

Retinopathy of Prematurity Screening Criteria and Work Load Implications at Tygerberg Children’s Hospital, South Africa: a Cross-sectional study

Dissertation Submitted By

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Dedication

This work is dedicated to Martin, Nicole and Grace Kift.

Declaration

I, Elsimé Visser Kift (VSSELS001) hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Signature:

Signed by candidate

Date: 10 March 2016

Abstract

ROP is an important cause of childhood blindness world-wide. Visual loss from ROP can be avoided through good neonatal care, and screening plus early treatment of infants at risk. ROP Screening guidelines used in high-income countries are not appropriate for detecting all ROP in middle-income countries, where more mature infants are at risk. Therefore, the first South African ROP screening guideline was published in 2013. Screening requirements are highly dependent on the quality of care provided and may vary widely between neonatal units. In addition, screening more mature infants may not be feasible where resources are limited. Therefore, ROP screening guidelines should be based on local data. The objectives of this research was to determine optimal screening criteria for retinopathy of prematurity at Tygerberg Children's Hospital (TCH), South Africa and to explore the workload implications of applying different criteria.

A complete literature review was performed and is summarized in section B of this dissertation. The study protocol (Section A) was drafted and sent for approval. The ethics committee of the Faculties of Medicine of both the University of Cape Town [924/2014] and Stellenbosch University [S14/10/218], as well as Tygerberg Hospital, approved the research. The complete study results are discussed in the manuscript (Section C), which will be submitted for publication in the South African Medical Journal. A short summary of the study follows below.

This was a cross-sectional study based on an existing database analysis. The study population was premature infants screened for ROP at TCH, from 1 January 2009 to 31 December 2014. Eligible infants with missing information were excluded from the analysis. The statistical analysis included logistic regression for prediction and classification. The predictors were

birthweight (BW) and gestational age (GA), and the main endpoints were clinically significant ROP (CSROP) and Type 1 ROP (T1ROP).

The cohort of 1104 infants had a median GA at birth of 28 weeks (IQR 27-29; range 24-37) and median BW of 930 g (IQR 820-1040; range 523-2600). ROP (any ROP) was found in 33% (369/1104), clinically CSROP was found in 9% (100/1104) and T1ROP in 2.45% (27/1104). The 27 infants with T1ROP all received laser therapy and were 29 weeks or 1060g and smaller (Median GA: 27 weeks (IQR26-28; range 24-29) and median BW: 815 g (IQR 763-940; range 640-1060)). The most mature infant in the dataset with CSROP that did not require intervention had a GA of 31 weeks and BW of 1530 g.

Among the 621 infants, for whom both GA and BW were recorded, GA was not a significantly better predictor of CSROP than BW ($p=0.521$). Neither were using GA in addition to BW in the prediction model better than using BW ($p=0.181$) alone. The number of screening examinations required was inversely correlated with GA and BW (spearman correlation coefficient -0.20 and -0.27; $p<0.001$). The median number of screening examinations per infant was 2 (IQR 1-3; range 1-11). The number needed to screen to identify one infant needing treatment was 41. Screening 41 infants entailed 83 screening examination visits, four screening hours, one technician and three doctors.

The main study points are:

- The prevalence of treatable T1ROP was low (2.45% (27/1104)).
- BW measurements were as good as GA in predicting CSROP, and are useful in our setting, where reliable GA estimates are often unattainable.
- Screening infants with a GA of ≤ 28 weeks or BW of < 1000 g would have detected all infants requiring treatment in the dataset, but missed two outliers with CSROP.

- Detection of the outliers would have been achieved with the wider screening criteria of GA of >32 weeks or BW>1500g only.
- Screening larger infants requires less work than screening smaller infants.
- Missing data limits the interpretation of the study results.

In conclusion, the avoidance of unnecessary ROP screening examinations is important since it is resource intensive. However, making the local screening criteria narrower on the basis of a limited evidence base may be dangerous. More research is required to develop screening criteria for the identification of more mature infants at risk of ROP in resource limited settings.

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PART A: PROTOCOL

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ABSTRACT

Background and Rationale

ROP is an important cause of childhood blindness world-wide. ROP accounted for 10.6% of blindness in children in schools for the blind in South Africa. Visual loss from ROP can be avoided through good neonatal care and screening plus early treatment of infants at risk of ROP. Screening guidelines are based on birth weight (BW) and gestational age (GA) values that detect infants requiring examination. Screening criteria used in the developed world are not appropriate for the detection of all infants at risk of ROP in middle-income countries, since higher BW infants in these countries may also develop ROP. Additional ROP screening of higher BW infants may not be feasible in resource limited settings or necessary in all middle-income institutions. Therefore, ROP screening guidelines should be based on local data. The purpose of this research is to determine optimal screening criteria for retinopathy of prematurity at Tygerberg Children's Hospital (TCH), South Africa and to explore the workload implications of applying different criteria.

Objectives

1. To determine the BW and GA cut-off values that maximizes the sensitivity of the prediction of ROP.
2. To determine the total number of screening examinations required at different cut-off values of birth weight and gestational age.
3. To determine the number of examinations required to identify one infant needing treatment according to screening criteria recommended by the study data.

Study Population and Eligibility Criteria

The study population is premature infants born in the drainage area of TCH, Western Cape, South Africa. All premature infants screened for ROP at TCH neonatal units from 1 January

2009 to 31 December 2014 for whom the required data are available on the existing ROP database or retrieved from hospital folders will be included in the study. Eligible infants with irretrievable missing information will be excluded from the study.

Study Design

This is a consecutive patient cross-sectional study based on an existing database analysis and retrospective folder review. The variables required for the data analysis for each infant is routinely recorded in the hospital folder on a ROP screening examination form and in the ROP screening Microsoft Excel database on the day of examination. The statistical analysis will include logistic regression for prediction and classification. The predictors are BW, GA and the main endpoint is clinically significant ROP as measured by the gold standard.

Sample size

A large existing database (all 2009-2014 TCH ROP screening examinations) will be statistically analyzed; the sample size is therefore fixed to number of infants with information recorded in the database.

BACKGROUND AND RATIONALE

Retinopathy of prematurity (ROP) is a vision-threatening vasoproliferative condition of premature infants worldwide. In addition to blindness, ROP is associated with an increased incidence of refractive errors, amblyopia, strabismus, cataracts and glaucoma.¹ Among the numerous associations described in the literature, the main accepted risk factors for ROP are low gestational age(GA), low birth weight(BW) poor oxygen management (ie. fluctuating hypoxia/hyperoxia/lack of monitoring) and lack of antenatal steroids. The mainstay of control of visual loss from ROP lies in primary prevention of the condition through good neonatal care and programs of secondary prevention whereby babies at risk of ROP are examined to detect those needing prompt intervention for treatable stages of the disease.² Most ROP Screening guidelines use BW and GA to identify infants needing examination, because these are major risk factors, are relatively straight forward to measure and are recorded routinely. Infants who meet the screening criteria are referred for indirect ophthalmoscopy by a trained ophthalmologist. Although indirect ophthalmoscopy is considered the gold standard for detecting ROP, retina photography with a retina camera (Retcam) has been shown to be a reliable, accurate and cost-effective alternative method of ROP detection.⁴⁻⁶ Detected ROP is classified according to the International Classification of Retinopathy of Prematurity (ICROP) system⁷ (Appendix B) and these infants are followed until ROP has progressed to treatable stages or has resolved spontaneously. Cryotherapy reduced the rate of adverse outcome in threshold ROP by 50%.⁸⁻⁹ Prompt treatment of type one high risk pre-threshold ROP with laser photocoagulation further improved short and long term visual outcomes and is now considered the standard of care for ROP treatment.¹⁰⁻¹¹ Early ROP screening and laser treatment is a resource intensive preventative strategy, but because of the high lifetime costs

of severe visual impairment it has been shown to be highly cost-effective in first world countries.¹²⁻¹³

ROP is responsible for blindness in an estimated 50 000 children throughout the world³ and is now often the leading cause of blindness in children in middle-income countries.¹⁴ The proportion of blindness due to ROP has been shown to be associated with the infant mortality rate (IMR) at country level.¹⁵ In countries with high IMRs, premature infants do not survive. In those with a low IMR ROP blindness is controlled through adequate ROP prevention programmes. In countries with IMRs in the mid-range (9-60/1000 live births) ROP is emerging as a major cause of blindness because improved neonatal care causes an increased premature infant survival rate which is disproportionate to primary and secondary ROP preventative strategy implementation. This phenomenon is known as the ‘third epidemic of ROP’ and is attributed to both an increase in premature infant survival (the cause of the ‘second epidemic’) and poor oxygen management (the cause of the ‘first epidemic’) in neonatal intensive care units (NICUs). Due to these oxygen management inadequacies in middle-income country NICUs larger infants than in high-income NICUs may be at risk and require screening.^{2,15} However, facilities lacking the staff and equipment for continuous infant oxygen monitoring might struggle to allocate resources towards ROP screening expansion or even establishment.

South Africa has an infant mortality rate of 53/1000 live births¹⁶ and has become part of the ‘third epidemic of ROP’.¹⁷ An estimated 16 000 infants in South Africa are at risk of ROP and require screening each year.¹⁷⁻¹⁸ In 1995, ROP accounted for 10.6% of blindness in children in schools for the blind in South Africa.¹⁹ The reported ROP incidence among infants with birth weights less than 1500g in South African academic centres remain low, with the incidence of any ROP ranging from 16.3-24.5% and clinically significant ROP

(CSROP) ranging from 1.56-4.4%.²⁰⁻²³ Those with sight threatening ROP requiring treatment range from 0.6-2.9%.¹⁸

The first South African guideline for the prevention, screening and treatment of ROP was published last year.¹⁷ It recommends the screening of infants with a GA<32weeks or a BW<1500g. Since larger middle-income country infants (GAs: 32-35weeks; BWs: 1500g-2000g) may be at risk of ROP², screening of infants with birth weights up to 2000g with additional features associated with an increased risk of ROP (poor oxygen monitoring, cardiac arrest, multiple blood transfusions, exchange transfusion, severe HIE, family history of HIE) is also recommended. Developing screening guidelines that is appropriate for all in institutions within a country is challenging since quality of NICU care and therefore ROP screening requirements are highly unit dependent.³ Screening higher weight infants may not be feasible in units where resources are limited. Most level 2 hospital NICUs in South Africa, where larger infants are likely to be at risk of ROP, do not even have access to screening facilities.¹⁷ On the contrary, screening larger infants in tertiary institutions in South Africa with high quality neonatal care may be an inappropriate application of scarce resource. Ideally, criteria and guidelines should be based on local evidence of the population of babies at risk of ROP, and these can be modified over time.²

Tygerberg Children's Hospital (TCH) reported a prevalence of any ROP of 31.1% and CSROP of 7.1 % among preterm infants ventilated for respiratory distress (1986-1987)²⁴ and a prevalence of any ROP of 21.8% and CSROP of 4.4% of preterm infants treated exclusively with non-invasive ventilation in the first week of life (2009-2010).²⁰ Only 1.5% of the latter cohort required laser therapy and no screened infants with BWs greater than 1250g had CSROP. The results from these subgroup analyses are instructive but insufficient to inform local screening policy and resource allocation. A focused analysis of the existing TCH ROP screening database is needed to determine optimal screening criteria for

retinopathy of prematurity at TCH and to explore the workload implications of using different BW and GA cut-off values. This work will set a platform for on-going surveillance and further research towards cost-effective intervention and scarce resource distribution.

OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Overall Aim:

To identify optimal screening criteria for retinopathy of prematurity at Tygerberg Children's Hospital(TCH), South Africa and to explore the workload implications of applying different criteria.

Primary objective:

To determine the BW (measured routinely at birth in grams) cut-off value and GA (as estimated using the date of last normal menstruation (LNMD), early ultra sound (EUS) or the New BALLARD score) cut-off value that maximizes the sensitivity of the prediction of ROP (as measured by the gold standard).

Secondary objectives:

- To determine the relationship between birth weight and number of screening examinations.
- To determine the total number of screening examinations required at different cut-off values of birth weight and gestational age.
- To determine the number of examinations required to identify one infant needing treatment according to screening criteria recommended by the study data.

METHODS

Study design

This is a consecutive patient cross-sectional study based on an existing database analysis and retrospective folder review. The variables required for the data analysis (BW, GA and

ROP zone and stage) for each infant is routinely recorded in the hospital folder on a ROP screening examination form (Appendix C) and in the ROP Screening Microsoft Excel database on the day of examination.

Setting and study population

The study population is premature infants born in the drainage area of TCH, Western Cape, South Africa.

Subjects

Premature infants managed at a TCH neonatal unit and referred for a ROP screening examination between 1 January 2009 and 31 December 2014.

Selection, Inclusion and Exclusion criteria

All premature infants screened for ROP at TCH neonatal units from 1 January 2009 to 31 December 2014 for whom the required data are available on the existing ROP database or retrieved from hospital folders. Eligible babies with irretrievable missing information will be excluded from the study.

Measures

Explanatory variables

BW (continuous), GA(continuous), Number of Screening Examinations (continuous), Sex(binary), Ward(categorical), Time of Examination(continuous).

Outcome variables

ROP zone (right eye), ROP stage (right eye), ROP zone (left eye), ROP stage (left eye). These categorical variables will be converted to the following binary (yes/no) variables: Any ROP, Clinically Significant ROP (CSROP), Type 1 ROP (treatable ROP) and LASER

treatment. CSROP is defined as ROP involving zone I, any stage 3 ROP or plus disease associated with any stage ROP in any zone. Type 1 ROP is defined as any stage zone I ROP with plus disease, zone I stage 3 with or without plus disease or zone II stage 2 or 3 ROP with plus disease.

Data management plan

Data collection and entering

The data are routinely collected by neonatologists and ophthalmologists and entered in an Microsoft Excel database which is kept by the paediatric ophthalmology consultant who heads the ROP screening programme at TCH. Since the data are collected routinely by various members of the ROP screening team it may contain a considerable degree of missing data and errors. Some data entering restrictions are in place to minimize recording errors.

Data storage and validation

Once the planned study receives ethics approval, the data sheet (1 January 2009 to 31 December 2014) will be cleaned and exported to STATA 13 for data exploration and statistical analysis. The extent of missing data and recording errors will be examined. Should these be non-random, hospital records will be accessed to retrieve or validate data. Once data collection is complete each infant will be assigned a unique study number for patient confidentiality purposes. The TCH ROP Screening Criteria Study database will be stored on the author's personal computer which is password protected.

Statistical considerations, sample size and power

A large existing database (all 2009-2014 TCH ROP screening examinations) will be statistically analyzed; the sample size is therefore fixed to number of infants with information recorded in the database. The 2009-2010 data alone was sufficient to show a significant

association between BW and CSROP ($p=0.023$, unadjusted odds ratio (OR) not reported) in a recent ROP risk factor finding study²⁰ (using the same dataset). The adjusted association was 1.002 (CI: 1.000 – 1.004; $p=0.038$; adjusted for severe apnoea and gender), which is small and just significant. This study included only infants who were treated exclusively with non-invasive ventilation in the first week of life. Among these 356 babies screened between 2009 and 2010 the prevalence of any ROP was 21.8% and CSROP 4.4%.

Data analysis plan

Descriptive Analysis:

Basic data exploration (univariate analysis) will be performed. Mean and standard deviations will be reported for normally distributed numerical variables and medians and interquartile ranges for skew data. Categorical data will be reported as proportions. The study sample characteristics will be summarized in tables and illustrated graphically (stratification according to number of examinations, ward and the various endpoints will be included).

Analytic Analysis:

Objectives with Analysis Plans

Objective 1: To determine the BW and GA cut-off values that maximizes the sensitivity of the prediction.

Endpoint: CSROP

Analysis: Logistic regression for prediction and classification (ROC curves)

Objective 2: To determine the relationship between birth weight and number of screening examinations.

Endpoint: Number of screening examinations per premature infant

Analysis: Bivariate analysis of two continuous variables (correlation and scatterplots)

Objective 3: To determine the total number of screenings required at different cut-off values of birth weight.

Endpoint: Total number of screening visits

Analysis: Subgroup analysis (exclude those not meeting the criteria). Descriptive statistics.

Objective 4: To determine the number of screening examinations required to identify one infant needing treatment according to screening criteria recommended by the study data.

Endpoint: Number of screening examinations

Analysis: Subgroup analysis (exclude those not meeting the criteria). Descriptive statistics.

Ethical considerations

Previous research protocols for retrospective studies on the existing ROP database were granted ethics approval by the Stellenbosch University in the past: N11-03-082 and S13-10-178.

Informed consent

Application for a waiver of informed parental consent

The study involves the retrospective analysis of the large ROP Screening database (2009-2014). The study subjects are premature infants who all received the TCH ROP screening and treatment standard of care. Contacting each infant's parent to gain informed consent to access and publish recorded data will not be feasible and may compromise the consecutive patient

cross-sectional design required for the diagnostic accuracy study. Parent contact details are not recorded in the database. Accessing this information via individual folder review will be time consuming, contact details are not recorded reliably and may have changed without notice and the study budget and calendar cannot allow for contacting parents.

This is retrospective, non-experimental, no-harm child research and will generate generalizable knowledge likely to minimize risk in local ROP screening and treatment programmes.

Confidentiality

Each infant in the TCH ROP Screening database will be given a unique study identity number. The infants' identities will not be exposed during data analysis and report. The study database will be stored on the PI's personal computer which is password protected.

Standard of care

All infants meeting the screening criteria (BW <1500 or GA < 32 weeks) and those with higher birth weights at increased risk for ROP are referred for early ROP screening and treatment. Examination and staging of infants are done according to the International Classification of Retinopathy of Prematurity (2005 revision)⁷ (Appendix B) by a trained ophthalmologist using a 28-dioptre condensing lens and an indirect ophthalmoscope (and/or specialist interpretation of retcam fundal photography). Infants are examined from 31 weeks corrected GA (4 weeks after birth) and then 1 - 3 weekly until vascularization of zone 3 is completed or the corrected GA of 41 weeks is reached. Infants with treatable stages of ROP (Type 1 ROP) receive laser therapy within 72 hours of diagnosis.

Conflict of interest

The investigator declares no conflict of interest.

STUDY TIMELINE

Calendar year	2014						2015											
	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Protocol development	x	x	x															
HREC submission and approval			x	x	x													
Data cleaning and analysis						x	x	x	x									
Maternity leave										x	x	x	x					
Manuscript preparation and publication														x	x	x	x	x
Dissemination of research results														x	x	x	x	x

STUDY LIMITATIONS

Since this study involves the analysis of data collected as part of routine care (not under rigorous study circumstances) measurement error, data entry errors and missing data may threaten the internal validity of the results. For example, GA is estimated in three different ways (LNMD, EUS and/or the New Ballard score²⁵) but the database does not discriminate which method was used for the recorded value or why. Since the routine of care was applied to all infants referred for ROP screening we hope that potential errors outlined above occurred at random. Non-random missing data or spurious results may necessitate a retrospective folder review to retrieve or validate the database information. This process may not be feasible to complete within the timeframe allowed since the existing database is very large (2009-2014). In this case the data for 2013-2014 only will be retrieved and/or validated.

FEASIBILITY

This is a straight forward, low cost study with a reasonable timeframe. Co-supervisor of this study and UCT MPH Clinical Research Tract student supervisor, Professor Landon Myer, confirmed the feasibility of the proposed study.

FUTURE DIRECTIONS

In addition to informing local ROP screening and treatment policy, this work will identify areas for improvement in current routine ROP screening data management and can create a platform for ongoing ROP surveillance and important further research in cost-effective ROP detection.

STUDY TEAM and INSTITUTIONAL RESEARCH ENVIRONMENT

The author/principle investigator is a MPH (clinical research tract) student with sufficient epidemiology and biostatistics knowledge to complete this study successfully. The supervisors are experienced researchers and experts in their fields. Strong research support structures for developing researchers exist at both the UCT School of Public Health and Stellenbosch University/TCH Centre for Evidence Based Health Care.

BUDGET

TCH ROP Screening Criteria Study Budget	
Personnel Compensation	
Investigators	The PI is a student and the supervisors are university/hospital staff (provide research supervision routinely)
Research Assistant*	R 3 000 – R 10 000
Consultation services	
Statistical Support	The PI has biostats III level training and additional statistical support is offered free of charge by School of Public Health staff to their students.
Computer and Software	
Laptop	The PI's personal equipment and software will be used for data storage and analysis.
External Hard drive	
STATA 13	The University of Cape Town is a STATA license holder and provides student access in designated computer laboratories.
Other direct Costs	
Phone	Broadband/wireless internet access is available at PI home and office. Paperwork and phone call communication will be kept to the bare minimum.
Internet	
Printing	
Office supplies	
Ethics review	Sponsored for students
Publication	The PI plans to publish in the South African Medical Journal. No costs were involved with recent previous publications in this journal.

Justification of budget

This student study is not funded. Costs will be kept to a minimum and covered by the PI.

* Should research assistantship be required for missing data collection or data validation the cost will be covered by the Division of Ophthalmology research fund and the PI.

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PART B: LITERATURE REVIEW

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OBJECTIVES OF THE LITERATURE REVIEW:

The first objective of this literature review was to present a short up-to-date overview of the complex disease entity, ROP. Secondly I aimed to discuss ROP as public health issue. Burden of disease, preventative strategies, organisation of case detection and care, cost effectiveness of interventions and the issues regarding the setup and improvement of ROP programmes. Finally, this review describes the gaps in the literature and rationale for the work presented in this dissertation.

LITERATURE SEARCH STRATEGY:

A search of the PubMed database was performed using the following search terms “retinopathy of prematurity”, ”ROP”, “ROP risk factors”, ”ROP Screening”, “ROP programmes”, “ROP guidelines”, “ROP treatment”, “VEGF”, ”gestational age”, “birthweight”, “retina camera”, “retcam”, ”telemedicine”, “postnatal growth”, ”cost effectiveness”, “incidence”, “burden “and “workload” in various combinations . Abstracts were reviewed and relevant English full text articles were retrieved. Mainly articles published in high impact journals in the past 10 years were selected, but highly regarded older publications were also included. The reference lists of the articles were then used to obtain further relevant literature.

SUMMARY OF THE LITERATURE:

Background

Retinopathy of prematurity is a vision-threatening vasoproliferative disorder that occurs in premature infants.(1) It has become a leading cause of childhood blindness world-wide. In

addition to blindness, ROP is associated with an increased incidence of refractive errors, amblyopia, strabismus, cataracts and glaucoma.(2)

The first, second and third ROP epidemic

In the late 1940s, ROP appeared suddenly in preterm infants. The disorder, initially called retrolental fibroplasia, was characterised by a complete retinal detachment behind the lens.(3) The cause of this ‘first epidemic’ of retinopathy of prematurity was the use of supplemental oxygen in closed incubators, which helped improve the survival of infants, but also contributed to blindness.(3, 4) Today, uncontrolled oxygen supplementation remains a major risk factor for ROP, and optimum oxygenation to balance the risk of ROP against improved survival is still unsettled.(3) Low infant gestational age at birth and low birth weight are other major risk factors for ROP. A ‘second epidemic’ of ROP arose due to first world technology allowing smaller and smaller premature infants to survive. The current ‘third epidemic’ of ROP is attributed to both the survival of more extremely premature babies, and the survival of babies in settings that lack the resources to prevent and manage the associated retinopathy.

ROP burden

Worldwide, 10% of births occur preterm (before the gestational age of 37 full weeks).(5) Recent global estimates of the incidence of blindness and severe visual impairment from ROP are much higher than formerly.(6) It was updated from 50 000 children under 15 years of age (estimated largely from blind school surveys and dubbed the ‘third epidemic’ of ROP) (7, 8), to a more alarming annual incidence of 20 000 infants blind from ROP and a further 12 300 with mild or moderate visual impairment.(9) This estimate comes from more rigorous methodology based on the published incidence of preterm birth, mortality rates and the proportion of ROP requiring treatment, and suggests the greatest burden of disease is now in

the rapidly developing economies of India, China and South East Asia (middle-income countries).(6)

Pre-term birth is the most common cause of neonatal death and the proportion of blindness due to ROP has been shown to be associated with the infant mortality rate (IMR) at country level.(10) In low-income countries with high IMRs, premature infants do not survive. In high-income countries with a low IMR, ROP blindness is controlled through adequate ROP prevention programmes. In middle-income countries with IMRs in the mid-range (9-60/1000 live births) ROP is emerging as a major cause of blindness, because improved neonatal care causes an increased premature infant survival rate, which is disproportionate to primary and secondary ROP preventative strategy implementation.

A comparison of the burden of ROP between countries is difficult because of substantial variability in study designs, gestational ages of included infants, survival rates and treatments used. As shown in table one, severe ROP prevalence estimates from population-based studies vary even among countries with similar neonatal intensive care facilities.(3) In addition, Zin et al. showed that the ROP burden can vary among neonatal units within one city.(8) Sweden has a register (SWEDROP) for all children screened for ROP, which is used to measure incidence.(11) Data from this registry show that the incidence of ROP did not change substantially over time in this first world setting. This may be due to an increased survival of very immature infants at high risk for the disease balanced against improved neonatal intensive care. (3)

Country	Author, year	GA at birth or BW	Any stage ROP	Severe ROP
Sweden	Austeng et al., 2009	<27 weeks	73% (368/506)	35%(176/506)
Norway	Markestad et al.,2005	<28 weeks	33% (95/290)	-
Belgium	Allegaert et al., 2004	<27 weeks	-	26%(45/175)
Australia and New Zealand	Darlow et al., 2005	<29 weeks	-	10%(203/2105)
Austria	Weber et al., 2005	<27 weeks	-	16% (50/316)
Finland	Tommiska et al., 2007	< 1000 g	-	5-10% (numbers not reported)

The two phase hypothesis for ROP pathogenesis

Currently the pathogenesis of ROP is best explained by the “two phase hypothesis”. In phase 1, suppression of growth factors due to hyperoxia and loss of the maternal-foetal interaction result in an arrest of retinal vascularisation. Subsequently in phase 2, the increasingly metabolic active, yet poorly vascularised, retina becomes hypoxic, stimulating growth factor-induced vasoproliferation.(3) So first insults arrest normal retinal neurovascular development, then pathological compensatory mechanisms lead to abnormal retinal vascularisation. The transition between phase 1 and 2 seems to depend on the post menstrual age of the infant independent of the postnatal age, which points to an association with programmed timing of development and disease pathogenesis.(3)

ROP Risk factors

Among the numerous associations described in the literature, the main accepted risk factors for ROP are low gestational age(GA) at birth, low birth weight(BW) for gestational age and poor oxygen management (i.e. fluctuating hypoxia/hyperoxia/lack of monitoring).

Gestational age and birth weight

Both GA and BW are related to the extent of immaturity of the retina and its vulnerability to insult. Low gestational age increases the duration of an infant's exposure to adverse postnatal insults and the lower the GA and BW, the more profound the loss of factors normally provided by the intrauterine environment.(3) When very preterm infants are born with a weight appropriate for gestational age, birthweight is likely to be a proxy for gestational age and not an independent risk factor.(12) However both GA and BW are considered major risk factors for ROP and used in ROP screening criteria and prediction models. A low BW for GA (i.e. intra-uterine growth restriction) may be associated with an increased risk of ROP (particularly in infants older than 29 weeks GA at birth) but more research is required to establish this association. GA, BW and intra-uterine factors are fixed at birth, then postnatal factors further influence retina vascularisation.

Oxygen

Oxygen supplementation is a known risk factor for ROP since the first wave of ROP, but teasing out at which concentrations it is harmful or beneficial in the preterm infant is an enduring challenge. The use of 100% oxygen made even some mature preterm babies blind during the first ROP epidemic and even room air can lead to hyperoxia compared with the intrauterine environment (where mean oxygen pressure is less than 50 mm Hg during the second half of pregnancy).(13) On the other hand, oxygen restriction to 50% of inspired O₂, resulted in 16 infant deaths per case of blindness averted.(14) Furthermore, Hellström et al.(3) point out that preterm infant oxygen requirements may be different in the two phases of ROP. In phase 1 high and fluctuating oxygen concentrations acts as an insult that arrests normal retina vascularisation, while in phase 2 the relative hypoxic retina requires higher oxygen concentrations due to poor vascularization. Oxygen saturation targets are discussed further under ROP related blindness control.

Other risk factors

Low Serum IGF-1 is strongly associated with poor postnatal weight gain and ROP in premature infants. (13) Postnatal weight gain is used in various models to predict the risk of severe ROP in premature infants.(14-16) Hyperglycaemia, neonatal infections, blood transfusions, genetic factors, Caucasian race and male gender are associated with ROP but not established risk factors.(3)

ROP related blindness control

Much severe ROP is preventable, but to achieve this, good organisation of neonatal care on a regional basis, a focus on implementing evidence-based practices and ongoing quality assurance and audit are required.(15, 16)The mainstay of control of visual loss from ROP lies in primary prevention of the condition through good neonatal care and programs of secondary prevention whereby babies at risk of ROP are examined to detect those needing prompt intervention for treatable stages of the disease.

Oxygen saturation targets

The optimum oxygenation to balance the risk of ROP against improved survival is still unclear.(3) To resolve this issue, five randomised controlled trials in infants with gestation <29 weeks have compared a SpO₂ target of 85–89% with 91–95% and will pool the results in an individual patient data meta-analysis (the Neonatal Oxygenation Prospective Meta-analysis Collaboration (NeOProM)).(17) Some NeOProM trials (the SUPPORT and the BOOST II Australia and UK) reported that the lower target was associated with a small but significant increase in mortality at hospital discharge.(6) An interim meta-analysis of mortality data confirms this, being 19.3% versus 16.2%, relative risk 1.18 (95% CI 1.04–1.34).(18) The lower target is also associated with a lower incidence of severe ROP but at 18-

to 24-month follow-up, the rate of severe visual disability was low with no differences between groups.(18) While awaiting the NeOProm final results, a saturation target of 90–95% plus efforts to avoid hyperoxaemia is recommended.(18) This may be best achieved with the upper target at 94% and the high alarm set at 95%.(6)

Case detection

Programs for detecting ROP are well established in most of the developed nations. These programs provide information on the population of babies needing treatment, and how this population is changing over time.(19) This information continues to be used to refine screening criteria, to ensure that programs are as cost effective and efficient as possible.(20) However, these are not “screening” programs in the true sense of the word, but are “case detection” initiatives. Screening would entail the use of a simple, safe, non-invasive and valid test which identified babies needing a “gold standard” diagnosis. (19) Aside from issues with nomenclature, there are many practical challenges secondary to the diversity of disease. Broadly these issues fall into 2 categories: (1) which babies should be screened, and (2) how the babies should be screened.(21) Further ROP screening challenges in need of resolution include ensuring that the manpower needed to perform the ROP examinations is available, and validating non-clinician lead screening, for example, using remote image transfer further assisted by arguable levels of computerized automation.(21) Problems with screening are a major source of medico legal concern.(22)

Screening guidelines vary with the characteristics of the premature population and neonatal intensive care practices in different countries and settings.(3) Most ROP Screening guidelines use BW and GA to identify infants needing examination, because these are major risk factors, are relatively straight forward to measure and are recorded routinely.(8) Screening cut-offs range from 30 to 35 weeks’ gestational age at birth and from birthweights of 1500 to 2000 g,

and depend on the extent and quality of neonatal intensive care available.(3) Guidelines should evolve according to changes in the local preterm population at risk. Infants who meet the screening criteria are referred for indirect ophthalmoscopy by a trained ophthalmologist. These eye examinations can be very painful for preterm infants, even when done by a skilled ophthalmologist.(23) In addition, the work load for ophthalmologists undertaking case detection is an enduring issue for ROP programmes.(6) In the context of high-quality neonatal intensive care, with existing screening criteria, only about 5–10% of infants examined will require treatment.(24) Also, a UK survey shows that in 1 year, 8208 infants had around 20 000 examinations by 152 ophthalmologists leading to 149 infants being treated; 55 infants were examined for every one treated, and there were 134 exams for each treated infant.(25) Safely decreasing the number of stressful and costly screening examinations would therefore be beneficial.

Although indirect ophthalmoscopy is still considered the gold standard for detecting ROP, retina photography with a retina camera (Retcam) has been shown to be a reliable, accurate and cost-effective alternative method of ROP detection.(26-30). Another way to safely reduce the workload is through clinical prediction methods based on post-natal weight gain.(31-33) One example is the WINROP algorithm which has been used for more than 10 000 babies in NICUs of various countries.(3) A multicentre study of about 2000 preterm infants substantiated the high sensitivity (98·6%) and negative predictive value (99·7%) of this algorithm, which suggests that the number of screening examinations can be substantially reduced if WINROP is used in combination with traditional screening.(34)

Classification

Detected ROP is classified in zones and stages according to the International Classification of Retinopathy of Prematurity (ICROP) system(35). Infants are followed until ROP has

progressed to treatable stages or has resolved spontaneously and the retina is fully vascularized. The investigators of the Early Treatment for Retinopathy Of Prematurity (ETROP) study(36) reclassified retinopathy of prematurity into type 2 (to be followed up) and type 1 (requires urgent treatment).(3) Type 1 now includes a more virulent form of retinopathy in extremely low-birthweight babies (aggressive posterior retinopathy of prematurity (APROP)), which involves very central neovascularisation with plus disease.(35) Clinically significant ROP (CSROP) is ROP of any grade, in an area of the retina that might threaten sight. CSROP can be defined as ROP involving zone I, any stage 3 ROP or plus disease associated with any stage ROP in any zone, for practical purposes.(37)

Treatment

Cryotherapy (ablation of the non-vascularized retina) reduced blindness in threshold ROP by 17% at age 10 years (70/227 in the treated group were blind, compared with 106/222 in the non-treated group of the CRYO-ROP study).(38-40) Prompt treatment of type one high risk pre-threshold ROP with laser photocoagulation (trans pupillary ablation of the non-vascularized retina), further improved short and long term visual outcomes, and is now considered the standard of care for ROP treatment.(36, 41) Early ROP screening and laser treatment is a resource intensive preventative strategy, but because of the high lifetime costs of severe visual impairment, it has been shown to be highly cost-effective in first world countries. (42, 43)¹²⁻¹³

A proportion of cases continue to progress despite laser treatment, and even a favourable early outcome may not mean normal vision.(6) Therefore other ROP treatment modalities such as lens-sparing vitrectomy(44) to preserve vision in early retinal detachment (stage 4) and intravitreal anti-VEGF injections are considered. A randomised controlled trial (BEAT-ROP) compared laser therapy to an intravitreal injection of 0,625mg bevacizumab in infants

with severe Zone I or posterior Zone II ROP and showed that the bevacizumide group required fewer retreatments before 54 weeks post menstrual age (4/70 (6%) bevacizumab versus 19/73 (26%) laser (OR 0.17 (95% CI 0.05 to 0.53) P = 0.002)).(45) However the benefit was confined to infants with Zone I disease and the study had several serious limitations.(46-48) In addition the dose, safety and long term outcome of bevacizumab has not been established in pre-term infants.(6)

The local setting and rationale for this dissertation

South Africa has an infant mortality rate of 53/1000 live births and has become part of the ‘third epidemic of ROP’.(49) As described above the ‘third epidemic of ROP’ is attributed to both an increase in premature infant survival (the cause of the ‘second epidemic’) and poor oxygen management (the cause of the ‘first epidemic’) in neonatal intensive care units (NICUs). Due to these oxygen management inadequacies in middle-income country NICUs, more mature infants than in high-income NICUs may be at risk and require screening.(10, 19, 50-52)

An estimated 16 000 infants in South Africa are at risk of ROP and require screening each year.(49, 53) In 1995, ROP accounted for 10.6% of blindness in children in schools for the blind in South Africa.(54) The reported ROP prevalence among infants with birth weights less than 1500g in South African academic centres remain low, with the prevalence of any ROP ranging from 16.3-24.5% and clinically significant ROP (CSROP) ranging from 1.56-4.4%.(37, 55-57) Those with sight threatening ROP requiring treatment range from 0.6-2.9%.(53)

The first South African guideline for the prevention, screening and treatment of ROP was published in 2013.(49) It recommends the screening of infants with a GA<32weeks or a BW<1500g. Since larger middle-income country infants (GAs: 32-35weeks; BWs: 1500g-

2000g) may be at risk of ROP, screening of infants with birth weights up to 2000g with additional features associated with an increased risk of ROP (poor oxygen monitoring, cardiac arrest, multiple blood transfusions, exchange transfusion, severe HIE, family history of HIE) is also recommended. Developing screening guidelines that is appropriate for all institutions within a country is challenging, since the quality of NICU care and therefore ROP screening requirements, are highly unit dependent.(8) Screening higher weight infants may not be feasible in units where resources are limited. Most level 2 hospital NICUs in South Africa, where larger infants are likely to be at risk of ROP, do not even have access to screening facilities.(49)¹⁷ On the contrary, screening larger infants in tertiary institutions in South Africa with high quality neonatal care may be an inappropriate application of scarce resource. Ideally, criteria and guidelines should be based on local evidence of the population of babies at risk of ROP, and these can be modified over time.

Tygerberg Children's Hospital (TCH) reported a prevalence of any ROP of 31.1% and CSROP of 7.1 % among preterm infants ventilated for respiratory distress (1986-1987)(58) and a prevalence of any ROP of 21.8% and CSROP of 4.4% of preterm infants treated exclusively with non-invasive ventilation in the first week of life (2009-2010).(37) Only 1.5% of the latter cohort required laser therapy and no screened infants with BWs greater than 1250 g had CSROP. The results from these subgroup analyses are instructive but insufficient to inform local screening policy and resource allocation. A focused analysis of the existing TCH ROP screening database is needed to determine optimal screening criteria for retinopathy of prematurity at TCH and to explore the workload implications of using different BW and GA cut-off values. This work will set a platform for on-going surveillance and further research towards cost-effective intervention and scarce resource distribution.

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PART C: MANUSCRIPT

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TITLE AND AUTHOR DETAILS

Title: Retinopathy of Prematurity Screening Criteria and Work Load Implications at Tygerberg Children's Hospital, South Africa: a Cross-sectional study

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ABSTRACT [235 words]**Background**

High-income country ROP Screening guidelines are not appropriate for middle-income

countries and screening requirements may vary even between units within one city. This study aimed to determine optimal ROP screening criteria, and its workload implications, for Tygerberg Children's Hospital (TCH), South Africa.

Methods

This cross-sectional study included premature infants screened for ROP, at TCH (1 January 2009 to 31 December 2014). Logistic regression for prediction and classification were performed. Predictors were birth weight (BW) and gestational age (GA). Endpoints were clinically significant ROP (CSROP) and Type 1 ROP (T1ROP).

Results

Among the 1104 eligible infants, 33% had ROP (CSROP=9%; T1ROP=2.45%). All T1ROP infants received laser therapy. The number of screening examinations was inversely correlated with GA and BW. The number needed to screen to identify one infant needing treatment was 41 (entailing 83 examinations, four screening hours, one technician and three doctors). Screening infants with a GA of ≤ 28 weeks and BW of < 1000 g would have detected all infants with T1ROP, but missed two outliers with CSROP. These outliers would only be detected with a GA of ≤ 32 weeks or BW < 1500 g.

Discussion

Detection of infants with T1ROP is resource intensive. Larger infants require screening to include a few outliers, but they require fewer examinations than smaller infants.

Conclusion

Making local screening criteria narrower on the basis of a limited evidence base may be dangerous. Larger infant risk factors for CSROP need to be researched.

FULL MANUSCRIPT [3009 words] [tables and figures – 339 words]**Introduction**

Retinopathy of prematurity (ROP) has an estimated global incidence of 20 000 infants per year.^[1] South Africa (SA) joined the ‘third epidemic of ROP’ which is attributed to both increasing premature infant survival and poor oxygen management in neonatal intensive care units (NICUs).^[2] Oxygen management inadequacies in middle-income country NICUs lead to larger infants being at risk than in high-income countries.^[3-5]

In SA an estimated 16 000 infants are at risk of ROP and require screening each year^[2,6] In 1995, ROP accounted for 10.6% of blindness in schools for the blind.^[7] The ROP prevalence among infants with birth weights less than 1500g in tertiary hospitals in SA remains low (any ROP 16.3-24.5%, clinically significant ROP (CSROP) 1.56-4.4%,^[8-11] and sight threatening ROP 0.6-2.9%.^[6])

The first SA ROP guideline was published in 2013.^[2] It recommends the screening of infants with a gestational age (GA) of less than 32weeks and a birth weight (BW) of less than 1500g, as well as larger infants (GAs: 32-35weeks; BWs: 1500g-2000g) with an increased risk of ROP.

Developing screening guidelines that are appropriate for all in institutions within a middle-income country is challenging, since ROP screening requirements are dependent on NICU quality of care and this varies widely between units.^[12-13] Screening higher weight infants may not be feasible in units where resources are limited. Most secondary level hospital NICUs in SA, where larger infants are likely to be at risk of ROP, do not even have access to screening facilities.^[2] In contrast, screening larger infants in SA tertiary institutions, with

high quality neonatal care, may be an inappropriate use of scarce resources. Ideally, ROP screening criteria should be based on local evidence.

Tygerberg Children's Hospital (TCH) reported a ROP prevalence of 31.1% (CSROP - 7.1%) among preterm infants ventilated for respiratory distress (1986-1987).^[14] Preterm infants treated exclusively with non-invasive ventilation in the first week of life (2009-2010), had a ROP prevalence of 21.8% (CSROP - 4.4%).^[11] Only 1.5% of the latter cohort required treatment and none with BWs greater than 1250 g had CSROP. The results from these subgroup analyses are instructive but insufficient to inform local screening policy and resource allocation. A focused analysis of the existing TCH ROP screening database was undertaken to determine optimal screening criteria for retinopathy of prematurity at TCH and to explore the workload implications of using different BW and GA cut-off values.

Methods

This was a cross-sectional study, based on a database analysis, of infants born in the drainage area of TCH, Western Cape, SA. Attending neonatologists identified premature infants (admitted to TCH neonatology wards) requiring ROP screening, and registered them in the ROP database. ROP screening activities at TCH commenced before the release of national screening criteria and were governed by local data and resources at the time. Infants were examined and staged according to the International Classification of ROP (2005 revision) by a trained ophthalmologist using a 28-dioptre condensing lens and indirect ophthalmoscope. The screening team consisted of one technician and three doctors (supervising paediatric ophthalmologist and two registrars in training). Retcam III imaging was performed in selected cases. Examination findings were recorded in hospital records and the database. Infants were examined from 31 weeks corrected GA (or four weeks after birth whichever is later). Follow-up screens were performed one to three weekly until vascularization of zone

three was completed or the corrected GA of 41 weeks was reached. Infants with treatable stages of ROP (T1ROP) received laser therapy within 72 hours of diagnosis.

The sample size was fixed to the number of infants with information recorded in the database. Screening examinations with missing outcome data were excluded from the study. The recorded findings (zone, stage and presence of plus disease for each eye) were converted to binary outcome variables: Any ROP, CSROP and T1ROP. CSROP was defined as ROP involving zone I, any stage 3 ROP or plus disease associated with any stage ROP in any zone. T1ROP was defined as any stage zone one ROP with plus disease, zone one stage three with or without plus disease or zone two stage two or three ROP with plus disease

Data were entered in a custom designed Microsoft Excel spreadsheet, and analysed using Stata 13. Ethical approval was obtained from the ethics committees of the University of Cape Town, Stellenbosch University, and Tygerberg Hospital.

Results

Between 1st March 2009 and 28th February 2014, 1104 infants were examined for ROP and the examination findings recorded in the ROP database at TCH. Of the 2643 ROP screening examinations (bookings) registered in the database 406 (15%) examination findings were missing, mostly due to infants not arriving for scheduled examinations (7%) or the inability to perform the examinations (3%) (due to poorly dilated pupils or clinical instability)(see figure 1).

The median GA at birth was 28 weeks (IQR 27-29; range 24-37). 95% had a GA of less than 32 weeks. The median BW was 930 g (IQR 820-1040; range 523 -2600). Median GAs and BWs were similar across five years of screening. The median postnatal age (PNA) of the

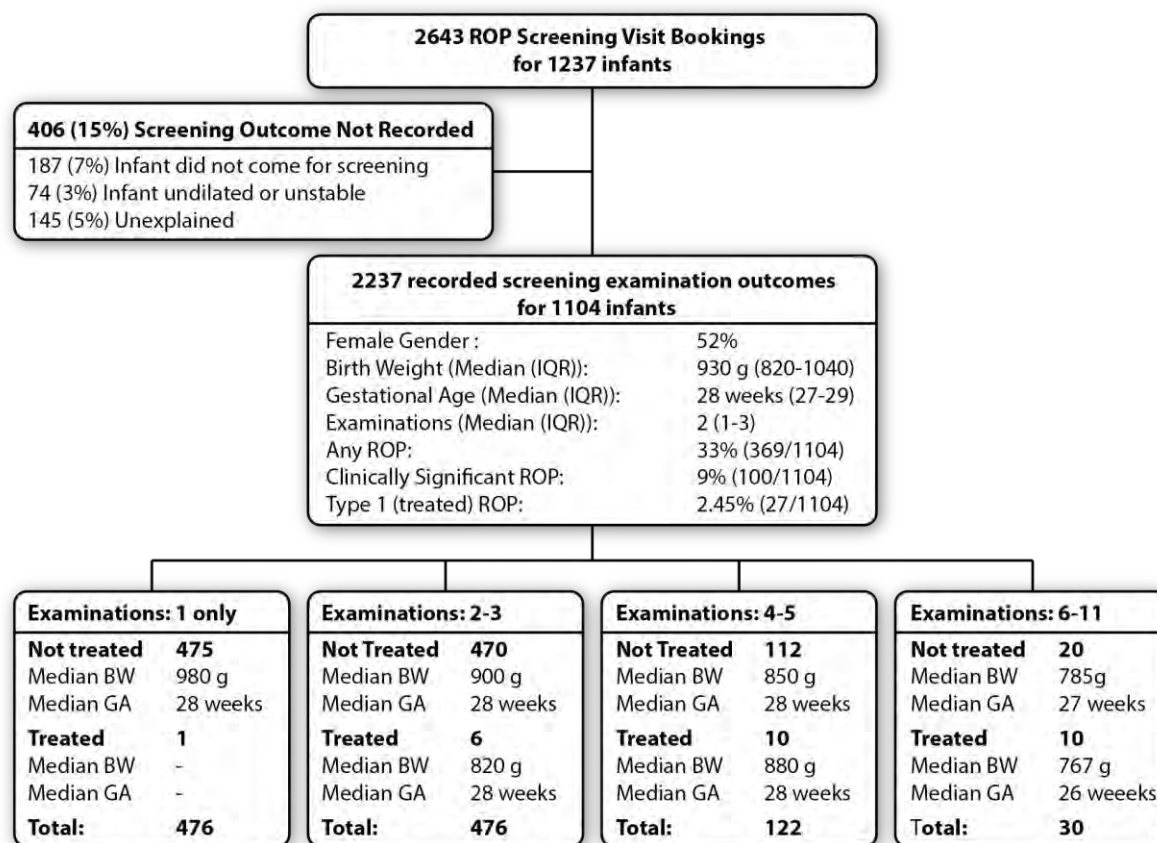


Figure 1: Overview of study population.

infants at the first screening examination was five weeks (IQR 4-7) and the post menstrual age (PMA) was 33 weeks (IQR 32-35).

Retinopathy of prematurity

ROP (any ROP) was found in 33% of the 1104 infants with recorded screening examination outcomes. CSROP was found in 9% and T1ROP in 2.45% (figure one). The prevalence of any ROP among infants with a gestational age of less than 27 weeks was 44% (44/98) and CSROP 18% (18/98). Overall, the median GA was 28 weeks in infants with ROP (27 weeks in CSROP) and the median BW was 865 g (826 g in CSROP). Rates of ROP according to GA and BW categories are shown in table 1 (among the subset of 621 infants with both GA and

BW recorded in the database). CSROP was detected in 2 infants with a GA of greater than 32 weeks or BW >1500g. The one infant

Table 1. Numbers and proportions of infants developing ROP by GA and BW group (n=621)

	Total	Any ROP	CSROP	Type 1 ROP
GA category				
24-25 weeks	15	8 (53%)	4 (27%)	2 (11%)
26-27 weeks	221	77 (35%)	28 (13%)	7 (3%)
28-29 weeks	292	88 (30%)	20 (7%)	5 (2%)
30-32 weeks	79	14 (18%)	3 (4%)	0 (0%)
33-37 weeks	14	4 (29%)	1 (7%)	0 (0%)
Total	621	191 (31%)	56 (9%)	14 (2.26)
BW category				
< 600g	10	3 (30%)	2 (20%)	0 (0%)
600 – 799g	112	49 (43%)	15 (13%)	6 (5%)
800 – 999g	284	93 (33%)	27 (10%)	6 (2%)
1000-1199g	171	37 (22%)	9 (5%)	2 (1%)
1200 -1399g	34	8 (24%)	2 (6%)	0 (0%)
>= 14 00g	10	1 (10%)	1 (10%)	0 (0%)
Total	621	191 (31%)	56 (9%)	14 (2.26)

had a BW of 866 g and GA of 35 weeks. Stage one zone one ROP was detected in the right eye only, four weeks after birth. The other had a BW of 1530 g and GA of 31 weeks. Pre-plus ROP was detected in zone two of the left eye at 34 weeks PMA (three weeks PNA).

Screening cut points

Among the 621 infants for whom both GA and BW were recorded GA was significantly associated with CSROP (OR 0.710 (CI 0.579 – 0.872; p = 0.001) and BW showed a trend (OR 0.998 (CI 0.996-0.9995; p = 0.013). Both GA and BW were predictors of CSROP and T1ROP (see figure two). GA was not a significantly better predictor of CSROP than BW (p=0.521) neither were using both GA and BW in the prediction model better than using either GA (p=0.412) or BW (p=0.181). A GA cut point of 30 weeks had a sensitivity of 97% and specificity of 9% in detecting CSROP. With this classification rule, two older infants

(Infant A: GA=35 and BW=866; Infant B: GA=31 and BW=1530) with CSROP would have been missed in the given dataset, but neither required treatment.

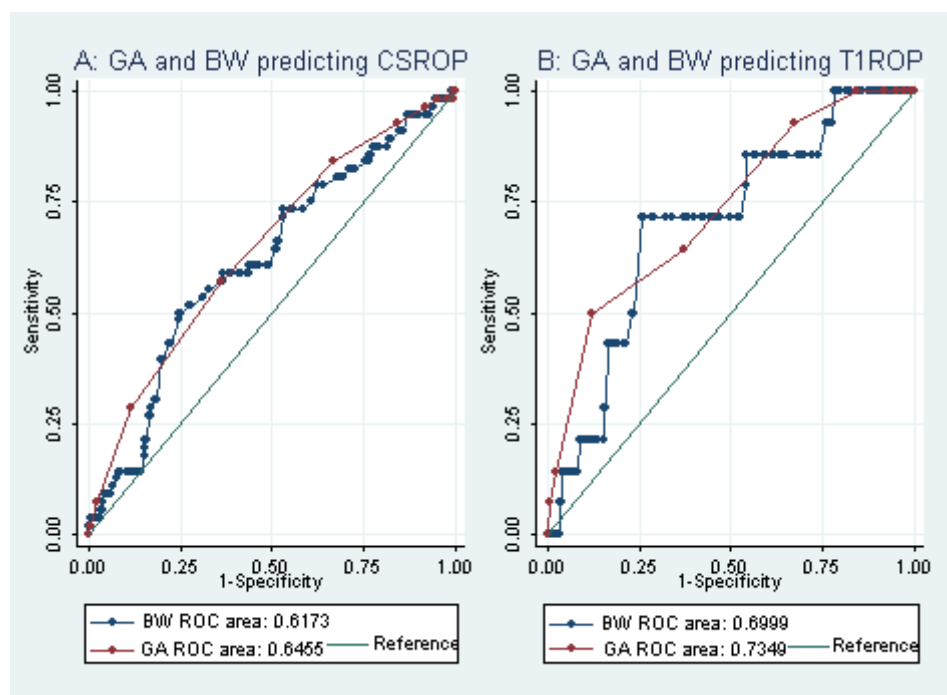


Figure 2: ROC curves show how prematurity predicts ROP.

A less sensitive cut point of older than 28 weeks would miss nine infants, one of which would have required treatment. At a cut point of 1200g the BW classification rule had a sensitivity of 96% and a specificity of 6%. With this classification rule three infants with a BW equal to and greater than 1200g and CSROP would have been missed but none of them required treatment (Infant B: GA=31 and BW=1530; Infant C: GA=28 weeks and BW=1200g; Infant D: GA=28 and BW=1220). A less sensitive cut point of 1000g would have missed 12 infants (two with T1ROP). Table three summarizes infants missed (false negatives) when BW and GA cut-offs are combined and applied. Screening criteria D ($GA \leq 28$ weeks or $BW < 1000$ g) would have detected all infants with CSROP requiring treatment (T1ROP). However, the most mature infant in the dataset with CSROP that did not require intervention had a GA of

31 weeks and BW of 1530 g (Infant B) and would have been detected with screening criteria B (GA >32 weeks or BW >1500g) only.

Table 3. Workload implications and false negatives with application different screening criteria (n=621).

	A: all infants	B: GA ≤ 32 weeks & BW < 1500 g	C: GA ≤ 30weeks & BW <1200 g	D: GA ≤ 28weeks & BW < 1000 g
Number of infants	621	618 (99.52%)	610 (98.23%)	530 (85.35%)
Number of examinations	1385	1382 (99.78%)	1367 (98.70%)	1236 (89.24%)
Examinations per infant	2.23	2.24 (100.45%)	2.24 (100.45%)	2.33 (104.48%)
Number of infants with CSROP	56	56 (100.00%)	55 (98.21%)	54 (96.43%)
Number of infants needed to screen to detect 1 infant with CSROP	11	11 (100.00%)	11 (100.00%)	10 (90.90%)
Number of examinations required to detect 1 infant with CSROP	25	25 (100%)	25 (100%)	23 (92%)
Number of infants with Type 1 ROP	14	14 (100%)	14 (100%)	14 (100%)
Number of infants needed to screen to detect 1 infant needing treatment	44	44 (100.00%)	44 (100.00%)	38 (86.36%)
Number of examinations required to detect 1 infant needing treatment	99	99 (100%)	97 (97.98%)	88 (88.89%)
CSROP missed (False negatives)	-	0	1	2
T1ROP missed (False negatives)	-	0	0	0

Infants needing treatment

Among the 1104 infants with recorded screening examination outcomes, all with T1ROP received laser therapy. The 27 infants (60% females) treated for ROP were 29 weeks or 1060 g and smaller (Median GA: 27 weeks (IQR26-28; range 24-29) and median BW: 815 g (IQR 763-940; range 640-1060)). The median PMA of the infants at the time of T1ROP detection was 35 weeks (IQR 33-38; range 31-43) and the PNA was seven weeks (IQR 6-10; range 5-15). Figure three reflects how those needing treatment changed over time, compared to those with CSROP and any ROP. 11/27 (41%) infants were treated during 2012. Any ROP and CSROP gradually increased over the study period from 14% to 48% and 4% to 14%. T1ROP had a baseline of 2% with a peak in 2012 (11/234 (5%) and returned to baseline in 2013.

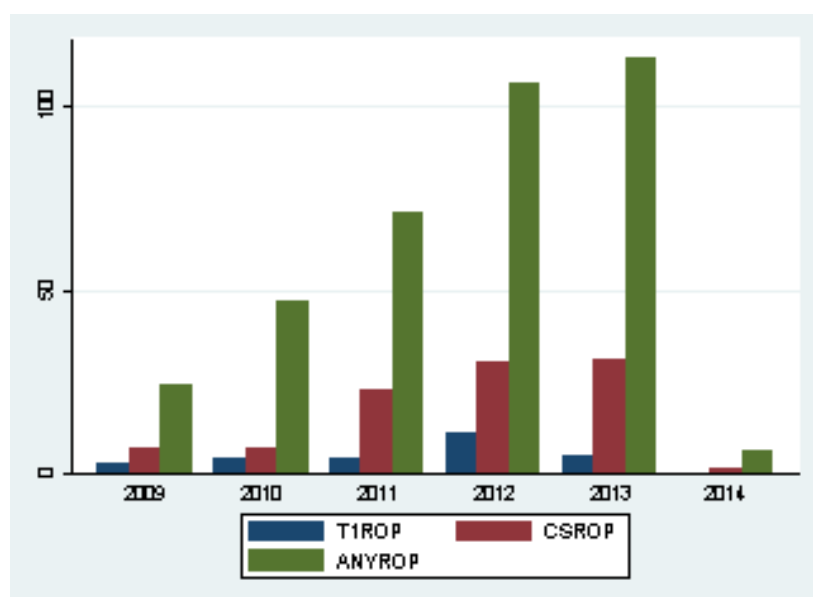


Figure 3: Number of infants with ROP at TCH, 2009-2014.

Work load implications

1104 infants required 2237 screening examinations. The median number of examinations per infant was two (IQR 1-3; range 1-11) with 26% (287/1104) having one examination only and

95% requiring less than six examinations. The median number of examinations for infants not needing treatment (T1ROP) was two (IQR: 1-3; range: 1-10) compared with six examinations (IQR: 4-9; range: 1-11) for treated infants. Thirteen infants (48% (13/27)) had reached the criterion for treatment at the first examination. However, the complete management of those treated involved four or more examinations in the majority of infants (74 % (20/27) (figure one)). The number needed to screen to identify one infant needing treatment was 41. Screening 41 infants entailed 83 examinations, four screening hours, one technician and three doctors.

The number of examinations required was inversely correlated with GA and BW (spearman correlation coefficient -0.20 and -0.27; $p < 0.001$). Table three shows the workload implications of applying different screening criteria (Option B to D) to the subset of infants with both GA and BW recorded (Option A). The tighter the screening criteria the smaller the number of infants to be screened but also the higher the screening examinations per infant. Therefore the workload, expressed as the total number of examinations, does not decrease proportionately to the number of infants screened. For example, the screening criteria in table three option D are $GA \leq 28$ weeks or $BW < 1000$ g. Narrowing the screening criteria to option D will lead to 14% reduction (6 less infants) in the number to be screened to detect one infant needing treatment, but only 11% (not 14%) reduction (11 less examinations) in the number examinations required to detect one needing treatment. Such a reduction in screening criteria would have decreased the workload by 91 less infants to be screened (149 less examinations) at the expense of missing two infants with CSROP.

Discussion

The prevalence of CSROP among infants with GAs less than 27 weeks at birth was 18% (18/98). Comparison with the ROP burden elsewhere is difficult, because of the substantial variability in study designs, gestational ages of infants, survival rates and treatments used.

Severe ROP prevalence estimates from population-based studies ranged from 5-35% among high-income countries with similar NICUs.^[15] The terms low-, middle-, and high-income countries does not always equate to the quality of care in every NICU in a particular country.^[13] In countries such as SA, India and Brazil, the standard of care may vary widely between individual NICUs. Zin and colleagues showed that in Rio de Janeiro the better NICUs were able to use narrower guidelines than other units in the same city.^[12] The prevalence of T1ROP in this middle-income city ranged from 2.1% -7.8% among NICUs.^[12] The TCH T1ROP prevalence of 2.45% compares with the estimate at the lower end of the range, which was measured at the Rio de Janeiro federal government research institute.

As expected, the smaller and younger the infants, the higher the rates of ROP (table one). A significant number of infants older than 32 weeks and 1200g and larger were examined. These infants had additional risk factors and therefore a higher yield of any ROP. However, few of them had CSROP and none required treatment. One infant with CSROP had a BW of 1530g and another a GA of 35 weeks. However, when BW and GA are taken into account simultaneously, as in the SA national ROP screening guideline ($GA \leq 32$ or $BW < 1500$),^[2] no infants with CSROP requiring follow-up fell outside the screening criteria. Also neither of the two more mature infants mentioned reached the criteria for laser treatment. This indicates well established neonatal care at TCH and that narrower guidelines may be applicable for this specific unit.

When planning ROP screening services it must be kept in mind that it is the immature and sick infants that require the most work.^[12] In this study most larger infants required only one or two examinations. Including more mature infants in the screening programme does not increase the workload to the same extent as screening the very immature infants.

Screening Criteria D ($GA \leq 28$ weeks or $BW < 1000$ g) would have detected all infants needing treatment. Screening Criteria D plus referral of all infants at increased risk of ROP might have included the two more mature infants with outlying measurements. However, making guidelines narrower, on a relatively small evidence base, should be undertaken with caution.

[13] Further investigation towards specific risk factors, or reasons for referral, is required in this cohort of infants. In addition, research is required to determine whether using this lower GA and BW plus a “sickness” criterion (risk factors) would be an effective and efficient method to include the outliers. For example, prediction methods based on GA, BW and post-natal weight gain (WINROP, ROPScore, and CHOP ROP) are employed to reduce ROP screening workload in high-income settings. Poor generalizability limits its use.^[15-16] Another tool has been developed by Binbaum, which can also be used in more mature infants at risk for ROP in countries with developing neonatal care systems.

In SA accurate GA estimates are not routinely available. GA in our study population was based on last normal menstrual date, early ultrasound or the new Ballard score calculation at birth. BW was as good as GA in predicting CSROP and using GA in addition to BW was not better at predicting CSROP. However, as was illustrated above with infant B in the dataset, using GA when it is available acts as a safety net to include those with high BW for GA (outliers).

Zin and colleagues showed that NICUs with a $< 80\%$ survival rate of infants with a $BW < 1500$ g should screen infants with a $GA \leq 35$ weeks and $BW \leq 1500$ g, and that NICUs with a survival rate of $\geq 80\%$ could adopt narrower screening criteria of $GA < 32$ weeks and $BW \leq 1500$ g.^[12] The TCH survival rate of infants with a $BW < 1500$ g gradually increased from 2009 to 2014 and was 90% on average during the study period (personal communication). We also showed that screening infants with $GA < 32$ weeks and $BW \leq 1500$ g is appropriate in a NICU with a < 1500 g infant survival rate of greater than 80%. Therefore, in third epidemic

settings, infant mortality rate is a useful proxy to indicate which infants should be examined. However, these findings need to be validated.

The Sweden ROP register (SWEDROP) showed that the incidence of severe ROP did not change substantially over time. [15] Perhaps an increased survival balanced against improved neonatal intensive care can explain this. In our study the numbers seen increased over time and the screening programme became more efficient in detecting any ROP and CSROP over time. The prevalence of T1ROP was 2% each year across the study period with an exception of a peak of 5% in 2012. An increase of very immature infants at high risk for T1ROP plus the sudden increase in the numbers of very low birth weight admissions (745 in 2012 and 801 in 2013 as opposed to 626 in 2011 and 632 in 2010) can explain the peak. An improvement in overall neonatal care may explain the return to the norm in 2013.

Study limitations

Incomplete data limit the data analysis and interpretation in this study. The exact ROP screening programme coverage is not known, but it appears to be insufficient. Not all infants <1500g were screened. Infants ≥ 1200 g were screened only if they had additional risk factors for ROP. A significant proportion, 15% (405/2670), of the examinations had missing outcomes and was excluded from analyses. Either GA or BW were not recorded for 44% (483/1104) of infants, however exploratory analysis revealed that these values were missing at random. Among the 621 infants (54%) with complete data, a small number required treatment. This may explain why the ROC curves were not very smooth and why we were unable to detect statistical differences between BW and GA in predicting risk of ROP. Improved routine data collection is needed for audit purposes and to establish the ROP program coverage.

Further studies are required to determine whether more mature infants should be screened routinely, or if the screening should be based on risk scores, in resource limited settings. Short and long term visual outcomes of infants are not recorded in the database and this requires further study to guide scarce resource allocation. Digital imaging of the retina is employed at TCH ROP screening ward rounds, but its role in ROP screening workload reduction is yet to be established.

Conclusions

Unnecessary ROP screening examination should be avoided since it is resource intensive, requires specially trained ophthalmologists, and is stressful for infants. In addition, neonatal management is continually changing, so screening criteria should be revised accordingly. Local audit is an essential component. However local guidelines should ideally be based on prospective studies.

At TCH no infants needing treatment were larger than 1060 g or older than 29 weeks, and no infant requiring follow-up for CSROP fell outside the current national screening criteria of GA less than 32 weeks and BW less than 1500g. However, making the local screening criteria narrower on the basis of a limited evidence base may be dangerous. More mature infants require less screening examinations than smaller infants, therefore modest broadening of current local inclusion criteria and screening infants >32 weeks at increased risk of ROP, should not result in an unmanageable workload. More research is required to develop screening criteria for the identification of more mature infants at risk of ROP in resource limited settings.

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Appendix A: Abbreviations and Glossary

BW:	Birth Weight
CSROP:	Clinically Significant ROP
EUS:	Early Ultra Sound
GA:	Gestational Age
LNMD:	Last Normal Menstruation Date
MPH:	Master of Public Health
PMA:	postmenstrual age
PNA:	postnatal age
ROP:	Retinopathy of Prematurity
TCH:	Tygerberg Children's Hospital
T1ROP:	Type 1 ROP
UCT:	University of Cape Town

Threshold ROP: Zone I or II, with 5 contiguous or 8 cumulative clock hours of stage 3 disease and plus disease

Pre-threshold ROP: Zone I or Zone II, stage 3 disease or Zone II, stage 2 disease with plus disease

Clinically Significant ROP: ROP involving zone I, any stage 3 ROP or plus disease associated with any stage ROP in any zone

Type 1 Pre-threshold ROP: Zone I, any stage ROP with plus disease (plus is ≥ 2 quadrants in the ETROP Study)
 Zone I, stage 3 ROP with or without plus disease
 Zone II, stage 2 or 3 ROP with plus disease

Appendix B: ROP staging and grading system

Appendix VIII. International classification of ROP

Stages (1 - 5)

1	Flat white demarcation line separates the vascular from the avascular retina
2	Ridge of fibrous tissue protrudes between the vascular and avascular retina
3	Blood vessels and fibrous tissue grow along the ridge and extend into the vitreous
4	Partial retinal detachment (4A – macula not involved; 4B – macula involved) is seen
5	Total retinal detachment has developed

Zones (I – III) and extent (clock hours)

I	The most central zone, centred on the optic nerve with a radius equal to twice the distance from the disc to the fovea
II	Extends concentrically from the edge of zone I to the nasal ora
III	The remaining temporal crescent

In addition, extent is denoted in the number of clock hours affected (1 - 12)

Plus disease

Blood vessels in the posterior pole appear tortuous and dilated. In addition, there may be vitreous haze, engorgement of iris vessels and poor dilatation of the pupil. The presence of plus indicates more severe ROP and rapid progression may follow.

Rush disease/AP-ROP (aggressive posterior ROP)

ROP in zone I with plus

Visser L, Singh R, Young M et al. Guideline for the prevention, screening and treatment of retinopathy of prematurity (ROP).S Afr Med J 2013;103(2):116-125.

Appendix C: TCH routine ROP screening examination form

Appendix VII. ROP screening form

Date booked for examination: _____ Hospital booked at: _____
 Name: _____ Hospital number: _____
 Date of birth: _____
 HIV-exposed/-unexposed/unknown: _____ Sex: _____
 Birth weight (g): _____ Multiple birth (1,2,3): _____
 Gestational age at birth: _____ Growth at birth – AGA/SGA/LGA: _____
 Duration of oxygen _____ IPPV: _____ CPAP: _____ Nasal O₂: _____

Indication for ROP screening in this patient: please tick appropriate box:

- weight <1 500g
- gestational age <32 weeks at birth
- weight 1 500 - 2 000 g with unstable clinical course

Examination

Date: _____ Examiner initials: _____ Current age: _____

Anterior segment: _____

Fundus

Stage: _____ Stage: _____
 Plan: _____

Visser L, Singh R, Young M et al. Guideline for the prevention, screening and treatment of retinopathy of prematurity (ROP).S Afr Med J 2013;103(2):116-125.

Appendix D: University of Cape Town study ethics approval



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



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24 December 2014

HREC REF: 924/2014

Prof L Myer
 Public Health & Family Medicine
 Level 5, Room 5.51
 Falmouth Building

Dear Prof Myer

PROJECT TITLE: RETINOPATHY OF PREMATURETY SCREENING CRITERIA AND WORK LOAD IMPLICATIONS AT TYGERBERG CHILDREN'S HOSPITAL, SOUTH AFRICA: A CROSS-SECTIONAL STUDY (MPH Candidate - Dr E Visser-Kift)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th December 2015.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Dr Elsime Visser-Kift will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

HREC 924/2014

Appendix E: University of Stellenbosch study ethics approval



UNIVERSITEIT STELLENBOSCH-UNIVERSITY
 (U) KENNISVERHOOD - your knowledge partner

Approved with Stipulations New Application

27-Nov-2014
 Visser Kift, Elsime E

Ethics Reference #: S14/10/218

Title: Retinopathy of Prematurity Screening Criteria and Work Load Implications at Tygerberg Children's Hospital, South Africa: a Cross-sectional study.

Dear Dr Elsime Visser Kift,

The New Application received on 15-Oct-2014, was reviewed by Health Research Ethics Committee 1 via Committee Review procedures on 05-Nov-2014.

Please note the following information about your approved research protocol:

Protocol Approval Period: 05-Nov-2014 -04-Nov-2015

Present Committee Members:

Weber, Franklin CFS
 Unger, Marianne M
 Sprenkels, Marie-Louise MHE
 Els, Petrus PJJS
 Potgieter, Sunita S
 Theunissen, Marie ME
 Kearns, Elaine E
 Barsdorf, Nicola N
 Whitelaw, David DA
 Botha, Paul JP
 Decloedt, Eric EH
 Rohland, Elvira EL
 Ferris, William WF

The Stipulations of your ethics approval are as follows:

Please give details of the misconduct and dates, as stipulated in the disclosure section of the ethics application.

Please remember to use your **protocol number** (S14/10/218) on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:

Please note a template of the progress report is obtainable on www.sun.ac.za/rds and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372

Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes

2004 (Department of Health).

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Department of Health (healthres@pgwc.gov.za Tel: +27 21 483 9907) and Dr Helene Visser at City Health (Helene.Visser@capetown.gov.za Tel: +27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and documents please visit: www.sun.ac.za/rds

If you have any questions or need further assistance, please contact the HREC office at 219389156.

Included Documents:

Request for waiver of consent

Application form

Protocol Synopsis

Request for expedited review

Declaration E Visser Kift

CV E Visser Kift

Checklist

CV N Freeman

Protocol

Declaration N Freeman

Cover letter

Sincerely,

Franklin Weber
HREC Coordinator
Health Research Ethics Committee 1

Appendix F: Tygerberg Hospital study approval**Tygerberg Hospital**

REFERENCE: Research Projects
ENQUIRIES: Dr G Marinus
TELEPHONE: 021 938-6267

ETHICS NO: S14/10/218

Retinopathy of Prematurity Screening Criteria and Work Load Implications at Tygerberg Children's Hospital, South Africa: a Cross-sectional study.

Dear Dr Visser Kift

PERMISSION TO CONDUCT YOUR RESEARCH AT TYGERBERG HOSPITAL

In accordance with the Provincial Research Policy and Tygerberg Hospital Notice No 40/2009, permission is hereby granted for you to conduct the above-mentioned research here at Tygerberg Hospital.

DR D ERASMUS
CHIEF EXECUTIVE OFFICER
Date: 23 December 2014

Appendix G: South African Medical Journal Author Guidelines

South African Medical Journal Author Guidelines

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.

AUTHORSHIP

Named authors must consent to publication. Authorship should be based on: (i) substantial contribution to conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual content; or (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org).

CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

RESEARCH ETHICS COMMITTEE APPROVAL

Provide evidence of Research Ethics Committee approval of the research where relevant.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to www.icmje.org.

ETHNIC CLASSIFICATION

References to ethnic classification must indicate the rationale for this.

MANUSCRIPTS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Research articles (previously 'Original articles') not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to clinical medicine and related fields. *References should be limited to no more than 15.* Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results, and Conclusion.*

Scientific letters will be considered for publication as shorter **Research articles**.

Editorials, Opinions, etc. should be about 1000 words and are welcome, but unless invited, will be subjected to the *SAMJ* peer review process.

Review articles are rarely accepted unless invited.

Letters to the editor, for publication, should be about 400 words with only one illustration or table, and must include a correspondence address.

Forum articles must be accompanied by a short description (50 words) of the affiliation details/interests of the author(s). Refer to recent forum articles for guidance. Please provide an accompanying abstract not exceeding 150 words.

Book reviews should be about 400 words and must be accompanied by the publication details of the book.

Obituaries should be about 400 words and may be accompanied by a photograph.

Guidelines must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed. A structured abstract not exceeding 250 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2. etc.) and summarised in a Table of Contents. References, appendices, figures and tables must be kept to a minimum.

Guidelines exceeding 8 000 words will only be considered for publication as a supplement to the SAMJ; the costs of which must be covered by sponsorship or advertising. The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

MANUSCRIPT PREPARATION

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - www.icmje.org. Manuscripts must be provided in **UK English**.

Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'.

Greater/smaller than signs (> and 40 years of age'. The same applies to ± and °, i.e. '35±6' and '19°C'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'

Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).

ILLUSTRATIONS AND TABLES

If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Tables may be embedded in the manuscript file or provided as '**supplementary files**'.

They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes or tabs), and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.

Figure legends: Fig. 1. 'Title...' All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable, but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached individually as '**supplementary files**' upon submission (not solely embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft Powerpoint or Excel must be accompanied by the original workbook.

REFERENCES

References must be kept to a maximum of 15. Authors must verify references from original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists must be generated manually and **not** with the use of reference

manager software. Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,^[2] and others.^[3,4-6] All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus. Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al. First and last page, volume and issue numbers should be given.

Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID). Authors are encouraged to use the DOI lookup service offered by [CrossRef](#).

Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. *Stat Med* 1998;289(1):350-355. [<http://dx.doi.org/10.1000/hgjr.182>] [PMID: 2764753]

Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101. **Chapter/section in a book:** Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. <http://www.who.int/whr/2002> (accessed 16 January 2010).

Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: publisher name, year; pages. Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'. Unpublished observations and personal communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

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A PDF proof of an article may be sent to the corresponding author before publication to resolve remaining queries. At that stage, **only** typographical changes are permitted; the corresponding author is required, having conferred with his/her co-authors, to reply within 2 working days in order for the article to be published in the issue for which it has been scheduled.

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2. The submission has not been previously published, nor is it before another journal for consideration.
3. The text complies with the stylistic and bibliographic requirements in [Author Guidelines](#).
4. The manuscript is in Microsoft Word or RTF document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (preferably TIFF or PNG). These must be submitted individually as 'supplementary files' (not solely embedded in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI) and PubMed ID (PMID)/PubMed Central ID (PMCID).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

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