Prospective evaluation of retinopathy of prematurity screening policy for neonatal units allied to the University of Cape Town

A dissertation submitted by Josephine Catherine Richards in fulfillment of the requirements of part III of the degree of Master in Medicine

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Declaration

I, Josephine Catherine Richards, 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 is being or is to be submitted for a degree at any other university.

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Date: 12/11/2002

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Abbreviations:

- AGA – Appropriately grown for Gestational Age
- CA – Age taken from date of birth
- EGA – Estimated Gestational Age (by obstetric examination)
- GA – Gestational Age.Duration of pregnancy taken from the first day of the last menstrual period. This term is usually used until the date of birth, after which the term postconceptional age is usually applied. (see discussion under PCA)
- GPH – Gestational Proteinuric Hypertension (known also as pre-eclampsia)
- HC – Head Circumference
- HCU – High Care Unit
- LGA – Large for Gestational Age
- NICU – Neonatal Intensive Care Unit
- PCA – Postconceptional Age. By convention this is taken from the first day of the last menstrual period so that term occurs on the first day of the 40^{th} week (although in reality the duration of gestation is 38 weeks if taken from the date of fertilisation). A Ballard score of 40 weeks has the same implication as a postconceptional age of 40 weeks. (Confusion has arisen since the North American Vermont-Oxford Network adopted the practice of defining PCA as illustrated in the following example: 30 weeks starts at

30 weeks minus 4 days and continues till 30 weeks plus 3 days.[1]) In this study the conventional meaning as used in the British as well as the Australian-New Zealand databases will be used.

- pO_2 - Partial Pressure of Oxygen
- ROP - Retinopathy of Prematurity
- Sc – Scored Gestational Age as assessed by the neonatologist within 72 hours of birth using the New Ballard score
- SGA – Small for Gestational Age. This term may be confused with abbreviations for scored gestational age for which reason the term "Underweight for Gestational Age" (UGA) is preferred. SGA is still used by some investigators particularly where the measure of growth is a parameter other than weight e.g. length or head circumference.
- St – Stage of ROP
- UGA – Underweight for Gestational Age. These babies fall below the 10th percentile when growth parameters are plotted on a Lubchenco chart (the standard chart used in the Western Cape public health sector)
- UCT – University of Cape Town
- VEGF – Vascular Endothelial Growth Factor
- Z – Zone

Terminology:

In order to facilitate discussion and comparison with other studies quoted in the literature:

- The screening component of this dissertation will be referred to as the **UCT-ROP study**
- The neonatal questionnaire will be referred to as the **UCT-SA-NICU survey**
- The blind school survey will be referred to as the **UCT-blind school survey**

Chapter 1: Introduction

1. Definition

Retinopathy of prematurity (ROP) refers to the pathologic vascularisation of the immature retina of premature babies. It is characterized by the development of neovascularisation and vascular shunts. This process may be followed by progression to cicatricial retinopathy and blindness. In the majority of cases, however, varying degrees of spontaneous regression occur and in many cases there is potential for normal visual development.

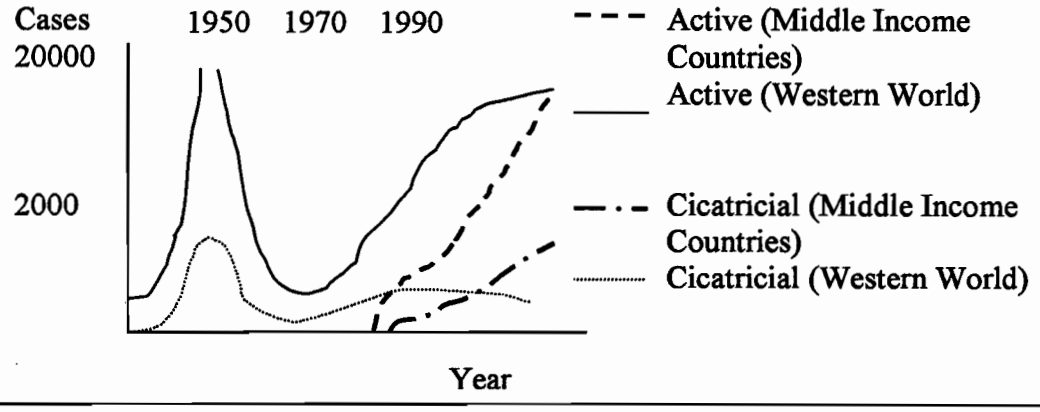
2. History

In 1942 Terry described a blinding retinopathy in babies, which he termed retrolental fibroplasia.[2] Eight years later Campbell noted that the incidence of ROP was higher in hospitals that could afford the cost of oxygen supplementation, than in poorer institutions.[2] In one of the first prospective randomized controlled ophthalmology trials Patz confirmed this link.[2] The association between the condition and prematurity, lead to the adoption of the term *Retinopathy of Prematurity* (ROP).[2]

Over the following decade ROP became the leading cause of childhood blindness in the USA, affecting 7000 children. When the link with oxygen therapy was confirmed, oxygen use was rapidly curtailed. As a result there was a dramatic rise in infant mortality and morbidity. As technology improved, oxygen supplementation under closer monitoring allowed survival of preterm babies with

a lower incidence of cicatricial ROP. Further advances, however, were accompanied by survival of much younger infants, and by a "second epidemic" of active ROP in developed countries described during and after the Cryo-ROP study of the 1980s.[3] (During the Cryo-ROP trial the incidence of ROP was 65.8%). Once again, however, advances in neonatal care appear to have resulted in a second lull in developed countries. [4, 5] This is in contrast with a growing epidemic in middle-income countries, the "third epidemic". [5, 6, 7]

Figure 1: ROP Trends



During the 1980's and 1990's there was a surge in interest in prevention of the complications of ROP in infants in whom the condition was unavoidable. It also became evident during this time that oxygen was not the only factor, which could be incriminated. Multiple studies have now implicated low gestational age and low birth weight as the greatest risk factors.[2, 3] The development of the International Classification of ROP allowed large scale pooling of data collected by screening programs. A clearer understanding of the natural history of the disease made it possible to evaluate treatment protocols. The landmark Cryo-ROP study demonstrated that it was possible to halve the incidence of serious cicatricial sequelae of the disease in cases with threshold active ROP.[8] More recently smaller scale trials have supported the use of laser in the treatment of the condition. [9-14,] Interest has now shifted to the problem of posterior ROP, which has a poor

prognosis, [15] as well as the possibility that treatment earlier than that described in the Cryo-ROP study may be advantageous. [16, 17]

3. Risk factors and protective factors influencing development of ROP

Besides low birthweight and gestational age [2, 3], the most important risk factors for ROP, the following factors appear to influence its development.

a. The role of oxygen

Although the link between oxygen therapy and ROP has been clearly established in the early, randomized trial by Patz, [2] to date only one study has demonstrated a direct relationship between oxygen measurements and ROP.[18] It showed that the length of time that the trans-cutaneously monitored $pO_2 \geq 80$mmHg was recorded correlated poorly with the incidence and severity of ROP. In infants with birth weight over 1000g, there did however appear to be a higher risk of ROP if their oxygen levels were not continuously monitored. In smaller infants the risk of ROP was conferred merely by birth weight with no effect of oxygen levels or monitoring. In this study, infants on > 40% oxygen were monitored and an attempt was made to run their trans-cutaneous pO_2 at 50-70mmHg. Interestingly an increased incidence of ROP in the neonatal unit concerned during the period of the study was attributed to picking up transient cases, which would have been missed during the usual more widely spaced examinations. This has important implications for the interpretation and comparison of incidence figures between different units. There is good evidence that fluctuations in oxygen levels within the first 2 weeks of life increase the severity of ROP (although the onset of ROP

remains most strongly influenced by post conceptional age). [19] Very high or low oxygen levels during transfer may be a reason why babies born outside study units have a higher incidence of ROP as was noted in the Cryo-ROP study. [20]

More recently the STOP-ROP trial assessed the use of supplemental oxygen at pulse oximetry saturations of 96-99% in babies with ROP. It was found that supplemental oxygen did not cause additional progression of prethreshold ROP but it also did not significantly reduce the number of infants progressing to threshold ROP. It also exacerbated pulmonary disease. [21]

b. The role of antenatal or postnatal steroids

A NIH consensus statement on the use of corticosteroids for fetal maturation was unable to offer conclusive evidence of their role in the prevention of ROP. [22] Indeed, the beneficial effects of antenatal steroids given between 24 and 34 weeks gestation, are so well established in reducing mortality, incidence of respiratory distress syndrome and intraventricular haemorrhage that it is unlikely that any trial will ever be performed to address this issue. Shortly after this NIH statement was published, a retrospective analysis of 8749 infants weighing between 502 and 1500g on the Vermont-Oxford Network Database showed a minimal (non statistically significant) protective effect. [23]

Prolonged postnatal dexamethasone used to treat bronchopulmonary dysplasia in babies with birth weight under 1000g has been shown to reduce the need for cryotherapy in a small retrospective trial. Prospective controlled trials would be needed in order to confirm this. [24]

c. The role of growth retardation

Literature review only identified one study assessing the role of growth retardation on the incidence of ROP. The study was conducted at a Jewish hospital in Canada. [25] It included only extremely premature babies born between 24 and $26^{6}/_{7}$ weeks gestation as determined by early ultrasound performed at 16-20 weeks gestation. Babies who were small for gestational age (SGA) were defined as having weights below the third percentile. These infants were at greater risk than those whose weights were appropriate for gestational age (AGA), for developing stage ≥ III ROP (65% vs.32%) and any ROP (65% vs. 12%). Severe intra-ventricular haemorrhage was commoner in AGA than SGA infants (23% vs. 12%). The authors speculate on a link between growth retardation and these outcomes related to altered levels of prostanoids, growth factors and endothelins, antioxidant deficiency and chronic intrauterine hypoxia.

In India it seems that ROP may be less common in growth-retarded babies. (Personal communication with Dr R Azad, Professor of Ophthalmology at Rajendra Prasad Centre for Ophthalmic Sciences, New Delhi). There is probably a greater similarity between South African public sector babies and Indian babies than those in the Canadian study as the former two groups are less likely to be admitted to neonatal units at such low gestational ages and are more likely to have been subjected to poor maternal nutrition. No study has specifically addressed the issue of growth retardation and ROP in less premature infants from developing countries.

d. The role of feeding with breast milk

Human milk is rich in inositol and other antioxidants and, in a retrospective analysis has been shown to reduce the incidence of ROP in very low birth weight infants. [26]

e. Other factors:

Given that premature infants are subject to a multitude of problems it is difficult to determine the significance of each possible risk factor or protective factor [2, 3].

Some of the many findings which appear to occur more frequently in babies with ROP include low birth weight, low gestational age, white race, multiple birth, birth outside the neonatal unit's hospital, [20] poor postnatal weight gain, [27] in vitro fertilization (possibly related to multiple birth), [28] blood transfusion, hypocarbia, ventilator hours, maternal bleeding and xanthine administration (e.g. theophylline / caffeine), hypoxia, hypercarbia, and mask and bag ventilation for apnoea, and parenteral nutrition. [2, 3]

During a prospective trial of surfactant prophylaxis against respiratory distress syndrome it was found that there was no significant effect on the incidence of ROP. The authors speculated that increased survival of extremely premature infants whose lungs benefit from the treatment may increase the incidence of ROP. [29]

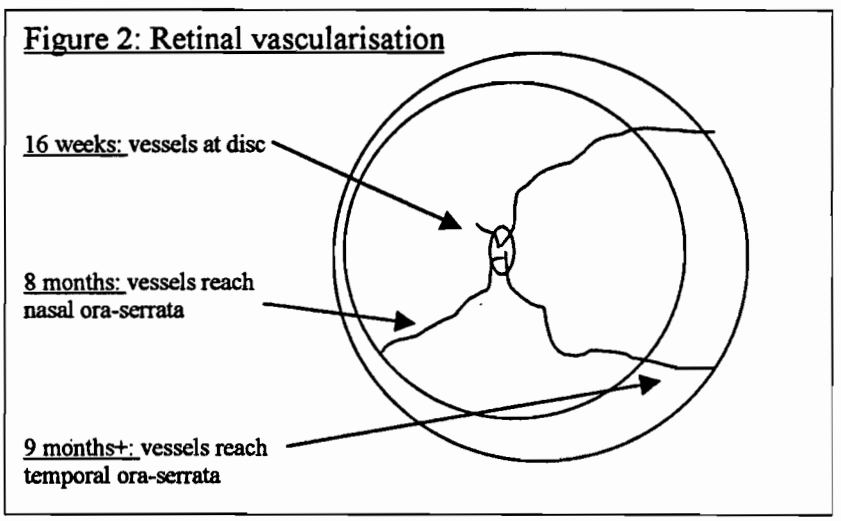
In recent years there has been much interest in the role of ambient light but the Multicentre Light-ROP study concluded that light reduction did not reduce the incidence of ROP. [30]

Despite many studies, the use of vitamin E remains controversial. Interest in its use started prior to knowledge of its antioxidant properties. Although premature neonates are known to be vitamin E deficient, supplementation has shown no consistent benefit. One intravenous preparation has been associated with the development of necrotising enterocolitis. At present although some studies have showed a beneficial effect in preventing ROP, its use is not recommended. [3, 13]

4. Development of normal retinal vasculature

Growth of mesenchyme onto the disc begins at 16 weeks. Vanguard tongues of spindle cells canalize to form rear guard primitive capillaries with differentiated endothelium and pericytes. These are remodeled into arteries and veins, which grow in a peripheral direction towards the zone of physiologic hypoxia. The process is normally only completed after birth. [3]

Figure 2: Retinal vascularisation



5. Pathogenesis of ROP

The understanding of normal vascularisation is increasing rapidly and creating a base for prevention and therapy. Vascular Endothelial Growth Factor (VEGF)

along with other angiogenic factors is currently a subject of great interest. [31] VEGF plays an important role in development of vessels from microvascular caliber to the great vessels of the body. Allelic VEGF insufficiency leads to agenesis of the great vessels. Abnormal expression of VEGF and other growth factors may be implicated in the pathology of diseases such as Norrie disease.

In the normal immature retina VEGF is found at the leading edge of vessels in the zone of physiologic hypoxia. The normoxic neonatal nursery is, in fact hyperoxic for the premature baby. It has been found that hyperoxia triggers disappearance of VEGF in the previous zone of physiologic hypoxia. Immature vessels are highly sensitive to withdrawal of VEGF and respond with apoptotic death of pericytes. In the second phase of ROP hypoxia results in upregulation of VEGF. These two mechanisms are likely to be responsible for the abrupt "broom-bristling" pattern of early ROP. [13] In addition it appears that there is a specific sequence of VEGF production by different layers of retina, which is responsible for normal full depth vascularisation of the retina. Derangement may lead to abnormal vertical growth of vessels. It is certain that that other growth factors play a role: If Insulin-like Growth Factor (IGF) is deficient proliferative ROP is more likely, [13] Platelet Derived Growth Factor (PDGF) is important for maintenance of endothelium, angiopoetins modulate neurovascular interaction and integrins influence VEGF expression. The mechanism by which the various risk factors for ROP up or down-regulate these substances has yet to be elucidated. [31] Complex interactions between these factors may be responsible for the high incidence of fundus abnormalities, which do not necessarily look like ROP, and which can be found in children who were originally born prematurely. [32]

Another aspect of pathogenesis, which is of particular relevance to our local population is the protective role of pigmentation. There is some evidence that oxidative damage may be a trigger to VEGF downregulation. Melanins are photoactive redox protective polymers. They act as free radical scavengers through the superoxide dismutase pathway. Their abundance in highly pigmented eyes may moderate the cascade of VEGF related responses. [33] Inositol, an antioxidant in breast milk may have a similar action. [26]

6. Histopathology of ROP

In the non-cicatricial stages of ROP, histopathology differs little from that of normal vascularising retina. Macroscopically the "broom-bristle" appearance and elevation are obvious features distinguishing it from the normal "chicken-wire" vascular pattern. Microscopically the normal migration of vanguard spindle cells and rear-guard endothelial cells into avascular retina appears similar to that of normal development. In the cicatricial stages, endothelial contraction occurs, initially intra-retinally. Later extra-retinal vascular proliferation takes place followed by extra-retinal endothelial contraction and vitreous base synchysis. [2]

7. Classification of ROP

a. The International Classification of ROP [2, 3]

In 1984 the Committee for the Classification of ROP published their international classification of ROP. This was of great importance in allowing observation of the natural history of the disease as well as in assessing the effectiveness of interventions.

Phases of the disease included in the Classification are:

- Active
- Cicatricial

These are further divided according to their severity:

i. Active ROP

The severity of active ROP is determined by its **Location, Extent, Stage** and the presence of **Plus disease**.

Location is described according to zones centered round the disc.

- Zone 1 has a radius twice the distance from the disc to the fovea.
- Zone 2 has a radius equal to the distance to the nasal ora serrata.
- Zone 3 includes the remaining temporal retina.

Extent is described according to the individual or continuous clock hours of involvement.

Stage refers to the pattern of the vascular abnormalities.

- Stage 1 disease shows a thin grey-white line separating immature peripheral retina from vascularised retina. The blood vessels straighten and

acquire a "broom-bristle "appearance instead of the normal "tree-like", or "chicken-wire like" branching pattern.

- Stage 2 disease refers to the formation of small, mesenchymal arteriovenous shunts along a ridge at the junction of vascularised and non-vascularised retina.
- Stage 3 disease shows extraretinal fibrovascular proliferation and often includes retinal and vitreous haemorrhage. Plus disease is frequently associated with this stage
- Stage 4 disease refers to the development of a subtotal retinal detachment starting from the periphery (4A is extrafoveal and 4B refers to foveal detachment)
- Stage 5 disease is marked by total retinal detachment.

Plus Disease is characterized by dilated tortuous vessels in the posterior pole. Features which are not included in the term "Plus Disease" but which frequently occur simultaneously include prominent iris vessels, poor pupil dilatation and vitreous haze.

ii. Cicatricial ROP

As active ROP undergoes involution approximately 20% of cases will progress to cicatricial ROP. This is staged as follows:

- Stage 1 disease patients have myopia, with minimal peripheral scarring and vitreous haze.
- Stage 2 disease shows temporal vitreoretinal traction often resulting in a pseudo-squint and a positive Angle Kappa.
- Stage 3 disease describes progression of peripheral retinal traction to the formation of falciform folds.

- Stage 4 traction includes a partial retrolental fibrovascular ring with retinal detachment.
- Stage 5 disease refers to total retinal detachment with a complete retrolental ring and secondary angle closure glaucoma in some cases.

b. New aspects of disease classification

It has now become evident that with the increased survival of smaller infants the International Classification has deficiencies in its description of posterior disease. In a series of extremely premature infants where mean birth weight was 845g, mean gestational age was 26.6 weeks and mean gestational age at treatment was 35.2 weeks the following observations were made: Zone 1 ROP has different characteristics and prognosis to that in zones 2 and 3. Unusual patterns seen may include a single vessel demarcating the zone between vascular and avascular retina, and flat peripheral morphology in the presence of marked plus disease. [15] ROP in zone 1 has more serious implications than more peripheral disease so that it is important to include it in definitions of prethreshold and threshold disease. [21]

c. Implications for follow-up and treatment

Treatment of threshold ROP in the Cryo-ROP study (discussed below) was based on previous experience of disease, which was mainly in zones 2 and 3. New definitions as included in the STOP-ROP [21] (Supplemental Therapeutic Oxygen for the Treatment of ROP) study are in italics. These are based on clinical judgement of ophthalmologists participating in this multicentre study that zone 1 disease, being more aggressive, needed earlier treatment.

Prethreshold disease:

- *Zone 1: Any number of clock hours of stage 1 without plus disease*
- Zone 2: Any number of clock hours of stage 3 without plus disease, any number of clock hours of stage 2 with plus disease, and plus disease with less than 5 contiguous hours of stage 3 disease

Threshold disease:

- *Zone 1: Any stage of ROP with dilatation / tortuosity in at least 2 quadrants (plus disease) or any stage 3 with or without plus disease*
- Zone 2: Presence of ≥5 contiguous or ≥8 composite clock hours of stage 3 disease with plus disease *as indicated by dilatation and tortuosity in at least 2 quadrants*

Plus disease: Two or more clock hours of vessel tortuosity and fullness at the optic nerve. Previously clock hours were not included in the definition of plus disease.

These definitions may change further based on the ETROP (Early Treatment of ROP) study, which seeks to determine the value of treatment of prethreshold ROP in infants at ≥15% risk of an unfavourable outcome. [17] Likelihood of an unfavourable outcome is assessed, using a Risk-factor Model (RM-ROP) based on the natural history cohort of the Cryo-ROP trial. [34]

8. The Cryo-ROP study

This landmark study, which started in 1986, has made a great impact on:

- Our knowledge of the natural history of the disease.
- The development of effective treatment.

- Our ability to narrow down screening to high-risk cases and to screen them at an appropriate stage.
- Our knowledge of long-term visual prognosis of premature babies.

The study took place in 23 centers and included 9751 infants weighing less than 1251g at birth. A total of 3862 infants survived 28 days from birth and met eligibility criteria. Threshold ROP was diagnosed in 291 infants whose average weight was 800g at birth. After randomization, cryotherapy was performed in half of the eyes with threshold disease. Threshold disease was defined as ≥5 continuous or ≥8 cumulative clock hours of stage 3 ROP in the presence of *plus disease*. It was treated within 72 hours of diagnosis. At this level the risk of blindness is predicted to be 50% if ROP is left untreated. Assessment of outcome was initially planned for 3 months, 1 year and 5½ years. It was to have been judged according to structural outcome. An unfavourable outcome included:

1) Posterior retinal detachment
2) Falciform fold in the macula
3) Retrolental mass.

Since initiation of the trial, modifications have taken place to include functional outcome, and follow up is ongoing 15-16 years later.

Important publications include:

1. Preliminary results: These showed that at 3 months, cryotherapy significantly improved the structural outcome (43% unfavorable outcome if untreated compared with 21.8% if treated). [8]

2. One-year structural and functional outcome: This study included photographic retinal assessment as well as grating acuity and behavioural

assessment. There was reduction in unfavourable structural appearance from 47.4% to 25.7%. Teller card acuity also demonstrated the beneficial effects of cryotherapy with 35.0% unfavourable visual outcome in treated eyes compared with 56.3% in the eyes not receiving treatment. [35]

3. 3½ year outcome: There was excellent follow up, which included 92% of the 256 survivors from the cohort of 291 infants who had originally been included in randomisation. Once again structural benefits were seen with posterior pole status being unfavourable in 26.1% of treated eyes compared with 45.4% of untreated eyes. Comparison between visual acuity of treated and untreated groups using HOTV crowded letters showed 46.6% favourable compared with 57.5% unfavourable outcome, and using Teller acuity showed 26.1% favourable compared with 45.4% unfavorable outcome.[36]

4. 5½-year outcome: Follow-up of 234 children showed continued reduction in unfavourable structural outcomes between treated and control groups (47.1% vs. 61.7%). It was now possible to measure Snellen acuity. Importantly, although testing of visual outcomes showed that blindness was less common in treated groups than controls (31.5% vs. 48%), fewer treated eyes than controls had a visual acuity of better than 20/40 (13% vs. 17%). The implication is that cryotherapy may reduce the potential for excellent vision. [37]

retinopathy should not be missed if the first examination is performed at at or just before 33 weeks and babies with ROP are followed up till at least 42 weeks (unless involution has already occurred).

In the same group of patients involution began at a mean of 38.6 weeks and in 90% of patients had started by 44 weeks. [40]

10. Screening for ROP

On the basis of the Cryo-ROP study as well as local epidemiological data, guidelines for screening of infants in the "upper-income country" setting have been drawn up. The most widely used in neonatal services in "Westernised" healthcare systems are the American and British Guidelines. Several publications have refined these as more data become available. At present great emphasis is being placed on cost effectiveness, and screening only of babies truly at risk. Number of examinations is being reduced to a minimum. It is probable that none of the currently available guidelines is applicable to the circumstances in the Western Cape public health sector.

The goal of screening is to identify potentially blinding ROP at a stage amenable to treatment

a. Guidelines

i. American Guidelines [41]

- Screen all infants ≤1500g and/or ≤28 weeks gestational age at birth (as well as babies >1500g with an unstable course)

- First examination at should be performed at week 4-6 after birth or week 31-33 PCA (whichever comes first)
- Babies should be examined every 2-4 weeks till vessels enter zone 3
- If ROP or immature vessels are seen in zone 1 babies should be examined every 1-2 weeks till vessels enter zone 3
- Threshold disease should be treated within 72 hours

ii. British Guidelines [42]

- Screen all infants ≤1500g and/or ≤31 weeks gestational age at birth.
- First examination should take place 6-7 weeks after birth
- Babies should be examined every 2 weeks till vessels enter zone 3
- Treatment should be given as soon as threshold disease is detected

The British guidelines appear safe for Britain [43] but the 1500g cut off may necessitate screening of large numbers of babies who are at very low risk of blinding disease. A 1250g cut off level of has been suggested as a more cost-effective option for future screening. [44]

A study applying the American and British guidelines to an American nursery suggested that the American 28 week cut off was too low as some babies with longer gestation developed ROP worse than stage 2. The authors considered the British 31 week cut off more acceptable. On examining the figures in the article, however, it appears that use of the 1500g birth weight cut off would have ensured that all the babies about whom concern was raised would have been screened and that in this study the American guidelines were quite safe. [45]

b. Timing

Based on more recent evidence the timing of first examination may be refined. Important factors in timing are Postconceptional age (PCA) and Chronological age (CA). It is important to include both where possible and a safe combination appears to be examination of infants of 7 weeks CA or 34 weeks PCA, whichever comes first, (but not younger than 5 weeks CA). Using chronological age alone may cause threshold disease to be missed in larger birth weight infants (1000-1250g). Using postconceptional age alone may cause threshold disease to be missed in smaller infants (<750g). [46] A recent audit of screening findings in a series of 258 extremely low birth weight infants (≤1000g) found that threshold disease developed at a range of 8-13.7 weeks after birth, which suggests that screening at 7 weeks chronological age should be safe even in this extremely high-risk group of babies. [47]

c. Examination Procedure

The pupils should be dilated with a low concentration preparation such as Cyclopentolate 0.2% and Phenylephrine 1% (Cyclomydril®, Alcon) at 1 hour, and at 30 minutes prior to examination. These drops have undesirable side effects such as tachycardia, bradycardia and feeding problems due to gastrointestinal stasis, which should be recognized and avoided as far as possible by punctual occlusion. A third application may be administered if the pupils fail to dilate (provided that the infant is stable). Topical anaesthesia, an eyelid speculum (preferably sterile) and scleral indentation are usual. Examination of the entire circumference of the retina is recommended unless the infant is particularly unstable in which case the temporal retina should be examined until more prolonged examination becomes safe. A 20, 25, 28 or 30 dioptre lens may be used. The 25D lens is useful in that 2

lens fields cover the distance between the disc and the edge of zone 2.[2,3,13] A 30D lens is useful in assessing the extent of posterior ROP. [1]

It is useful to have an assistant to hold the infant's head. Failing this swaddling is usually necessary. "Nesting" (supporting the infant in a flexed position by means of a soft padded surface with boundaries) may reduce distress experienced by the infant. [48]

Monitoring of unstable infants is important, as apnoea and cardiac arrest have been reported as a result of the stress of being examined as well as vagal stimulation during indentation. [2]

11. Treatment

a. Cryotherapy

Screening and cryotherapy have been assessed as being cost effective in saving approximately 320 American children from blindness per year. [49] Cryotherapy for threshold ROP is the longest established therapy although laser treatment is acquiring increasing popularity. Treatment entails freezing of the peripheral non-vascularised retina in one or more session depending on the regression noted subsequent to treatment. The lens cryoprobe used for intracapsular lens extraction is most suitable for the therapy. Usually the full circumference is treated confluently with one row nasally and two rows temporally. In the Cryo-ROP trial 291 babies had cryotherapy and 17 required additional treatment for persistent plus disease adjacent to untreated avascular retina 3-17 days after treatment. During the Cryo-ROP trial the decision on whether to use local or general

anaesthetic was left to the clinicians involved. Only one eye per infant received cryotherapy.[8] As a result of the findings of the trial most centres now treat both eyes at the same sitting especially if general anaesthetic is used. As a long available treatment the advantages and disadvantages of cryotherapy are well established.[2, 3, 14]

i. Advantages of cryotherapy

1. Cryotherapy is well tested and has been proven to be effective.
2. Almost all centers have access to a lens cryoprobe.
3. Peripheral disease can be treated even if there is poor dilatation of the pupil.

ii. Operative disadvantages of cryotherapy

1. Cryotherapy is a painful procedure, which leads to considerable local reaction with prolonged lid swelling and a theoretical risk of amblyopia.
2. The cryotherapy apparatus is not as easily portable as most laser units.
3. Zone one disease is poorly accessible and responds less favourably to treatment.
4. Conjunctival incision is required for the treatment of posterior disease.
5. Increased intraocular pressure may cause corneal clouding.

iii. Ocular complications of cryotherapy

- Intra-operative
  1. Conjunctival haematoma or laceration
  2. Haemorrhage (retinal, pre-retinal or vitreous)
  3. Central retinal artery occlusion

4. Freezing of an area larger than planned

- Postoperative
  1. Myopia
  2. Amblyopia from prolonged lid closure
  3. Pre-retinal membrane formation
  4. Late retinal detachment
  5. Constricted visual field

iv. Systemic complications of cryotherapy

1. Bradycardia
2. Acquired or increased cyanosis
3. Seizure
4. Cardio-respiratory arrest

b. Laser

Other modes of therapy such as diode laser are currently gaining increased popularity as a result of what appears to be an improved side effect profile. Both transpupillary argon and indirect or trans-scleral diode laser [9-14] have been found to be as effective in treating threshold ROP as cryotherapy. Diode laser, being more portable has become more widely used than argon laser. It is probably less likely than argon laser to be absorbed by other undesirable anatomical structures in the eye (e.g. tunica vasculosa lentis or lens) as a result of its absorption spectrum. [14]

Laser therapy may offer advantages over cryotherapy. These include superior results with posterior prethreshold disease, ease of application under local

anaesthetic, and lower risk of subsequent rhegmatogenous retinal detachment. The latter is thought to be as a result of the practice of leaving a ½ burn diameter between burns so that the remaining retina can stretch with growth of the eye.

i. Complications of laser therapy [14]

- Intra-operative
    1. Anterior segment ischaemia following inadvertent photocoagulation of the long posterior ciliary arteries [10]
    2. Iris, retinal or corneal burn
    3. Pre-retinal or choroidal haemorrhage
    4. Inadvertent photocoagulation of the fovea
- Post-operative
    1. Choroidal neovascularisation
    2. Pre-retinal membrane formation
    3. Cataract formation (particularly if using argon laser in the presence of a persistent tunica vasculosa lentis)
    4. Late retinal detachment

c. Scleral buckling

Small-scale studies have shown that anatomical reattachment of the retina may be achieved following scleral buckling for stage 4 or 5 active disease. Some isolated good visual results have been recorded but in general the prognosis for this stage of disease is poor. In interpreting these small studies the possibility of spontaneous resolution must be taken into consideration. [2, 3]

d. Vitreoretinal surgery

Vitrectomy with membrane peeling using an open or closed sky approach, may allow anatomical restoration of some previously unsalvageable eyes. Unfortunately the visual results have been universally dismal with visual acuity as good as 6/60 being unusual. This is because of ocular, and organic neurological causes as well as amblyopia. [2, 3]

12. Sequelae and Follow up

Close follow up is needed until regression occurs or until the cicatricial process reaches its end point. In the case of regression it must be borne in mind that the following conditions are commoner in babies who have regressed ROP than in controls: [3, 50, 51]

- Myopia: In infants not receiving cryotherapy the incidence of myopia is about 20% at one year. Refraction may increase by age 12 months to ≥ 5D in 4.6% of children with regressed ROP. After this, progression appears to stabilize. Risk factors for higher myopia include lower birth weight, increasing severity of ROP (e.g. macular heterotopia and folds), astigmatism and anisometropia. It seems that the cause of myopia is related both to retarded anterior segment growth and increased axial length. Although this may be seen in infants with untreated ROP it is more marked in babies who have received cryotherapy and may also occur after laser treatment although it is usually less severe. [50, 51]
- Astigmatism
- Anisometropia

d. Strabismus

In the case of cicatricial disease and incomplete regression there is an increased risk of:

- Glaucoma:
  1. Angle closure caused by small anterior segment / anterior displacement of the iris lens diaphragm by retrolental fibrosis. This may occur at any stage in life. [2]
  2. Ciliary block glaucoma may occur at any stage in life.[2]
  3. Inflammatory glaucoma usually occurs in infancy.[2]
  4. Neovascular usually occurs in infancy.[2]

- Late Retinal Detachment: The risk of retinal detachment persists throughout life in infants with regressed ROP. At this stage no increased risk has been seen following cryotherapy although it is expected that this may change with long-term follow up. Risk factors for late retinal detachment include: abnormal peripheral vascular changes, avascular peripheral retina, temporal vascular straightening, vascular tortuosity, Retinal Pigment Epithalial changes, vitreoretinal changes, retinal folds, vitreous membranes, retinal breaks, and lattice-like degeneration. In patients with detachment in the presence of vitreoretinal and vascular changes there is often a need for vitrectomy.

13. Differential diagnosis

During a screening program for neonates few other conditions present a similar picture and the diagnosis is usually obvious. In our setting, however, where there is no large-scale ROP screening program, some patients may present late. In these cases the differential diagnosis becomes broader and dependant on the cicatricial stage reached.

Other conditions associated with retinal detachment and/or vitreous fibrosis in infants and children include: [2, 3]

- Norrie Disease: Initially this progressive disease may appear very similar to ROP, presenting as bilateral leucocoria with total retinal detachment. Neurological degeneration, mental retardation, and deafness, become evident in the first few months of life. Leucocoria is usually present earlier than in patients with ROP. It is inherited in an X-linked recessive pattern associated with a mutation on the short arm of the X chromosome.
- Coats Disease: This condition is usually unilateral and occurs later in life than ROP. Gross intra-retinal exudation is usually obvious.
- Posterior Hyperplastic Primary Vitreous: This congenital abnormality is present from birth, is usually unilateral and is often associated with anterior segment abnormalities and microphthalmos.
- Familial Exudative Vitreoretinopathy: This follows an autosomal dominant pattern and includes marked subretinal exudation with temporal dragging of the macula, retinal breaks and detachments, and organized vitreous membranes. It usually occurs in non-premature individuals and develops several years after birth in an asymmetric fashion.

- Retinoblastoma: Although this condition should be considered in the differential diagnosis, the lack of history of prematurity, asymmetry of findings, and usual characteristic appearance generally allow clinical differentiation. The presence of calcification on CTscan is further evidence in support of retinoblastoma.

15. The future

a. Prevention

Advances in neonatal care have already had a significant impact on the incidence of ROP. They may continue to do so although any additional preventive effect is unlikely to be dramatic.

b. Risk assessment

Genetic studies may eventually play a role in risk assessment. [1, 13] Diseases such as Norrie disease, X- linked retinal dysplasia, familial exudative vitreoretinopathy, and some cases of posterior hyperplastic primary vitreous have been mapped to loci in contiguous areas of the X chromosome. Expression of the disease is dependant both on the location of the mutation and on whether this results in nonsense translations, mis-sense translations or deletions. The first African American female with advanced ROP was found to be positive for the Norrie gene and this finding has been present in other infants with ROP.

In less affluent countries genetic testing is unlikely to be financially viable in the foreseeable future. For this reason easily identifiable physical or clinical

characteristics would be more useful for risk identification (e.g. skin or fundus pigmentation).

c. Screening

In the future telephotoscreening may become possible using the RetCam (Massie Research Laboratories Inc, Dublin, California).This fibreoptic device uses a contact camera to provide a 120° view of the retina. It is currently being improved to allow a 130° view. The major limitations of the system at this stage are its high cost and low sensitivity of 46-89%. [52-54]

d. Treatment

The future of treatment of this, and other vascular diseases may lie in modulation of growth factors. These are already proving successful in switching off neovascularisation in animal models. Areas of possible intervention include controlling VEGF production, VEGF neutralisation, receptor modulation, and modification of VEGF-endothelial interaction. [31]

Chapter 2:Background to this project

1. International screening trends

Screening for ROP has evolved dramatically since the Cryo-ROP trial. Possible changes to screening strategies, which are currently of interest include: [53]

1. Elimination of superfluous examinations
2. Abbreviation of the screening process in low risk infants (e.g. direct ophthalmoscopy of the posterior pole looking for plus disease)
3. Use of technology other than conventional indirect ophthalmoscopy for screening.

Strategy 1, the elimination of unnecessary examinations is clearly a priority. Although most first world neonatal units follow the British and American guidelines, it is recognized that protocols must be tailored to local circumstances. High-tech computer generated models such as RM-ROP are still far from able to improve screening criteria [55] and would be out of the reach of units with limited resources. Since babies are usually discharged prior to completion of screening, follow-up represents a major challenge. Even in a "first-world" situation, ensuring compliance with follow-up requires considerable resources in terms of time and effort. [56] In an upper-income country such as the United Kingdom where 648 consultants are registered for a population of approximately 60 million, skills in this specialized aspect of ophthalmology are not always considered optimal. Screening and management of babies are time consuming and do not always receive priority. Training and better organisation of services are considered vital.[57] In South Africa there are only approximately 250 ophthalmologists serving about

45 million people and concerns about examiners' skills and distribution of screening raised in the UK are probably equally valid. Ways of limiting the number of babies who need screening are clearly of great importance, but as yet only partially understood.

Strategies 2 and 3 seem remote possibilities in our circumstances given the current failure of both inexpensive direct ophthalmoscopy, and expensive photographic devices to impact on our much greater problem of blinding diabetic retinopathy.

2. Current status of screening in South Africa

Screening for ROP in South Africa is currently done on a sporadic basis. Referral depends on partially evidence based neonatal unit policy rather than clinical audit or local epidemiological data. Many neonatologists and ophthalmologists feel that the disease is so rare in our population that screening may not be cost effective at all.

3. Occurrence of ROP in South Africa

The possible sources of information on ROP occurrence in a population include:

a. ROP incidence figures from neonatal screening programs

b. Blind school statistics

c. Blind registration statistics / Patients presenting to ophthalmologists for diagnosis

d. Cohort studies

e. Large population based longitudinal studies

Current information is as follows:

a. ROP incidence figures from neonatal screening

In South Africa there are limited numbers of ophthalmologists to do screening and very few clinical audit figures are available. Straker et al found in 1991, that of 141 babies weighing ≤1500g at birth, 19.2% developed ROP but only 1.56% developed prethreshold ROP in the Groote Schuur Neonatal ICU. None required treatment. [58] The most recent figures are those from a study at Kalafong Hospital in Pretoriaof 122 black infants with birth-weight <1500g. In this group of babies ROP incidence was 26% with 3.5% developing stage 3 disease in 1999. (Personal communication with Dr Odendal, Dept. Ophthalmology, Pretoria)

b. Blind school statistics

In South Africa this source of figures has several disadvantages. O'Sullivan et al in 1997 found that 10.6% of childhood blindness in blind schools was caused by ROP. More than 50% of children in the blind schools, however, had visual acuity of >6/60 (i.e. were partially sighted and not blind). In addition at the time of the study only 10.1% of blind children were in schools for the blind and disproportionately few of these were black. [6] Some schools were in inaccessible areas so that the sample was taken from the more urban, accessible schools (personal communication with Jane O'Sullivan). Many blind schools do not keep statistics on causes of blindness or birthplace of children with ROP blindness.

c. Blind registration / Patients presenting to ophthalmologists for diagnosis

In South Africa, blind registration statistics on ROP are not available. It is hoped that this will change following the resolutions of the 2002 Cape Town childhood blindness workshop. At present information exists only in the form of individual ophthalmologists impressions. There are plans to make ophthalmology consultation mandatory prior to blind school admission. Following that assessment the diagnosis would be registered in a centralized database.

A negligible number of children blind from ROP are seen at the Red Cross Children's hospital ophthalmology clinic. Most blind children whose parents make use of the public sector would be expected to present to this facility as it is the only unit in the Western Cape with a paediatric ophthalmologist. For this reason it is thought that the prevalence of ROP blindness in our region is not very high.

d. Longitudinal and cohort studies

No large longitudinal or cohort studies have been performed in the last 8 years on the subject of ROP or childhood blindness in South Africa.

4. South Africa (and specifically the Western Cape) compared with other countries and regions

In the blind school study the 10.6% prevalence of ROP blindness in South African blind schools in 1997 was lower than those in Latin America, Asia and Eastern

Europe (38.6% in Cuba, 25.9% in Bulgaria, 16.9% in Thailand). [7] The authors of this study point out that incidence of childhood blindness due to ROP is 0% in most African countries and 0.2% in India. They feel that this is strongly linked to infant mortality although only limited figures on this subject are quoted (for many of the countries these figures may not be available). In 1998 the British Oxford registry reported that ROP cases comprised 5.4% of the childhood blind, resident in the region. [59] There is also evidence that the incidence and severity of ROP may be declining in the upper income country setting. [4]

At the start of the UCT-ROP study the decline in the South African health care system was a matter for concern. Staff shortages were worsening in the tertiary public health sector so that intensive monitoring (e.g. of oxygen therapy) was becoming increasingly difficult. It was conceivable that the previously first world standards maintained in our top units may be declining and that ROP trends may have begun to mirror those of the other middle-income countries (listed above) more closely. It was not known if Straker's findings (discussed previously) [58] were still applicable. In the event that the incidence of blinding ROP was still negligible it was felt that analysis of possible reasons for this, might guide decisions on how to limit the number of infants needing screening.

5. Risk factors for and protective factors against ROP and their possible significance to screening policy in South Africa

a. The pigmentation theory:

In the blind school study 6/26 (31%) of Asian children, 41/145 (28%) of white children, 7/69 (10%) of coloured children and 4/138 (1%) of black children in

South Africa were blind from ROP. In this study, black children made up 56.7% of the blind school population. [6] The authors of the study note the possible protective effect of racial pigmentation although they feel that socio-economic factors are more likely to account for the disparity between population groups. [7] Interestingly Cuba with its 25.9% incidence of ROP, defies the pigmentation theory, despite the expected, significant number of pigmented neonates of mixed Afro-Hispanic ancestry. [7]

In the Cryo-ROP study, of the 4099 infants enrolled in a "natural history cohort", 7.4% of 2158 white infants developed threshold ROP vs. 3.2% of 1584 black infants. [60] Unfortunately it is not clear what is meant by the classification "black".

Monos et al found that in a mixed population of 161 Bedouins and Jews originating from Europe, Asia and North Africa, dark fundus pigmentation halved the risk of developing acute ROP. In addition none of the babies with stage 3 disease had dark fundus pigmentation. [33] Our black population, which shares a similar ancestry with West African tribes who migrated south, probably has greater genetic similarities to Black Americans of slave origin than North African Bedouins.

In the public health sector neonatal population of the Western Cape, a very high proportion of babies are pigmented. It was felt that if the role of pigmentation in our babies could be determined it may be possible to reduce the numbers requiring screening. Skin pigmentation would be more useful to neonatologists than fundal pigmentation as a referral criterion.

b. Growth retardation

It is known that the Western Cape public health sector neonatal population has a very high proportion of growth retarded and wasted babies. This may reduce the incidence of ROP in that intrauterine nutritional compromise is thought to be responsible for accelerated maturation of neurological and respiratory systems. On the other hand, deficiency in antioxidants in babies with intra-uterine malnutrition may increase the risk of ROP. [56] As discussed previously the only information available on growth retardation is in the form of 1) a study on extremely premature Canadian Jewish babies [56] and 2) anecdotal impressions from India.

Two possible explanations for our large numbers of small babies are 1) poor maternal health (including malnutrition, alcoholism and HIV) and 2) the high incidence of caesarian section for gestational proteinuric hypertension (GPH). Groote Schuur Hospital (GSH) where Straker's audit was performed [58] is a referral centre for GPH. Other units allied to UCT such as Mowbray Maternity Hospital serve as general tertiary referral centres and hence only encounter causes of growth retardation other than GPH.

Chapter 3: Evaluation of retinopathy of prematurity screening policy

1. Aim

To identify characteristics of babies who need to be screened for ROP in order to develop a cost effective screening policy appropriate to the population and resources of the neonatal units allied to the University of Cape Town. In addition, to assess the potential for application of findings to other South African centres in order to provide information useful to other units wishing to develop their own protocols.

2. Methods

a. Inclusion criteria

Babies under the care of Groote Schuur and Mowbray Maternity Neonatal Intensive Care Units between 14/7/1999 and 13/12/2000 were eligible for inclusion in this study. Scored or Estimated Gestational Age $\leq$ 28 weeks or birth weight $\leq$1500g were prerequisites. Babies who were transferred to outlying hospitals were excluded from the study.

b. Timing of examination

Babies were examined 5-7 weeks after birth or at 34 weeks EGA or before discharge, whichever came first, but not before 5 weeks of age. [41, 42, 46] If immature vasculature in zone 2 was detected, examination was repeated every 2 weeks until Zone 3 was vascularised. If ROP in zone 2 or was detected, weekly examinations were performed until regression occurred, with a view to treatment if it became necessary. [41, 42] (International guidelines on zone 1 disease proved irrelevant to this study as no babies had low enough gestational age at birth to develop zone 1 disease). Mothers whose babies were discharged before they became eligible for examination or before vascularisation was complete were offered the option of outpatient screening. It became evident that almost no mothers were bringing their babies to follow up visits. As a result funding was obtained to improve attendance. Two research assistants (trained ophthalmic assistants) fluent in English, Afrikaans and Xhosa (as well as the author) provided written and verbal counseling to mothers in the neonatal unit. The research assistants also took care of mothers and babies during the follow up clinics and attempted to trace mothers who failed to bring their babies back on the booked date. Mothers received payment sufficient to cover the cost of transport and a hospital lunch if they attended their appointment. It was decided that the greatest priority was to determine the presence or absence of potentially blinding ROP and that this would be evident by the time babies reached their due date of delivery. [39] For this reason the remunerated follow-up visit was arranged to coincide with the baby's 40th postconceptional week unless closer follow up was necessitated by prior clinical findings. In the many cases where mothers still did not return on the appropriate date, they were phoned every week until they did come in. As a result these babies were older than 40 weeks PCA at the time of their final examination.

c. Examination technique

The author's examination technique was checked and findings were verified during the first 6 months of screening through supervision by a departmental consultant, or by a visiting ophthalmologist, both of whom were experienced in screening for ROP.

Pupils were dilated with cyclopentolate 0.2% and phenylephrine 1% (Cyclomydril®, Alcon) at 1 hour, and at 30 minutes prior to examination. In the case of failure to dilate, a third application was administered if the infant was stable. Topical anaesthesia and use of a scleral depressor to turn the eye were routine. Although some ophthalmologists confine their examination to the temporal retina if no posterior ROP is detected, it has been shown that significant disease may occasionally be missed using this practice. [61] For this reason, and because the study aimed to detect any ROP, examination was not confined to the temporal retina. An eyelid speculum was used in most cases. Neonatal speculums were disinfected in chlorhexidine, based on evidence that this was more effective than isopropyl alcohol. Insufficient speculums were available to allow autoclaving. [62, 63]

Depending on the availability of an assistant the baby was either swaddled or examined in the "Nesting" position. [48]

d. Collection of Risk Factor Data

Birth characteristics including weight, head circumference (HC), estimated gestational age (EGA) and Ballard scored gestational age (Sc) were obtained from

the hospital notes on the day of recruitment. Details from the patient notes were transcribed to the data sheets (Appendix 1) either by the author or by a research assistant. EGA was assessed by the obstetrician prior to birth according to pre-natal findings such as menstrual history, size and growth. Sc was assessed using the Ballard score by the admitting neonatologist. The use of the new Ballard score [64] is a routine practice in Western Cape neonatal units and is expected to be accurate to within 2 weeks on either side of true gestational age when performed by an experienced examiner. Its accuracy is likely to be lower in an academic setting where some junior doctors are still in the process of acquiring proficiency in neonatal assessment. Availability of gestational age as predicted by early ultrasound was very rare so that the **Sc was deemed the most accurate of the available age estimates** (note that for this reason the results will be based as far as possible on the Ballard score). These parameters were then used to determine the presence of and type of growth retardation.

Pigmentation was assessed at the first eye examination. Fundus pigmentation was graded as light, medium, or dark by the author using as a reference, photographs in Monos et al.[33] Iris pigmentation was graded as light (blue), medium (any intermediate degree of pigmentation), and dark (obvious brown pigmentation).

In a dermatological study looking at actinic skin damage, there was moderate correlation between patient-reported or dermatologist-reported skin colour and automated measurement of reflectance. [65] There was a higher correlation between this subjective impression and presence of actinic lesions than between these lesions and reflectance i.e. clinical assessment in this study had better validity than laboratory assessment. For this reason it was felt that clinical assessment of skin

colour in the neonatal unit should be evaluated as an inexpensive and easy tool for risk factor assessment. Skin pigmentation was assessed using a simplified modification of the Fitzpatrick score as follows: [66]

- Light = pale translucent skin which turns red on exposure to light.
- Medium = skin which has some pigmentation at birth and which acquires a golden or light brown colour when exposed to light.
- Dark = skin which is obviously pigmented from birth and becomes darker with minimal redness on light exposure.

In the first few months of the study the neonatologist assessed skin pigmentation independent of the ophthalmologist in order to determine whether there would be reasonable correlation between the opinions of two doctors should this attribute be included in future screening protocols.

Presence of maternal Gestational Proteinuric Hypertension (GPH), and use of antenatal steroids to accelerate fetal maturation was recorded.

Other parameters such as systemic complications, oxygen use, administration of postnatal xanthines and steroids etc. were recorded when present in the hospital notes. Availability of these factors in the neonatal record was inconsistent. It was felt that this would make them less useful as referral criteria under the current system of record keeping and for this reason they were not included in final analysis of risk factor data.

3. **Results:**

TheUCT-ROP study

a. Population characteristics of the group of babies studied

Overview (see table 1 in iii. for more detailed information):

During the entire duration of screening 9 cases of ROP were detected. One of these was seen amongst the 38 babies examined during the pilot phase. This baby was excluded from risk factor analysis. No babies developed threshold ROP and hence no treatment was needed. No stage 3 ROP (i.e. disease with the potential to progress to threshold or even blindness) was seen above 31 weeks gestational age or 1100g birth weight.

i. Recruitment and drop-out

A total of 269 babies were recruited of which 37 babies died or were transferred out of the neonatal unit (usually to hospitals in outlying areas) before they became eligible for screening. Note that because babies were not recruited at birth, these figures should not be used as early mortality indicators for the nursery as some babies died prior to the recruiting ward rounds, held once a week alternating between neonatal units. This left 232 babies available for screening which started on 6/7/1999. During the 10 week pilot phase while examination technique was being refined 38 babies were examined. They were excluded from the final incidence statistics in order to avoid the influence of the learning curve.

After the pilot phase, 194 babies were examined starting on 21/9/1999. Virtually no mothers of the first 83 babies returned for follow-up. The only babies receiving

follow-up examinations in this group were the ones in whom ROP had been detected in the neonatal unit. In these cases the parents were contacted as many times as was necessary to persuade them to bring their babies to the scheduled appointments.

After funds became available to educate and remunerate mothers, 111 babies were examined. These babies were eligible for final examination between 14/7/2000 and 13/12/2000. Of these 29/111 (26.1%) did not attend final follow up i.e. there was only 73.9% follow up despite the efforts of the 3 recruiters.

ii. Groupings

No new cases of ROP were detected at the 40 week follow-up visit. In addition, Fisher's exact test showed that there was no statistically significant difference in the rate of detection of ROP prior to funding (3/83 = 3.6%) and after funding was obtained (5/111 = 4.5%) $p = 0.53$. For this reason all of these 194 patients seen after the pilot phase were analysed for risk factors as a single group. In this group of 194 patients a total of 85 were followed to term or beyond, giving a follow-up rate of 46%.

iii. Characteristics of the 9 babies with ROP

Table 1: Characteristics of the 9 babies with ROP

Baby	**Score (Sc)**	**Estimated Gestational Age (EGA)**	**Size for gestational age A – appropriate S – small**		**Stage & Zone of ROP**	**Birth weight (g)**
			By Weight	By Head Circumference		
Ad	31	29	S	A	St1 Z3	910
Ba	31		S	A	St2 Z3	1050
Be Ý§	33	27 Ý§	S	S	St3 Z2	920
Br ‖¶** ÝÝ	29	31 ‖¶**	A	A	St3 Z3	1100 ÝÝ
Da	27		A	A	St3 Z2	950
Mz Ý	27	30	A	A	St1 Z3	1175 Ý
Na *Ý	*32*	*30* Ý	*S*	*S*	*St3 Z3*	*870*
Sm	24	28	A	A	St1 Z3	790
Ts	29		A		St2 Z3	910

**Seen during pilot phase and hence excluded from incidence statistics*

Ý Gestational ages were reviewed by a senior neonatologist. In these cases the babies were re-assessed and the postnatal course reviewed following the diagnosis of ROP. It was felt that the estimated gestational (EGA) age as assessed by the

Note on the following results:

The following results illustrate the risk factor profile of babies in the neonatal service. It is important to use the best available assessment of gestational age in order to compare certain parameters. The purpose of charts 1 and 2 in section b as well as charts 3 and 4 in section c is to illustrate trends in gestational age distribution as well as the logic behind the way in which the Ballard score is applied in subsequent results.

b. Gestational ages of the babies at birth measured by neonatologist's Ballard score (Sc) and obstetrician's Estimated Gestational Age (EGA)

Chart 1

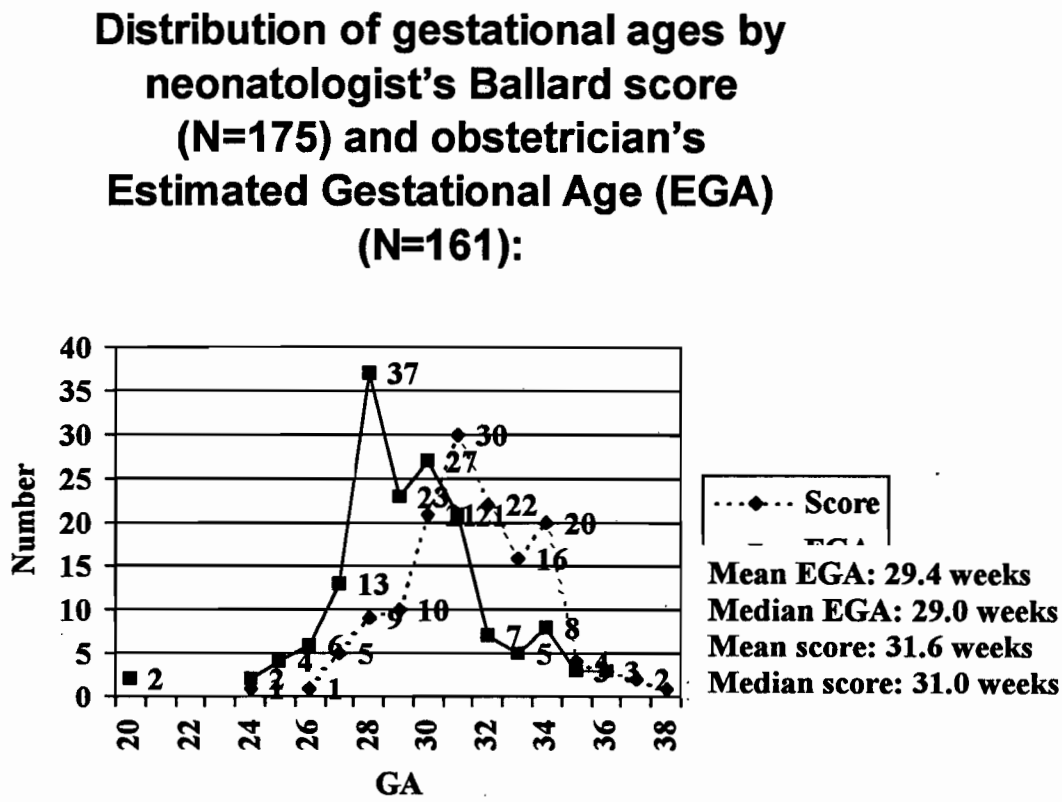
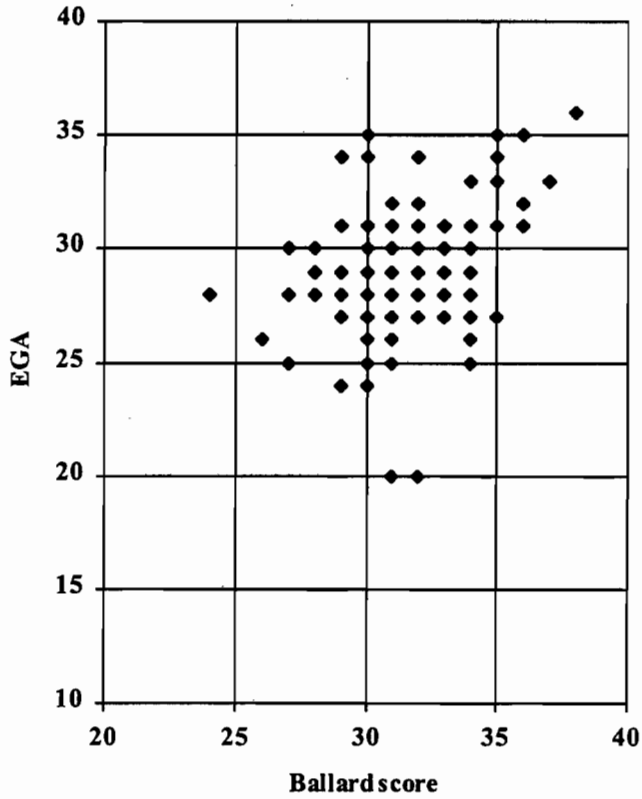


Chart 2:

Scatter Plot showing Ballard score and estimated gestational age



- The correlation between estimated and scored gestational age value distributions was 0.33 indicating that the distributions were statistically significantly different.
- On chart 1 a left shift in the distribution of EGA was evident, indicating that EGAs were overall lower than scores. This reflects the high incidence of intrauterine growth retardation (as discussed previously, EGA relies mainly on size and growth in-utero and is less accurate than the Ballard score).
- The scatter plot (chart 2) demonstrates the clustering of babies in the 30-35 week Ballard scored range corresponding with the 25-32 week estimated gestational age range.

c. Results relating to risk factors for and protective factors against ROP, illustrating their potential as possible screening criteria

i. The Ballard score as a screening criterion

Table 2: Composition of the group by Ballard scored gestational age when divided into groups fitting 3 proposed screening criteria

Proposed screening cut-off (weeks PCA at birth)	**Total Scored = 150/194**	**% Babies eligible for screening**
≤33 (UCT)	115	76.7
≤31 (British)	77	51.3*
≤28 (American)	16	10.67 Ý

*Note that the incidence of extreme prematurity < 28 weeks is low in the UCT neonatal population with almost 50% of babies being > 31 weeks postconceptional age at birth.

Ý If babies ≤ 33 weeks were screened 76.7 % of this group would have been examined. The proposed 33 week level is based on the conservative British 31 week cut-of plus 2 weeks to allow for inaccuracy of the Ballard score.

In some cases, for logistical reasons such as medical staff shortages, the Ballard score (or Estimated Gestational Age) was not available. In order to facilitate discussion on the entire group of 194 babies it was necessary to correct for the number of babies who were not allocated a score. It was hence important to demonstrate that the distribution of gestational age of babies not allocated a Ballard score was similar to that of the group overall.

Table 3: Incidence of ROP by Ballard scored Gestational Age (with correction[§] allowing for number of babies allocated a score)

Note on results to be presented in Table 3: By chance, all babies who had ROP had been allocated a Ballard score (and Estimated Gestational Age). If calculations of ROP incidence were based only on the number of babies scored this would have resulted in false inflation of the incidence of ROP in each gestational age group. It was hence necessary to correct for number of babies scored as described above.

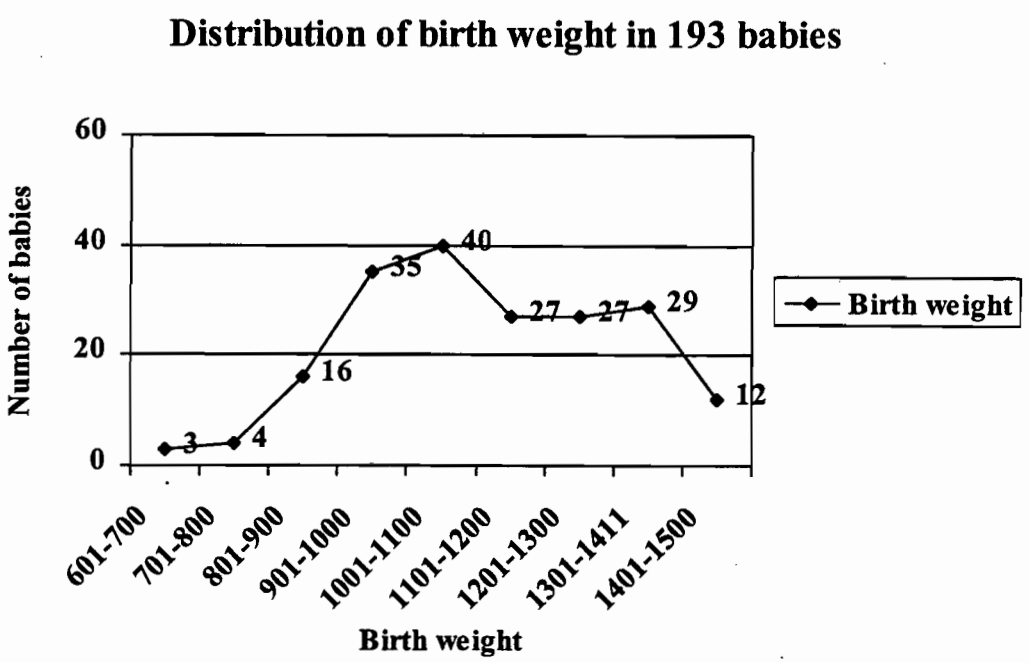
	Total	**≤33 wk**	**≤31 wk**	**≤28 wk**
All babies screened after pilot phase (uncorrected)	8/194 (4%)	8/115 (7%)	6/77 (7%)	3/16 (19%)
Incidence using correction factor[§] of 194/150=1.293		5.4%	7.0%	14.5%

As expected the incidence of ROP was higher in the babies with lower Ballard scores. An incidence of 14.5% was lower than that expected for babies of ≤28 weeks gestational age. Possible reasons for this will be presented in the discussion.

ii. Birth weight as a screening criterion

Chart 5

(The birth weight of one baby was unavailable)



The American criteria for screening are ≤1500g or ≤28 weeks PCA at birth and British criteria are ≤1500g or ≤31 weeks PCA at birth. Hence all babies in this study would have been screened in a "first world" situation by virtue of their weight.

Some ophthalmologists have suggested reducing the birth weight criterion to 1250g or1100g. If this were applied to the population in this study, babies of 31 or 28 weeks by score would have been missed in some cases as illustrated in table 4

Table 4: Number of babies who would have been missed in a screening program based on other possible birth weight criteria

Birth weight used as screening criteria	**Number of babies eligible for screening**	**Number of babies ≤ 31 weeks GA who would have been missed**	**Number of babies ≤ 28 weeks GA who would have been missed**
≤1250 *	138/193 = 71.5%	13	1
≤1100 [Ý]	98 /193= 50.7%	30	2

* If only babies ≤1250g had been screened, 71.5% of babies would have been eligible for examination at the expense of missing 13 (6.7%) babies ≤ 31 weeks and 1 (0.05%) baby ≤ 28 weeks.

[Ý] As illustrated in Table 1 (and in keeping with figures previously discussed from Kalafong hospital) no baby with stage 3 ROP or worse had a birth weight over 1100g. If 1100g were used as a cut off, only 50.7% of babies in this series would have required screening. It should, however, be noted that babies eligible for screening by the American or British criteria as well as babies with ROP less severe than stage 3 would have been missed.

iii. Combination of birth weight and Ballard score as screening criteria

If a Ballard score of ≤31 weeks OR birth weight ≤1250g were applied to the study group 117.6[§]/194 (60.6%) babies would have required screening and no babies with any stage of ROP would have been missed.

iv. Head circumference as a screening criterion

Table 5: Number of babies who would require screening by proposed head circumference measurements

Head Circumference (HC) proposed as screening criterion	**Number of babies eligible for inclusion by proposed criteria. (Total for whom HC was measured = 174)**	**Percentage of the 174 babies eligible for screening**
≤28 cm (largest HC of babies with ROP)	134	86.8%*
≤30cm (29.5cm is 90th percentile for 28 weeks as in the American criteria)	169	97.1%Ý
≤32cm (31.5cm is 90th percentile for 31 weeks as in the British Criteria)	169	97.1% Ý

*If only babies with head circumference higher than that of the largest circumference of the babies with ROP had been screened, 13.2 % of babies in this series could have been eliminated from screening.

Ý If either the head circumference applicable to the 90th percentile for babies of gestational age by the American or British criteria were used, only 2.9% of babies could have been excluded from screening.

See distribution of head circumference for gestational age (Table 6).

v. The Role of Growth retardation

Table 6: Growth retardation as assessed using weight and head circumference for each scored gestational age

	Total measured	**Number of small babies**	**% Small babies**	**Small babies with ROP out of total babies with ROP whose Wt and HC were measured**	**% Babies with ROP who were small by Wt or HC**
Wt/Sc	144/194	83/144	57.6	3/8	37.5
HC/Sc	127/194	54/127	42.5	1/7	14.2

Note in table 6 that 37.5% of babies were small for gestational age by weight but only 14.2% were growth retarded by head circumference. Head circumference is less affected by late intrauterine wasting so that only babies with severe prolonged intrauterine insult are likely to have reduced head circumference. This will be dealt with in the discussion

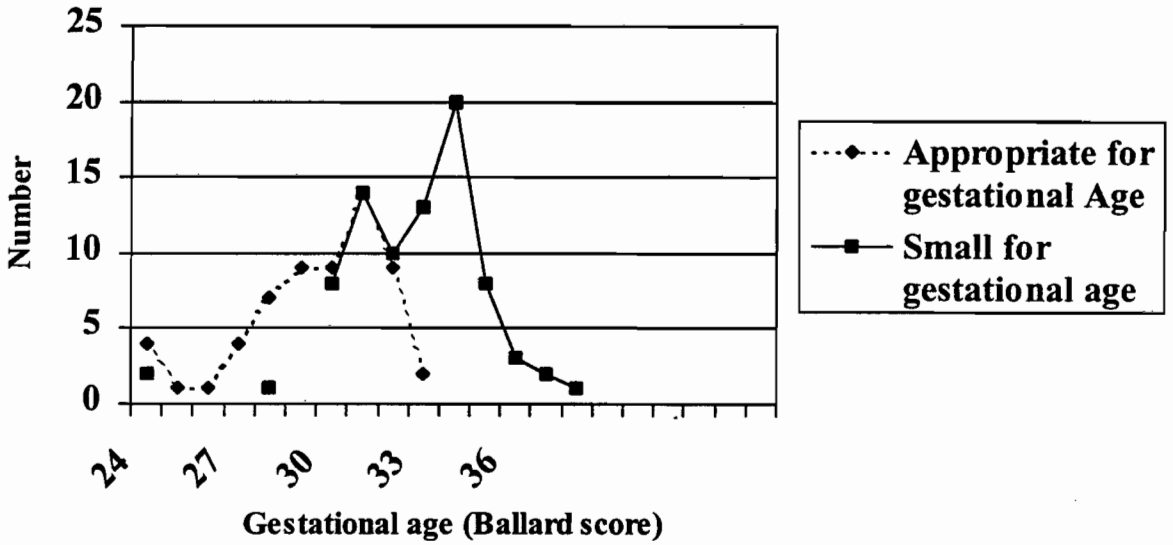
Symmetry of growth retardation using weight and head circumference

Head circumference had been measured in 127 babies who were then assessed for growth retardation. All these babies had been also been assessed for growth retardation using birth weight. The babies who had been assessed using both criteria were then compared:

- A total of 27/127 babies (21.3%) were small for gestational age by weight but not head circumference. This asymmetry indicates late intrauterine wasting. A similar proportion of babies in the group of those who had ROP, 2/8 (25%) fell into this group. Fisher's exact test showed that there was no significant difference in the incidence of asymmetric growth retardation between babies with ROP and the total group (p=0.5).
- A total of 50/127 (39.4%) were small for gestational age by weight **AND** head circumference. This symmetry indicates prolonged growth retardation. Only 1/8 babies who had ROP (12.5%) fell into this group. This suggested that prolonged intrauterine insult may accelerate maturation or in some way protect against ROP. Because of very small numbers, however, Fisher's exact test was unable to demonstrate a statistically significant protective effect of symmetrical growth retardation against ROP (p=0.12).

Chart 6

Trends in growth retardation as measured by birth-weight

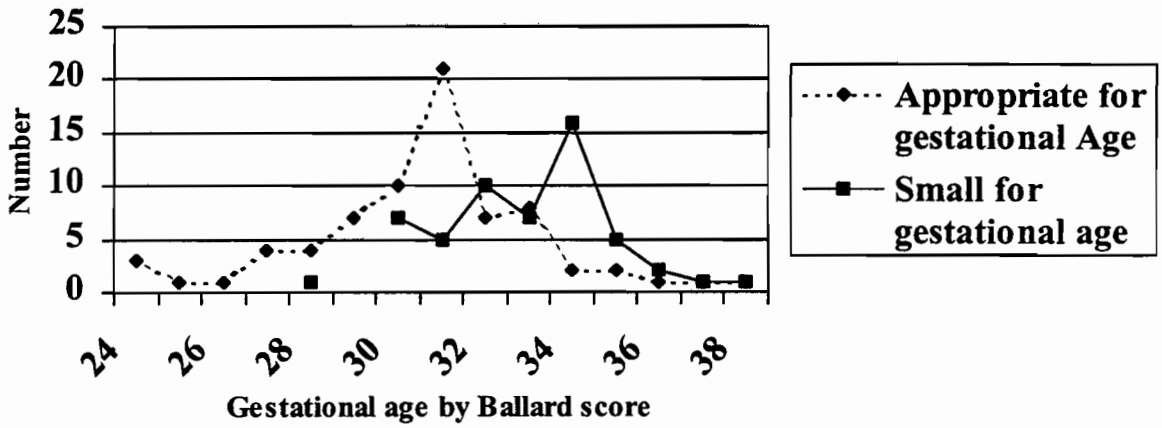


- The mean gestational age at birth of babies who were **small** for gestational age was 32.9 weeks with a standard deviation of 1.94.
- The mean gestational age at birth of babies who were **appropriately grown** for gestational age was 29.8 weeks with a standard deviation of 1.87.
- The t test showed a statistically significant difference in the distribution of the 2 groups with $t=9.13$ and $p<0.00001$.
- In babies with GA ≥ 32weeks, 84.1% (58/69) babies in whom birth weight and GA were available, had weight below the 10^{th} percentile.
- In babies with GA ≤ 31weeks, 33.3% (23/69) babies in whom birth weight and GA were available had birth weight below the 10^{th} percentile.

This indicates that babies of higher gestational age were more commonly underweight in the neonatal service studied.

Chart 7

Trends in growth retardation as measured by head circumference



- The mean gestational age at birth of babies whose head circumference was **small** for gestational age was 32.81 weeks with a standard deviation of 1.87.
- The mean gestational age at birth of babies whose head circumference was **appropriately grown** for gestational age was 30.87 weeks with a standard deviation of 2.44.
- The t test showed a statistically significant difference in the distribution of the 2 groups with t=4.85 and p=0.05.
- In babies with GA ≥ 32 weeks, 66.6% (40/60) of babies in whom both head circumference and GA were available, had head circumference below the 10^{th} percentile.

- In babies with GA ≤ 31weeks, 20.3% (13/64) of babies in whom both head circumference and GA were available, had head circumference below the 10th percentile.

This indicates that babies of higher gestational age more commonly had small head circumference. In the upper gestational age range, many babies have small head circumferences. If head circumference were used as a screening criterion these babies would be eligible for examination because they fall within the normal limits for babies of lower gestational age. This option will be explored in the discussion.

vii. The role of pigmentation

Table 7: Pigmentation as assessed by the author

Note on figures in the following table: In some cases pigmentation was not recorded on the data sheet. The most common reason was that the author omitted to record these at the same time as noting presence or absence of ROP when the research assistants were busy with the data sheets i.e. the omission was by chance. All babies who had ROP had been assessed for pigmentation (by chance).
As discussed, in respect of score, it was necessary to apply a correction factor to prevent false elevation of the incidence of ROP in each category. This was calculated as follows: Number of babies in the series (194) / Number of babies assessed for pigmentation.

*Correction factor for skin pigmentation: (1.13). This was based on the total number of babies screened (194) divided by the number of babies allocated a pigmentation category (171).

[Ÿ] Correction factor for fundus pigmentation: (1.15). This was based on the total number of babies screened (194) divided by the number of babies allocated a pigmentation category (168).

	Total	**%**	**% with ROP**
Skin pigmentation	**Total classified=171**	**%**	**Corrected* for number classified 194/171**
Light	16	9.4	11.0
Medium	83	48.5	5.3
Dark	72	42.1	1.2
Fundus pigmentation	**Total classified=168**		**Corrected [Ÿ] for number classified 194/168**
Light	20	11.9	13.0
Medium	72	42.9	4.8
Dark	76	45.2	1.1 [ÿ]

- In the initial phase of the study there was agreement between the ophthalmologist and neonatologist in 49/56 cases (88%). This represented a good correlation with a Chi squared value of 70.9 and $p<0.00001$. The coefficient of concordance was 0.46. Because the correlation was good and it proved difficult to ensure that neonatologists completed the assessment of pigmentation, the assessment was performed by the investigator for the remainder of the study.
- When ophthalmologist assessment of skin versus fundus colour was compared there was agreement in 152 out of the 171 cases (89%) in which

both of these variables were assessed. This represented an excellent correlation with a Chi squared value of 208.7 ($p<0.00001$).

- There was a trend towards a lower incidence of ROP with increased skin pigmentation although this was not statistically significant. Only one baby with ROP had dark skin[ŷ]. For this reason the results could only be analysed by grouping this baby with those of medium pigmentation and then comparing this composite group with the group of babies with light pigmentation. Fisher's exact test revealed no statistically significant protective effect of pigmentation ($p=0.11$).
- Again, because only one baby[ŷ] with ROP had dark fundal pigmentation it was necessary to group dark with medium coloured fundi in performing Fisher's exact test. There was a non statistically significant protective effect of pigmentation ($p=0.055$).
- Very few babies had light pigmentation and there were almost equal numbers of babies with medium and dark pigmentation.
- All except one baby had dark brown irises at the time of examination. This baby had light brown irises. For this reason no analysis was performed on the link between iris colour and ROP.

Table 8: Ethnic group as recorded by the admitting clerical staff

	Total	**%**
Population group	**n=194**	
Black	96	49.5
Mixed ancestry	98	50.5

The numbers of babies assessed by the clerk as being of black or mixed ancestry were almost equal. No babies were assessed as being white.

viii. Other possible factors influencing the incidence of ROP

Table 9: Presence of other risk factors / protective factors

	Total 194	**%**
Antenatal steroids (2 or 3 doses)	61	31.4
Antenatal steroids (1 dose)	15	7.7
Maternal GPH	51	26.3

A substantial number of mothers received antenatal steroids and / or suffered from GPH. This was a small series and lack of complete detailed records made it difficult to assess possible pharmacological confounding variables (e.g. both betamethasone and dexamethasone were in use during the study and use of postnatal steroids was not always certain as medication charts went missing). It was also not possible to assess the exact nature and severity of the GPH. For this reason these factors were not analysed for statistical significance. They have been included in this series of results in order to facilitate comparison between this group of babies and those in proposed future audits.

The UCT-Blind School Survey

Of 10 schools listed in the ophthalmologic directory at the time of the survey, information was obtained from 7 following one written request, 1 faxed request and as many telephone calls as were necessary, according to the means of communication available at each school. These data are summarized in table 10. The 3 schools from which no information could be obtained were in under-resourced areas: Umtata, Nkandla and Mpundule. At the time of the study, schools were in the process of being re-assigned as schools for the handicapped and it is not certain whether these schools catered for blind children at all as no contact (including telephonic) could be made despite multiple attempts.

Table 10: Origin and year of birth of babies who were blind from ROP

Each child with ROP blindness, along with the year of birth of that child is shown under columns indicating which school supplied the information. The hospital at which the child was born is shown on the left.

Hospital	**Athlone School (11 children)**	**Pioneer School (32 children)**	**Prinshof School (20 children)**
Tygerberg	'85	'75	
	'86	'89	
Groote Schuur	'85		
	'88		
Red Cross	'85		
	'86		
	'87		
	'93		
Somerset	'92		
Knysna	'82		
Eben Donges (Worcester)		'86	
Johannesburg General		'89	
Bloemfontein		'84	
		'92	

Provincial (Port Elizabeth)		'79	
		'83 (2 babies)	
		'91	
		'92	
Mossel Bay		'91	
Gordonia (Upington)		'92	
Ontdekkers (Roodepoort)		'88	
Middelburg		'90	
Klerksdorp			'88
			'89
Louis Leipoldt (Cape Town)		'86	
JS Marais		'83	

- A total of 69 children blind from ROP were identified in this survey. This probably represents almost all ROP blind children at blind schools in the country. Figures are comparable with those from the blind school study by O'Sullivan, Gilbert and colleagues [5,7] in which 564 children were examined between 1991 and 1996. At that time the 60 children with ROP blindness were identified.
- Athlone, Prinshof and Pioneer schools admit children at age 5 so that these figures reflect the neonatal population born prior to 1996.

- The hospital of origin was only known in 28 out of the 69 (40.5%) cases. Information was notably lacking in the cases of white children attending Prinshof and Pioneer schools.
- The last ROP blind child admitted to Athlone School (in Cape Town) was born in 1993. In all children blind from ROP, the hospital at which they were treated is included in the table.
- The last ROP blind child at Pioneer School (in Worcester) was born in 1992. Hospital of birth was unknown in 15 children. Twenty-five children were white, 5 were of mixed ancestry and one was black.
- The last ROP blind child admitted to Prinshof School (Pretoria) was born in 1995. In total 19 children were white and 1 was black.
- Arthur Blaxall School (in Pietermaritzburg) was unable to supply any birth details on the 7 ROP blind children attending the school besides dates of birth between 1983 and 1994. Of the children, 6 were Asian and one black.
- Siloe School (in Pholokwane) had admitted no children with ROP blindness.
- Lethaba School (in Lethaba) and Bartimea School (in Selosesha) were unable to supply confirmation of having admitted ROP blind children and did not keep information on birth details.

Table 11: Results of countrywide NICU survey

Characteristics	Cape Town	Bloem-fontein	Pretoria	Johannes-burg	Durban
Minimum weight ventilated	800g if beds available but obstetric history taken into account	800g	800g	1000g	1000g or less if mother has bad obstetric history
Acceptable Oxygen range in NICU (measured on pulse oximeter)	86-92%	92-94% (ELBW babies 90-92%)	88-93%	90-95%	88-93%

Is this usually achieved?	Yes	Yes	No	Yes	Probably not
Number of pulse oximeters in unit	5 (currently 3 function)	ICU 10 HCU 3	6	ICU 4 HCU 2 Transitional 2	6 but only 3 function
Are more pulse oximeters needed?	Yes	Yes	Yes	Yes	Yes
On which babies are arterial blood gasses measured?	Unstable babies and ventilated babies		Babies in ICU 2-4x per day	Newborns, ventilated & unstable babies up to every 2 hrs	Depends how busy the unit is. Up to 4 per day on sick babies
Number of beds in the Neonatal unit excluding Kangaroo Care	ICU 12 HCU 12		ICU 6 HCU 15	ICU 8 HCU 20 Low care 15 Transitional 8	ICU 4 HCU 4 Special care 6 but in reality 50-60 (over-loaded)

Number of Kangaroo Care beds	10 and 6 beds for boarding mothers who are breastfeeding		13	None	No but this type of care is encouraged
Number of babies per year with birth weight					
500-999g	40	33		60	100-150
1000-1249g	45	58		293	200-300
1249-1500g	45 approx	48			100-200 approx
Are babies screened for ROP	Yes at time of study	Yes	Yes	Yes	Yes

What are the criteria?	During study: <1501g or <29weeks at 5-7 weeks (before discharge)		Babies less than 1501g, twins of these babies screened at 4-6 weeks	<32 wks gestation or <1500g screened as close to 36 weeks as possible (or at 6 weeks)	Oxygen therapy for more than 2 weeks. Ventilated babies on >70% oxygen Screened when stable before discharge
Number of babies blinded by ROP per year	0 in study		1 baby blind in 1 eye but poor follow-up	None known since 1991	Aware that babies exist but unknown numbers
Available ROP figures	See figures above		Feb 1999-Dec 2000 – St3 6%, Threshold 3.2%	1-2 treated per year	5-6 babies with ROP detected per year

Ethnicity of babies admitted to unit	Black ~50%, Mixed ancestry ~50%	Black 97%, Mixed ancestry 2.5%, White 0.5%	Almost all black	80% black, 20% Other	99% black
Proportion of babies under-weight for gestational age	35-40%	16%	Unknown	10%	Unknown
Discharge criteria	Feeding well and weigh >1700g		When feeding well No definite weight		

The most noteworthy discrepancies between units were:

- Admission criteria
- Acceptable range of oxygen for each nursery
- Resources and ability to maintain desired oxygen levels
- Proportion of growth retarded babies in the unit
- The use of kangaroo maternal care allowing very early discharge

All units served a population of babies of whom a substantial proportion would be darkly pigmented.

Specifically of note in the Groote Schuur unit is that oxygen control receives a high level of priority. Despite the small number of pulse oximeters, the unit is able to perform readings every 1 to 3 hours by keeping the machines on trolleys and allocating nurses to wheel them between babies on a semi-continual basis. If necessary, a machine may be used for continuous monitoring while the remaining machines are wheeled around. This is clearly very labour intensive but ensures that the readings on the pulse oximeter are not overlooked.

All units indicated that they were desperate for more working pulse oximeters which would allow much closer monitoring and would free nursing staff to attend to other important aspects of care.

Chapter 4: Discussion

1. Discussion of findings and comparison with other studies

a. The low incidence of ROP

It is probable that one of the main reasons for the low incidence of ROP detected in this study (4%: Table 3) is that the group consisted predominantly of babies of higher gestational age than in western-world series. In the Cryo-ROP study the mean gestational age was 26 weeks. In the UCT-ROP study only 2 babies had gestational ages ≤ 26 weeks.

Importantly most babies in the UCT-ROP study were only examined 1-3 times. As an example it would be common for a 30 week PCA baby to be examined at age 5-6 weeks (35 weeks PCA) immediately prior to discharge and then again at 40 weeks PCA (or later if it took several weeks to trace the mother and persuade her to return for follow-up). When analysing the Cryo-ROP natural history cohort it was found that the larger babies (900-1300g), who would probably have characteristics similar to babies in the UCT-ROP study population, had onset of ROP at a mean of 5.7 +/- 3.4 weeks. [39] This means that many of the babies in the UCT-ROP study would have had onset of ROP after discharge from hospital. In the Cryo-ROP group, mild disease tended to regress within 2-3 weeks. [39] This implies that in our population these cases would have had resolution of ROP by the time they were examined at 40 weeks PCA. Had it been possible to examine babies 2-3 weeks after discharge it is probable that a significantly higher incidence of ROP would have been noted.

It is possible that the predominance of pigmented babies in the study group contributed to a true lower incidence of ROP. (Only one baby with dark pigmentation had ROP: Table 7). Unfortunately, the numbers of babies in this study were insufficient to draw definite conclusions in this regard.

The effect of intrauterine growth retardation on retinal vascular maturation is poorly understood particularly in babies with gestational ages close to term. As discussed previously, the only figures available on this subject apply to babies <27 weeks gestational age with birth weight below the 3rd percentile. [25] Babies in the UCT-ROP study were mainly older than 28 weeks gestational age at birth and growth retardation was defined as growth below the 10th percentile.

It was particularly interesting to note that while the incidence of asymmetric, late intrauterine wasting in babies with ROP was similar to that of the whole group this was not the case for symmetric growth retardation. While 39.4% of babies in the whole group showed symmetric, prolonged intrauterine growth retardation only 12.5% of babies with ROP exhibited this finding. There were insufficient babies with ROP in this study to demonstrate a statistically significant effect of prolonged intrauterine growth retardation.

It is possible that prolonged exposure intrauterine nutritional stress was responsible for accelerated retinal maturation as is postulated by neonatologists to occur in other organs. Equally it is possible that a deficiency in antioxidants in older growth retarded babies could be a risk factor for the development of ROP as was postulated for babies < 27 week gestational age.[25]

The low incidence of ROP in the ≤ 28-week group (14.5%) is almost certainly in part due to poor follow-up as 7 out of the 16 (44%) were only seen on one occasion for reasons discussed under "follow-up". Coats et al point out differences in reported incidence of ROP in extremely premature infants. [67] In the Cryo-ROP study the incidence of ROP in babies ≤27 weeks was 83.4%. With each additional week of decreased gestational age at birth there was a 19% increase in the risk of developing threshold disease. In Coats's series, 100% of babies ≤ 25 weeks gestational age at birth developed ROP. In other series, figures such as 58% incidence in babies ≤ 25 weeks, and 58% in babies ≤29 weeks have been reported. The figures are difficult to compare because of differing standards of care and varying proportions of extremely premature babies. [67]

It is important not to use figures from the UCT-ROP study for comparison with other neonatal units who are able to examine babies on several occasions before 40 weeks PCA because of longer admission. It is, however, likely that the incidence of ROP remains low in UCT units. In light of the absence of newly detected ROP at the final visit, or ROP requiring treatment it is almost certain that blinding ROP is not a significant problem in this neonatal service. The evidence for lack of blinding ROP is further supported by the findings of the UCT-blind school survey.

b. Follow-up

In the UCT-ROP study the follow up rate of 73% during the funded phase was poor despite the best efforts of the project team. In total when the non-funded phase was included in the follow-up figures the follow-up rate was only 46.2%. There were several possible reasons: The tertiary care facilities in which the study

was performed serve a population with addresses mostly located 5-25 km away. Most paediatric follow-up takes place at baby clinics in the community, so that it is a great inconvenience for mothers who are almost all reliant on public transport to have to travel to a tertiary care center for an eye appointment.

Although many mothers were able to give a mobile telephone contact number, most of them could not afford to pay for a phone contract and it was usually difficult to contact them via this means. Many mothers from the Eastern Cape travel over 1000km in order to give birth and quote the local address of a friend in Cape Town in order to be eligible for the better standard of care available in the Western Cape. They then travel home again once their babies are discharged. It was common to phone a contact number and be told that the mother was no longer at that address. After the long period babies spend in the NICU, working mothers have often used up their maternity leave. Several mothers were unable to attend for this reason. Examples of the difficulties with follow-up include those found in the 7 babies ≤ 28 weeks score who were not brought for follow-up: One mother presented in labour (her first medical visit during the pregnancy) and then disappeared from follow up, one mother died, following which the baby was taken to the Northern Province by extended family, one mother left for the Eastern Cape upon discharge and the other four were not contactable using the contact details in the folder. In a non-research setting where a dedicated team is not available to keep reminding mothers to attend, the follow-up rate is likely to be much worse.[56]

c. The local incidence of blinding ROP in the context of international blind school surveys

It is interesting to consider trends in ROP around the world in the context of socioeconomic conditions, primary health care standards and the state of tertiary

facilities. Most developed countries, along with a low incidence of extreme poverty have good primary and tertiary care and a low incidence of blinding ROP. Cuba has an excellent primary health care system but tertiary care is still not of the same standard as may be found in westernized countries. This means that although oxygen, for example, is available, its use is not accompanied by adequate ability to monitor and control its use. Premature infants have a very good chance of surviving but are at risk of long-term sequelae such as blindness. [7]

The University of Cape Town units are in the unusual situation of serving a mixed population some of which has access to excellent primary peri-natal care and some of which migrates into the region transiently from communities in which there is extreme poverty with little or no primary care. Obstetric and neonatal facilities are world-class so that babies have a high chance of survival without the sequelae of substandard care. After discharge, however those babies born into extreme poverty are likely to suffer a similar or higher mortality rate to that of non-premature babies in these under-serviced communities. Thus some of the babies in the UCT-ROP study would be in the same category as those in the upper income countries where there is a declining incidence of ROP. Others would probably fall into the group described by Gilbert et al in which infant mortality is so high that they do not survive long enough to be admitted to blind schools. In the face of the AIDS epidemic this group is likely to form an increasing proportion of all premature babies. The following infant mortality figures illustrate the disparities present in South African society in 1996: 54.3/1000 for Blacks, 36.3/1000 for Coloureds, 9.9/1000 for Indians and 7.3/1000 for Whites. [6]

Analysis of the UCT-blind school survey (Table 10) showed that the last child with ROP blindness originating from UCT neonatal services was born in 1993. The survey represents children born prior to 1996. Importantly, 4 children came from Red Cross Children's Hospital (not included in the UCT-ROP study). Children admitted to the Red Cross Children's Hospital service are usually transferred there for purposes of surgical management. This means they are more likely to be very sick in addition to being exposed to the risk factor of fluctuating oxygen levels[19] during transfer and peri-operatively.

Unfortunately in the UCT-blind school survey, neonatal unit of origin was only known in 40.5% of cases. Information about white children was particularly lacking. However in the context of South African society in the late 1980's and early 1990's when these children were born, it is likely that many of them would have been managed in the private sector. In this case they may have formed part of the "second epidemic" as described in upper income situations. This commonly used term refers to the increased incidence of ROP because of increased survival of extremely preterm babies.

Many of the ROP blind children in the UCT-blind school survey came from secondary level neonatal units in small towns. In these situations, a paediatrician rather than a neonatologist provides the neonatal care service and facilities for stringent oxygen monitoring may not be available. Babies from these units may represent the "third epidemic" as described by Gilbert et al. [5, 7]

d. The decrease in incidence of ROP since the early 1990's

Although there has been a documented declining incidence of ROP in developed countries it is unlikely that this would account for such a low incidence of ROP as that found in the UCT-ROP study.

In all Western Cape neonatal units, Kangaroo Maternal Care is now strongly encouraged. It allows babies to be removed from incubators to be kept warm through their mothers' body heat. Bonding and breastfeeding are promoted and babies grow faster than those receiving care in incubators. It also allows discharge of most babies weighing more than 1700g for paediatric follow up in day hospitals out in the community. In 1991 at Groote Schuur, babies stayed in hospital until their weight reached 2000g and, were hence followed longer and more frequently by the ophthalmologist so that mild later cases would have been detected. As discussed above it is probable that in the UCT-ROP study, mild ROP developed and regressed in the time between initial screening and the single follow up visit at term.

Data from the 1991 audit are no longer available so that it is not possible to compare the study populations. Most of the senior staff of the neonatal unit have moved on or assumed new roles so that it is also difficult to be certain what care practices are different from those in 1991. It is conceivable that the population admitted is a lower risk group, technology has advanced, or that care has improved over the last decade.

2. Appropriate risk factor based screening criteria in a developing country situation

a. The Ballard score

This is currently the most accurate way of assessing gestational age at birth in our setting. It is accurate to within approximately 2 weeks depending on the experience of the examiner. In one baby with ROP in this study, the Ballard score as assessed by a junior doctor was felt to be overestimated by 3-4 weeks when reviewed by a professor. Allowances need to be made for the presence of junior staff in the setting of an academic hospital.

If birth weight were abandoned as a criterion in our situation (because of the high incidence of growth retardation), it would be necessary to include a safe margin of error when using the Ballard score in isolation. Use of a Ballard score of ≤33 weeks (the conservative British 31 week cut-off plus the addition of 2 weeks) would have rendered only 77% of babies eligible for screening (Table 2).

b. Birth-weight

This is currently the most commonly used screening criterion in the developing world because gestational age is usually unknown. Early ultrasound is not commonly available and mothers infrequently have an accurate recall of their last menstrual period. The latter is a particular problem in our population where injectable contraceptives frequently render patients amenorrhoeic and may cause marked weight gain. If women become pregnant after forgetting to attend the clinic for their injection it may be several months before they realize they are pregnant.

In the UCT-ROP study 37.5% of babies (Table 6) were underweight for gestational age (and were hence not as premature as expected for their weight). Of special note was that babies who were underweight for gestational age (Chart 6) were more common (84.1%) in the group with longer gestation (≥ 32weeks) than in the more premature group ≤ 31weeks (33.3%).

In considering the safety of screening only babies ≤1250g it is important to characterise the babies with weights above this level. Specifically in the birth-weight category between 1251g and 1501g, the majority of babies were underweight for gestational age rather than being extremely premature. In this group all but one baby had gestational age over 28 weeks (the American gestational age cut off for screening). Thirteen babies in this weight group who had gestational age ≤ 31 weeks (the British cut-off) would have been missed if babies weighing between 1251g and 1501g had been excluded from screening. If only babies ≤1250g were screened, 71.5% of babies in the UCT-ROP trial would have been eligible for examination (Table 4). No babies with ROP would have been missed. These findings suggest that in circumstances similar to ours with a high prevalence of growth retardation or wasting, use of a birth weight cut-off of 1250g would be relatively safe.

c. The combined use of birth weight and Ballard score as screening criteria

This method of reducing the number of babies who require screening, as practiced by the Americans and British, is found cumbersome in units where staff limitations do not allow for a screening coordinator. Nursing policy makers request that the simplest criteria possible (preferably only one criterion) be given. In the UCT-ROP study if a Ballard score of ≤31 weeks OR birth weight ≤1250g

had been used, 117.6[§]/194 (60.6%) babies would have required screening and no babies with any stage of ROP would have been missed. Because more than one criterion is being used, there is less cause for concern about the inaccuracy of the Ballard score, particularly as the 31 week cut off is more conservative than the American cut off of 28 weeks.

The reduction in numbers would be slightly less than the reduction allowed by using a Ballard score of ≤33 weeks (Table 2) as a cut off (77% eligible). It would require fractionally more thought on the part of the referring clinician but would lower the risk of missing babies because of mis-assessment of the Ballard score by inexperienced staff.

d. Pigmentation

The findings of this study indicate a non statistically significant trend towards a protective effect of pigmentation against ROP (Table 7). Interestingly, one of the reasons that grouped analysis had to be performed was that there was only one baby with dark skin and fundal pigmentation who developed any stage of ROP. The findings relating to fundal pigmentation were in agreement with those of Monos. [33] Small numbers of babies with ROP limited the statistical power of the study. Specifically the protective effect of skin pigmentation was not sufficient for this characteristic to be used as a referral criterion by neonatologists. It is unlikely that pigmentation will ever be useful in the South African setting as a screening criterion in light of the significant incidence of ROP found in black babies at Kalafong Hospital. Only after a large trial such as the Cryo-ROP study, could it ever be applied and then only as part of a sophisticated risk-analysis model.[55]

e. Estimated Gestational Age (EGA)

This is based on growth and size in-utero. It is unable to detect the presence of growth retardation unless serial estimates are made from an early stage in pregnancy. It is preferable to use early fetal ultrasound as a baseline. Because patients in our population tend to present late in pregnancy and resources do not allow for universal fetal ultrasound, EGA represents a very rough guess. Upon delivery a much larger range of physiological responses and findings can be used to arrive at a more accurate estimate of maturation. In a growth retarded population such as this one, EGA will be lower than age estimated by scoring after birth as can be seen from the Charts 1-4. For this reason EGA is useful only in the absence of more accurate parameters and should be used only in combination with other forms of assessment. It is not an ideal screening criterion.

f. Head circumference

Head circumference is routinely recorded in UCT neonatal admission notes for several reasons including its usefulness in assessing growth retardation and fetal wasting. It is most helpful in combination with birth weight or body length. In mild to moderate growth retardation, brain growth is usually preserved at the expense of body weight so that head circumference is appropriate for gestational age. [68] This situation would also be seen in late fetal wasting such as might occur in GPH. In severe intrauterine compromise of long duration, brain development is adversely affected so that head circumference and weight would both be low for gestational age. Situations where this might be expected include chronic maternal under-nutrition, maternal alcoholism (common in the Western Cape), and maternal illness such as HIV (increasingly prevalent in the Western Cape). Head circumference would theoretically be a more useful measure of prematurity as a

screening criterion than birth weight because it is affected less than weight by intrauterine adversity: In the UCT-ROP study 37.5% of babies had low birth-weight for gestational age compared with only 14.2% who had small head circumference for gestational age. If the head circumference of 29.5cm (90^{th} percentile for 28 weeks PCA) were chosen as a screening criterion it would, by definition, cause examiners to miss 10% of the babies of 28 weeks PCA who had head circumference above the 90^{th} percentile for their age. Unfortunately, in this study, only 2.9% of babies had head circumference above 29.5cm (Table 5). This is because a much higher proportion of babies with longer gestation had small heads compared to the babies with shorter gestation as seen on Chart 7. In order to reduce the number of babies needing screening by 2.9% one would theoretically miss the 10% of babies whose head circumference was larger than the 90^{th} percentile for PCA. For this reason head circumference would not be an appropriate screening criterion in our setting.

3. Appropriateness of screening in UCT neonatal units

In order for a screening program to be worthwhile the following criteria should be met (Community Eye Health Workshop, Pretoria, 1999)

1. The condition should be an important public health problem
2. The natural history of the disease should be well understood
3. There should be a suitable screening test in terms of validity and specificity
4. There should be an accepted treatment

5. There should be a recognized latent stage when early treatment will provide an improved outcome

6. There should be an agreed policy on who to treat

7. Facilities for diagnosis and treatment should be available

8. The test should be acceptable to the population

9. Cost effectiveness and opportunity cost to be considered

10. Case finding should be an ongoing process

Fulfillment of these criteria:

1. The blind school publications [6, 7] would suggest that ROP is responsible for 10% of childhood blindness in South Africa. In the Western Cape, blind school statistics although not complete, suggest that the problem may be of lesser significance (Table 10).

2-6. As already discussed these have been well defined in the International Classification of ROP, the Cryo-ROP trial and numerous subsequent studies. New knowledge is constantly allowing refinements.

7. Excellent tertiary care facilities are available including trans-pupillary diode laser or cryotherapy for treatment.

8. The examination can be distressing for mothers and babies, particularly in the situation of a follow-up clinic. It has been found in this study that factors such as the harsh Cape Town winters make mothers reluctant to venture out with their very low birth weight babies in order to access this examination. Much neonatal follow-up is done in the community and this is definitely the most convenient

option for mothers. Unfortunately ROP screening is currently a specialized skill performed by an experienced ophthalmologist. It is not possible to offer correctly timed screening examinations in the community because there are too few ophthalmologists available. There seems little that can be done to make ROP screening acceptable enough to the population who use UCT tertiary healthcare services, to improve their use of the service.

9. Accurately calculated evaluation of cost-effectiveness and cost-opportunity is beyond the scope of this study. Most of the necessary figures needed for calculating cost-effectiveness (e.g. cost of screening and treatment, blind schooling, disability grant, treatment of secondary glaucoma, etc) are simply not available in our fragmented healthcare service. The issue of HIV limits the ability to calculate quality adjusted life years. It is likely that opportunity cost is favourable as all the facilities for treatment are already available and the cost per case would be similar to that of the many other surgical interventions commonly undertaken in this group of babies. In the era of HIV, resources for tertiary healthcare (including ophthalmology) are static or declining. For this reason it is valid to compare the values of possible services to which an existing ophthalmologist might be allocated. In the example of prevention of diabetic blindness (an under-staffed aspect of our service), one ophthalmologist allocated to diabetic evaluation and laser treatment on alternate weeks would be able to save more than one diabetic from blindness or visual loss per week. In contrast, if allocated to ROP screening, not even one baby would have been saved from blindness in more than 18 months. In a population with a higher incidence of blinding ROP it would be possible to raise the argument that childhood blindness causes many more years of disability than adult diabetic blindness. This may make it possible to justify screening in other under-resourced services.

10. During the project, registrars in the department were trained in ROP screening and were shown the cases that were detected. Following the project the senior retinal registrar screened for a few sessions, attempting to see babies between 5 and 7 weeks after birth. In the absence of a coordinator it was impossible to ensure correct timing and obtain any follow-up. No cases of ROP were detected and the service was abandoned in favour of other services with more potential for saving sight.

A neonatal ROP evaluation service was then offered only on the basis of named patient referral. Because of the perception amongst neonatologists that ROP is not a major problem very few referrals have been received. Of the 2 babies who have been referred on the basis of low gestational age and stormy postnatal course, both had stage 1-2 ROP in zone 3 which regressed totally.

In summary: ROP screening in the UCT tertiary referral service only fulfills 7 of 10 criteria necessary for a viable screening program. For this reason an alternative approach is needed.

4. A proposed approach to ROP evaluation for the UCT neonatal service

In the face of declining resource allocation to tertiary care services it is vital to be aware of any changes, which might increase the incidence of ROP blindness. It seems certain that there is very little chance that increasingly premature babies will be admitted to the service. Since prematurity is the major risk factor for ROP this is reassuring. Probably the only other area of concern is that of facilities and staff to monitor oxygen therapy. At present this aspect of care is very tightly controlled.

As a result of the 2002 Cape Town Childhood Blindness Workshop it is hoped that notification of cases of ROP blindness after mandatory examination prior to admission to blind schools will be introduced. This will provide a source of information 5 years after the event.

More timeous information could be provided by sampled screening audits performed every 2-3 years or sooner if neonatologists suspect an important decline in the quality of care.

5. Applying the findings of this study to services in South Africa and other developing country situations

The only other unit in South Africa where audit results are available is Kalafong. For reasons already discussed it is not possible to compare the incidence of ROP between the two units because of differences in timing of examinations. It is probable though, that the incidence is lower in UCT units. Possible factors contributing to this difference (Table 11) are the higher incidence of growth retardation (i.e. different risk profile of population) and greater emphasis on oxygen monitoring in Cape Town. The Kalafong unit has established that ROP is a problem for which reason screening takes place with audited screening criteria. Since the prevalence of growth retardation is unknown in that population it is not possible to comment on the use of the Ballard score to refine screening criteria.

ROP audit figures are not available in other parts of the country. Blind school figures do not point to any particular unit in which audit is vital. For units wishing to establish the need for screening and to evaluate screening criteria the following

(in addition to ROP figures and details) would be relevant on the database concerned:

- birth weight
- gestational age by the most accurate method available (probably the Ballard score)
- head circumference.

This would allow critical analysis of birth weight as a screening criterion as well as facilitating understanding of the effects of late and prolonged growth retardation. A better understanding of the role of growth retardation in older preterm babies could be obtained from the study of populations with a higher incidence of ROP, and would be of value worldwide.

It would of interest, although probably not clinically useful to repeat evaluation of pigmentation. All public sector neonatal units in the UCT-NICU survey serve mainly pigmented babies so that it may be difficult to find sufficient lightly pigmented babies to perform meaningful analysis. In units where the incidence of ROP is higher and babies are kept in the unit for longer it may be easier to prove statistical significance.

It would be informative to include details of feeding with breast milk. In the era of HIV where some infants are offered formula feeding it may be possible (and ethical) to obtain similar sample sizes of babies fed breast milk and those given formula feeds. This would improve understanding of the role of breastfeeding in preventing ROP in developing country situations.

Of importance would be knowledge of the current oxygen policy in the unit. It would be informative to note the effects of any changes in oxygen management on the babies with different risk profiles (our circumstances clearly differ from those in which most oxygen studies were performed).

An important aspect of ROP blindness prevention that has become evident is the aspect of resources for oxygen monitoring. All units indicated that they were in need of more machines in order to provide truly effective monitoring. It came to light at the 2002 Cape Town Childhood Blindness Workshop that rural primary healthcare clinics are increasingly becoming able to keep very small babies alive under care of primary care nurses in incubators with unmonitored oxygen. Some of these babies apparently have birth weight under 1000g. This is of great importance in the light of the findings of the blind school studies that ROP blindness is a real problem in middle-income countries with this kind of facility. Pulse oximeters cost approximately R10 000. It seems that they are a resource worthy of greater priority both in the primary and tertiary care setting.

The UCT-blind school survey (Table 10) failed to reveal any clustering of cases in certain hospitals in recent years. Both Provincial Hospital in Port Elizabeth and Red Cross Children's Hospital cared for 4 babies with ROP blindness prior to 1993.

The Red Cross Children's Hospital figures are entirely expected as this is the only children's hospital in Africa, south of the Sahara and is a referral center for the sickest babies, most of whom would be in the ICU for purposes of surgery. It should also be noted that oxygen policy in the surgical ICU service differs from that in the NICUs run by neonatologists. In the surgical service, oxygen saturations of 95% are considered ideal (compared with 86-92% in the neonatal

service). It is important that, since the Red Cross Children's Hospital ICU can be identified as a potential source of blind children, special attention should be given to examining babies at risk. This should be easily within the capabilities of the hospital as it has a dedicated paediatric ophthalmology department with the only paediatric ophthalmologist in Africa. Oxygen control for babies being transferred to and from theatre as well as from referral units should be given particular priority.

The reason for the regular presentation of ROP blind babies from Provincial Hospital is less clear. It is possible that it represents a "third epidemic" type situation with paediatricians capable of keeping babies alive but without the resources for intensive oxygen monitoring and super-specialist care. Since Port Elizabeth is a referral center for rural areas the issue of fluctuating oxygen levels[19] during transfer may be relevant. The hospital does not have an academic ophthalmology department with retinal specialist capabilities so that it will probably be difficult to assess and manage the situation from an ophthalmic point of view.

The sporadic cases from the private sector probably represent examples of survival of extremely premature babies because of advanced neonatal care. It is, however, known that some units do not routinely refer their babies to ophthalmologists. It would be of value to ensure awareness amongst private sector neonatologists of the American and British ROP screening criteria.

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In Summary:

Summary

- Although skin and fundus pigmentation appeared to have some protective effect this was not statistically significant because of the small size of the study, the low incidence of ROP (particularly in darkly pigmented babies) and the uncommonness of light pigmentation in the study population. These findings were interesting in the light of those in the Cryo-ROP study, [60] those of Monos, [33] and the evidence from the worldwide blind school studies. [6, 7]

- The very low incidence of ROP in this study could be explained by predominance of less premature babies in the study population, timing of examination, world class neonatal care with particular attention to oxygen monitoring, difficulties with follow-up, and possibly, a predominantly pigmented group of babies. Although it is presumed that the actual incidence of transient ROP in the UCT units is higher than reported in the UCT-ROP study, it seems safe to conclude that the incidence of blinding ROP is negligible.

- Gestational age assessed using the Ballard score represents the simplest screening criterion. Ballard score ≤33 weeks would be safe in the UCT service and would minimise unnecessary examinations. Combination of Ballard score ≤31 weeks OR birth weight ≤1250g could further help refine referrals. Other units with similar circumstances could evaluate screening policy using these parameters as a starting point.

- Based on neonatal screening and the UCT blind school survey ROP blindness does not appear to be a problem in the UCT neonatal service with the possible exception of Red Cross Children's Hospital (for reasons of it's unique position as a children's hospital with super-specialist referral patterns). For this reason the current utilisation of scarce human resources for providing ophthalmological services in other fields of greater need seems appropriate. This situation requires regular review. The audit of neonatal screening and improved childhood blindness notification are essential.

- There are disparities between the public sector neonatal services around the country with respect to policy, resources and clinical outcome. For this reason each center needs to define its own care and referral priorities. Vigilance is needed in order to prevent the "Middle income country" "third epidemic" situation from happening in South Africa. Adequate provision of oxygen monitoring equipment and staff are vital. Awareness of international ROP screening criteria needs to be promoted amongst private practice neonatologists who are dealing with the babies in the "second epidemic" risk group.

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Appendices

Appendix 1: Datasheet

Sticker

Mother's Folder No
Contact Tel No
Reason Prem
Antenatal Dex

Date of Recruitment
Delivery 1° Delivery 2° Delivery 3°
Birth weight Score EGA HC AGA UGA LGA
Duration on Oxygen Date of DC Hospital Stay

Problems

Resp	Neuro	CVS
Renal	Metabolic	Jaundice
Haem	GIT	Infection
Other		

Intervention

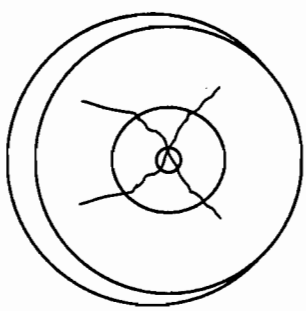
Transfusion Postnatal steroid Other

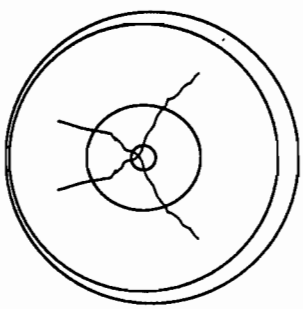
Trial data

SkinOph L M D SkinPaed L M D Fundus L M D Iris colour

Date

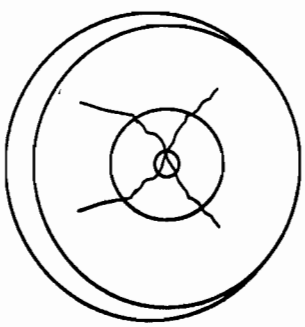
Draw ROP with label for stage in each zone
---Plus disease Present---

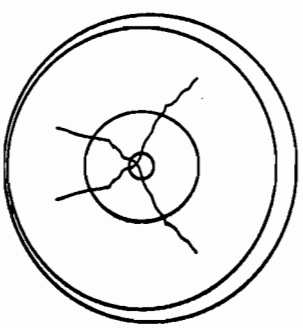




Date

Draw ROP with label for stage in each zone
---Plus disease Present---





Appendix 2: Blind School Questionnaire

School:

Name	**Date of Birth**	**Population group: Black (B) White (W) Asian (A) Mixed (M) Other (O)**	**City of Birth**	**Hospital of birth/ neonatal unit providing care**	**Birth weight and duration of pregnancy if known**	**Address of parents**

Appendix 3: NICU Questionnaire

I would be most grateful if you could answer the following questions where the data is available to you. Brief and approximate answers will be fine if you do not have access to detailed statistics.

1. What is the minimum weight of babies eligible for ventilation in your NICU?
2. What is the ideal range of % oxygen saturation within which you attempt to keep your babies?
3. Do you think you achieve this range in the majority of babies with the resources and staff available to you?
4. How many pulse oximeters are available in your unit?
5. Do you think you need more pulse oximeters?

6. On which babies are arterial blood gasses measured and how often (e.g. very sick babies 2x /day…)?
7. How many beds do you run in the neonatal unit excluding Kangaroo Care?
8. Do you have extra beds for Kangaroo Maternal Care, and if so how many?
9. How many babies per year are admitted to your unit weighing between
    - ❖ 500-999g
    - ❖ 1000-1249g
    - ❖ 1249-1500g
10. Are your babies screened for ROP?
11. If so what are the criteria and at what age are they screened?
12. Are you aware of any babies from your unit blinded by ROP and if so, how many over what time period?
13. Do you have any figures for incidence of ROP in your unit any time in the last 10-15 years? If possible please supply total incidence, number reaching pre-threshold, and number requiring treatment.
14. What is the approximate genetic make-up of your NICU's population? Black (+Language): Mixed ancestry: Asian: White? E.g. GSH=3(Xhosa):4:2:1
15. Approximately what proportion of your babies is underweight for estimated Gestational Age?
16. What are the discharge criteria in your unit?