UK Retinopathy of Prematurity Guideline

Royal College of Paediatrics and Child Health,
Royal College of Ophthalmologists &
British Association of Perinatal Medicine

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EXECUTIVE SUMMARY

Retinopathy of prematurity (ROP) is one of the few causes of childhood visual disability which is largely preventable. Many extremely preterm babies will develop some degree of ROP although in the majority this never progress beyond mild disease which resolves spontaneously without treatment. A small proportion, develop potentially severe ROP which can be detected through retinal screening. If untreated, severe disease can result in serious vision impairment and consequently all babies at risk of sight-threatening ROP should be screened.

This evidence-based guideline for the screening and treatment of ROP was developed by a multidisciplinary guideline development group (GDG) of the Royal College of Paediatrics & Child Health (RCPCH) in collaboration with the Royal College of Ophthalmologists (RCOphth), British Association of Perinatal Medicine (BAPM) and the premature baby charity BLISS. The guideline was produced according to RCPCH standards for guideline development.[1]

The guideline provides 25 evidence-based recommendations and 21 good practice points. Recommendations are graded A-D using SIGN grading hierarchy,[2] according to the strength of the evidence underpinning them. The good practice points (GPP) are a consensus of the GDG. This Executive Summary highlights those recommendations and good practice points considered by the GDG to be priorities for implementation.

This guideline has been produced specifically for use within the UK and supersedes the previous guideline.[3] It will not be applicable in countries where more mature babies are at risk of sight threatening ROP.[4]

Not all the recommendations are included in this Summary. The full Guideline should be consulted which also contains complete details of the Guideline methodology. Appendices A, B, C and D give a standardised sheet for recording screening results, an algorithm for ophthalmic criteria for screening and treatment, the International Classification of ROP Revisited, and parent information leaflets respectively. All the documents are available on the websites of the Royal College of Ophthalmologists www.rcophth.ac.uk, the Royal College of Paediatrics and Child Health www.rcpch.ac.uk or the British Association of Perinatal Medicine www.bapm.org.

Key Recommendations/Good Practice Points for Implementation

Screening Criteria

▪ All babies less than 32 weeks gestational age (up to 31 weeks and 6 days) or less than 1501g birthweight should be screened for ROP. One criterion to be met for inclusion.	**GPP**
▪ All babies less than 31 weeks gestational age (up to 30 weeks and 6 days) or less than 1251g birthweight must be screened for ROP. One criterion to be met for inclusion.	**B**

Screening Protocol

▪ Babies born before 27 weeks gestational age (i.e. up to 26 weeks and 6 days) - the first ROP screening examination should be undertaken at 30 to 31 weeks postmenstrual age	**B**
▪ Babies born between 27 and 32 weeks gestational age (i.e. up to 31 weeks and 6 days) - the first ROP screening examination should be undertaken between 4 to 5 weeks (i.e. 28-35 days) postnatal age.	**B**
▪ Babies >32 weeks gestational age but with birthweight <1501 grams – the first ROP screening examination should be undertaken between 4 to 5 weeks (i.e. 28-35 days) postnatal age.	**B**
▪ **Minimum frequencies** of screening should be **weekly** when: ▪ the vessels end in zone I or posterior zone II; **or** ▪ there is any plus or pre-plus disease **or** ▪ there is any stage 3 disease in any zone	**B**

▪ **Minimum frequencies** of screening should be **every 2 weeks**: ▪ In all other circumstances until the criteria for termination have been reached	**D**
▪ All babies <32 weeks gestational age or birthweight <1501g should have their first ROP screening examination prior to discharge.	**D**

Although screening for all babies at risk should follow the above protocol, it is acknowledged that there may be clinical or organisational circumstances which prevent this. In these circumstances the following is recommended as good practice to ensure that subsequent screening examinations are not missed.

▪ Where a decision is made not to screen a baby, the reasons for doing so should be clearly stated in the baby's medical record and the examination should be rescheduled within one week of the intended examination**.**	**GPP**

Screening Examination

The screening examination can be stressful for both babies and parents. The full guideline gives recommendations on preparation and care of the baby. The examination requires a well-dilated pupil so the peripheral retina can be fully visualised. The following are key recommendations and good practice points for this area.

▪ In addition to oral communication, parents should be given written information about the screening process prior to the first examination of their baby.	**GPP**
▪ It is important that the periphery of the retina can be seen and this may be facilitated by the use of an eyelid speculum and scleral indentor suitable for neonatal use.	**B**
▪ Ophthalmological notes should be made after each ROP examination, detailing zone, stage, and extent in terms of clock hours of any ROP and the presence of any pre-plus or plus disease. These notes should include a recommendation for the timing of the next examination (if any) and be kept with the baby's medical record.	**GPP**
▪ Comfort care techniques (e.g. administering sucrose solution, nesting, swaddling and/or the use of a pacifier) during the screening examination may be considered.	**B**

Termination of ROP screening

Screening can be stopped when a baby is no longer at risk of sight-threatening ROP.

In babies who never develop any ROP, the risk of sight-threatening ROP developing is minimal once the retinal vessels have entered zone III. That vessels are in zone III can be difficult to determine, but it is unlikely to occur before 37 weeks postmenstrual age and a decision to stop screening before this must be carefully evaluated.

▪ In babies without ROP, there is minimal risk of developing sight-threatening ROP when vascularisation has extended into zone III and eye examinations may be stopped when this happens, usually after 36 completed weeks postmenstrual age.	**B**

In babies developing ROP which does not meet the criteria for treatment, screening can be safely stopped when there are clear signs that the active progression of ROP has halted and regression has commenced.

▪ In the presence of ROP, screening for progressive active disease may be discontinued when any of the following characteristics of regression are seen on at least 2 successive examinations:
  ▪ Lack of increase in severity
  ▪ Partial resolution progressing towards complete resolution
  ▪ Change in colour in the ridge from salmon pink to white
	D

▪ Transgression of vessels through the demarcation line ▪ Commencement of the process of replacement of active ROP lesions by scar tissue	

ROP Treatment

Timely treatment for ROP is effective at preventing severe vision impairment. Previous guidance recommended treatment when the disease reached 'Threshold', as defined in section 8 of the main document. Recent evidence shows benefit from earlier treatment.

Ophthalmic criteria for treatment

▪ Treatment for ROP should be undertaken if any of the following indications are reached:
  ▪ Zone I, any ROP with plus disease,
  ▪ Zone I, stage 3 without plus disease,
  ▪ Zone II; stage 3 with plus disease.
	B

▪ Treatment for ROP should be seriously considered if the following indication is reached: ▪ Zone II, stage 2 with plus disease	**B**

Although there is no specific evidence to inform the interval between reaching treatment criteria and treatment taking place, it is the view of the GDG that, given the encouraging results for early treatment obtained by treating within 48 hours, this should be the target standard.

▪ Babies with aggressive ROP (as defined in ICROP revisted) should be treated as soon as possible and within 48 hours. ROP requiring treatment but which is not aggressive posterior ROP should normally be treated within 48-72 hours.	**GPP**
▪ Transpupillary diode laser therapy is recommended as the first line treatment for ROP.	**B**
▪ Treatment with near-confluent (0.5-1 burn-width) laser burn spacing should be administered to the entire avascular retina.	**D**
▪ The unavailability of diode laser equipment or the inability to transfer to another centre should not prevent or delay the treatment of ROP. In these situations, treatment with cryotherapy or argon laser may be completed by an ophthalmologist experienced in these techniques.	**GPP**

Severe ROP requiring treatment is relatively infrequent and treatment is a specialised procedure. Although there is no research literature on treatment outcomes according to operator expertise, it is likely that those with the greatest experience will be the most skilled practitioners in the procedure.

▪ Babies with ROP should be treated by ophthalmologists who have the appropriate competency.	**GPP**
▪ Each network should have identified individuals for ROP treatment	**GPP**

Post Treatment Review

Post operative review is important to monitor disease regression and to determine if retreatment is necessary. The GDG have agreed the following GPP in the absence of good quality evidence to inform these timings.

▪ The first examination post treatment should take place 5-7 days after treatment and should be continued at least weekly for signs of decreasing activity and regression.	**GPP**
▪ Re-treatment should be performed usually 10-14 days after initial treatment when there has been a failure of the ROP to regress.	**GPP**

Follow-up after Screening or Treatment

▪ After the acute phase, eyes that have reached stage 3 or have been treated should be monitored at a frequency dictated by the clinical condition to determine the risk of sequelae.	**GPP**

Organisation of Services

Effective services for ROP screening and treatment must be embedded in a robust organisational structure, with individual responsibilities identified. Particular efforts must be made to ensure that the service is delivered appropriately for all those at risk, as there is evidence that babies transferred or discharged home before screening is complete are at risk of poor outcomes as a result of lack of follow-up.

▪ All units caring for babies at risk of ROP should have a written protocol in relation to the screening for, and treatment of, ROP. This should include responsibilities for follow-up of babies transferred or discharged from the unit before screening is complete, which should be the responsibility of the named consultant Neonatologist for each baby.	**GPP**
▪ If babies are transferred either before ROP screening is initiated or when it has been started but not completed, it is the responsibility of the consultant neonatologist to ensure that the neonatal team in the receiving unit is aware of the need to start or continue ROP screening.	**GPP**
▪ There should be a record of all babies who require review and the arrangements for their follow-up.	**GPP**
▪ For babies who meet the ROP screening criteria, screening status and the need and arrangements for further screens must be recorded in all transfer letters so that screening may be continued.	**D**
▪ For babies discharged home before screening is complete the first follow-up out-patient appointment must be made before hospital discharge and the importance of attendance explained to the parents/carers.	**D**
▪All babies <32 weeks gestational age or birthweight <1501g should have their first ROP screening examination prior to discharge.	**D**

Work commitment

▪ Ophthalmologists regularly completing ROP screening and/or treatment should have sessional commitments allocated within their work plan.Ophthalmologists treating ROP need to have specific time allocated in their job plans for travel to the neonatal unit for treatment, for talking to parents/carers, pre-treatment preparation of the eye, treating the baby, and appropriate follow-up.	**GPP**

References

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2. Scottish Intercollegiate Guidelines Network. Sign 50: A Guideline Developers' Handbook. 2001.
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5. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol 2005; 123(7):991-999.

6. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity. Preliminary results. Arch Ophthalmol 1988; 106(4):471-479.

CONTENTS

Definitions and Acronyms

BAPM	British Association of Perinatal Medicine
BNF-C	British National Formulary for Children 2007
BW	Birthweight
CRYO-ROP study	Multicenter Trial of Cryotherapy for Retinopathy of Prematurity[13]
ETROP trial	Early Treatment for Retinopathy of Prematurity Randomized Trial[46]
Gestational age (GA)	Time between the first day of the last menstrual period and the day of delivery
GDG	Guideline Development Group
ICP	Integrated care pathway
ICROP revisited	International Classification of Retinopathy of Prematurity Revisited[6]
LIGHT-ROP	Multicenter Trial of Light Reduction in Retinopathy of Prematurity[146]
NICU	Neonatal Intensive Care Unit
PIPP	Premature Infant Pain Profile
Postconceptional age (PCA)	Time from conception
Postmenstrual age (PMA)	Gestational age plus chronological age
Postnatal age	Time from birth
RCOphth	Royal College of Ophthalmologists
RCPCH	Royal College of Paediatrics and Child Health
RCT	Randomised controlled trial
ROP	Retinopathy of prematurity

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Screening examination sheet
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1. Introduction

1.1 Background

The first UK guidelines for the screening and treatment of Retinopathy of Prematurity (ROP) were drawn up in 1990 by the Royal College of Ophthalmologists (RCOphth) and the British Association for Perinatal Medicine (BAPM).[1] In 1995 the guidelines were revised and extended to cover treatment, parent information and counselling, and the management of end-stage ROP.[2] Recent advances in the methodology of guideline development and new research into ROP have provided an opportunity to review the 1995 guidelines to develop evidence-based recommendations for health professionals caring for babies who are at risk of developing ROP**.**

The development of this guideline, which was led by the Royal College of Paediatrics & Child Health (RCPCH) in collaboration with the RCOphth and BAPM, has been undertaken by a multidisciplinary guideline development group (GDG) of ophthalmologists, neonatologists, paediatricians, a paediatric anaesthetist, neonatal nurses, parents and representatives from the premature baby charity BLISS. The membership of the GDG is listed on page 4.

1.2 Clinical Need

Evidence that the 1995 guideline needed updating has come from several sources. An audit of UK ophthalmologists in 1999 established that although many of the 1995 recommendations were being followed, practice varied in relation to when screening should stop and at what stage ROP should be treated.[3] Concerns were also expressed that the recommendations in the 1995 guideline resulted in too many babies being screened, causing a heavy workload for ophthalmologists and distress to babies receiving unnecessary retinal examinations.[4,5]

The recent publication of the revised international ROP classification (ICROP revisited)[6] and the preliminary results of the large multicentre Early Treatment for ROP Trial (ETROP)[7] provide an opportunity to incorporate the most up-to-date evidence in the guideline.

1.3 Aims

The aims of the guideline are:

- To evaluate and summarise the clinical evidence relating to the management of ROP.
- To provide evidence-based recommendations for the screening and treatment of ROP.
- To produce good practice points based on the consensus of the GDG in areas where the research evidence is lacking.

1.4 Guideline Scope

The scope of the guideline covers all aspects of the screening and treatment of ROP. The management of end-stage disease (including treatment of the disorganised anterior segment and retinal re-attachment) and the requirements for long-term ophthalmic follow-up were considered to be outside the scope of this guideline. Although the guideline aims to cover the majority of situations where ROP has developed, it does not cover rare, complex or unusual cases.

1.5 Guideline Methodology

The guideline was developed according to standards produced by the RCPCH Quality of Practice Committee (QPC).[8] The process included the development of clinical questions, a systematic search of the literature to answer these questions, selection of the evidence according to pre-arranged inclusion criteria, critical appraisal of the included papers and formulation of graded recommendations using the SIGN grading hierarchy[9] indicated below. Where there was no strong evidence, the GDG agreed good practice points (GPP) although there was no formal consensus process.

SIGN Grading Hierarchy:

A	At least one meta analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

GPP	Good practice point based on the consensus of the GDG in areas where the research evidence is lacking

Levels of evidence:

1++	High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1 -	Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2 -	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Inclusion criteria applied to all papers were:

- Studies reporting primary data on children with sight-threatening ROP;
- Studies on populations with similar characteristics to the UK population (i.e. studies conducted in top 30 countries on the United Nations Human Development Index);
- Studies of good methodological quality assessed using a standardised check list; and
- Studies classifying stages and severity of ROP according to ICROP revisited criteria.

For some clinical questions additional quality criteria were agreed which are identified in the relevant section. Full details of the search strategy and clinical questions are available on request.

Studies were reviewed by members of the GDG and volunteer clinical reviewers. At a draft stage the QPC identified five significant recommendations and independently appraised the underlying evidence. The draft guideline was also sent out for independent stakeholder consultation and the comments received discussed at a meeting of the GDG. A list of consultees is available on request.

1.6 Audience and Guideline Limitations

The guideline has been developed for ophthalmic and neonatal teams caring for babies who are at risk of developing sight-threatening ROP, **within the UK**. It is not intended for use outside of the UK and caution must be applied when using the guidance for babies transferred (antenatally or postnatally) from healthcare settings outside of the UK. This is because a recent study[10] established that the characteristics of babies developing ROP in less developed countries are significantly different from those in more developed countries. The evidence reviewed for the guideline was restricted to studies undertaken in the top 30 countries in the United Nations Human Development Index to be consistent with this finding.

It should also be noted that the UK guidelines differ from those recently published in the USA which were subsequently corrected.[11]

It is hoped that the guideline will be a resource for all those involved in the organisation and management of ROP services, including anaesthetic teams, managers and commissioners. The guideline is also accompanied by information leaflets for parents on screening and treatment (Appendix D).

Wherever possible the recommendations and good practice points have been drafted so that they can be implemented in all UK healthcare settings where ROP is managed. However, it is appreciated that service provision and organisation may differ according to local needs and resources and some good practice points may need to be adapted to reflect these local circumstances.

1.7 Guideline Definitions

The ophthalmic and neonatal terms used in this guideline are defined in section 7, and glossary of abbreviations and acronyms can be found on page 3. Where the research evidence is discussed the terminology employed is that used in the original research studies.

1.8 Updating the Guideline

This guideline will be updated within 5 years of the publication date, or earlier if additional evidence which has the potential to impact the recommendations becomes available.

1.9 Conflicts of Interest

No conflicts of interest were declared from any member of the Guideline Development Group or any of the reviewers assisting with the critical appraisal of the literature for this guideline.

1.10 Guideline Dissemination

Copies of this document can be downloaded from the RCPCH website. The Executive Summary highlighting the key recommendations for implementation is available as a separate document (www.rcpch.ac.uk and www.rcophth.ac.uk). The recommendations in relation to the ophthalmic criteria for screening and treatment have also been compiled as a separate algorithm which is incorporated in the Executive Summary and at Appendix B.

2. Background to ROP

Retinopathy of prematurity, a condition confined to the developing retinal vascular system of preterm babies, is one of the few largely preventable causes of childhood vision impairment. Babies at risk of ROP require ophthalmic screening to identify disease requiring treatment and this, together with meticulous neonatal management can reduce, although not entirely eliminate, the risk of vision loss due to the disease.

ROP is described by severity (6 stages), location by zone (I-III) (Figure 1), extent by clock hours or sector quadrant and by the presence of pre-plus and plus disease.[6] Severity stages 1 and 2 and any acute phase without plus disease are usually considered mild because most resolve spontaneously without major visually disabling sequelae.[12] ROP with plus and stages 3 - 5 are referred to as severe, as stage 3 is the first that presents a significant risk of poor visual outcome. Stage 4a eyes that remain stable can maintain good vision but progression through to stages 4b and 5 (being associated with retinal detachment) always carries a poor prognosis for vision. A subdivision of stage 3, 'threshold' ROP, carries a risk of blindness of about 50% if untreated and was the indication for treatment[13] until 2003 when the results of a trial investigating earlier treatment were published.[7]

The zone of disease appears to be important because ROP in zone I or posterior zone II is associated with progression requiring treatment.[14] Some authors have suggested that there may be two distinct mechanisms between the development of posterior and peripheral ROP.[15]

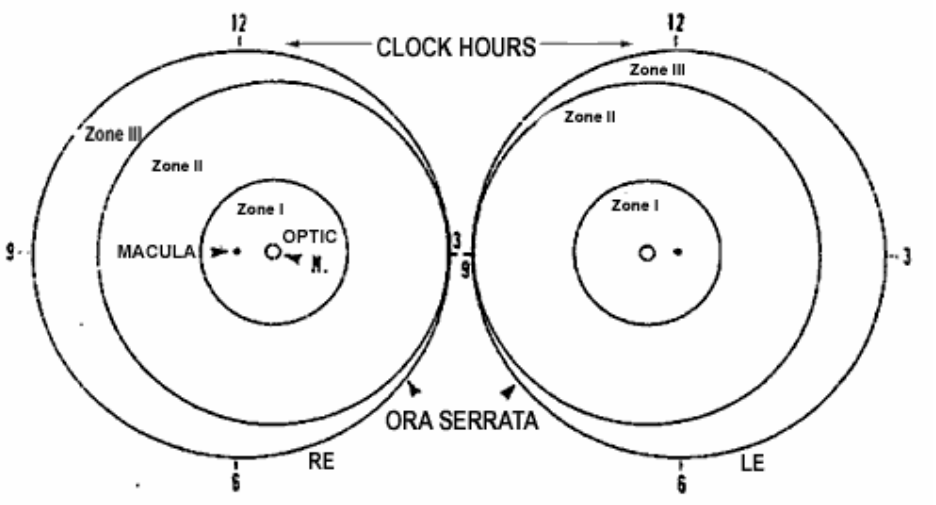


Figure 1: Retinal zones

Reproduced with permission from the International Committee for the Classification of Retinopathy of Prematurity Revisited.[6]

2.1 Epidemiology

Many extremely preterm babies develop some degree of ROP, and incidences of 66-68%[14] have been reported in babies of less than 1251g. However, in the majority of these babies the ROP never progresses beyond mild disease and resolves spontaneously without treatment.[16,17] Severe disease is relatively infrequent; the CRYO-ROP multicentre study found that only 18% of babies <1251g developed stage 3 with only 6% reaching threshold and requiring treatment.[13]

In the UK, ROP-induced complete or partial blindness constituted around 5-8% of childhood vision impairment in 1985-1990 and was confined mainly to babies below 1000g.[18] The incidence had decreased to 3% in 2000.[19] In a 16-month, UK-wide study only 19% of babies with stage 3 ROP had severe vision loss or blindness at one year of age.[20] ROP is more often associated with an increased risk of less serious ophthalmic problems associated with prematurity such as strabismus and myopia. In a study of babies with birthweights under 1701g, 29% of babies with stage 3 had strabismus at 6 months compared with 3% with no ROP.[21]

As the number of screened babies developing severe ROP is so low, many ophthalmologists rarely see sight-threatening disease and a national audit identified this as a cause of concern.[3] Although some,[22,23] but not all,[24] single centre studies suggest the incidence of ROP is declining in the developed world, improvement in survival of extremely preterm babies is leading to an increase in the number of babies needing screening.

3. ROP Screening

3.1 Screening Criteria

The literature was reviewed to establish the criteria for identifying which babies should be routinely screened for ROP in the UK. The 1995 guideline recommended screening babies of birthweight less than 1501g or gestational age less than 32 weeks.[2] In addition to the criteria listed in section 1.5, included studies met the following criteria:

- a primary study reporting birthweights and/or gestational ages of babies developing sight-threatening ROP (defined in section 7)
- study population included babies of birthweight up to 1500g

Twenty-three studies met the inclusion criteria and data were extracted for analysis.[4,5,23,25-44]

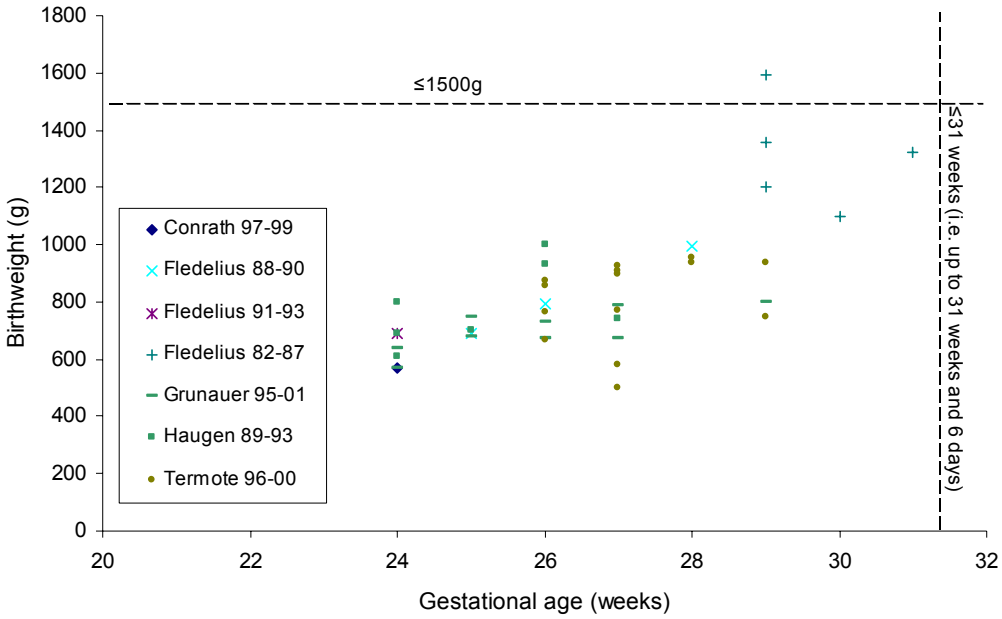
The numbers of babies developing sight-threatening ROP by birthweight and/or gestational age (GA) were entered onto an MS Excel spreadsheet. Most of the included studies only presented birthweight and gestational age data, particularly birthweight, as ranges rather than by individual baby. Where this was the case the assumption was made that all babies within in a particular category were at the highest end of the range. As the individual birthweight and GA data was of particular importance in the 8 studies reporting larger or more mature babies developing sight-threatening ROP, the principal study authors were contacted with a request for individual data. Three authors responded.

The 23 papers reported a total of 10,481 screened babies, 643 (6.1%) of whom developed sight-threatening ROP. Twenty studies reported both GA and birthweight; one study only reported GA and the two remaining studies reported no extractable birthweight or gestational data, one because no study babies developed sight-threatening ROP.[35]

Gestational age data were available for 630/643 babies with sight-threatening ROP (98.0%); 593 (94.1%) had a GA of ≤ 29 weeks, 29 (4.6%) had a GA of 30-31 weeks and 8 (1.2%) had a GA ≥32 weeks. Birthweight data were available for 584/643 (90.8%) babies who developed sight-threatening ROP. Of these, 532 (91.0%) had a birthweight <1251g; 29 babies in birthweight groups which crossed the 1250g boundary were placed at the highest possible birthweight, although in reality some of these may have been less than 1250g. In addition, another 15 (2.6%) babies had a birthweight between 1251 and 1500g and 8 babies (1.4%) had a birthweight >1500g (range between 1520g – 2300g).

A separate analysis was undertaken for the 7 studies which provided complete birthweight and GA data for all babies (n=40) with sight-threatening ROP[27,32-34,37,38,43] as the possibility of selection bias does not arise with these studies.

Figure 2: Individual birthweight and gestational age of babies developing sight-threatening ROP



The data which are presented in figure 2 show that all babies fell within the 1995 screening criteria (as indicated by the dashed lines). However one baby requiring treatment[32] would have been missed if either the GA criterion was reduced by one week or the birthweight criterion reduced by 250g. This recommendation is supported by the clinical experience of the ophthalmologists on the GDG who were aware of 8 babies in four UK regions developing sight-threatening ROP since 2000 who had a birthweight of >1250g and gestational age of ≥30 weeks. On the basis of this evidence the GDG recommendation is that the criteria for ROP screening should remain at less than 32 weeks or less than 1501g birthweight. These criteria may need to be re-assessed when there is a body of evidence in relation to the birthweight and gestational ages of babies meeting the earlier ophthalmic criteria for treatment (section 4.2).

All babies less than 32 weeks gestational age (up to 31 weeks and 6 days) or less than 1501g birthweight should be screened for ROP. One criterion to be met for inclusion.	**GPP**

All babies less than 31 weeks gestational age (up to 30 weeks and 6 days) or less than 1251g birthweight must be screened for ROP. One criterion to be met for inclusion.	**B**

3.2 Timing of Screening

Studies of the natural history of ROP suggest that a number of factors affect the severity and rate of development of the disease. This presents a challenge when defining an appropriate screening protocol. In babies at risk, the screening must be initiated soon enough to detect the earliest possible onset of potentially severe disease and continue at intervals which allow for the timely detection of disease requiring treatment until the risk of sight-threatening ROP has passed. This means that some babies require only one eye examination whereas others require many. As examination of the retina can be distressing to the babies and their families (see section 3.3.2) and consume significant ophthalmic time and expertise they need to be kept to the minimum required.

Several studies provide evidence that the development of ROP is closely related to postmenstrual age.[30,39,40,45] Although this implies that all babies developing ROP would do so at the same postmenstrual age, a study which corrected for the degree of prematurity suggests that ROP onset is slightly accelerated in the most immature thus occurring at a slightly earlier postmenstrual age.[30]

Although the terms used in the guideline are defined in section 7, the terminology relating to the age of the baby was felt to be sufficiently confusing as to warrant further explanation. There was considerable variation between studies in how the age of the babies was reported. Studies used one, or a combination, of the following terms in their discussions around timing; postnatal age, chronological age, postmenstrual age (PMA) and postconceptional age (PCA). Although not strictly accurate, PCA and PMA have generally been considered in the literature to be synonymous. For the purpose of the review it has been assumed that where onset is described in terms of PCA that this is equivalent to PMA **unless this is explicitly defined otherwise in the paper**. The other terms of postnatal and chronological age are unambiguous.

The guideline presents data as they appear in the original papers. Where a paper expresses the time of an event in partial weeks with a decimal point, the number after the point could mean either the number of days into the following week or a decimal fraction of the next week (e.g. 24.3 could mean 24 weeks and 3 days or 24 weeks and 3 tenths of a week, ie 2.1 days). The GDG agreed that either interpretation allows the determination of the time to an acceptable level of accuracy of one week and have included data as they appear in the paper.

In addition to the inclusion criteria provided in section 1.5, studies included in this section also met the following criteria:

- a primary study reporting timing of screening of babies developing sight-threatening ROP where babies had the first screen at 6 weeks or earlier and subsequent examinations at a maximum of 2 weekly intervals); ***or***
- A primary study on the natural history of potentially sight-threatening ROP.

Much of the evidence for this section comes from the natural history cohorts of two very large, well-conducted randomised controlled trials investigating the treatment of ROP, CRYO-ROP study[13] and ETROP trial [46] which have generated a number of publications. Although care has been taken not to include duplicate data from these study populations, papers reporting on different aspects of the same populations have been included where appropriate in order to provide the best possible evidence.

3.2.1 First Screening Examination

The timing of the first ROP screening examination must be early enough to identify the first signs of sight-threatening disease but late enough to ensure that the ophthalmologist has a good view of the retina which can be obscured by vitreous haze in the very preterm eye.[30]

Of the nine included studies only one,[30] where screening began at 3 postnatal weeks, reported any vitreous haze which was present in 13.8% of screened babies (79/572) although this was not associated with the development of sight-threatening ROP. The other eight studies began screening later than 3 weeks and none reported any vitreous haze in study babies. This suggests that, if present, the haze would normally be expected to clear by 4-5 postnatal weeks.

Four papers[16,17,45,47] reported the onset of prethreshold ROP. In the ETROP trial[16] 5% of cases developed prethreshold disease before 32.1 weeks PMA and in the CRYO-ROP study[47] 1% of cases did so before 30.9 weeks PMA. One study of babies <1000g[45] reported earlier onset of prethreshold disease, with 3.2% of babies developing prethreshold before 30 weeks PMA and 11% before 31 weeks PMA with the earliest diagnosis at 28.9 weeks PMA, although the definition of prethreshold in this study differed from that used in the ETROP trial and CRYO-ROP studies. In relation to postnatal age, the ETROP trial showed that 95% of babies develop prethreshold at 7 postnatal weeks or more[16] and in the CRYO-ROP study no prethreshold (or worse) was detected in 99% of eyes before 4.7 weeks postnatal age.[47]

Three studies reported the onset of threshold disease,[45,47,48] and the earliest onset reported was between 31.0 – 32.6 weeks PMA and 6.6 – 8.0 weeks postnatal age. For stage 3 disease, 6 studies[16,17,29,30,39,40] reported earliest age of onset as between 30.3 – 35.6 weeks PMA, and 3.8 – 6.7 weeks postnatal age.

The evidence that sight-threatening ROP is extremely unlikely to develop prior to 31 weeks postmenstrual age or 4 to 5 weeks postnatal age informs the time frame for the first screening examination. However, in developing the recommendations the GDG also considered the evidence that ROP develops at an earlier postmenstrual but later postnatal age[30,39] in the less mature babies.

There is good evidence that the screening programme is less likely to be completed once babies have been discharged from hospital (section 3.2.5). Therefore in the most mature babies, which are at lowest risk of sight-threatening ROP (>28 weeks), the timing of the first screening examination

should be brought forward to ensure that at least one eye examination is completed prior to the baby going home, and for this pragmatic reason the timing of the first exam is given as postnatal rather than postmenstrual age.

Babies born before 27 weeks gestational age (i.e. up to 26 weeks and 6 days) - the first ROP screening examination should be undertaken at 30 to 31 weeks postmenstrual age.	**B**

Babies born between 27 and 32 weeks gestational age (i.e. up to 31 weeks and 6 days) - the first ROP screening examination should be undertaken between 4 to 5 weeks (i.e. 28-35 days) postnatal age.	**B**

Babies >32 weeks gestational age but with birthweight <1501 grams - the first ROP screening examination should be undertaken between 4 to 5 weeks (i.e. 28-35 days) postnatal age.	**B**

Babies <32 weeks gestational age or birthweight <1501g should have their first ROP screening examination prior to discharge.	**D**

The suggested timing for the first screen for babies at risk of developing sight-threatening ROP in relation to the baby's gestational age has been compiled into the table below.

Table 1: Timing of first screen by gestational age

	Timing of first ROP screen	
Gestational Age (Weeks)	Postnatal Weeks	Postmenstrual Weeks
22	8	30
23	7	30
24	6	30
25	5	30
26	4	30
27	4	31
28	4	32
29	4	33
30	4	34
31	4	35

3.2.2 Subsequent Screening Examinations

The ophthalmic findings at the first eye examination will determine if and when subsequent examinations are required. The ETROP trial[7] found that the presence of plus disease, vessels ending in zone I or posterior zone II, and stage 3 ROP are all associated with progression to requiring treatment and the same factors were associated with adverse outcomes in the CRYO-

ROP study natural history cohort.[14] The CRYO-ROP study[49] found that the rate of progression of ROP (mean ± standard error) was faster in eyes with an unfavourable outcome (8.2 ± 1.2 days between first observation of ROP to prethreshold) compared with those with a favourable outcome (12.3 ± 1.2 days), suggesting that in some situations 2 weekly examinations are not frequent enough. Furthermore there have been case reports of aggressive ROP progressing from onset to zone II, stage 4 ROP in less than a week.[50] This type of quickly progressing, severe ROP, historically termed 'rush' disease, has recently been defined by ICROP revisited[6] as aggressive posterior ROP and is noted for its rapid progression to stage 5 disease without treatment.

On the basis of this evidence the GDG concluded that when the characteristics of rapidly progressing disease are observed, or when aggressive posterior ROP is present, the baby should be monitored closely and screening should be undertaken at least weekly.

In other situations where there is no ROP and the vessels have only progressed to zone II or there is stage 1 or 2 disease without plus in zone II or III screening can be completed every two weeks as the risk of progressing to sight-threatening disease is low.

Minimum frequencies of screening should be: **Weekly when:** • **The vessels end in zone I or posterior zone II; or** • **There is any plus or pre-plus disease; or** • **There is any stage 3 disease in any zone**	**B**

Every 2 weeks: • **In all other circumstances until the criteria for termination have been reached (section 3.2.3).**	**D**

3.2.3 Termination of Screening Examinations

Screening can stop when the baby is no longer at risk of developing sight-threatening ROP. As ROP is a disease of immature retinal vascularisation, the risk has passed once full vascularisation to the periphery of the retina has occurred, and there is only a minimal risk of sight-threatening disease once vascularisation has progressed into zone III.[14,30] However it is acknowledged that the identification of zones, particularly the boundary between zones II and III, can be problematic. The ICROP revisited classification[6] provides advice regarding distinguishing the zones of ROP but it is important to note the guidance that ROP in zone III can only be determined with confidence when the nasal retina is vascularised.

Terminating screening in babies not developing ROP

One study[47] reported on the progression of vascularisation into zone III in babies without ROP and found that the median was 35.6 weeks PMA with only 1% of eyes becoming vascularised in zone III before 30.4 weeks PMA or after 45.9 weeks PMA.

Given that it can be difficult, particularly for less experienced ophthalmologists, to accurately identify zone III, it is important to know when zone III vascularisation is likely to occur. In the study cited above the retina had vascularised into zone III in around 70% of babies by 37 postmenstrual weeks.[47] Although ROP can develop after 37 weeks (5% of babies developed stage 1 disease after 39.1[47] postmenstrual weeks) it is most unlikely to develop into disease requiring treatment.

In babies without ROP, there is minimal risk of developing sight-threatening ROP when vascularisation has extended into zone III and eye examinations may be stopped when this happens, usually after 36 completed weeks postmenstrual age.	**B**

Terminating screening in babies with ROP

When a baby has ROP which does not progress to requiring treatment, a decision has to be made as to when the risk of sight-threatening ROP is so low that the eye examinations can be safely stopped.

The CRYO-ROP study[47,51] found that babies developing stage 1 or 2 ROP in zone III, are at extremely low risk of developing sight-threatening ROP. In babies with moderate ROP once regression occurs and the vascularisation of the retina continues into zone III, the risk to the baby's sight is minimal.[47] However in a very small number of babies (3% of eyes[51]) regression and zone III vascularisation had still not occurred by 3 months post term. The GDG felt therefore that ophthalmic criteria for terminating screening should be the presence of signs of regression of active ROP rather than vascularisation.

The signs of ROP regression have been defined by ICROP revisited.[6] These are a lack of increase in severity, complete or partial resolution, reduction of pre-plus/plus disease, transgression of vessels through the demarcation line and the commencement of the process of replacement of active ROP lesions by scar tissue. Additionally the ridge may change in colour from salmon pink to white. These signs should be confirmed by at least two examinations.

The process of regression may differ between individuals and ophthalmologists should err on the side of caution when they believe that there is still the possibility of sight-threatening ROP.

Once the risk for progressive active disease has passed, the ophthalmologist may wish to continue to monitor the eyes for treatable ophthalmic sequelae.

In the presence of ROP, screening for progressive active disease may be discontinued when any of the following characteristics of regression are seen on at least 2 successive examinations: • **Lack of increase in severity** • **Partial resolution progressing towards complete resolution** • **Change in colour in the ridge from salmon pink to white** • **Transgression of vessels through the demarcation line** • **Commencement of the process of replacement of active ROP lesions by scar tissue**	**D**

Examinations for significant ophthalmic sequelae which might require treatment should be continued once screening for potentially treatable ROP has stopped.	**GPP**

3.2.4 Delaying Screening

Although all babies at risk should be screened according to the protocol outlined above, there may be clinical or organisational reasons why this does not happen. None of the studies reviewed reported the outcomes for babies not screened at the appropriate time. It is clear that delaying or postponing a screening examination could mean that the window of opportunity for treatment is missed. Where the decision to postpone a screening examination is made on clinical grounds this should be a joint decision between the ophthalmic and neonatal team, balancing the risks of late diagnosis of sight-threatening ROP against the risks to the baby of undergoing the screening examination. A junior member of the team should not make this decision. Where a decision is made not to screen a baby, the reasons for doing so should be clearly stated in the baby's medical record and the examination should be rescheduled within one week of the intended examination.

Where a decision is made not to screen a baby, the reasons for doing so should be clearly stated in the baby's medical record and the examination should be rescheduled within one week of the intended examination.	**GPP**

3.2.5 Screening Babies Transferred Between Units or Discharged Home

Studies in the UK[52] and USA[53,54] show that as many as 75% of babies will require initiation or continuation of ROP screening after transfer or discharge home from the neonatal unit and that the compliance with follow-up arrangements is low. For these babies, arrangements need to be made to ensure that screening continues until either treatment is required or until the termination criteria have been met (section 3.2.3). Ensuring that these babies do not get forgotten relies on robust service organisation. The issues associated with the service organisation and communication for transfer and discharge are discussed in section 5.1.

3.3. Screening Examination

3.3.1 Preparation of the Eye

Effective mydriasis of the pupil is essential as a well-dilated pupil enables the periphery of the retina to be examined and facilitates accurate diagnosis and staging of ROP. Mydriatic eye drops are either parasympathetic blockers which affect the pupillary sphincter muscle (e.g. tropicamide, cyclopentolate) or sympathetic stimulants which affect the pupillary dilator muscle (e.g. phenylephrine).[55] A typical mydriatic regimen will use a combination of the two types.

A range of different combinations of mydriatic regimen is reported in the literature, many of which appear to provide adequate pupil dilation without significant adverse effects. A small RCT[56] (comparing phenylephrine1%/cyclopentolate 0.2% with phenylephrine 2.5%/tropicamide 0.5%) and two cohort studies[57,58] compared the safety and efficacy of different regimens. An observational study using tropicamide 2.5%/phenylephrine 2.5% reported no adverse systemic effects.[59] Two studies concluded that a combination of phenylephrine 1% and cyclopentolate 0.2% administered on two[60] or three[56] occasions at 5 minute intervals, 60 minutes before the examination provided the best balance of efficacy and safety although the RCT[56] was only conducted on babies with dark irides. This combination has been also used in other studies without notable adverse effects.[39,61,62] The other cohort study[58] comparing mydriatic regimens only tested two different concentrations of cyclopentolate (0.25% and 0.5%).

As the mydriatic regimen evaluated in these studies (phenylephrine 1% and cyclopentolate 0.2%) is currently not available in the UK, the closest available combination, phenylephrine 2.5% and cyclopentolate 0.5%, should be used as an alternative. Although no studies have compared the two combinations, two cohort studies have investigated the systemic effects of screening[62,63] using a phenylephrine 2.5%/cyclopentolate 0.5% combination and found no evidence of severe adverse events. Further well-conducted trials comparing different regimens are needed to determine the optimal mydriatic regimen for ROP screening in the UK.

There have been reports[56,64] that heavily pigmented irides are more difficult to dilate than lightly pigmented ones. It is the experience of the GDG that the mydriatric regimen proposed is also effective in babies with dark irides although three doses of the mydriatics may facilitate better dilation in these cases.

A mydriatic combination of phenylephrine 2.5% and cyclopentolate 0.5%, instilled one drop each in 2 to 3 doses, each five minutes apart, 1 hour prior to examination is a suitable mydriatic regimen for preterm babies undergoing ROP screening examinations. This recommendation should be reviewed in the event that the optimal mydriatic combination evaluated in a RCT is licensed for use in infants in the UK	**GPP**

No major adverse effects have been reported from the phenylephrine/cyclopentolate regimen recommended. There are case reports of renal failure with tropicamide 0.5%/phenylephrine 0.5%,[55] transient paralytic ileus with cyclopentolate 0.2%/phenylephrine 1%,[65] bradycardia with tropicamide 1%[66] and heart failure with phenylephrine 10%/cyclopentolate 1%.[67] Mydriatric eye drops can also be absorbed into other parts of the body through contact with the skin around the eye, the cornea, the conjunctiva, nasal mucosa and the nasolacrimal canal.[55] Reducing this absorption may reduce the risk of adverse events. Proposed methods of reducing absorption include using smaller drops,[68] wiping off any excess or closing the eyelid after instillation[55] although no high quality studies have tested their effectiveness.

The evidence that some mydriatic regimens can have systemic effects on premature babies, led the GDG to suggest using only the smallest amount possible to achieve effective mydriasis.

When instilling mydriatic eye drops, care should be taken to use the minimum possible concentrations and doses to achieve effective mydriasis and to minimise the possibility of absorption into areas other than the eye.	**GPP**

Mydriatric regimens in ROP screening have also been shown to have an effect on gastric function. Slow gastric emptying, emesis, abdominal distension and feeding related bradycardia were all significantly greater 24 hours after screening and effects on duodenal motor activity and gastric emptying have been demonstrated up to 3 hours after screening using phenylephrine 1%/cyclopentolate 0.2%.[60] Another study[57] concluded that placebo and cyclopentolate 0.25% eye drops had no significant effect on the tested gastric function. However, 0.5% eye drops significantly decreased gastric acid secretion and volume.

3.3.2 Care of the Baby during Screening

Observations of babies being screened suggest that it is an uncomfortable and distressing procedure especially when an eyelid speculum and scleral indentor are used.[69]

Three cohort studies investigated the responses of babies undergoing screening where indirect ophthalmoscopy, topical anaesthesia, and an eyelid speculum were used. Two[62,70] found no significant difference in blood pressure during the examination compared with the pre-examination baseline whereas the third[63] found a significant increase in diastolic pressure 15 minutes after instillation of eye drops and during examination which returned to baseline level within 10 minutes after the examination. A recent RCT compared Newborn Individualized Developments Care and Assessment Programme and standard support for babies undergoing screening and reported no difference in pain responses, but faster recovery as measured by salivary cortisol in the former group. Babies examined by RetCam compared to indirect ophthalmoscopy experienced less pain.[71]

Four studies have investigated the effect of screening on the baby's heart rate. Two[63,70] recorded a significant increase in pulse rate which returned quickly to a level slightly lower than baseline after

the examination. The third study[62] showed no difference in heart rate compared with base level either at 30 minutes or 24 hours after the examination. One study[66] showed that 31% of babies demonstrated significant bradycardia at some time during the examination, with the instillation of eye drops and insertion of the eyelid speculum being a major cause. However, none of the events were life-threatening.

Oxygen saturation levels during screening were recorded in two studies.[63,70] These both found that the level fell during the insertion of the eyelid speculum and during the physical manipulation of the eye, returning to the baseline 5-10 minutes after the examination. Reduced oxygen saturation and cyanosis resulted in the examination being abandoned in 2/57 infants.[69]

There has been one case report of an episode of severe apnoea and bradycardia during screening examination which required resuscitation[72] and the GDG provided anecdotal evidence that this is not an exceptional occurrence when screening the most fragile babies. The group suggested that adequately skilled staff and resuscitation equipment should be immediately available when examining such vulnerable babies.

The evidence indicates that although systemic effects may occur during ROP screening, they are usually transient and therefore unlikely to require additional monitoring above that provided as part of the baby's neonatal care.

ROP screening examinations can have short-term effects on blood pressure, heart rate and respiratory function in the premature baby. The examinations should be kept as short as possible and precautions taken to ensure that emergency situations can be dealt with promptly and effectively.	**D**

3.3.3 Pain Relief

Evidence that ROP screening examination has systemic effects on the baby suggests that the examination, particularly when a eyelid speculum is used, is painful and that pain relief is necessary.[62,63,70,73] Two small RCTs in the USA[61,74] investigated the effect of topical anaesthesia proparacaine hydrochloride 0.5% (1 or 2 drops, 30-60 seconds pre-examination). One concluded that topical anaesthesia reduced pain, as assessed by Premature Infant Pain Profile (PIPP),[61] whereas the second[74] observed no difference in subjective measures of pain pre and post examination. Neither study suggested that the topical anaesthesia caused any harm or interfered with the examination in any way.

In the UK proparacaine hydrochloride is known as proxymetacaine. The British National Formulary for Children 2007[75] advises that proxymetacaine is contraindicated in preterm neonates because of the immaturity of the metabolising enzyme system. According to the BNF-C oxybuprocaine hydrochloride (also known as Benoxinate or Novesin®) is the only local anaesthetic not contraindicated in the preterm infant although its use for ROP screening has not been formally

evaluated. Members of the GDG have experience of using both proxymetacaine and Benoxinate without harmful effects.

Given the guidance in the BNF-C and lack of research evidence, the GDG felt unable to recommend a specific topical anaesthetic for ROP screening. However the evidence does suggest that eye examinations with an eyelid speculum are painful for babies (and would not be undertaken in older children or adults without a local anaesthetic) so a topical anaesthetic of choice should be used prior to ROP screening.

Topical anaesthesia should be used prior to screening of babies for ROP if an eyelid speculum is to be used.	**B**

3.3.4 Other Comfort Care

Other techniques used to comfort babies during the screening examination include pacifiers, sucrose, nesting or swaddling. Five RCTs have investigated the use of sucrose to reduce pain during screening.[76-80] Two[77,80] found no significant difference in the PIPP score with sucrose compared with sterile water although it is not clear if topical anaesthesia was also used. The other two studies[76,79] using topical anaesthesia found that 24% sucrose placed on the tongue or onto a pacifier during screening significantly decreased the PIPP score compared with sterile water. Other studies have reported that use of a pacifier (RCT)[80] and nesting[81] (placing on a soft padded surface with boundaries) (cohort study)[79] reduced pain and stress (measured by BP and O_2) during the examination although both were small, unrepeated studies. No adverse events were recorded in any of the trials reviewed.

Comfort care techniques (e.g. administering sucrose solution, nesting, swaddling and/or the use of a pacifier) during the screening examination may be considered.	**B**

3.3.5 Screening Technique

In recent years new technology has opened up the possibility of using alternatives to the indirect ophthalmoscope for ROP screening such as wide field digital fundus photography with a specially adapted camera, for example the RetCam. Proponents of this technique argue that it is easier to use than the indirect ophthalmoscope and provides a permanent, electronically transmissible record of the retina, thus offering the potential for screening by less specialised staff with images reviewed by an expert either on site or remotely.

Five studies compared the RetCam with the indirect ophthalmoscope in consecutive contemporaneous examinations in the same babies.[82-86] Although the methodology varied slightly, RetCam sensitivity and specificity rates for detection of ROP were 82.4% and 93.8% in one study[82] but only 46% and 100% in another where eyes were examined at 32 weeks, although this improved to 76% and 100% by the second examination and the low rates were partially ascribed to technical

problems.[84] A third study[83] found that when digital photos were read remotely the RetCam had 100% sensitivity and 96% specificity in detecting ROP. One study not aiming to grade the ROP but to identify severe disease requiring treatment[86] concluded that although the sensitivity and specificity of remotely read images were 100% and 97.5% respectively, 21% of the initial images were not able to be evaluated due to poor image quality. Interpretation of RetCam images has been found to have good inter/intra-reader reliability[85,87] which enhances its potential for use in telemedicine.

There is not a sufficient body of research evidence at the present time to demonstrate that wide field digital fundus photography is as effective as the indirect ophthalmoscope for ROP screening. For some UK screeners the RetCam is already the technique of choice although the cost is likely to remain a deterrent for many units. Staff training is an important issue and no studies have yet demonstrated that cameras operated by non-ophthalmologists are as sensitive at detecting ROP as the indirect ophthalmoscope in the hands of a skilled ophthalmologist.

One cohort study compared the systemic effects of the RetCam and binocular indirect ophthalmoscopy.[88] Babies undergoing RetCam screening at one hospital (n=52) were compared with 34 babies undergoing indirect ophthalmoscopy at another site. Both groups showed an increase in heart rate and respiratory rate, but the increase was significantly greater in the indirect ophthalmoscopy group. There were no significant differences with respect to the change in oxygen saturation or blood pressure although the RetCam examination took significantly longer than that using indirect ophthalmoscopy (7.8 minutes vs. 3.9 minutes).

There are two case reports of retinal haemorrhages on consecutive occasions after screening with a RetCam.[89,90] Clearly further research is needed to evaluate the effectiveness of the RetCam although some questions may be answered with the multicentre 'PhotoROP' trial.[91]

Use of Eyelid Speculum and Scleral Indentor

The use of an eyelid speculum and scleral indentor in screening examinations improves the scrutiny of the peripheral retina and their use was standard practice in the CRYO-ROP and ETROP studies. A study[69] comparing binocular indirect ophthalmoscopy with and without the eyelid speculum and scleral indendor concluded that the view of the retina, particularly in peripheral regions, was more complete when the eyelid speculum and scleral indentor were used i.e. determining if vascularisation is in zone II or zone III. The systemic effects on the baby which have been associated with the use of the speculum have already been documented (section 3.3.2).

It is important that the periphery of the retina can be seen and this may be facilitated by the use of an eyelid speculum and scleral indentor suitable for neonatal use.	**B**

Equipment Sterilisation

If the eyelid speculum and/or a scleral indentor comes into contact with mucous membrane there is a risk of spreading infection. The single use of autoclave-sterilised instruments for each patient will reduce this risk although a survey of NICUs in the USA[92] found practice was inconsistent. There have been no comparable surveys of UK practice but it is likely that similar variations exist.

Two small RCTs compared the effectiveness of 70% isopropyl alcohol[93] and 4% chlorhexidine gluconate[94] in disinfecting eyelid specula used in ROP screening examinations after laboratory culture for adenovirus and herpes simplex-2 virus (HSV-2). These showed that although isopropyl alcohol is effective against HSV-2, it is ineffective against bacteria and against adenovirus serotype 5 which can cause potentially life threatening infections in neonates. Chlorhexidine gluconate had a broad spectrum of activity against bacteria and was effective against HSV-2, but was also ineffective against adenovirus.

The use of isopropyl alcohol (70%) and chlorhexidine gluconate (4%) are not recommended for use as disinfectants for eyelid specula and scleral indentors in ROP screening.	**B**

3.3.6 Recording the Results of a Screening Examination

There is no universally used standardised sheet for recording the results of the ROP examination and anecdotal evidence from the GDG indicate that units use different sheets with varying levels of detail.

It is clearly important that accurate records are made for each screening examination in relation to the stage, zone and extent of any ROP and the presence of any pre-plus (as defined by ICROP revisited[6]) or plus disease. Notes should also record any adverse events experienced by the baby during the screening. If a further examination is required the need for and time of this examination should be documented. The documentation of clear, easy to interpret information on ROP screening status should form a separate part of the baby's medical record so that it is available if the baby is transferred between examinations.

A standardised examination record sheet developed by the GDG to capture the minimum information which should be recorded at each examination is included in this document (Appendix A). This sheet can be downloaded, adapted, printed and photocopied as required. An electronic version is available from www.rcpch.ac.uk.

Ophthalmological notes should be made after each ROP examination, detailing zone, stage and extent in terms of clock hours of any ROP and the presence of any pre-plus or plus disease. These notes should include a recommendation for the timing of the next examination (if any) and be kept with the baby's medical record.	**GPP**

3.3.7 Informing Parents about Screening

Parents are usually the best advocates for their child and parents of a baby with an extended stay in the neonatal unit are likely to have a keen interest in their baby's clinical progress. They have often developed considerable expertise and confidence in talking to nurses and doctors. Parents need to be informed that their child will be screened for ROP prior to the first examination. The parents should be provided with written information about why their baby is being screened, about the screening procedure, and about the risk and consequences of severe ROP developing. A suggested example of a leaflet on ROP screening for parents is provided with this guideline (Appendix D) although written information should supplement and not replace oral communication with the parents.

If their baby requires screening after discharge or transfer, informing parents about the potential implications of undiagnosed or untreated ROP, and that their baby will need further screening examinations, should help to ensure that these examinations take place. If an appointment is not kept a combined effort is needed to encourage attendance. As well as sending parents the details of a rearranged appointment, a copy should go to their GP and/or Health Visitor asking them to contact the parents to stress the importance of the screening examination.

In addition to oral communication, parents should be given written information about the screening process prior to the first examination of their baby.	**GPP**

Screening for ROP is considered to be a routine procedure within the neonatal unit. As such, informed written consent for screening is not required although it is important that parents are informed that this procedure will take place and have a chance to ask any questions.

3.4. Follow-up after Screening or Treatment

The outcome of preterm babies without ROP and those who developed stages 1 or 2 are similar and the GDG do not recommend, unless there is specific concern, follow-up other than the routine national screening that is undertaken between 41/2 and 5 years of age.

The GDG agreed that all babies with stage 3 ROP in which ROP resolved spontaneously and those babies requiring treatment require ophthalmic review at least until 5 years of age.[95]

After the acute phase, eyes that have reached stage 3 or have been treated should be monitored at a frequency dictated by the clinical condition to determine the risk of sequelae.	**GPP**

4. ROP Treatment

4.1 Introduction

Although treatment for ROP by laser ablation of the avascular peripheral retina was first explored in Japan in the 1960s,[96] the first robust evidence of successful treatment came from the multi-centre CRYO-ROP study which reported in 1988.[13] This study, which compared cryotherapy at threshold (defined in section 7) with no treatment, followed up treated and non-treated eyes over 15 years so providing the first evidence for long-term structural and functional outcomes.[97]

Ophthalmic outcomes of treatment

The CRYO-ROP study reports at 3 months and 1, 3.5, 5.5, 10 and 15 years showed that unfavourable structural outcomes (defined by categorising ROP residua in the posterior retina and which include retinal detachment) were less in the treated group than in the untreated group at all time points. However the percentage of eyes with unfavourable outcomes increased over time in both groups from 25.1% at one year[98] to 30.0% at 15 years for treated eyes,[97] compared with 44.7% vs. 51.9% for untreated eyes.[97,98]

When visual acuity as a measure of functional outcome was tested at 15 years,[97] 44.7% of treated eyes had unfavourable visual acuity (blind or a Snellen acuity score equal to, or worse than, 20/200) compared with 64.3% ($p<0.001$) of control eyes. At 10 years[99] 38.9% of eyes with bilateral ROP treated with cryotherapy and 29.3% of untreated control eyes were highly myopic (≤-8 D) although this was not statistically different and there was no significant difference in the distribution of refractive errors between groups with both exhibiting a range of refractive errors from highly myopic (i.e.≤-8D) to hyperopic (+4-6 D).

It was the CRYO-ROP study findings at 10 years[98] which first prompted a debate about whether earlier treatment would improve functional outcomes and led to the ETROP trial which evaluated outcomes with treatment at prethreshold (defined in section 7) compared with conventional management.[46] Detailed results from the ETROP trial are discussed in section 4.2.

Both the CRYO-ROP and ETROP studies also present the results according to the retinal location and severity of ROP at treatment. In the ETROP trial,[46] the risk of an unfavourable structural outcome at 9 months when treated at prethreshold ranged from 7.3% - 29.6% according to the zone, stage and the presence of plus disease and the rate of unfavourable visual acuity from 14.7% - 30.8%.[46] CRYO-ROP and ETROP studies concur that the risk of unfavourable outcomes increases with more posterior location, increasing severity and the presence of plus disease.[13,46]

Other short-term ophthalmic morbidity

Other ocular morbidities reported after ROP treatment include intraocular haemorrhage following diode laser,[46,101-105] argon laser[101] and cryotherapy[106,107] treatment. Haemorrhages ranged from

transient,[107] those clearing within 3 days[101] to a vitreous haemorrhage clearing after 2 weeks.[101] The ETROP study[46] reported haemorrhage (retinal, preretinal or vitreous) in 3.9% (14/361) of eyes treated at prethreshold and 5.1% (12/236) eyes treated conventionally, lower than in the CRYO-ROP study where haemorrhages occurred in 22.3% of babies undergoing cryotherapy. Similarly the rate of conjunctival or subjunctival haematomas was lower in the ETROP trial compared with CRYO-ROP study at 8.3% of in eyes treated at prethreshold, 6.8% in conventionally treated eyes and 11.7% of CRYO-ROP eyes.[14]

Cataracts have also been reported after cryotherapy, argon and diode laser treatment.[108] Retrospective case note reviews give cataract rates after diode laser as 0.64% (1/156)[109] and between 1% (4/374)[110] and 6% (6/100)[111] after argon laser treatment. Both the latter studies involving argon laser treatment noted that all 10 eyes developing cataracts had tunica vasculosa lentis at treatment, although other studies have noted cataract formation in the absence of this condition.[103]

In the ETROP trial, cataract and aphakia (loss of lens) not associated with total retinal detachment or vitrectomy occurred in 1.2% (4 eyes) of both the prethreshold and the conventionally managed group, although the treatment modality is not recorded.[46] One study reported a high incidence of phthisis bulbi (shrinkage of the eyeball) after cataract formation subsequent to treatment of threshold ROP by laser.[112]

Other treatment complications reported include vitreous detachment at 5 weeks,[107] iris atrophy,[113] hypotony,[113] corneal haze,[110,113] rupture of Bruch's membrane,[114,115] conjunctival lacerations[46,106] and nystagmus.[46] There have also been case reports of angle closure glaucoma in babies after argon and diode laser treatment,[116-118] serous macular detachment immediately after argon laser treatment,[119] and serous retinal detachment with pigmentary macular change following diode laser treatment.[120] Features noted during post-treatment involution which greatly increase risk of later retinal detachment include vitreous organisation and vitreous haemorrhage.[120]

In summary, although treatment of severe ROP is associated with better long-term visual and structural outcomes, it carries a risk of both short- and long-term ophthalmic morbidities.

4.2 Treatment Criteria and Timing

The research evidence was reviewed to identify any high quality RCTs comparing the safety and efficacy of at least two different ophthalmological criteria for treatment. The only study identified to be of sufficient methodological quality was the ETROP trial involving 26 centres in the US which compared early treatment of high-risk prethreshold (see Table 2) with conventional threshold treatment.

Table 2: Definition of prethreshold ROP used in the ETROP trial

Term	Definition
Prethreshold	**Zone I, any stage ROP less than threshold** **Zone II, Stage 2 with plus disease** **Zone II, Stage 3 without plus disease** **Zone II, Stage 3 with plus disease, but less than the criteria for threshold disease.**

In this trial, 401 babies meeting the criteria for 'high-risk' of an unfavourable outcome with prethreshold in at least one eye were randomised to receive either early or conventional treatment.[46,122,123] The level of risk was determined by a risk analysis programme (RM-ROP2)[122] which used, among other factors, degree of ROP (stage, zone and presence of plus), rate of ROP progression, birthweight, gestational age and ethnicity to classify eyes as at either 'high-risk' (i.e. ≥15% chance) or 'low-risk' (<15% chance) of an unfavourable outcome without treatment.

At the time of writing, functional outcome at 9 months has been reported.[46] The results showed an overall significant benefit for the early treatment of eyes with high-risk prethreshold disease, with unfavourable visual acuities (i.e. grating detection on the low vision card only or worse) in 14.3% of early treated eyes compared with 19.8% of eyes treated conventionally at threshold ($p<0.05$).[46] Two-year structural outcomes showed that significantly fewer high-risk eyes treated at prethreshold had an unfavourable outcome (presence of posterior retinal fold involving the macula, a retinal detachment involving the macula, or a retrolental tissue or 'mass' obscuring the view of the posterior pole), 9.1% compared with 15.4% of eyes undergoing conventional treatment ($p=0.002$).[124] Refractive error at 9 months[125] showed no significant difference in the distribution of myopia with 25.5% of eyes treated prethreshold and 28.3% of eyes managed conventionally being highly myopic (≥5 D).

Although these results show significant benefits of early treatment the study definition of high-risk was based on a complex risk analysis model. In order to assess their relevance to clinical practice the ETROP trial authors[46] mapped the 9 month ETROP outcomes to the ICROP classification, and discussed the impact on the study findings if the 329 babies deemed to have 'low risk' prethreshold (i.e. <15% chance of developing unfavourable outcomes) had also been treated. A clinical algorithm was developed which distinguished two types of prethreshold eyes (Table 3) for use where the risk model is not available, based on the outcomes of untreated eyes from the CRYO-ROP study[46] rather than the ETROP trial data.

Table 3: Definition of Type I and type II prethreshold disease from the ETROP trial[46]

Type I Prethreshold ROP	**Zone I, any Stage ROP with plus disease** **Zone I, Stage 3 with or without plus** **Zone II, Stage 2 or 3 ROP with plus disease**
Type II Prethreshold ROP	**Zone I, Stage 1 or 2 ROP without plus disease** **Zone II, Stage 3 ROP without plus disease**

The ETROP trial recommendation that treatment should be considered in any eye meeting the criteria of type I prethreshold has considerable implications for UK practice as it would clearly increase the total number of babies treated. The ETROP trial paper[46] estimated that treating babies <1251g with type I prethreshold would increase the percentage of screened babies needing treatment from 6% to 8%. In real terms this means that in the UK ophthalmologists would expect to treat 33% more babies than currently.

There was considerable debate, both within the GDG and in the stakeholder consultations, regarding the ETROP trial findings and the classification of type I and type II prethreshold ROP suggested by the trial (Table 3[46]). The greatest concern was in relation to the treatment of stage 2, zone II ROP with plus disease. The ETROP trial data on this subgroup report unfavourable 2 year structural outcomes in 16.7% of those treated at the conventional threshold criteria and 20.0% with early treatment.[124] The GDG were aware of the evidence from the CRYO-ROP study natural history study that only 56% of eyes with stage 2, zone II ROP with plus would progress to threshold or unfavourable outcomes if left untreated (Appendix A[46]). This means that if all babies in this group were treated early, 44% would probably have been treated unnecessarily. The ETROP trial authors,[126] in response to concerns that the subgroup analysis suggested little benefit for early treatment of stage 2, zone II ROP with plus disease, emphasised that the trial had not been designed for post-hoc subgroup analysis, and there were insufficient participants in each subgroup to be confident that these results were not due to chance.

After careful deliberation of the evidence and the ETROP trial authors' response the GDG felt able to accept the overall results of the ETROP trial and to recommend early treatment for prethreshold ROP occurring in zone I, or zone II, stage 3 ROP with plus disease. For ROP occurring in zone II, stage 2 with plus disease, the evidence suggests that treatment should be seriously considered but clearly more research is needed. The group emphasised that these recommendations do not negate the application of clinical judgement by experienced and competent ophthalmologists.

The following ophthalmic criteria are therefore recommended to identify babies requiring ROP treatment.

Treatment for ROP should be undertaken if any of the following indications are reached: • **Zone I, any ROP with plus disease,** • **Zone I, Stage 3 without plus disease,** • **Zone II, Stage 3 with plus disease.**	**B**

Treatment for ROP should be seriously considered if the following indication is reached: • **Zone II, Stage 2 with plus disease**	**B**

Ophthalmologists should be aware that earlier treatment will result in treating less mature and consequently more unstable babies. Potential complications in treating this population are discussed in section 4.3.5. Negotiation with the PCTs and Trusts will need to be held to increase the necessary capacity of all staff and cots at the appropriate location for treatment to occur in a timely fashion.

Treatment of fellow eye

The evidence suggests that that the rate of progression and severity of ROP between the eyes in the same baby is closely related. In the CRYO-ROP study natural history study in more than 90% of cases the severity did not vary between eyes by more than one category (categories used were: 1, no ROP; 2, less than prethreshold; 3, prethreshold ROP; 4, threshold ROP). Over 90% of cases had ROP in the same zone in both eyes. There was also a high degree of concordance between eyes with regards to plus disease.[127]

In situations where one of the baby's eyes reaches the criteria for treatment before the other, a clinical decision needs to be made regarding the treatment of the opposite eye, balancing the risk of treating an eye unnecessarily against the risks of exposing the baby to the possibility of two treatment sessions in close proximity.

4.2.1 Window of Opportunity for Treatment

Data from the CRYO-ROP study[49] indicate that the faster the progression of ROP the greater the risk of unfavourable outcome. Although the ETROP trial papers[16,46] do not report the interval between the onset of prethreshold and the onset of threshold disease or worse, the study protocol required a time interval between the treatment indications being reached and treatment of 48 hours.[46] As this protocol gave successful results it seems appropriate to adopt a similar interval although the ETROP trial papers do not provide data on how many cases met this standard and any difference in outcome when this standard was not met.

The GDG felt that adopting a standard of 48 hours between identification of ROP requiring treatment and treatment taking place highlights the importance of quick treatment, especially for those babies developing aggressive posterior ROP. Comments from the consultation described situations at present where treating within 48 hours would be difficult, such as when the ophthalmologist identified the need for treatment at the end of the week but treatment could not be organised until after the weekend. The GDG felt that some of these problems could be resolved by reorganising the screening programme to screen at the beginning of the week ***as this would hopefully reduce the pressure on the ophthalmologist having to organise treatment over the weekend.*** It was acknowledged that the timing may still provide a challenge in some areas, particularly where transfer of the baby for treatment is necessary. ***Where such reorganisation proves impossible babies who require treatment over the weekend should be treated within the appropriate time recommendations.***

Babies with aggressive posterior ROP (as defined by ICROP revisited) should be treated as soon as possible and within 48 hours. ROP requiring treatment but which is not aggressive posterior ROP should normally be treated within 48-72 hours.	**GPP**

A summary of the screening and treatment recommendations can be found in the algorithm at Appendix B.

4.2.2 Informing Parents about Treatment

The recommended timescales between the baby reaching the criteria for treatment and the scheduling of treatment are very short. However, parents should be given the chance to speak to the ophthalmic surgeon conducting the treatment prior to the procedure, preferably face-to-face, although if this is not possible a documented telephone consultation may be substituted. Parents should also be provided with written information about the treatment, such as the parent leaflet with this guideline (Appendix D), although this should never replace oral communication. Parents should receive information regarding the anaesthetic technique to be used and associated risks, which should be discussed with the anaesthetist conducting the procedure where appropriate. As ROP treatment is a surgical procedure informed consent must be gained before treatment.

The treating ophthalmologist should speak to the parents/carers of a baby requiring treatment for ROP and should gain informed consent prior to the procedure taking place.	**GPP**

4.3 Treatment Procedure

This section reviews the evidence in relation to treatment techniques and covers preparing the baby for treatment and postoperative care.

The evidence review identified few good-quality, high-powered RCTs comparing treatment techniques, probably due to the relatively small number of babies treated in a single centre. Most of the literature consisted of cohort studies, case series and case reports from single centres and a few small RCTs. Furthermore these studies almost all used what were, until recently, universally accepted treatment criteria of 'threshold' ROP. With the recent publication of encouraging results with earlier prethreshold treatment (section 4.2) there is an urgent need for new studies using these criteria.

4.3.1 Place of Treatment

Before laser treatment is undertaken consideration needs to be given to the provision of a "laser safe" environment to protect the treated baby, other babies, staff and equipment from inadvertent exposure to laser energy.

Most babies undergoing treatment for ROP will require some level of supportive care at the time of treatment because of their prematurity. In these circumstances it seems sensible for treatment to be undertaken within the neonatal unit, where appropriate continuity of care and post procedure monitoring for adverse events can be ensured.

It is acknowledged that the facilities required for treatment will depend on a number of factors including the method of treatment and anaesthesia, local resources, preferences of the neonatal and ophthalmic team as well as the clinical stability of the baby. However, as a minimum, ROP treatment will require an adequately heated environment where the baby can be safely cared for (adequate physiological monitoring with facilities and staff for any rapid intervention needed) while the room is darkened during treatment.

4.3.2 Treating Discharged Babies

A very small number of babies may need treatment after discharge. If these babies cannot be re-admitted to, and treated on, the neonatal unit they will need to be treated in a suitable unit with experience of caring for babies after neonatal surgery.

Babies who require treatment for ROP after discharge from hospital should be admitted to a suitable neonatal or paediatric unit with intensive care facilities.	**GPP**

4.3.3 Mydriatic Regimen

No studies were found that investigated the efficacy and safety of different mydriatic regimen used for the treatment of ROP. Having reviewed the evidence in relation to mydriatic regimens for ROP screening (section 3.3.1), the GDG felt that the regimen recommended for screening examinations was also appropriate prior to treatment. It is important that pupils remain well dilated throughout the

procedure to ensure the treatment is completed in a reasonable time frame and to reduce the risk of under treatment which may result in the need for re-treatment.

4.3.4 Treatment Anaesthesia

Ensuring that babies are appropriately prepared for treatment is crucial; with appropriate anaesthesia, analgesia and mydriasis, treatment is more likely to be completed satisfactorily with the minimum of distress to the baby and the need for re-treatment reduced.

Two regional UK surveys of 30 treating ophthalmologists[128] and 15 regional neonatal units[129] revealed significant variations in anaesthetic practice for ROP treatment. The most common anaesthetic regimens reported were either sedation with analgesia, paralysis and ventilation in the neonatal unit or general anaesthesia in an operating theatre. Other techniques included sedation with or without local or topical analgesia. Written protocols in relation to anaesthetic practice were uncommon[129] and the choice of anaesthetic regimen often dictated by surgeon or neonatologist preference and the availability of facilities or staff.[128] Sedation with analgesia, paralysis and ventilation under supervision of a neonatologist allows a baby to be treated in the neonatal unit whereas procedures under general anaesthetic are usually completed in operating theatres. Treatment in an operating theatre (requiring a paediatric anaesthetist) resulted in longer delays than when babies were treated on the neonatal unit.[128]

There is little evidence to support any one single method of sedation, analgesia or anaesthesia for ROP treatment. One retrospective study showed that babies undergoing treatment can be supported by nasophyrngeal prongs so avoiding the need for intubation.[130] Babies undergoing ROP treatment may be physiologically unstable and at risk of adverse cardio-respiratory events during and after treatment.[131] One observational study of 30 babies[131] treated by cryotherapy recorded the effects of using general anaesthesia; sedation and analgesia with elective ventilation; or topical anaesthesia alone. There were more severe and protracted complications in the topical anaesthesia group with 3/12 babies requiring resuscitation during treatment and 75% (9/12) of babies becoming unstable during or after treatment. Complications in the general anaesthesia and sedation/analgesia groups were generally less severe and none was life threatening. Despite the small size of the study, which used cryotherapy as the treatment modality, the GDG felt strongly that topical anaesthesia alone should not be used as anaesthesia for ROP treatment.

Babies may be treated more rapidly in the neonatal unit with sedation, analgesia, paralysis and ventilation.	**D**

Babies may be treated with general anaesthesia in a theatre if this can be arranged in a timely way.	**D**

Topical anaesthesia alone provides insufficient analgesia for ROP treatment and should not be used.	**D**

Further studies are required to determine the efficacy and safety of various sedation and anaesthetic regimens used when treating babies at prethreshold.

4.3.5 Monitoring during Treatment

No studies have specifically compared the systemic complications during treatment associated with different treatment and/or anaesthetic methods, although some have reported these as study outcomes. Factors affecting the risk of systemic events include the clinical stability of the baby, the type of analgesia and the treatment method. Treatment is generally considered to be relatively safe and some studies record no systemic[115,131] or ocular complications during or after treatment.[132] No reports of mortalities as a result of ROP treatment were found in the literature. Where systemic complications have been reported they include intraoperative pulmonary distress[134,135] and apnoea[50] during diode laser treatment under topical anaesthesia. One RCT[136] comparing argon laser with cryotherapy reported bradycardia in both treatment groups (3/16 (19%) and 3/12 (25%) respectively), but this was transient and normal heart rate resumed when manipulation of the globe ceased. In a study comparing diode laser with cryotherapy[137] one baby (4%) developed apnoeic spells during laser treatment and one during cryotherapy (4%).

The ETROP trial[46] found a significantly higher rate of systemic complications (apnoea, bradycardia, or the need for reintubation within 10 days of treatment after stopping artificial ventilation) in babies undergoing early treatment (84 events in 361 babies (23.2%)), compared with 26 events in 261 conventionally treated babies (11.0%). This is probably explained by less mature babies being treated.

Treatment for ROP is a surgical procedure. Effective monitoring and the presence of adequately skilled individuals during treatment can minimise both the risk of events occurring and the severity of events if they do occur. The GDG agreed that the extent of the monitoring should be determined by the local team and will largely be dictated by the baby's clinical condition.

Monitoring during treatment for ROP should follow local protocols for safe surgical procedures in neonates.	**GPP**

4.4 Treatment Modality

Although cryotherapy was the standard method of treating ROP in the CRYO-ROP study, 810nm diode laser therapy is now the technique of choice in the UK.[20] A similar preference was indicated in the ETROP trial where most of the ophthalmologists selected laser.[46] Laser therapy has been cited as causing lower rates of postoperative ocular and systemic complications and less damage to the adjacent tissues compared with cryotherapy.[138] Other advantages are that the laser spots are visible during treatment minimising the risk of missing areas requiring treatment, and that laser equipment is portable allowing use outside of the operating theatre.[138] However as the move to laser therapy away from cryotherapy appears to have been based on preference rather than evidence, the literature was reviewed to establish if the evidence exists to support this change.

4.4.1 Cryotherapy vs. Laser Treatment

Two RCTs[114,139] comparing short- and long-term outcomes of laser therapy with cryotherapy at threshold were identified One compared argon green laser (16 eyes) with cryotherapy (12 eyes)[136] in one part of the trial and diode laser (28 eyes) and cryotherapy (24 eyes)[137] in the second part. The second RCT[114] compared cryotherapy (15 eyes) with diode laser therapy (18 eyes). Both RCTs were included in a later meta-analysis[140] which was excluded from the review as there was insufficient methodological detail about the process used to compare the studies.

Both Hunter and Repka[114] and McNamara et al[136,137,139] report 'favourable' and 'unfavourable' structural outcomes as defined in the CRYO-ROP study[91] within 8 weeks of treatment. There were no significant differences in the McNamara et al study between structural outcomes with cryotherapy and laser therapy with favourable outcomes in 83% and 89% of patients undergoing cryotherapy and diode laser treatment respectively,[137] and in 75% and 94% (cryotherapy treatment and argon laser respectively).[136] Similarly, in the trial of Hunter and Repka,[114] favourable outcomes were reported as 94% both in cryotherapy and in diode laser treated eyes. In both studies there were more systemic complications with cryotherapy, although this did not reach statistical significance. Systemic complications of treatment have been discussed in section 4.3.5.

Babies treated in these studies have been followed up 10 years later although the results for diode and argon laser treatment are combined.[141,142] There was a relatively low follow-up rate (52.6% and 37.9% respectively) so bias cannot be ruled out. However, the results suggest that laser therapy is associated with significantly better corrected visual acuity compared with cryotherapy at 10 years and with significantly less macular dragging (29.4% with laser vs. 75% with cryotherapy).[142] A trend towards reduced refractive error with laser treatment was found in both studies but only reached statistical significance in one.[141]

4.4.2 Diode Laser vs. Argon Laser Treatment

No good quality studies have compared the safety and efficacy of diode and argon laser treatment. Both techniques have been shown to be effective in halting progressive disease in the short term.[136,137] Long-term results[112,139] (mean follow-up 5.8 years) found that there was no significant difference in refractive outcomes between the diode and the argon laser treated eyes.

The diode laser offers the advantages of greater portability and is easier to use. There is no need for ancillary cooling making it more suitable for use on neonatal units compared with argon laser.[101] Furthermore, argon laser energy can be absorbed by structures in the anterior segment, resulting in corneal epithelial oedema, burns of the cornea and iris, and coagulation of the tunica vasculosa lentis with secondary miosis.[114] The suggestion that argon laser treatment is associated with a higher rate of cataract formation is discussed in section 4.1.[111]

Transscleral or Transpupillary Laser Treatment

Diode laser treatment is traditionally completed through the pupil (i.e. transpupillary) but it has been suggested that transscleral treatment provides larger burn-widths resulting in significantly fewer laser spots.[105] One RCT compared safety and efficacy of transscleral and transpupillary laser treatment[105] in 25 babies and concluded that the two were equally effective although transscleral coagulation was associated with a higher risk of complications such as intraocular bleeding.[103] Transscleral treatment for posterior ROP sometimes requires conjunctival incisions, for which a general anaesthetic is required, and can result in trauma including fundus bleeding and swelling of eyelids and conjunctiva.[105] A small cohort study of 8 babies undergoing transscleral diode laser photocoagulation also concluded that it was safe and effective, although no long-term outcomes were investigated in either study.[143]

The evidence suggests that diode laser treatment is likely to be associated with better long-term functional and structural outcome when compared with cryotherapy. Although there is a lack of conclusive evidence demonstrating significant short-term benefit of one laser treatment technique over the other, diode laser treatment is associated with fewer ocular morbidities and is considered to be more practicable.

It should be noted that there may be some circumstances where it is not possible to complete diode laser treatment, for example where the visibility of the retina is obscured by corneal or lens opacities. In such circumstances the GDG felt that cryotherapy should be completed by an ophthalmologist experienced in this technique.

Transpupillary diode laser therapy is recommended as the first line treatment for ROP.	**B**

The unavailability of diode laser equipment or the inability to transfer to another centre should not prevent or delay the treatment of ROP. In these situations, treatment with cryotherapy or argon laser may be completed by an ophthalmologist experienced in these techniques.	**GPP**

4.4.3 Retinal Area Treated

There are no studies comparing the structural or functional outcomes when different areas of the retina are treated, and few studies give this level of detail. Where treated area has been recorded burns were mostly administered in the retinal area anterior to, but excluding, the ridge and throughout the entire avascular region.[50,114,136,137,144,145] In the ETROP trial the treatment area was not specified,[123] although the study design states that treatment excluded the neovascular ridge and in zone I cases the fovea was avoided even when anterior to the ROP/avascular retina demarcation line.

One prospective cohort study[135] which treated prethreshold ROP with diode laser burns adjacent to the lesions and not throughout the avascular retina reported favourable outcomes in all eyes although 50% (4/8) required re-treatment. A retrospective cohort study[104] treated 43 babies (82 eyes) at threshold with confluent diode laser treatment to the avascular retina and the ridge, including associated extra-retinal fibrovascular proliferation characteristic of stage 3 ROP. This study reported favourable outcomes in (96% of eyes), with a mean follow-up of 18 months, although intraoperative complications included the frequent appearance of small, localised ridge haemorrhages and 10% of eyes developed postoperative intraocular haemorrhage substantial enough to obscure the fundus, clearing within 3-4 weeks. No long-term results have been reported.

4.4.4 Laser Pattern and Burn Intensity

One small cohort study[146] compared the efficacy of treatment with a near confluent pattern of diode burns compared with less dense burn spacing of 1-1.5 burn-widths apart. The study concluded that, with respect to ROP progression in threshold ROP zone II disease, active disease was more likely to be halted with the near confluent laser burns compared with burns 1-1.5 burn-width apart. Similar results were achieved with zone I eyes, although the trial was too small to give significant results. Another retrospective study confirmed the efficacy of near confluent laser.[147] In the ETROP trial laser burns were placed no more than one burn-width apart.[123]

On the basis of this evidence and personal experience, the GDG recommended that treatment for ROP should include the entire avascular retina anterior to the ridge with burn spacing of between 0.5 to 1 burn-widths apart.

Treatment with near-confluent (0.5-1 burn-width) laser burn spacing should be administered to the entire avascular retina.	**D**

4.5 Post Treatment

4.5.1 Post Operative Recovery

Anecdotal evidence suggests that babies may require admission to an intensive care or high dependency unit after treatment. A cohort study of 25 babies[148] not ventilated for 7 days prior to cryotherapy found 30% needed post-operative ventilation. Any baby electively ventilated for treatment of ROP will require intensive monitoring post-operatively.

4.5.2 Post Treatment Eye Drops

No studies were found which compared outcomes with different post treatment regimens and a number of different protocols are recorded in the literature. Steroid, antibiotic and mydriatic eye drops are used separately or in combination for a few days[114] to two weeks.[149] The practice of members of the GDG varied similarly. However, due to the increased risk of complications such as hyphaema, posterior synechiae and transient cataract in very immature babies, the GDG felt that

the prophylactic use of steroid and mydriatic eye drops may be justified for up to 7 days in these babies and longer if problems develop.

Members of the GDG reported anecdotal evidence from their own practice of a very low rate of post operative infection after diode laser treatment and prophylactic antibiotics are rarely administered. However as the risk of infection is greater with cryotherapy, which is an open treatment (requiring conjunctival incisions), the use of prophylactic antibiotics may be of greater importance. There were no reports in the literature of any harm caused by the instillation of post-operative drops.

4.5.3 Post Operative Examination

The post-operative examination has two purposes: to determine whether re-treatment is necessary and to monitor disease regression to determine the frequency of medium to long-term follow-up. No high quality studies were found which investigated the optimal timing for this review but post-operative examination schedules reported ranged from examination the day after treatment to check for adverse effects and to measure intraocular pressures,[144] to a review at 10 days.[115]

One prospective cohort study[50] noted that regression occurred a mean of 5 days after diode laser therapy (range 2-14 days). In another study of 13 patients[133] both plus disease and ROP had resolved in 61.5% (8/13) babies one week after diode laser treatment, increasing to 84.6% (11/13) after 2 weeks.[133]

The GDG noted that inflammation is likely to occur after treatment,[148] but from their own practice they reported that this is likely to have reduced by 5-7 days after. A post-operative examination at this stage would be suitable to determine if the ROP has regressed.

The first examination post treatment should take place 5-7 days after treatment and should be continued at least weekly for signs of decreasing activity and regression.	**GPP**

4.6 Re-treatment

Where the active ROP fails to regress after the first treatment, re-treatment is required. The re-treatment rate in the ETROP trial was 13.9% for prethreshold treatment and 11%[46] when treated at threshold; both rates were higher than the 6.4% re-treatment rate in the CRYO-ROP study.[13]

No papers were found which specifically helped to inform a recommendation in relation to the ophthalmic criteria, timing of, or method for, re-treatment.

The time of re-treatment reported in the literature ranges from 1 week[144] to 3 weeks[151] after initial treatment. In the experience of the GDG, if re-treatment is required, it is usually undertaken between 10-14 days after initial treatment.

Re-treatment should be performed usually 10-14 days after initial treatment when there has been a failure of the ROP to regress.	**GPP**

4.7 Follow-up

See section 3.4.

5. Organisation of Services

Since the demonstration in the late 1980s that treatment could reduce the likelihood of severe visual disability and blindness, ROP screening programmes have been established throughout the UK.[3] Although this has resulted in fewer babies suffering visual impairment as a result of ROP[19] it is clear from a national audit[3] and from litigation reports that cases of babies not being screened or treated appropriately continue to occur.[152] Adherence to the evidence-based clinical guidance in this document should reduce the likelihood of poor outcomes for babies developing ROP but to be effective, screening and treatment services must be embedded in a robust organisational structure. In this section the GDG draws on evidence from the literature and from their own experience to define the components of a good screening and treatment service for babies at risk of developing sight-threatening ROP.

5.1 Communication and Responsibilities

A good service will have a number of components; it has to ensure that all babies at risk are identified and are screened at the appropriate times by an ophthalmologist with appropriate expertise. If treatment is required, it should be delivered in a safe environment in a timely manner by a specialist. Such a service will require co-ordination and communication between the neonatal and ophthalmic teams and parents. Yet studies suggest that this communication can break down. A UK regional audit[52] found that information about ROP screening was included in the transfer letter in only 44% of cases and 80% of those discharged home had no information about arrangements for ROP screening in the discharge summary.

A national UK audit found there was no clear agreement between ophthalmologists and clinical directors about who should take responsibility for the ROP screening programme. This is essential for a seamless programme of screening for all babies, including those transferred between units or discharged home before screening is finished.[3] Units should consider using an integrated care pathway (section 5.4) to improve the clinical governance of this process. The GDG agreed that the overall responsibility for the ROP programme within a unit should be at a consultant level and not be delegated to less experienced trainees. Cross cover for sickness and annual leave needs to be established.[153]

The responsibility for arranging follow-up of babies discharged home is often not clear. Parents need to be well informed about the need for follow-up, but may need reminding or encouragement to do this. A US study asking parents to sign written information about the risk of blindness without follow-up, together with oral advice to make appointments, did not increase the spontaneous follow-up rate.[53] Factors which did improve this however included written recommendations for follow-up examination in the transfer letter[52] and/or the discharge summaries[52,54] and scheduling of outpatient appointments by hospital staff at discharge.[53]

Neonatal units clearly need to have a robust mechanism for identifying babies needing screening and ensuring that this screening continues until the baby is no longer at risk or requires treatment. It is essential that there is local accountability and identification and documentation of the individual responsible for ensuring that the screening protocol is completed for all babies at risk.

Although the most appropriate way of organising ROP services will clearly depend on local circumstances and resources, the GDG wanted to highlight some key components as good practice.

All units caring for babies at risk of ROP should have a written protocol in relation to the screening for, and treatment of, ROP. This should include responsibilities for follow-up of babies transferred or discharged from the unit before screening is complete, which should be the responsibility of the named consultant Neonatologist for each baby.	**GPP**

Displaying the protocol in the unit and ensuring that parents are informed if their baby meets the requirements of the protocol should help to make certain that all are aware of the importance of ensuring that screening is continued post transfer and discharge

A protocol for contacting those who do not attend may encourage attendance and it is also important to document all efforts made to inform parents/carers of the need to bring their baby back. *The GDG is aware of a case where a claim of negligence succeeded because the ophthalmologist did not personally contact the parents who failed to bring their baby back for a screening examination.* Appropriate administrative support and time must be allowed for this.

If babies are transferred either before ROP screening is initiated or when it has been started but not completed, it is the responsibility of the consultant neonatologist to ensure that the neonatal team in the receiving unit is aware of the need to start or continue ROP screening.	**GPP**

Whenever possible ROP screening should be completed prior to discharge.	**D**

There should be a record of all babies who require review and the arrangements for their follow-up.	**GPP**

For babies who meet the ROP screening criteria, screening status and the need and arrangements for further screens must be recorded in all transfer letters so that screening may be continued.	**D**

For babies discharged home before screening is complete the first follow-up out-patient appointment must be made before hospital discharge and the importance of attendance explained to the parents / carers.	**D**

If babies are not brought back for the out-patient appointment, parents / carers should be contacted by telephone and then by letter to re-arrange the appointment and to reinforce the importance of the eye examination with a copy sent to the GP, Health Visitor and Consultant Neonatologist. **The rearranged appointment needs to be within 1-2 weeks depending on severity and level of concern.**	**D**

5.2 Ophthalmologists' Work Commitment

The time an ophthalmologist requires to screen and treat babies will depend on the number of babies requiring screening. A survey of UK ophthalmologists[154] found that ROP screening is an infrequent activity for many ophthalmologists, with 55% of respondents screening fewer than 40 babies per year. In terms of sessional commitment 34% of those who screened babies spent more than half a session a week ROP screening. Of those ophthalmologists who screened more than 70 babies in 1994, 43% did not have ROP screening identified in their work plan. ROP screening should be included in the work plan for those ophthalmologists completing screening and should be based on the number of babies admitted to the unit meeting the screening criteria (birthweight of <1501g or gestational age of <32 weeks) per year.

Although treatment of severe disease is relatively infrequent, the time commitments for each treatment session are large and will include travel, preparation, consultation with parents, treatment and follow-up. Arrangements should be made for inclusion of this work into the ophthalmologist's work plan.

Ophthalmologists regularly completing ROP screening and/or treatment should have sessional commitments allocated within their work plan.Ophthalmologists treating ROP need to have specific time allocated in their job plans for travel to the neonatal unit for treatment, for talking to parents/carers, pre-treatment preparation of the eye, treating the baby, and appropriate follow-up.	**GPP**

5.3 Ophthalmologists' Training and Expertise

The training of ophthalmologists for the screening and treatment of ROP is an important issue, but is outside the scope of this guideline.

ROP treatment is a specialised procedure. In a surveillance study conducted in the late 1990s, 131 babies were treated in the UK by 39 individuals in a 15 month period.[20] The number of treating ophthalmologists is now much less than the 65 ophthalmologists who reported themselves as treating ROP in 1995.[153] These figures suggest that at the turn of the century UK treatment services were already covering relatively large geographical populations and, because of the rarity of ROP requiring treatment, most ophthalmologists treat very few babies each year. However if the recommendations in this guideline for earlier treatment are adopted throughout the UK, the number of babies requiring treatment is likely to increase (section 4.2).

Babies with ROP should be treated by ophthalmologists who have the appropriate competency.	**GPP**

Each network should have identified individuals for ROP treatment.	**GPP**

5.4 Integrated Care Pathways

The care journey for a premature baby is often complicated. Transfers between hospitals and even regions are not unusual with babies often discharged home requiring ongoing ophthalmology follow-up. At these times the potential for miscommunication between the neonatal and ophthalmology services is high. High quality care may be promoted by the use of integrated care pathways (ICP).

The key difference between an ICP and a guideline, protocol or flowchart is the element of variance reporting. A system is set up (ideally electronically) that identifies to a clinician when the agreed local arrangement has not been followed. This provides an important element of clinical governance to the pathway. There may be entirely legitimate reasons for variance but the process should identify all variance and therefore, in this instance, any babies where ophthalmic follow-up has stopped before the ophthalmologist has discharged the patient.

More information on how to develop an ICP and examples from other areas of clinical care can be found in the Knowledge Zone of the Protocols and Care Pathways Specialist Library (http://www.library.nhs.uk/pathways) or from a trust clinical governance department.

6. Audit Standards

It is suggested that the following recommendations and good practice points are regularly audited in units:

Key priority for implementation	**Audit Measure**	**Standard and justification**
Completeness of screening programme	% of babies <32 weeks GA **or** <1501g birthweight who receive at least one ROP eye examination	100% - this standard is also included in the National Neonatal Audit
Timing of first screen	% of babies < 27 weeks GA receiving a first ROP screening exam by 31 completed weeks postmenstrual age.	95% - clinical or other reasons may require postponement of screening but must be documented
	% of babies 27 –32 weeks receiving a first ROP screening exam before 5 completed weeks postnatal age.	95% - clinical or other reasons may require postponement of screening but must be documented
Screening before discharge	% of babies admitted to the unit at <32 weeks GA who have at least one eye examination on the unit	100%
ROP Treatment	% of babies with any zone 1 ROP who receive treatment	100%
Timing of treatment	% of babies needing ROP treatment for their ROP who are treated within 48 hours of the decision to treat being made.	100% (although it is acknowledged that there will be circumstances where this is difficult to achieve)
Parent information	% of parents/carers of babies meeting screening criteria provided with written information about ROP screening prior to first examination	100%
Transferred infants	% of babies transferred after at least one eye examination with details of screening status and the need/arrangements for further screens documented in transfer letter	100%
Discharged infants	% of infants discharged home before screening is complete for whom an out-patient appointment has been made before discharge	100%

7. Ophthalmic Definitions and Photo Glossary

Aggressive Posterior ROP (AP-ROP) * (Figure 1)
An uncommon, rapidly progressing, severe form of ROP characterised by its posterior location, prominence of plus disease and the ill-defined nature of the retinopathy.

Plus Disease (Figure 2)
Increased venous dilatation and arteriolar tortuosity of the posterior retinal vessels in at least two quadrants of the eye.

Pre-Plus Disease (Figure 3)
Vascular abnormalities of the posterior pole which signifies the presence of ROP, but which are insufficient for the diagnosis of plus disease

Regression
The process of ROP changing from active, progressive disease to inactive disease. Also called involution.

Sight-Threatening ROP
Presence of stage 3 disease as defined in ICROP revisited,[6] prethreshold (type 1 or type 2) or threshold disease as defined below..

Stage
Six stages (1, 2, 3, 4a, 4b and 5) which describe the severity of ROP from very mild disease (stage 1) to stage 5 which is complete retinal detachment. Stages are defined in the ICROP revisited classification[6]

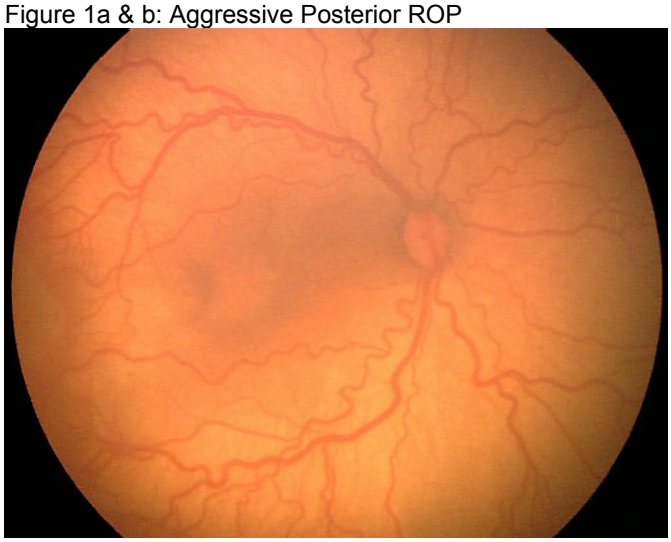
Threshold
5 contiguous or 8 cumulative clock hours of stage 3 ROP with plus disease in zones I or II

Prethreshold

Type 1:	Zone I, any Stage ROP with plus disease
	Zone I, Stage 3 ROP with or without plus disease
	Zone II, Stage 2 or 3 ROP with plus disease
Type 2:	Zone I, Stage 1 or 2 ROP without plus disease
	Zone II, Stage 3 ROP without plus disease

Zone
The areas of the retina used to describe the location of ROP (Figure 4)

Figure 1a & b: Aggressive Posterior ROP



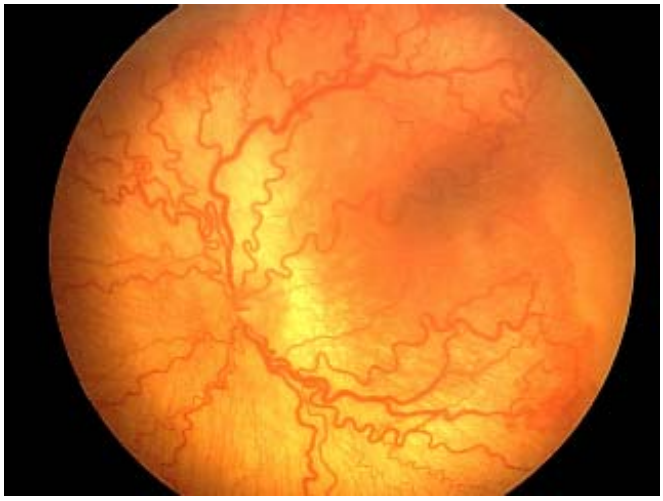


Figure 2: Plus Disease

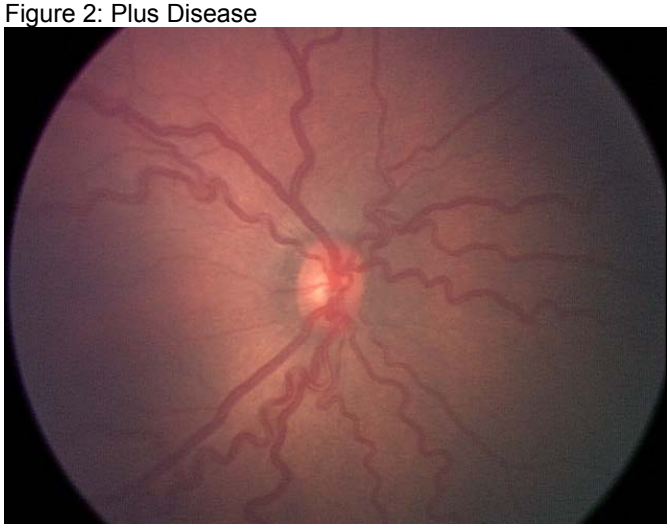


Figure 3: Pre-Plus Disease

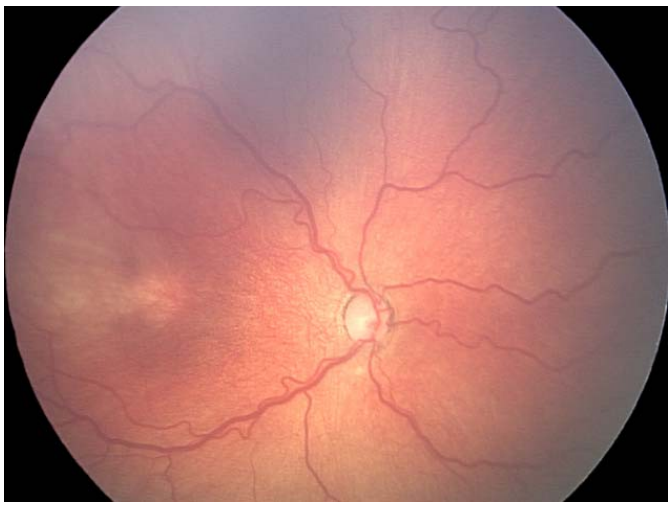
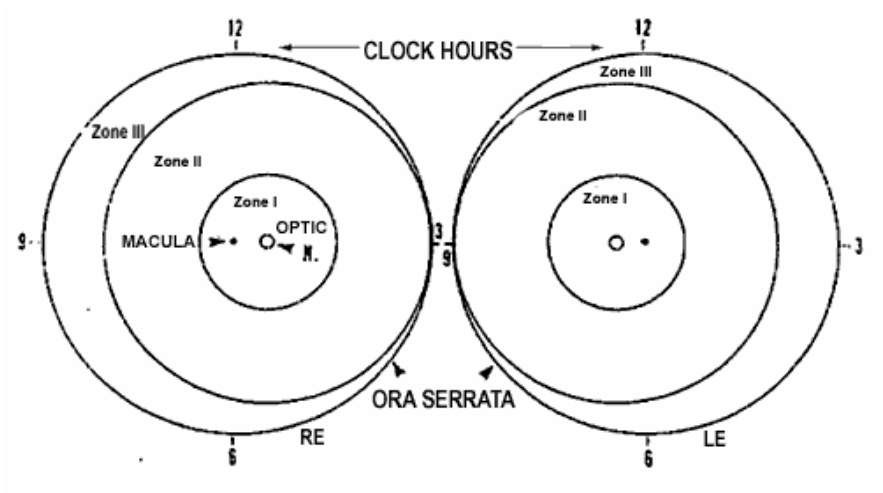


Figure 4: Retinal zones**



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