% of infants screened[11].

At Chris Hani Baragwanath Academic Hospital, Mayet et al found the mean birth weight of neonates with ROP to be 1093.7g, compared to those without ROP at

1215.6g. No severe ROP was found in infants above 1250g. Although ROP was found in 16.3% of infants threshold disease was only found in 1.6%. A significant number were lost to follow up thus limiting the study. The study showed that gestational age was an unreliable factor to assess risk in our population due to infrequent first trimester ultrasound scans and often uncertain last menstrual periods[11].

The rates of severe ROP have been found to be lower in infants of African descent populations in studies in the United States of America and United Kingdom by Saunders for the Cryotherapy for Retinopathy of Prematurity Cooperative Group[12], Ying for the e-ROP Cooperative Group[13] and Husain in London[14]. In Israel, Monos also found that African infants were less likely to develop ROP, but also that this may be related to the amount of melanin in the choroid and retina. Infants with darker pigmented retinas have been found to have lower incidences of ROP. Dark skinned individuals have increased concentrations of melanin, which is a known free radical scavenger. As a significant part of the pathogenesis of ROP consists of oxygen toxicity and the generation of superoxide free radicals, the increased melanin may have a protective effect[15].

Another study in the United Kingdom found that the infants of African descent, along with Asian infants had a higher rate of ROP when compared to white infants even after adjustments were made for birth weight and gestational ages. It has been suggested that this difference may be due to more African infants being

small for gestational age, as well as having better survival rates than their white counterparts[16].

1.3 Pathophysiology of Retinopathy of Prematurity

Vasculogenesis of the retina usually starts at approximately 12 weeks gestation in utero when the vascular precursor cells lay down the framework. The increased metabolic demands of the maturing retinal neurons spur on angiogenesis at approximately 17 weeks gestation, building onto the vascular framework and radiating outward from the optic nerve. The relative physiological hypoxia from this metabolic demand results in the release of Vascular Endothelial Growth Factor (VEGF) stimulating new vessel formation. In the retina Insulin-like Growth Factor – 1 (IGF-1) regulates VEGF, and a minimum level is required for maximum signalling of the pathways involved [17, 18].

The pathophysiology of ROP is understood to be due to abnormal vascularisation of the retina which takes place in two phases postnatally. Firstly at birth the relative hyperoxia of the ex-utero environment, with or without supplemental oxygen, leads to down regulation of hypoxia-driven growth factors and results in vascular obliteration[17]. In addition the lack of optimal levels of IGF-1 and essential fatty acids found in utero seem to contribute to the first phase of ROP[4].

Secondly at 30 – 32 weeks pathological neovascularisation develops. As metabolic demands from the retina increase causing hypoxia, there is an upsurge in the release of growth factors in response resulting in neovascularisation. These new vessels remain on the border between the vascular and avascular retina and do not perfuse the avascular portion of the retina[17]. The abnormal vessels are also more permeable and result in fibrosis, scarring and at the most severe retinal detachment. The degree of ROP is dependent on the balance between the oxygen demand of the retina and the supply. In most cases ROP regresses spontaneously as the vascularisation of the retina progresses[4].

Thus, abnormal levels of postnatal growth factors such as VEGF and IGF-1, that impact on both vascular growth and weight gain would have an impact on the second stage of ROP. The degree of avascularisation from the first stage of ROP has an influence on the extent of the second stage of ROP.

1.4 Risk Factors

Risk factors can be classified into prenatal and postnatal as represented in Table 1.1.

Table 1.1 Risk factors for Retinopathy of Prematurity [4,17,18,19,20]

Prenatal	Postnatal
• Birth weight • Gestational age	• Hyperoxia • Poor postnatal nutrition • Low IGF-1 levels and poor postnatal growth • Neonatal infection • Hyperglycaemia, insulin use

Prenatal factors determine how vulnerable the retina is to the stresses that could result in abnormal vascular development. The more premature the infant is, the more immature the neural and vascular tissues, and so the higher the risk of damage. In addition, a very premature infant will be hospitalised for a longer period, which exposes them to more postnatal risks [4, 17]. It has also been found that poor intra-uterine growth resulting in being born small for gestational age is an additional risk for ROP[18].

As the prenatal factors are determined at birth, the postnatal risks are modifiable targets for prevention and therapy. The first risk factor is the relative hyperoxia at birth and the secondary suppression of the growth factors. The balance between prevention of ROP and mortality guide oxygen saturation targets and the strict management of oxygen therapy is a known important strategy in avoidance of ROP[4, 17, 19].

Secondly factors lacking in the postnatal environment usually found in-utero that support normal retinal development during the third trimester are more recent subjects of research. Premature infants have increased metabolic requirements than they would have had in utero having to generate heat, adapt to the postnatal environment and overcome complications such as chronic lung disease. Enteral feeding is also complicated with an immature gastrointestinal tract, and intravenous nutrition only provides the basic nutritional requirements[18]. Premature infants do not receive the large amount of omega 3 and omega 6 fatty acids transferred transplacentally during the third trimester. The balance between these two essential fatty acids is vital in the survival in both the vascular and neural cells in the retina[17]. Hyperglycaemia and treatment with insulin have been shown to increase the risk of both mild and severe ROP[20] emphasising the importance of a balanced approach to nutrition.

Low IGF-1 levels are also associated with poor postnatal weight gain and brain growth as measured by head circumference. In utero IGF-1 levels increase mostly during the third trimester[4]. After a preterm delivery the loss of the maternal-foetal

interaction results in a rapid decrease in these levels and a very slow increase due to reduced liver production secondary to immaturity and inadequate nutritional substrates[18].

Neonatal infections, in particular fungal infections also increase the risk of the development of ROP. This may be due to systemic inflammation associated with sepsis, which may worsen the effects of the hyperoxia[4].

By definition, ROP occurs only in preterm infants, as it requires an incompletely vascularised retina. In certain circumstances, however more mature infants can be at risk as well. Prenatal risks include pregnancy related hypertension. Postnatal asphyxia and hypoxia-ischaemic encephalopathy along with the infections mentioned previously can put term infants at risk of retinopathy.[21].

1.5 Classification of Retinopathy of Prematurity

The International Classification of Retinopathy of Prematurity was initially developed in 1985 to provide a standardised description of the staging and location of disease. It has been updated in 1987 and 2005[22].

The location is described in zones, which are concentric circles centred on the optic nerve, and includes the hours of a clock face to indicate the areas involved. The staging of the disease is determined by the most severe manifestation of the disease in the eye. These are described in more detail in Table 1.2 and Figure 1.1. Stage 1 and Stage 2 ROP are likely to spontaneously resolve, but Stage 3 is at risk of progressing and causing vision loss.

Table 1.2. Staging of ROP

The International Classification of Retinopathy of Prematurity[22]

	Definition	Description
Stage 1	Demarcation Line	Thin flat white line between vascular and avascular retina
Stage 2	Ridge	White or pink line with height extending above the plane of the retina
Stage 3	Extraretinal Fibrovascular Proliferation	Neovascularisation extending into the vitreous makes ridge appear ragged
Stage 4	Partial Retinal Detachment	Extrafoveal (4A) or Foveal (4B)
Stage 5	Complete Retinal Detachment	Funnel-shaped usually
Plus Disease	Arterial tortuosity of posterior retinal vessels and venous dilatation	
Aggressive Posterior (AP-ROP or Rush disease)	Severe form of ROP with rapid progression. Posterior prominence of plus disease that does not always follow the usual stepwise progression in severity	

Figure 1.1 Zones of Retinopathy of Prematurity[4]

Right eye

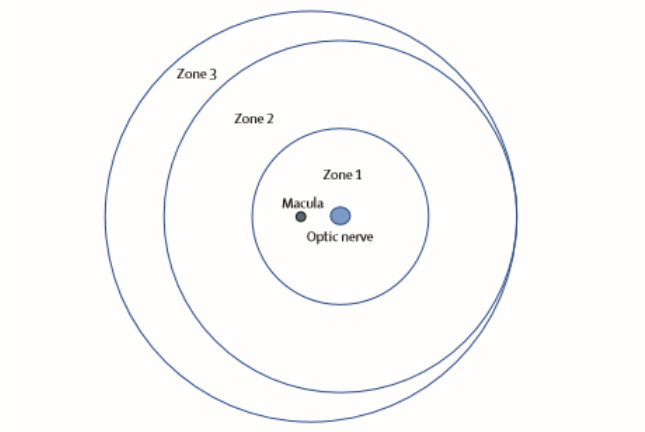
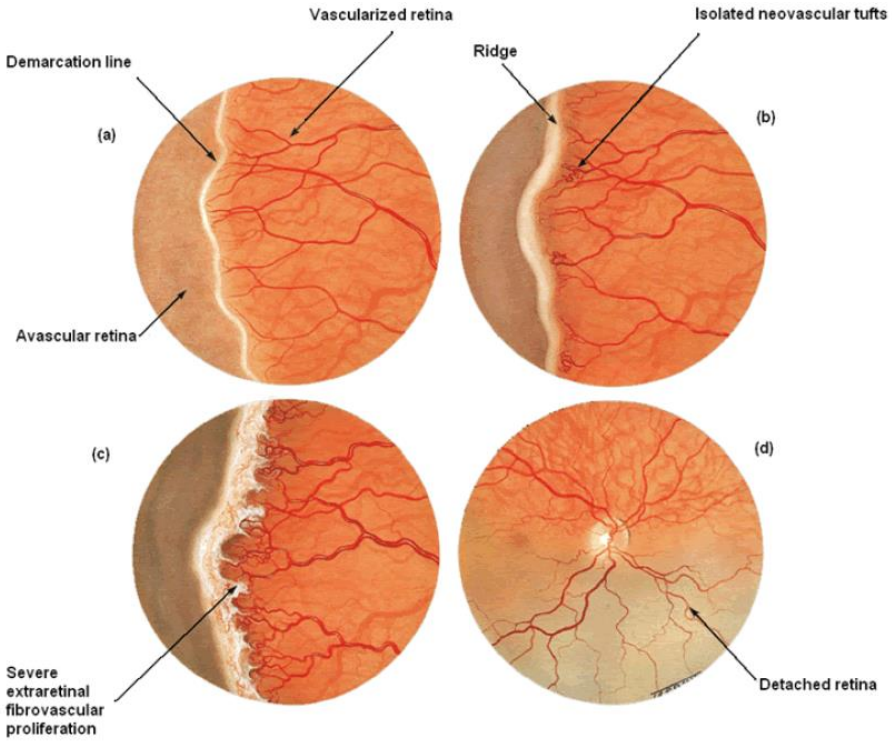


Figure 1.2 Stages of Retinopathy of Prematurity[23]

(a) Stage 1 ROP; (b) Stage 2 ROP; (c) Stage 3 ROP; (d) Stage 4 ROP



Following on the The Early Treatment for Retinopathy of Prematurity (ETROP) study severe ROP was classified into Type 1 and Type 2 as described in Table 1.3. Type 1 ROP requires treatment, whereas Type 2 requires serial follow up examinations with treatment if it progresses to Type 1[24].

Table 1.3 The Early Treatment for Retinopathy of Prematurity (ETROP) Study[24]

Type 1 ROP	Type 2 ROP
• Zone I, any stage ROP with plus disease • Zone I, stage 3, with or without plus disease • Zone II, stage 2 or 3 ROP, with plus disease	• Zone I, stage 1 or 2 with no plus disease • Zone II, stage 3 with no plus disease

1.6 Retinopathy of Prematurity Screening

ROP screening programmes have a high sensitivity but low specificity. The aim is to prevent blindness in any child, but as a result only a very small proportion of those screened have positive findings, and an even smaller minority require treatment.

The WHO VISION 2020 targets for the control of blindness in children include ensuring that all infants at risk of ROP have a fundus examination by a trained observer 6–7 weeks after birth. Cryo or laser treatment should be provided for all those with threshold disease[1]. Worldwide screening guidelines vary. There are two main approaches to developing guidelines for screening: firstly, using gestational age and birth weight alone, and secondly using gestational age and birth weight along with illness criteria[25]. This second method takes the clinical course of the infant and the impact of known risk factors such as prolonged oxygen exposure into account.

The timing of screening examinations is also not consistent. Some guidelines calculate the examinations to be done at postnatal ages regardless of gestational age at birth, for example WHO Vision 2020 suggests screening at 6 – 7 weeks postnatal age[1]. However most guidelines plan the examinations based on corrected gestational age (CGA). A schedule was developed from a meta-analysis which suggested first screening at a CGA of 31 weeks or postnatal age of 4 weeks, whichever came latest. This also correlates with the natural history of ROP[26]. Screening is continued until the risk of ROP developing is minimal, usually at a CGA of 37 weeks or when zone 3 is vascularised clinically. If ROP is present on initial screening, the premature infant examinations continue at 1 – 2 weekly intervals until regression is seen on at least two occasions[25].

In the United Kingdom the guidelines recommend all infants born at ≤1500 g and/or less than 32 weeks gestation should have an ophthalmology screen[27]. In

the USA Infants with a birth weight of ≤1500 g or gestational age of 30 weeks or less, and selected infants with a birth weight between 1500 - 2000 g or gestational age of >30 weeks with an unstable clinical course are recommended to be screened[28]. Both follow the schedule of examinations based on CGA of the patient.

These screening programmes developed in first world settings are not always appropriate for middle and low-income countries. Thirteen percent of infants in middle and low income countries that were found to have ROP had birth weights and gestational ages greater than that of the United Kingdom screening criteria[7].

To compound the problem, a shortage of specialised ophthalmology services and screening programmes in South Africa resulted in only 19.2% of infants that fulfil the screening criteria being examined by an ophthalmologist[29]. In the future telemedicine might improve coverage with the use of digital retinal imaging done by trained technicians rather than ophthalmologists and referral to centralised ophthalmology centres as required[30].

The South African guidelines suggests screening for all neonates born below 32 weeks gestation, weighing < 1500g at birth or with risk factors such as family history, cardiac arrest, multiple blood transfusions, exchange transfusions and hypoxic ischaemic encephalopathy (HIE). It is recommended that examinations are done between 31 and 32 weeks corrected gestational age or between 4 and 6 weeks chronological age, whichever is later[31]. The rates of ROP requiring

treatment from available screening programmes were low at 0.6 – 2.9% with all infants weighing <1200g at birth[29].

At Chris Hani Baragwanath Academic Hospital previous studies have shown that gestational age is an unreliable factor to assess risk in our population due to infrequent first trimester ultrasound scans and often uncertain last menstrual periods. For this reason the screening criteria at Chris Hani Baragwanath Academic Hospital is based on birth weight[11].

The screening guidelines for retinopathy of prematurity as per Chris Hani Baragwanath Academic Hospital ROP guidelines are as follows:

1. All infants with a birth weight of below 1500g
2. Infants with a birth weight of 1500 – 2000g who received mechanical ventilation for more than 7 days
3. Infants with a birth weight of 1500 – 2000g who received supplemental oxygen for more than 2 weeks
4. Infants with any birth weight who received supplemental oxygen for more than 6 weeks will be included.

1.7 Treatment of Retinopathy of Prematurity

The Cryotherapy for Retinopathy of Prematurity Study (CRYO-ROP) determined that a 50% reduction in retinal detachment was achieved with treatment at a specific time during the course of disease, referred to as threshold disease. It is defined clinically as at least five contiguous or eight cumulative clock hours of stage 3 ROP in zone I or II in the presence of plus disease [32].

However visual acuity was still poor, with less than 20% of infants having a visual acuity better than 20/40. Subsequently The Early Treatment for Retinopathy of Prematurity Study (ETROP) found that earlier treatment results in improved visual outcomes. This is referred to as prethreshold disease. Following on the study it is recommended that peripheral retinal ablation should be considered for any eye with Type 1 ROP, defined as:

- Zone I, any stage ROP with plus disease or
- Zone I, stage 3, with or without plus disease or
- Zone II, stage 2 or 3 ROP, with plus disease.

Continued serial examinations as opposed to peripheral retinal ablation, should be considered for any eye with Type II ROP, defined as:

- Zone I, stage 1 or 2 with no plus disease or
- Zone II, stage 3 with no plus disease[24] .

Cryotherapy was initially the treatment of choice to ablate the non-vascularised retina, but laser ablation has subsequently replaced it as the gold standard of management[33]. Both these therapies prevent progression of ROP by destroying retinal cells producing VEGF. Inhibitors of VEGF such as bevacizumab have begun to gain favour as they have been shown to require repeat treatments less frequently[34], and have fewer ocular complications when compared to laser ablation. Intravitreal VEGF inhibitors such as bevacizumab injections do not permanently damage the retina as laser does, and allows the retina to continue to develop. This results in better visual fields and refraction. Concern does exist however regarding the systemic effects of these treatments on the developing organs in preterm infants, and further trials are needed to study their safety[35].

1.8 WINROP (Weight, IGF-1, Neonatal Retinopathy of Prematurity)

WINROP is an algorithm developed by The Sahlgrenska Center for Paediatric Ophthalmology Research in Gothenburg, Sweden. A model was sought that took known postnatal risks into consideration when predicting ROP along with prenatal factors of birth weight and gestational age. WINROP works from a reference model calculated using logistic regression with expected values from the weights and IGF-1 levels of infants with no or mild ROP. Alarms for the possible development of ROP were developed for deviations from the expected weight gain over time. Initially the algorithm required both weekly blood IGF-1 levels as well as weekly weights. Now the only data required is sex, gestational age at birth and the weekly weights to calculate the risk[36].

WINROP showed 100% sensitivity for stage 3 ROP in the Swedish population[37]. This algorithm was then incorporated into a web-based computer program to calculate the alarms. A further prospective study of the online surveillance system again showed a sensitivity of 100%, specificity of 32% and positive predictive value of 24% for stage 3 ROP. For sight-threatening ROP the sensitivity was again 100% with a specificity of 54% and a positive predictive value of 41%, thus indicating its usefulness as a screening tool[38].

The algorithm is accessed online after registration with the WINROP website (https://winrop.com) with a password protected login. Patients can either be entered anonymously or as named patients. Once the weekly weights have been entered risk is indicated as red or green lamps indicating high or low risk respectively. The timing of a high risk alarm is also indicated in gestational age in weeks. The final ophthalmology examination is also inserted into the online database.

A retrospective study in the USA using the WINROP online statistical surveillance program with only weekly weights still showed 100% sensitivity with all infants with severe ROP infants triggering an alarm. These infants triggered an alarm at a median of 3 weeks of age, 9 weeks before the diagnosis of severe ROP. In the infants that did not trigger an alarm or triggered a low risk alarm, none developed more than mild ROP and all regressed without treatment. As all the infants that developed severe ROP triggered a high risk alarm, and these patients totalled

25% of those screened, it was postulated that the number of screens could be reduced by 75%[36].

WINROP has been validated using retrospective cohort studies for the prediction of severe ROP in Switzerland (sensitivity 90%)[39], Brazil (sensitivity 90.5%)[40], North America (sensitivity 100% and 98.6% in two studies) [36, 41], Mexico (sensitivity 84.7%)[42], China (sensitivity 87.5%)[43], South Korea (sensitivity 90%)[44], and Scotland (sensitivity 87.5%)[27]. The prediction tool is simple to use and is implemented in 47 countries by 256 caregivers. It has been useful in highlighting the patients at highest risk in order to prioritise and initiate early interventions, and thus managing resources appropriately[45]. No data has been published regarding the efficacy of WINROP in an African population, which is the objective of this study.

CHAPTER 2

2. AIM, OBJECTIVES AND METHODS

2.1 Aim

This study aimed to assess the efficacy of WINROP as a screening tool in predicting ROP in infants undergoing ROP screening at Chris Hani Baragwanath Academic Hospital.

2.2 Objectives

We used the following objectives to evaluate WINROP as a screening tool in our population:

2.2.1 Sensitivity

In order to evaluate the proportion of true positives correctly identified by the WINROP screening algorithm, sensitivity was calculated. This reflects the rate of pick-up of ROP by WINROP.

2.2.2 Specificity

The specificity was calculated to assess how efficiently the WINROP screening

algorithm excluded the possibility of ROP by calculating the proportion of true negatives.

2.2.3 Positive Predictive Value

The proportion of those with a high risk alarm on the WINROP screening algorithm who have ROP was calculated and reflected in the positive predictive value.

2.2.4 Negative Predictive Value

The negative predictive value was used to assess the proportion of those without high risk alarms on the WINROP screening algorithm who did not have ROP.

2.2.5 Positive likelihood Ratio

The positive likelihood ration was used to determine the effect of a high risk alarm on the WINROP screening algorithm on the odds of having ROP.

2.2.6 Mean time of Alarm

When inserting data into the online algorithm those infants that deviate from the growth predicted trigger an alarm depicted as a red lamp on screen. This indicates that they are at high risk of ROP. Note was made of the corrected gestational age when the alarm was triggered. This was to determine if this occurred earlier than the scheduled ophthalmology screening examinations.

2.2.7 Comparison of Complete and Incomplete Weights

Not all the infants were weighed consistently every week. In order to determine the effect of incomplete weights on the efficacy of the screening tool we compared infants with complete weights with those with missing weekly weights.

2.2.8 Rates of ROP

The rates of ROP were calculated using the number of infants diagnosed with ROP born over a two year time period. This is described in more detail below. The rates may not be a true incidence rate as this was a retrospective record review of inpatient files. Some notes may have been missing, and some infants may have missed ophthalmology screening or completed their screening as outpatients.

2.3 Methods

2.3.1 Study Design

This study was a retrospective review of the records of patients who underwent ROP screening as per guidelines at Chris Hani Baragwanath Academic Hospital. Registration for WINROP was undertaken prior to commencement of the study with The Sahlgrenska Center for Pediatric Ophthalmology Research, allowing us access to the online programme with a password protected login.

Weekly ROP screenings are performed by registrars in ophthalmology, and referred to consultants as required. ROP was classified according to the International Classification of ROP[22]. The ophthalmology reports of the routine ROP screenings were reviewed along with the patient records to obtain the required data. As only the inpatient records were available for review, only screens done as an inpatient could be recorded. Not all patients had completed ROP screening by the time of discharge and so the type or severity of ROP diagnosis at time of discharge was used for the study. This data was entered into a modification of the current ophthalmology request form for ROP (see Appendix A).

The gestational age, date of birth, weekly weights and final ophthalmology screening results were entered into the online WINROP algorithm. Patient identifiers such as names and hospital numbers were recorded in a separate document to ensure confidentiality.

The ETROP study[24] was the basis for the categorisation in the study. This was in order to maintain uniformity with other studies evaluating ROP. Patients were classified as follows:

1. No ROP (immature or mature vascularization)
2. Mild ROP (stage 1 or 2 ROP in zone II or III, without plus disease)
3. Severe ROP (any prethreshold, any stage 3, or threshold ROP)[35].

2.3.2 Study Population

2.3.2.1. Inclusion criteria

1. Premature infants born between 1 January 2013 and 31 December 2014 who underwent at least one ophthalmology ROP screening examination
2. Premature infants with a gestational age at birth equal to or less than 32 weeks

   WINROP can only be used reliably for a gestational age at birth of 23 weeks + 0 days to 31 weeks + 6 days. For this reason infants screened by the ophthalmology unit as per the guidelines at 32 weeks were included to fulfil the criteria of 31 weeks. Due to the majority of the gestational ages in our study being calculated by examination with the New Ballard Score[46], which estimates gestation to full weeks, those at 32 weeks were included as 31 weeks + 6 days.

3. Premature infants with a birth weight below 1500g, as per Chris Hani Baragwanath Academic Hospital guidelines

   The screening guidelines for retinopathy of prematurity as per Chris Hani Baragwanath Academic Hospital ROP guidelines are as follows:

   - All infants with a birth weight of below 1500g
   - Infants with a birth weight of 1500 – 2000g who received mechanical ventilation for more than 7 days

- Infants with a birth weight of 1500 – 2000g who received supplemental oxygen for more than 2 weeks
- Infants with any birth weight who received supplemental oxygen for more than 6 weeks will be included

2.3.2.2 Exclusion criteria

Neonates that were noted to have conditions leading to disproportionate weights such as hydrocephalus were excluded.

2.3.3 Statistical analysis

A required sample size of 207 was calculated using a frequency of 16.3% for any ROP, allowing a margin for error of 5% and a total of 220 patients were included.

Once the data was compiled in the online programme, the database was exported as a spreadsheet. The outcomes of the ophthalmology clinical examinations were then compared to the alarms triggered on the system. Sensitivity and specificity, as well as positive predictive and negative predictive values were calculated based on high risk alarms and clinical findings of ROP. The mean time of alarm and average weight gain per week was also calculated. The average weight gain per week was calculated using the difference between subsequent average weights per gestational and chronological age.

Results were compared between those patients with complete weekly weights and those with missing weekly weights. Statistical software package Dell Statistica (Version 12) was used to analyse the characteristics of these two groups, using Chi-square tests for categorical variables and Student's t-test for continuous data.

CHAPTER 3

3. RESULTS

3.1 Patient Characteristics

A total of 220 infants were included in the study. The gestational age, birth weight, gender and ROP diagnosis are included in Table 3.1. The complete weight group consisting of 193 infants was also analysed as a group to evaluate the effect of missing weights on the efficacy of WINROP. The mean birthweight of all the infants was 1115g (standard deviation 201.0 grams). Birth weights were normally distributed. Gestational ages were slightly skewed towards the larger gestational ages although not significantly so with a median of 29 weeks (interquatile range 28 – 30 weeks) and a mean of 29.1 weeks (standard deviation 1.8 weeks). This is likely because more mature infants have better survivial rates. For comparison with previous studies of WINROP the mean gestational age was used.

There was no statistical difference in gestational age and weights between the infants with complete weights as compared to the infants with incomplete weights (p=0.32 and p=0.96). There were slightly more females (112, 50.9%) than males in the study population although not statistically significant. Almost 95% of the study population had no ROP when screened. There was no statistical difference

(p=0.60) in the rate of ROP between the complete weight and incomplete weight groups. (Table 3.1).

Table 3.1 Patient Characteristics and Rates of ROP

	All infants	Complete weights	Incomplete weights	P value
Number	220	193	27	
Mean gestational age (weeks) (±SD)	29.1 (±1.8)	29.1 (±1.8)	28.7 (±2.0)	0.32*
Mean birth weight (grams) (±SD)	1115.5 (±201.0)	1115.8 (±201.2)	1113.7 (±203.5)	0.96*
Male gender n (%)	108 (49.1%)	92 (47.7%)	16 (59.3%)	0.25#
No ROP n (%)	207 (94.1%)	181 (93.8%)	26 (96.3%)	0.60#
ROP mild n (%)	8 (3.6%)	7 (3.6%)	1 (3.7%)	
ROP severe n (%)	5 (2.3%)	5 (2.6%)	0	
ROP treated as inpatient n (%)	2 (0.9%)	2 (1.0%)	0	

* Students t-test, # Chi-square

3.2 Rates of Retinopathy of Prematurity

The rates of ROP in our population were low with any severity of ROP at 5.9% and severe ROP at 2.3% (Table 3.1). Most of the patients with ROP were in the complete weight group, with only one patient with mild ROP missing weights. Two patients were treated with bevacizumab injections by the ophthalmology unit as inpatients.

3.3 Average weight gain

Using the database of weekly weights, an estimation of weekly weight gain had been created. The weekly weight gain ranged between 4.6 to 83.8g/kg per chronological week. This is represented in Table 3.2 and Figure 3.1 shows the average weight gain per week. The number of infants per chronological week is included to demonstrate the reduction in numbers as the chronological weeks progress, which may have resulted in the average weight gain being less significant as seen in week 9 in Table 3.2.

Figure 3.1 Average Weight per Chronological Week

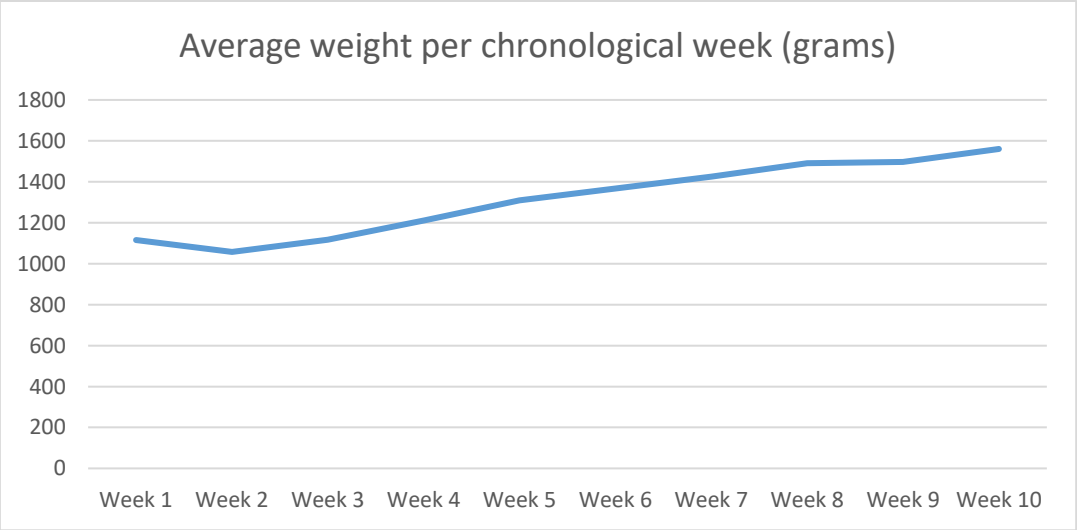


Table 3.2. Average Weight per Chronological Week

Chronological week	Number of infants	Average weight (g) Mean (±SD)	Average gain per week (g)	Average gain per week (g/kg)
1	220	1115.5 (±220.6)		
2	197	1057.6 (±192.7)	- 57.9	-51.9
3	210	1117.4 (±196.8)	59.8	56.5
4	211	1211.1 (±217.2)	93.9	84.0
5	214	1309.4 (±231.1)	98.3	81.2
6	154	1366.8 (±232.1)	57.4	43.8
7	114	1413.6 (±244.0)	58.2	42.6
8	71	1490.7 (±286.9)	65.7	46.5
9	20	1497.5 (±184.0)	6.8	4.6
10	9	1560.6 (±236.7)	63.1	40.4

The weekly weight change ranged from a loss of 79.6g to a gain of 83.7g when calculated on weights according to corrected gestational age. This is represented in Figure 3.2 and Table 3.3. The number of infants per gestational age in weeks is included to demonstrate the reduced numbers in the earliest corrected gestational ages, which may have impacted on significance of the calculations at these corrected gestational ages.

Figure 3.2 Average Weight per Corrected Gestational Age

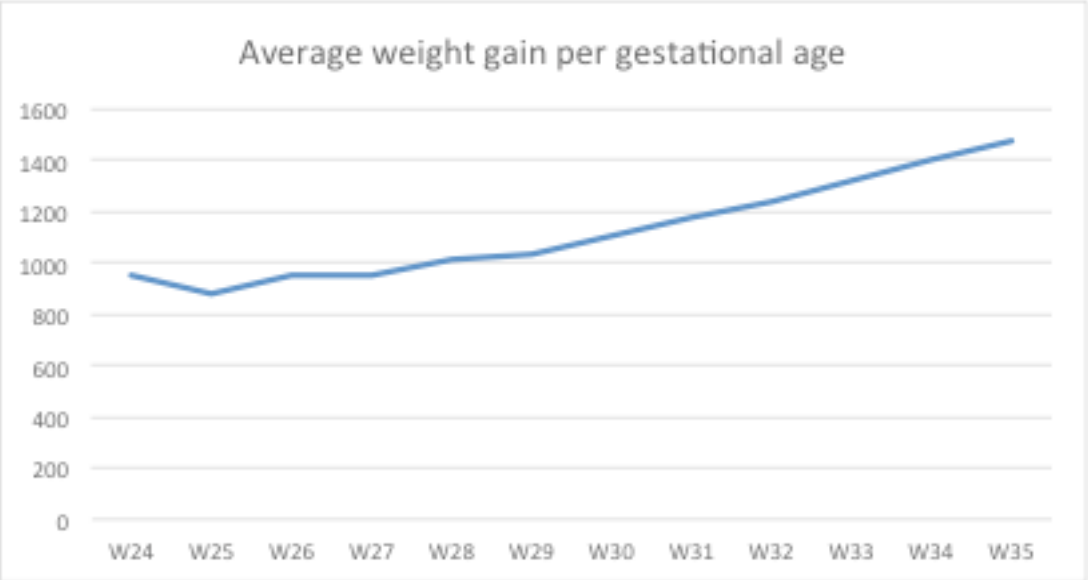


Table 3.3. Average Weight Gain per Corrected Gestational Age

Corrected gestational age (weeks)	Number of infants	Average weight (g) (±SD)	Average gain per week (g)	Average gain per week (g/kg)
24	1	955		
25	3	875.3 (±68.3)	-79.7	-83.5
26	21	954.4 (±145.7)	79.0	90.3
27	37	950.8 (±145.1)	-3.6	-3.8
28	94	1016.9 (±164.7)	66.1	71.3
29	113	1030.2 (±173.9)	13.3	13.1
30	162	1103.4 (±182.2)	73.2	71.1
31	210	1176.7 (±202.9)	73.3	66.4
32	209	1238.0 (±208.7)	61.3	52.1
33	212	1321.7 (±232.4)	83.7	67.6
34	197	1403.5 (±243.2)	81.8	61.9
35	165	1472.1 (±255.3)	68.6	48.9

3.4 Efficacy of WINROP

3.4.1 Alarm

The WINROP programme triggered a high risk alarm in 155 out of 220 infants (70.5%) at a mean of 30.7 weeks gestational age. Seventeen infants triggered an alarm at birth for being significantly small for gestational age; although none went on to develop any ROP.

3.4.2 Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Values

The sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and positive likelihood ratios were calculated for all infants as well as for those with complete weights, and for all stages of ROP and severe ROP (Table 2.3). All the severe ROP patients triggered a high risk alarm. Compared to the sensitivity for severe ROP (100%), the sensitivity for all stages ROP was reduced at 76.9% in all infants and 83.3% in the complete weight group. The specificity was low in all groups, with such a large number of the total infants triggering alarms, due to poor weight gain. The positive likelihood ratios were 1.1 for all stages of ROP, and 1.4 for severe ROP.

All patients with any stage of ROP were due for follow up with the ophthalmology department as outpatients at one to three weeks after the last screen. These records were unavailable for the purposes of this study, so it is unknown if the ROP regressed or worsened.

Table 3.4. Results for all patients with any stage of ROP

	Disease	No Disease	
Test positive	10	145	155
Test negative	3	62	65
	13	207	220

Sensitivity = 10/ (10+13) = 76.9%

Specificity = 62/(62+155) = 30.0%

PPV = 10/(10+145) = 6.5%

NPV = 62/(62+3) = 95.4%

Table 3.5. Results for patients with complete weights with any ROP

	Disease	No Disease	
Test positive	10	133	143
Test negative	2	48	50
	12	181	193

Sensitivity = 10/(10+2) = 83.3%

Specificity = 48/(48+133) = 26.5%

PPV = 10/(10+133) = 7.0%

NPV = 48/(48+2) = 96%

Table 3.6. Results for all patients with severe ROP

	Disease	No Disease	
Test positive	5	150	155
Test negative	0	65	65
	5	215	220

Sensitivity = 5/(5+0) = 100%

Specificity = 65/(65+150) = 30.2%

PPV = 5/(5+150) = 3.2%

NPV = 65/(65+0) = 100%

Table 3.7. Results for patients with complete weights with severe ROP

	Disease	No Disease	
Test positive	5	138	143
Test negative	0	50	50
	5	188	193

Sensitivity = 5/(5+0) = 100%

Specificity = 50/(50+138) = 26.6%

PPV = 5/(5+138) = 3.5%

NPV = 50/(50+0) = 100%

Table 3.8 WINROP performance in predicting ROP

	Severe ROP		All ROP	
	All infants	**Complete weights**	**All infants**	**Complete weights**
Sensitivity	100%	100%	76.9%	83.3%
Specificity	30.2%	26.6%	30.0%	26.5%
NPV	3.2%	3.5%	6.5%	7.0%
PPV	100%	100%	95.4%	96%
Positive likelihood ratio	1.4	1.4	1.1	1.1

CHAPTER 4

4. DISCUSSION

The rates of ROP in our population were found to be low at 5.9% for any severity of ROP and 2.3% for severe ROP, when compared to other populations in the upper middle income countries[47].

The patient population at Chris Hani Baragwanath Academic Hospital is largely African with the vast majority of patients being of black race. A study by Mayet et al from 2001 – 2003 found that 99% of infants screened for ROP at Chris Hani Baragwanath Academic Hospital were of black race, and only those of black race were used for analysis. Rates of ROP were low compared to other upper middle income countries with ROP of any severity at 16.3% and stage 3 ROP at 2.5%[11]. This is despite the neonatal unit having far fewer oxygen blenders and less stringent oxygen targets at the time.

A study done at Kalafong Hospital in 1999 by Delport et al also only analysed the black infants screened. The rates of ROP were higher in comparison in this population with any stage of at ROP 24.5% and stage 3 ROP at 6.4%[10]. This is still lower than the rates in most upper middle income populations. Unfortunately, other studies on ROP in South African populations have not commented on race for further comparison.

High risk alarms were triggered by a large proportion of infants at Chris Hani Baragwanath Academic Hospital (70%) despite the low rate of ROP (5.9%), resulting in a low negative predictive value. As a comparison in other countries who have studied WINROP, only Mexico had more alarms at 79.2%, but also found severe ROP in 56.3% of their infants. In this population, ROP was found in larger more mature infants. It was also disclosed that gestational age estimates, antenatal care, oxygen monitoring were suboptimal[42]. Elsewhere the rates of alarms were lower but still with higher rates of ROP than our population as demonstrated in Table 4.1.

Table 4.1: Comparison of WINROP Alarms, Rates of Severe ROP, Gestational Age and Birth Weight from Studies Conducted Worldwide

	WINROP Alarms	ROP severe	GA (weeks)	BW (grams)
CHBAH	70.5%	2.3%	29.1	1115.5
Mexico[42]	79.2%	56.3%	31	1420*
China[43]	18.5%	9.8%	30	1416
Brazil[40]	47%	5.7%	30	1215
Korea[44]	52.9%	12.7%	29.3	1263.7
Scotland[27]	43.4%	12.3%	28.8	1201.8
USA[36]	25.5%	8.8%	29	1050
Sweden (ELBW)[48]	78.4%	69%	25+4	784

* Only gives the birth weight and gestational age of Stage 1 ROP.

The sensitivity of WINROP in our study was 100% for severe ROP with or without complete weights, but reduced for any stage of ROP at 76.9%. The subgroup with complete weights did however show an improved sensitivity of 83.3% for any stage of ROP. However, when calculating the positive likelihood ratios the range of 1.1 – 1.4 only indicates a minimal increase in the likelihood of disease with a high risk alarm.

The high number of alarms appears to be related to our poor growth rates postnatally, which deviate from the algorithm used by WINROP. The average weight gain of 0.66g to 12g per day is far below the 15 – 17g/kg per day recommended[49] . The small numbers of infants found on the extremes of both chronological and gestational age made the calculations of average weight gain per week distort from the middle age averages, although all the averages were still far below the recommended average weight gain per day. What seems to be unique in our study is despite the high rate of alarms our numbers of ROP remain low.

At Chris Hani Baragwanath Academic Hospital it is often challenging obtaining expressed breast milk (EBM) in the first few days of life. The mothers of the preterm infants are often unwell, and have difficulties producing milk. For this reason we make use of a donor expressed breast milk (DBM) reserve for those with insufficient maternal EBM. This is unfortunately often inadequate for the large number of preterm infants that are treated in the neonatal unit. Although DBM is

donated, screening and processing the milk is costly. In a study in the United States of America the cost was quoted as $4 (approximately R48 at current exchange rates) per 30ml, excluding transport in 2011. It was calculated that in a population of infants <1500g and <33 weeks gestational age, the average cost for DBM ranged from $27 to $590 (approximately R327 – R7138 at current exchange rates) depending on the available maternal milk[50]. The Neonatal Unit at Chris Hani Baragwanath Academic Hospital gets 20 bottles of 200 mls each per week. This is not enough to cater for the ever-growing premature population. There is a unit policy of which infants are eligible for DBM and once screened to be eligible for DBM the infant only receives the DBM for two weeks.

The large burden of HIV in our population also affects preterm infant feeding and growth. In 2015 Statistics South Africa estimated 18.99% of woman between the ages of 15 and 49 years were HIV positive[51]. Mixed feeding has been found to increase HIV transmission and decrease survival[52]. This forces us to depend on EBM from the mother or the limited breast milk reserve. As a referral hospital many patients are transferred from distant centres, and inadequate lodger facilities results in insuffient EBM from mothers who often do not have the finances to travel into our centre daily. This places further burden on the breast milk reserve. Further study into the factors affecting our poor postnatal growth rates would be helpful.

A study conducted in a multiracial London neonatal unit showed that black infants had lower levels of IGF-1 at 32 and 33 weeks gestation when compared to white patients. The mean IGF-1 levels for black infants were 9.7 µmol/L, 8.8 µmol/L and

9.4 µmol/L at 31, 32 and 33 weeks CGA respectively. This was significantly lower when compared to non-black infants' levels at 14.3 µmol/L, 17.2 µmol/L and 22.3 µmol/L over the same age range. As expected, along with the lower IGF-1 levels they had lower absolute postnatal weight gain. Despite these known risk factors the black infants still needed less treatment for ROP than the white infants[53]. It is known that the adult black population has lower IGF-1 levels than white populations[54] and this seems to be confirmed in infants too[53]. This would suggest that screening algorithms relying on growth and IGF-1 levels are population and race dependent which may account for the differences in efficacy of WINROP outside of Sweden, including in our study.

Although black infants may not show the same growth as the white infants, our study does highlight an important deficiency in care with our growth rates being inadequate. Meta-analysis showed that human milk feeding might play a protective role in the prevention of any ROP as well as severe ROP[55]. Thus the promotion of early expressed breast milk for preterm babies is an area for improvement.

In our resource scarce setting patients do not have the transport funds for repeated outpatient appointments. WINROP may assist in predicting those who are at highest risk of ROP and so need to prioritise screening, although the low positive likelihood ratio only gives a minimal increase in the likelihood of disease. With such a high number of alarms WINROP would only potentially reduce the numbers for screening by 30%. The alarm was triggered at a mean of 30.7 weeks

gestational age, which is before the routine screening by ophthalmology. This could perhaps assist in the planning of discharges and follow up visits in infants discharged before the screen, as frequently happens in our hospital with a discharge weight of 1650g. A database tracking the infants receiving ROP screening, including their WINROP risk alarm would assist in not only the management of these infants, but also give more accurate statistics on ROP.

There is potential for further study in more rurally based health facilities where patients would require travel for the ophthalmology screening, as an alternative to telemedicine as the equipment and trained personnel are not yet available in our setting.

CHAPTER 5

5. LIMITATIONS

A required sample size of 207 was calculated using a frequency of 16.3% for any ROP, allowing a margin for error of 5% and a total of 220 patients were included. In our study, the rates of ROP were lower than the previous study at 5.9% for any ROP. This would influence the accuracy of the sample size calculation, and therefore the power of the results.

As this study was a retrospective record review it included only the files that were located. Only inpatient ROP screening examinations were used in this study as no outpatient records were available. Many preterm infants were discharged prior to their first screening examination and were referred to the ophthalmology unit as outpatients. Some infants had initial screening examinations as inpatients, but were discharged prior to follow up examinations as outpatients. In these cases we could only include the screens documented in the inpatient file and not their final review by the ophthalmology unit. This may have influenced our results as I am not certain of the final diagnosis or stage of ROP in these infants, but rather using the diagnosis or stage at time of discharge.

The examinations are done by the ophthalmology registrars and referred to consultants as required. There is rotation of the registrars and so perhaps no

consistency with regards to examiners doing the screening examinations which may create some bias.

In the vast majority of our infants early antenatal ultrasounds were not performed. Gestational ages antenatally are often based on last normal menstrual peroid or symphasis-pubis measurements during pregnancy. Postnatally infants are expected to have a New Ballard Score performed to estimate their gestational age. This is usually undertaken by junior doctors working in the labour ward. The inexperience of these doctors may cause erroneous estimations of gestational age, which influences the performance of WINROP as an algorithm.

Race was unfortunately not documented as part of the data collected. This would have been useful considering the findings related to rates of ROP and growth of African infants. There is no data available regarding the race of patients admitted to the unit during the time period, although the vast majority of our population is black. As this was a retrospective study limited by incomplete records, data regarding the severity of illness and duration of oxygen therapy was not collected This may have provided interesting comparison to the severity of ROP.

CHAPTER 6

6. CONCLUSION AND RECOMMENDATIONS

Rates of ROP are low at Chris Hani Baragwanath Academic Hospital. This may be due to the vast majority of patients being African, which is known to be a protective factor against ROP due to the anitioxidant properties of melanin pigments.

WINROP showed 100% sensitivity but a low specificity and low negative predictive value secondary to a large proportion of high risk alarms. The likelihood of disease was only minimally increased with a high risk alarm. It appears that the test would be of limited benefit in our population.

The increased alarms were due to poor postnatal weight gain that differed from the expected weights calculated for the WINROP algorithm. The cause of poor growth in our infants is multifactorial and requires further investigation.

Our study seems to confirm that IGF-1 levels and growth are population and race dependent, resulting in differences in the performance of WINROP compared to those in other parts of the world. This could form the basis of a future prospective study.

A future prospective study would be useful at a district or rural hospital where ophthalmology review is logistically difficult or not available as some benefit may be offered by reducing the number of referrals.

A database containing the ROP screening examinations and WINROP alarms of infants could be a helpful tool, and perhaps be part of a prospective study in the future. Such a database may be useful in creating a complete ROP report for each infant, thus ensuring that fewer infants are lost to follow up. The high risk alarms would assist in prioritising patients for screening and early intervention. As our hospital is a tertiary referral centre it would be important to plan down referrals to centres without on site ophthalmology more carefully in high risk infants.

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APPENDICES

APPENDIX A: DATA SHEET

ROP DATA SHEET Study no:

Gestational age:_____weeks CGA at screening_____weeks

Birth weight:_____g

Rh: Pos/Neg RPR: Pos/Neg HIV: Pos/Neg

Ventilated: Yes/No Date started: _____; stopped: _____

Oxygen: Yes/No Date started: _____; stopped: _____

NEC: Yes/No TPN: Yes/No

Culture positive sepsis: Yes/No

Organism _____ date of culture _____

Organism _____ date of culture _____

Organism _____ date of culture _____

Weights:

Date	CGA	Weight

Date of ROP Screen____/____/____ (day/month/year)

1st Screen/2nd Screen

Results:

Zone1/Zone 2/Zone 3/Zone 4/Zone 5

Preplus Disease /Plus Disease /Rush Disease

Other:

Discharge: Yes/No Date of Rescreen: _____/_____/_____

APPENDIX B: HUMAN RESEARCH ETHICS COMMITTEE APPROVAL

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH 10005, 10th floor.
Medical School Secretariat: PV Tobias Building 2nd Floor.
Private Bag 3, Wits 2050, www.wits.ac.za

Tel +27 (0)11-717-1252
Tel +27 (0)11-717-2700
Fax +27 (0)11-717-1265

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Office of the Deputy Vice-Chancellor Research & Post Graduate Affairs

MEMORANDUM

TO: **Dr. Samantha Jane Kesting**
Department of Paediatrics
E-mail: sjkesting@gmail.com

FROM: **Mr Rhulani Mkansi**
Administrative Officer: Human Research Ethics Committee (Medical)
Tel: 011 717-1234
E-mail: Rhulani.Mkansi@wits.ac.za

DATE: 30 November 2015

REF: ***R14/49***

PROTOCOL NO: M151123 *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

The protocol below was considered at a meeting of the Human Research Ethics Committee (Medical) **on Friday 27 November 2015.** The Committee requires the following amendments/corrections/information from you before your application can be approved.

Project Title: Prediction of Retinopathy of Prematurity using the WINROP (Weight, IGF-1, Neonatal Retinopathy of Prematurity) screening algorithm in a South African Population

Conditions: **Approved subject to:**

- *Application Form:*
  - January 1, 2013 – December 31, 2014 but section 6.3 indicates that follow up examinations may still be conducted. Clarifying that all follow up examinations to be included will have been conducted before December 2015.
- *Data Collection Sheet:*
  - Provided, please remove identifiers – name, surname, and substitute date of birth with age placing this information into a separate file linked to a study number on the data sheet.

1. **Please submit a covering letter (list all the conditions above and write your response below the each condition and attach relevant documentation), highlight any changes made and send two hard copy to this office. The default for submission is hardcopies – Amendments send by email will not be considered.**
2. **Amendments must be delivered at Faculty of Health Sciences, Phillip Tobias Building, second floor, Cnr York Road and Princess of Wales Terrance**
3. **Office hours: 07h30-16h00**

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH 10005, 10th floor. Tel +27 (0)11-717-1252
Medical School Secretariat: PVT Building, Parktown, 2nd Floor. Tel +27 (0)11-717-2700
Private Bag 3, Wits 2050, www.wits.ac.za. Fax +27 (0)11-717-1265
email: Zanele.ndlovu@wits.ac.za Office email: HREC-Medical.ResearchOffice@wits.ac.za

16 March 2016

Dr Samantha Jane Kesting
Department of Paediatrics

Sent by email to: sjkesting@gmail.com

Dear Dr Kesting

Re: **Protocol Ref no: M151123**
Protocol Title: Prediction of Radiotherapy of Prematurity Using the WINROP (Weight, IGF-1, Neonatal Retinopathy of Prematurity) Screening Algorithm in a South African Population
Principal Investigator: Dr Samantha Jane Kesting
Protocol Amendment

This letter serves to confirm that the Chairman of the Human Research Ethics Committee (Medical) has approved the amendments on the above mentioned study, as detailed your letter dated 03 March 2015

The following document was received:

- Amended Protocol

Thank you for keeping us informed and updated,

UNIVERSITY OF THE WITWATERSRAND
OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH
16 MAR 2016
RESEARCH OFFICE HREC (Medical)
JOHANNESBURG

Yours Sincerely,

.....
Ms Zanele Ndlovu
Administrative Officer
Human Research Ethics Committee (Medical)

APPENDIX C: TURNITIN REPORT

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ORIGINALITY REPORT

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