The ROYAL COLLEGE of OPHTHALMOLOGISTS

Clinical Guidelines

Treating Retinopathy of Prematurity in the UK

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The UK Special Interest Group for ROP forum (ROP-SIG) were consulted during guideline preparation to reach consensus. Questions were sent to the group by email and following discussion, consensus was used to refine practice points. Members of ROP-SIG are listed in Appendix G.

Stakeholder Organisations

The following organisations were formally consulted during the guideline development:

Fellows and Members of RCOphth
British Association of Perinatal Medicine
Royal College of Paediatrics and Child Health
Bliss (The charity for babies born premature or sick)

2. Definitions and Acronyms

BAPM	British Association of Perinatal Medicine
BNF-C	British National Formulary for Children
BOSU	British Ophthalmic Surveillance Unit
BW	Birthweight
CRYO-ROP study	Multicenter Trial of Cryotherapy for Retinopathy of Prematurity
ETROP trial	Early Treatment for Retinopathy of Prematurity Randomized Trial
GA	Gestational age – Time between the first day of the last menstrual period and the day of delivery
GDG	Guideline Development Group
ICP	Integrated care pathway
ICROP	International Classification of Retinopathy of Prematurity
MDT	Multidisciplinary team
NICU	Neonatal Intensive Care Unit
PIPP	Premature Infant Pain Profile
PMA	Postmenstrual age – 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

2.1 Ophthalmic Definitions

Threshold ROP (Cryo-ROP)[1]

The severity of ROP treated in the Cryo-ROP study, based on a 50% risk of retinal detachment if left untreated.

5 contiguous or 8 cumulative clock hours of Stage 3 ROP in Zone I or Zone II, with plus disease.

Prethreshold ROP (Cryo-ROP)[1]

Zone I any ROP less than threshold,

Zone II stage 2 with plus,

Zone II stage 3 without plus,

Zone II stage 3 with plus but less than the extent defined for threshold disease.

ETROP Type 1 Prethreshold ROP[2]

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

ETROP Type 2 Prethreshold ROP[2]

Zone I Stage 1 or 2 ROP without plus disease

Zone II Stage 3 ROP without plus disease

Referral-warranted ROP

For telemedicine studies, forms of ROP that are treatment-requiring, or almost treatment-requiring have been combined under the term "referral-warranted". This is defined as any ROP in Zone I, any plus disease, any stage 3 ROP. [3,4]

Sight-threatening ROP

Any Stage 3 ROP OR Prethreshold (type 1 or type 2) OR threshold disease.

Treatment-Requiring ROP

ETROP Type 1 Prethreshold ROP OR A-ROP

Aggressive ROP (A-ROP)

An uncommon, rapidly progressive, severe form of ROP, typically posteriorly located in zone I or posterior zone II, but in some healthcare settings or in atypical cases may occur more anteriorly, and predominance of plus in all four quadrants of the retina. Progression may not pass through stage 1-3 as in classic ROP, although hybrid forms may exist.

3. ROP Treatment Guideline

3.1 Background to the guideline

Retinopathy of Prematurity is a potentially blinding condition. While most infants screened for ROP do not require treatment, an important minority do. Timely intervention will prevent blindness in most cases. The 2008 ROP screening and treatment guideline was produced by the Royal College of Paediatrics & Child Health (RCPCH) in collaboration with the RCOphth and BAPM. When considering the most appropriate approach to revision of the guideline, the RCPCH and the RCOphth decided to develop two complementary guidelines. The Screening guideline has been developed by the RCPCH, and the Treatment guideline by RCOphth.

3.2 Clinical need for an updated guideline

Clinical studies of the criteria for ROP screening, and developments in telemedicine have prompted the need to review ROP screening, which impacts arrangements for treatment. Major changes in the treatment of ROP occurred following the publication of the Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity (BEAT-ROP) trial in 2011,[5] and the Ranibizumab Compared With Laser Therapy for the Treatment of Infants Born Prematurely With Retinopathy of Prematurity (RAINBOW) trial in 2019.[6] While these trials demonstrated anti-Vascular Endothelial Growth Factor (VEGF) agents are effective in the treatment of ROP, they raised questions on the systemic safety of the agents and of patterns of disease regression and reactivation following the use of these agents. The recent publication of the third iteration of the international classification of ROP (ICROP3),[7] along with the two anti-VEGF trials necessitate a fresh approach to clinical practice, using an updated guideline.

3.3 Guideline objectives

The aims of the guideline are:

- To evaluate and summarise the clinical evidence relating to the treatment of ROP.
- To provide evidence-based recommendations for the treatment of ROP.
- To provide information for parents and carers on the treatment of ROP.
- To produce good practice points based on the consensus of the Guideline Development Group (GDG) in areas where the research evidence is lacking.

3.4 Guideline Methodology

Detailed methodology is given in appendices F-J. Recommendations are graded A-D using SIGN grading hierarchy (Appendix G, page 60), according to the strength of the evidence underpinning them. Good practice points (GPP) are a consensus of the GDG.

3.5 Background and epidemiology

ROP screening should identify the small number of infants who require treatment, in a timely way. There is a much higher risk of unfavourable outcome with late treatment. In 1988 the CRYO-ROP study showed there was a 49.3% reduction in unfavourable retinal structural outcomes in eyes treated with cryotherapy at "threshold" ROP compared to no treatment.[1] This was the first evidence that an intervention improved outcome. The 2003 ETROP study of "prethreshold" treatment showed better outcomes; 14% had unfavourable acuity and 9% had unfavourable structure at 9 months of age.[2]

Most infants screened for ROP do not require treatment. A UK national prospective surveillance study in 2014 found that only 4% of an estimated 8,112 screened infants required treatment.[8] Other developed countries have reported a treatment rate up to 10%. In the UK study, 90.5% of treated infants received laser and 8% anti-VEGF therapy. Only one infant had cryotherapy, combined with laser due to the presence of vitreous haemorrhage. The median gestational age of infants requiring ROP treatment was 25 weeks, and the median birth weight was 706 grams. 57.8% of the infants were male. 69.7% of the infants were white, 13.8% Asian, 5.5% black and 5.2% mixed. The study noted an increase in the number of infants treated compared to a British Ophthalmic Surveillance Unit (BOSU) survey performed in 1998. In addition, a change in treatment modalities was noted; in the earlier survey 22% of infants were treated with cryotherapy and no infant was treated with an anti-VEGF agent.[9]

The dominant risk factors for ROP are low gestation and low birth weight.[10] Additional factors are ethnicity (higher risk in Asian infants and lower risk in black infants when compared with white infants).[11] Postnatal oxygen supplementation, poor postnatal weight gain, blood transfusions and a range of complications associated with preterm delivery have been associated with ROP.[11]

The pathophysiology and treatment rationale of ROP may be understood in terms of two phases of postnatal retinal development in preterm infants.[12] Before approximately 30 weeks PMA therapeutic oxygen supplementation and low circulating Insulin-like Growth Factor 1(IGF-1) lead to reduced retinal blood vessel growth. From approximately 31 weeks PMA increased retinal metabolic activity in the anterior, avascular retina leads to increased retinal production of VEGF. A high level of intraocular VEGF in the presence of increased circulating IGF-1 level stimulates abnormal angiogenesis, leading to ROP. Treatment of ROP is targeted to reduce intraocular VEGF – laser ablation of VEGF-producing avascular retina or anti- VEGF antibody binding of intraocular VEGF.

3.6 Overview of major clinical trials: ophthalmic outcomes of treatment

Cryotherapy vs. No treatment

The CRYO-ROP study showed that unfavourable structural outcomes (fibrotic changes involving the macula, including retinal detachment) were less in the treated group than in the untreated group at all follow-up time points. At 15 years, unfavourable retinal structure was present in 51.9% untreated eyes and 30% treated eyes, and visual acuity was 6/60 or worse in 64.3% untreated and 44.7% treated eyes, providing the first evidence for long-term benefit in structural and functional outcomes.[13]

Laser

The CRYO-ROP study findings at 10 years[14] prompted a debate about whether earlier treatment would improve functional outcomes and led to the Early Treatment of ROP (ETROP) trial, which evaluated outcomes with treatment at prethreshold (defined in ophthalmic definitions) compared with conventional management.[15] Detailed results from the ETROP trial are discussed in section 4.1, "What are the indications for ROP treatment?". The ETROP trial allowed treatment with either cryotherapy or laser, but only one infant in the trial had primary cryotherapy. In practice the trial measured the effects of laser treatment. 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 ranged from 14.7% – 30.8%.[15] 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.[1,15] At 2 years follow-up, ETROP showed unfavourable structural outcomes were reduced from 15.4% in conventionally managed eyes to 9.1% in earlier-treated eyes.[16]

Anti-VEGF agents

Bevacizumab is a monoclonal antibody that binds VEGF-A, and was licensed in 2004 for the treatment of colorectal cancer. It was reported to be beneficial for the treatment of neovascular macular degeneration in 2005 but its ocular use remains off-label. The Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity (BEAT-ROP) trial reported in 2011.[5] Infants with stage 3 ROP with plus disease in Zone I or in posterior Zone II were randomised to receive intravitreous bevacizumab (IVB) 0.625mg (half adult dose) in 0.025 ml (75 infants) or laser (75 infants), to both eyes. The primary outcome measure was changed prior to data analysis. The original outcome was treatment success: absence of Stage 3 with plus disease recurrence in one or both eyes, to PMA age 54 weeks. The primary outcome measure used for analysis was treatment failure, defined as recurrence of neovascularization in one or both eyes requiring retreatment, to PMA age 54 weeks. Four infants (6/140 eyes, 4%) failed in the IVB group and 19 infants (32/146 eyes, 22%) failed in the laser treated group, P = 0.002. In subgroup analysis the difference was significant for Zone I ROP: IVB (2/62 (3%) eyes vs. laser 23/66 (35%) eyes, p = 0.003, but not for posterior Zone II ROP: IVB (4/78 (5%) eyes vs. laser 9/80 (11%) eyes, p = 0.27. Unfavourable retinal structure was also reported. 3/140 (2%) eyes treated with bevacizumab and 24/146 (16%) eyes treated with laser had abnormal structure at PMA 54 weeks. The difference was most marked in eyes with Zone I disease at baseline:1/62 (2%) bevacizumab treated eyes and 18/66 (27%) laser treated eyes had abnormal structure at PMA 54 weeks. In eyes with posterior Zone II disease at baseline: 2/78 (3%) bevacizumab treated eyes and 6/80 (7.5%) laser treated eyes had abnormal structure at 54 weeks PMA.

Ranibizumab is a monoclonal antibody fragment (Fab), developed and licensed for ocular use. The RAINBOW trial published in 2019 used a composite primary outcome: survival with no active retinopathy, no unfavourable structural outcomes, or need for a different treatment modality at or before 24 weeks post baseline.6 Infants with Type 1 ROP (excluding Zone II Stage 2 with plus disease) in both eyes were randomised to intravitreous ranibizumab (IVR) 0.2mg (40% adult dose) in 0.02ml (74 infants), IVR 0.1mg (20% adult dose) in 0.01ml (77 infants) or laser (74 infants) in both eyes. Treatment success occurred in 56/70 (80%) infants in the IVR 0·2 mg group, 57/76 (75%) infants in the IVR 0·1 mg group and 45/68 (66%) infants in the laser group. The difference between IVR 0.2mg and laser was P = 0.051. The primary outcome successes for infants with Zone I were 19/28 (68%) and 14/23 (61%) for IVR 0.2mg and laser respectively, and with Zone II 37/42 (88%) and 31/45 (70%) respectively. Unfavourable retinal structure was present in at least one eye of 1/74 (1%) infants treated with ranibizumab 0.2mg, 5/77 (6%) infants treated with ranibizumab 0.1mg and 7/74 (9%) infants treated with laser therapy, at 24 weeks post baseline. The conclusion of the study was that ranibizumab 0.2mg was as effective as, and might be superior to, laser for all forms of Type 1 ROP; Zone II stage 2+ was not studied. Currently ranibizumab is the only anti-VEGF licensed for ROP treatment.

Functional outcomes have not yet been reported in a systematic way from either trial. Five-year visual acuity outcomes are planned for the RAINBOW study.

Different anti-VEGF agents

Ranibizumab is the only anti-VEGF that has been subjected to a clinical trial that included systemic safety outcomes. No direct comparison trials between anti-VEGF agents for ROP have been performed. A RCT of aflibercept compared to laser has been completed, but results have not yet been published.

Anti-VEGF dose

Concerns about possible systemic side effects of bevacizumab (see section 3.7 below "Systemic morbidity: Neurodevelopment following anti-VEGF") might be mitigated using lower doses.[17] The BEAT-ROP trial used half the adult dose (0.625mg), but pilot "de-escalating" dose studies have investigated the short term efficacy of much lower doses.[17] To date, the lowest dose reported to have short term efficacy was 0.004mg.[17] A small case series in the UK reported the use of 0.16mg.[18] The optimal dose of bevacizumab for ROP remains unknown.

In the RAINBOW trial, the efficacy of ranibizumab 0.1mg and 0.2mg were compared. While not statistically different, results with 0.2mg were slightly better than those with 0.1mg. In the small CARE-ROP trial, infants with bilateral Type 1 ROP were randomised to ranibizumab 0.12mg (10 infants) or ranibizumab 0.20 mg (9 infants).[19] The primary outcome was the number of infants who did not require rescue treatment by 24 weeks post baseline. 8/9 infants in the IVR 0.12mg group and 6/7 in the IVR 0.2mg group reached 24 weeks without rescue treatment.

The dose of ranibizumab licensed to treat ROP in UK is 0.2mg.

3.7 Treatment related morbidity

Short-term ophthalmic morbidity

The ETROP study reported haemorrhage (retinal, preretinal or vitreous) in 3.9% of eyes treated at prethreshold and 5.1% eyes treated conventionally.[2,15] In the RAINBOW trial, retinal haemorrhages occurred in at least one eye of 11% infants treated with ranibizumab and 10% infants treated with laser.[6] The rate of conjunctival or subconjunctival haematomas in the ETROP trial was 8.3% in eyes treated at prethreshold, and 6.8% in conventionally treated eyes.[15] This compares with subconjunctival haemorrhage in at least one eye of 3% infants for laser and 8% for ranibizumab in the RAINBOW trial.[6] Corneal opacity was reported following laser in 2% infants in RAINBOW[6] and 0.6% eyes in the G-ROP study,[20] but not following anti-VEGF treatment in these studies. Hyphaema was reported in 1.6% eyes treated with laser in the G-ROP study.[20] Importantly, endophthalmitis occurred in one eye treated with ranibizumab in the RAINBOW trial, but the eye had recently been treated for bacterial conjunctivitis.[7]

In the ETROP trial, 1.9% (eight eyes of seven patients) developed cataracts by six months corrected age, including two eyes that had not undergone laser treatment.[21] Only one infant was reported to have developed cataract within 10 days of treatment. In the G-ROP study, 0.3% of 970 eyes treated with laser developed cataract.[20] In the RAINBOW trial no eyes treated with laser developed cataract, but one eye treated with ranibizumab developed cataract, thought to be due to needle trauma.[6] An Iranian case series reported 0.23% of 865 eyes treated with bevacizumab developed cataract.[22] In the UK national study at one year follow-up, cataract was reported in two children, one after laser and one in a child who had both laser and anti-VEGF and was awaiting vitrectomy.[23] The ocular abnormalities following standard dose and reduced dose bevacizumab have been reported as similar.[24]

Systemic morbidity: neurodevelopment following anti-VEGF

Bevacizumab

Two recent metanalyses of possible neurodevelopmental effects of bevacizumab treatment produced conflicting results.[25,26] Tsai used up to 700 participants from seven comparative case series and one small RCT.[25] Kaushal used up to 974 participants from 12 comparative case series and the same small RCT.[26] Five of the comparative case series appeared in both metanalyses. Tsai found no increase in neurodevelopmental morbidity when compared with laser treatment or with no treatment, and

a possible small increase in motor morbidity.[25] Kaushal found a higher risk of moderate cognitive impairment, lower Bayley III cognitive and language composite scores and a higher risk of death, compared to laser.[26] Both authors commented that adjustment for confounders was limited and that bevacizumab was used in sicker infants in some studies. Systemic data from the BEAT-ROP trial were limited to 18 infants from one trial centre, reported to 2 years.[27]

Ranibizumab

To date the only RCT comparing systemic safety of an anti-VEGF and laser treatment has been the RAINBOW trial. There have been no systemic safety concerns to 2 years follow-up.[28] However, the trial was powered for ocular treatment effect to 24 weeks, not for safety measures.

Systemic VEGF

An indirect measure of the possible risk of anti-VEGF morbidity is measurement of serum or plasma VEGF following anti-VEGF treatment. VEGF is known to have an important role in the development of several tissues, [29,30] including the central nervous system (CNS).[31] Serum VEGF is reduced for a number of weeks following intravitreal bevacizumab injection.[32] In contrast, while one small study showed reduced serum VEGF during the first week following intravitreal ranibizumab injection,[33] in the RAINBOW trial[6] plasma VEGF was not reduced from 9 – 30 days.[34]

Summary of Neurodevelopment following anti-VEGF

To date there is no clear evidence that anti-VEGF agents do or do not affect neurodevelopment. Ranibizumab causes less suppression of systemic VEGF levels than bevacizumab and to date ranibizumab is the only anti-VEGF that has been subjected to an RCT that includes neurodevelopmental and other systemic outcomes at the age of 2 years. On this basis, any theoretical risk of developmental impairment attributable to administration of anti-VEGF agents can, and should, be balanced against any advantages that anti-VEGF use might bring to an individual case. Ranibizumab is currently the only anti-VEGF licensed for use in preterm infants.

Systemic hypertension following intravitreal bevacizumab in infants

One uncontrolled retrospective study found a high rate of new onset systemic hypertension following intravitreal bevacizumab.[35] In the RAINBOW trial, there were no differences between treatment groups for the mean change in blood pressure between baseline and Day 85 but blood pressure was not measured systematically soon after treatment.[7]

Mortality

ROP treated with laser or surgery was not associated with increased mortality.[36]

In summary, although treatment of severe ROP is associated with better long-term visual and structural outcomes than no treatment, it carries a risk of both short- and long-term ophthalmic morbidities. There are some concerns related to systemic morbidity following anti-VEGF treatment.

4. Recommendations

4.1 What are the indications for treatment of ROP?

Evidence Grade A

Treat infants in whom a screening examination has detected:

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

Plus disease should be present in at least two quadrants. Vessel changes should be assessed within Zone I. GPP: Zone II stage 2 with plus ROP, is borderline for treatment and close watching is an acceptable alternative approach.

Closely monitor infants (weekly review and if concerned discuss with the network treating ophthalmologist) in whom a screening examination has detected:

- Zone I stage 1 or 2 without plus disease
- Zone II stage 3 without plus disease

Indications for treatment in the 2008 guideline were based on the ETROP trial.[15] No subsequent studies were identified. The recommended indications for treatment have therefore not changed. As these criteria are central to ROP management, much of the discussion of the ETROP trial given in the 2008 guideline is repeated here.

The ETROP trial involved 26 centres in the US which compared early treatment of high-risk 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) with conventional threshold treatment.

In this trial, 401 infants 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.[15] The level of risk was determined by a risk analysis programme (RM-ROP2) 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.[37]

Reported functional outcome at 9 months 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 ($p<0.05$).[15] 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).[16] Refractive error at 9 months 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 (level of myopia given as ≥5 Dioptres).[38]

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 mapped the 9-month ETROP outcomes to the ICROP classification, and discussed the impact on the study findings if the 329 infants deemed to have 'low risk' prethreshold (i.e. <15% chance of developing unfavourable outcomes) had also been treated.[15] A clinical algorithm was developed which distinguished two types of prethreshold eyes (Table 1) for use where the risk model is not available, based on the outcomes of untreated eyes from the CRYO-ROP study rather than the ETROP trial data.[15] It should be noted that in the ETROP trial, blood vessel changes were required in at least 2 quadrants to be considered "plus".

Table 1: Definition of type 1 and type 2 prethreshold disease from the ETROP trial[15]

Type 1 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 A-ROP
Type 2 Prethreshold ROP	Zone I, stage 1 or 2 ROP without plus disease Zone II, stage 3 ROP without plus disease

There has been continued debate in relation to the treatment of stage 2, zone II ROP with plus disease. The ETROP trial data on this subgroup reported unfavourable 2-year structural outcomes in 16.7% of those treated at the conventional threshold criteria and 20.0% with early treatment.[16] The GDG were aware of the evidence from the CRYO-ROP 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.[15] This means that if all infants in this group were treated early, 44% would probably have been treated unnecessarily. The ETROP trial authors, 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.[39]

The disease category AP-ROP (aggressive-posterior ROP) was included in the International Classification of ROP in 2005, after the ETROP trial was completed.[40] It is now termed A-ROP (aggressive ROP).[7] As A-ROP is regarded as an uncommon, rapidly progressive form of ROP that generally occurs in zone I or in posterior zone II, with prominence of plus disease in all four quadrants, and generally has a form of ill-defined stage 3 ROP, it is included as a treatment criterion. The term "posterior" was removed in recognition of the fact that in some challenged healthcare settings or in very atypical cases aggressive ROP could be seen in more anterior zones of the retina.[7]

The GDG continues to accept the results of the ETROP trial and to recommend 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 more research is needed. The group emphasised that these recommendations do not negate the application of clinical judgement by experienced and competent ophthalmologists. There are reports

in the literature of the treatment of eyes that have a variety of borderline treatment criteria.[41] Plus disease is a significant driver for treatment, and it is recognised that there is inter-observer variability in the identification of plus disease and of the less severe change of pre-plus disease. Pre-plus disease carries a high risk of progression to plus disease, with 70% of those with pre-plus at 33-34 weeks PMA progressing to require treatment.[42] Pre-plus in multiple quadrants, higher stages of ROP and lower zones is associated with a higher risk of disease progression.[43] Fluorescein angiography has been reported to be useful in borderline or difficult cases in identifying disease progression and the need for treatment.[44] The presence of shunts on fluorescein angiography at the avascular/ vascular border at less than 34 weeks gestational age are reported as predictive of the development of treatment requiring ROP.[45] In the UK national study 27% of infants were treated for non-type 1 ROP but the vast majority had pre-plus disease (called type 2 plus in the report).[8]

4.2 Treatment of fellow eye

The evidence suggests that the rate of progression and severity of ROP between the eyes in the same infant is closely related.[46] In the CRYO-ROP natural history study in more than 90% of infants 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 infants had ROP in the same zone in both eyes. There was also a high degree of concordance between eyes for plus disease.[47]

In situations where one of the infant's eyes reaches the criteria for treatment before the other, a clinical decision needs to be made regarding the treatment of the fellow eye, balancing the risk of treating an eye unnecessarily against the risks of exposing the infant to the possibility of two treatment sessions in close proximity. The GDG and the SIG-ROP group were of the view that in general when ROP in one eye requires laser treatment and ROP of a lower severity is present in the fellow eye, both eyes should be treated. If one eye has treatable ROP and the other has no or minimal ROP (e.g., as may occur in infants undergoing late treatment post term) it would be inappropriate to treat the fellow eye. This is an uncommon situation. A similar risk / benefit assessment is required for anti-VEGF treatment.

4.3 How urgently should treatment for ROP be given?

Evidence Grade B

> Infants with A-ROP or zone I stage 3 with plus ROP should be treated as soon as possible and within 48 hours. Infants with zone I stage 1 or 2 ROP with plus disease, zone I stage 3 ROP without plus disease zone II stage 2 or 3 with plus disease should be treated within 48-72 hours.

Data from the CRYO-ROP study indicate that the faster the progression of ROP the greater the risk of unfavourable outcome.[48] More recent studies have raised concerns of rapid progression of ROP in extremely immature infants with aggressive forms of ROP. A-ROP progresses faster than Type 1 ROP with a median of 5 days from onset to treatment compared with 21 days for Type 1 disease.[49] Treatment for AP-ROP was required earlier at a mean of 34.7 weeks' PMA compared with a mean of 36.9 weeks' PMA for infants who required treatment but did not have AP-ROP.[50] 8% infants in the UK survey had AP-ROP.[8]

Infants with A-ROP and Zone 1 disease should be treated as soon as possible because of the risk of rapid disease progression. An interval of 48 hours was used in the ETROP trial protocol. This has been widely adopted in clinical practice and is compatible with the literature. Treatment should therefore be within 48 hours of the decision to treat. For infants with Type 1 disease in zone II there would appear to be a slightly slower rate of disease progression and treatment by 48-72 hours from diagnosis is recommended. These times should allow the infant to be treated within a safe therapeutic window.

4.4 Treatment Setting

What information should be provided to parents of infants with ROP?

GPP

The treating ophthalmologist should have a consent discussion with the parents/carers of an infant requiring treatment for ROP and should gain informed explicit consent prior to the procedure taking place.

The recommended timescale between the infant reaching the criteria for treatment and the scheduling of treatment is short. Parents should be informed as soon as possible that their infant may need treatment for ROP. Parents should also be informed where the treatment would likely take place if it needs to go ahead, particularly if this would necessitate transfer to a different centre. Although there may be an element of uncertainty around when or if this might occur, it would be appropriate to do so if an infant has reached type 2 ROP or if there are signs of progressive ROP in zone I or posterior zone II. Early discussion and information sharing using written and verbal communications provides an early opportunity for parents to ask questions and for clinicians to alleviate concerns and discuss options.[51]

As ROP treatment is a surgical procedure explicit informed consent must be obtained before treatment. This should be both verbal and written. Areas to cover include:

- treatment rationale
- how and where treatment is to be carried out and by whom
- treatment options and potential adverse effects
- follow-up and the need for family compliance with this
- the potential need for further treatment
- the possibility of visual impairment (ocular and/or cerebral).

Parents should be given the chance to speak to the ophthalmic surgeon conducting the treatment prior to the procedure, preferably face-to-face. It can be helpful and good practice for a member of the neonatal team to be present when consent is obtained by the ophthalmologist. If an in-person meeting with the treating ophthalmologist is not possible a documented telephone or video-consultation may be substituted.

A parental information leaflet written in the form of a frequently asked questions in clear and simple language is a useful way of providing information.52 It is important to be sensitive to the level of understanding of parents. Written information should complement a verbal discussion with parents and on its own is not enough to enable parents to make an informed decision. Parents with limited English proficiency or low health literacy are at risk of having poorer understanding and knowledge about ROP.[53] Verbal discussion with the parents, with the assistance of appropriate translation services and ideally complemented by translated written information should be available under these circumstances.

Location of Treatment

All infants undergoing treatment for ROP will require some level of supportive care at the time of treatment. In the UK 67% of infants were treated in the neonatal unit.[54] It is acknowledged that the facilities required for treatment will depend on several factors including the method of treatment and

anaesthesia, local resources and preferences of the neonatal and ophthalmic team as well as the clinical stability of the infant. An ROP co-ordinator can be helpful in ensuring that parents have a point of contact at the receiving hospital if transfer is required and for ensuring that they have information about facilities at the hospital. Before laser treatment is undertaken consideration needs to be given to the provision of a "laser safe" environment to protect the treated infant, other infants, staff and equipment from inadvertent exposure to laser energy. A room should be used where the infant can be safely cared for (adequate physiological monitoring with facilities and staff for any rapid intervention needed) while the room is darkened during treatment.

Anti-VEGF injections must be performed using fully sterile conditions. As with other sterile procedures performed in NICUs, adequate staffing and equipment for appropriate sedation and monitoring should be in place, along with adequate space and lighting for the performance of a brief but difficult sterile procedure. Very accurate placement of the needle during injection is vital.

Treating discharged infants

GPP

> Infants who require treatment for ROP after discharge from hospital should be admitted to a suitable neonatal or paediatric unit with facilities and experience of caring for infants after neonatal surgery.

Some infants will need treatment after discharge. If these infants cannot be re-admitted to, and treated on, the neonatal unit they will need to be treated in a suitable unit with facilities for and experience of caring for infants after neonatal surgery.

Mydriatic regimen

The regimen recommended for screening examinations is also appropriate prior to treatment. This consists of phenylephrine 2.5% and cyclopentolate 0.5%, one drop of each in 2 doses, each 5 minutes apart, 1 hour prior to treatment. For laser 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. The pupils should also be dilated for anti-VEGF treatment, so that the fundi may be examined immediately after treatment for adverse effects.

Sedation, anaesthesia and monitoring

Ensuring that infants 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 infant and, for laser treatments, with the minimum need for re-treatment. In the UK national study, three (0.9%) infants suffered significant respiratory distress during or immediately after treatment, all 3 infants had laser (one also had anti-VEGF therapy).[54] One case was performed under general anaesthetic, one under sub-Tenon's block and the third under intravenous sedation. Two of these infants subsequently died but both had pre-existing severe lung disease with pulmonary hypertension and the deaths occurred more than one week after treatment. There were no adverse events reported in relation to anti-VEGF injection treatment.

Following general anaesthesia for the treatment of ROP using laser, apnoeic episodes have been reported after 29% of extubations, and careful monitoring is required.[55] Importantly, it should be noted that there are significant concerns about brain volume and neurodevelopment effects of GA in preterm infants.[56]

For laser treatment, sedation with analgesia, paralysis and ventilation under the supervision of a neonatologist allows an infant to be treated in the neonatal unit whereas procedures under general anaesthetic are usually completed in operating theatres. In the UK national study, 89% laser treatments

and 50% anti-VEGF treatments were performed with the infant intubated.[54] Treatment in an operating theatre (requiring a paediatric anaesthetist) resulted in longer delays than when infants were treated on the neonatal unit.[57] For anti-VEGF treatment, monitored sedation and topical anaesthesia are sufficient to provide satisfactory conditions for the infant and the treater.

4.5 How should ROP be treated?

Evidence Grade A

Zone I and Posterior Zone II

Treatment-requiring AP-ROP and ROP in zone I should be treated with an intravitreous injection of an anti-VEGF agent that has been demonstrated to be safe and effective for use in ROP. Anti-VEGF agents must NOT be administered if there are any signs of periocular infection.

In the view of the GDG, posterior Zone II (2 disc diameters anterior to the junction of Zone I and Zone II) or any "notch" of ROP that encroaches backwards into Zone I, may behave in a similar way to Zone I and may be treated accordingly.

Zone II (except posterior zone II)

Treatment-requiring ROP in zone II should be treated with transpupillary laser, to produce near-confluent ablation of the entire avascular retina.

Anti-VEGF treatment results in fewer eyes with high myopia compared to laser treatment,[28] but requires more intensive follow-up and carries a higher rate of retreatment.[23] Anti-VEGF agents must NOT be administered if there are any signs of periocular infection.

Cryotherapy

Although cryotherapy was the standard method of treating ROP in the CRYO-ROP study, 810nm diode laser therapy has for some time been the preferred technique in the UK.[9] Laser was preferred over cryotherapy in the ETROP trial, in which only one infant received primary cryotherapy.[15] In the UK national study performed in 2014, 90.5% of infants were treated by laser.[8] One infant had cryotherapy as well as laser because of the presence of vitreous haemorrhage. The GDG were of the view that cryotherapy has a very limited role in ROP treatment in the UK.

Laser

Wavelength

There have been concerns that argon laser energy can be absorbed by structures in the anterior segment, resulting in cataract formation.[58] However, cataracts can occur following treatment with the 810nm diode laser, and results reported with the frequency doubled YAG at 532 nm have been comparable to those of the 810 nm diode laser.[59,60] It appears that either infrared or green wavelength lasers may be used to treat ROP.

Retinal area treated and burn pattern

In the ETROP trial the treatment area was not specified, although the study protocol stated 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.[61] One small cohort study 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.[62] 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. In the ETROP trial laser burns were placed no more than one burn-width apart.[61] 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 no more than 0.5 burn-widths apart, or with "near confluent" spacing. Before starting to laser, the surgeon should identify the location of the macula and ensure that they are orientated to avoid any inadvertent macular burn. Care should be taken not to apply too much pressure with the indenter as this can cause a false ridge with the risk of applying laser too posterior in vascularised retina. Laser burns should be applied to give a cloud grey appearance and not a deep white colouration. At the end of treatment, the retina should be carefully checked to ensure there are no skip lesions or gaps in the retinal cover, preferably with wide angle photography.

Anti-VEGF agents

Administration

Anti-VEGF injections must be performed using fully sterile conditions. They must NOT be used if there are any signs of periocular infection. Key differences to intravitreal injection in adults are:

1. The injection should be performed 1.00 – 1.50mm from the limbus. The pars plana is extremely narrow in preterm eyes.
2. The needle should be directed in a vertically backward manner to avoid damaging the relatively large crystalline lens. A 30g needle should be used. Use of a low volume high accuracy syringe (0.02ml) should be considered.

The treating ophthalmologist should be gowned, masked and gloved as for a surgical procedure. A masked and gloved assistant may help with drawing up the drug. For ranibizumab, specialised low volume high accuracy syringes are available to more precisely deliver the small volume of drug used (0.02ml), adding confidence that the full dose has been delivered. The infant should be sedated, topical anaesthesia should be used, the skin and conjunctiva prepped with 5% povidone-iodine and an eyelid speculum used. The injection site should be measured with callipers and the eye held steady with forceps while the drug is injected. After injection, the fundus should be examined for adverse effects, and the central retinal artery observed for closure due to raised intraocular pressure. Injecting 0.025 ml fluid into a premature eye typically elevates the IOP to an average of 40mm Hg initially, recovering over 10-15 minutes[64]. While prolonged central retinal artery closure might prompt consideration of paracentesis treatment, in practice this has not been reported and would be exceptionally hazardous, even when performed under the operating microscope. Each eye should be treated entirely separately. Treatment of the second eye should be undertaken as if treating a separate patient, with the surgeon descrubbing, and rescrubbing, and a new treatment tray set up to eliminate any shared equipment between eye. A new drug vial must be used for the second eye.

Choice of Treatment modality in the UK

In the UK national study performed in 2014, 90.5% of infants were treated by laser and 8% with anti-VEGF agents. One infant had cryotherapy as well as laser because of the presence of vitreous haemorrhage. A recent survey of UK ROP treaters, which received 23 responses, reported the use of anti-VEGF injection treatment for ROP in 14 units with 85% using it as primary therapy in less than 1/3rd of cases. Two units performed primary anti-VEGF therapy in over 80% of cases.[64]

In trials, for Zone I ROP bevacizumab produced better outcomes than laser treatment[5] and ranibizumab produced similar results to laser.[6] For Zone II ROP bevacizumab and ranibizumab gave similar results to laser.[5,6] Additional information may be obtained from a secondary analysis of 1167 eyes in 640 infants from the postnatal growth and ROP (G-ROP) cohorts.[65] Fewer eyes developed retinal detachment following ant-VEGF (1/164, 0.6%) than laser treatment (49/1003, 4.9%).[65]

Anti-VEGF agents are simpler to administer than laser. However, they require much more intense follow-up (see Table 4), retreatment is more often required (see Table 4), and there are some concerns about potential systemic morbidity, especially for bevacizumab (see section 3.7). Laser is a more "definitive" treatment, with no systemic effects. Anti-VEGFs result in a lower rate of high myopia than laser therapy.[66,67] In the RAINBOW study, high myopia (> 5.00 dioptres) occurred in 5% eyes treated with ranibizumab 0.2mg, compared to 20% eyes treated with laser.[28] A recent metanalysis comparing anti-VEGF (1289 eyes) and laser (2412 eyes) treatments found no difference in disease regression, vision outcomes or safety measures, but anti-VEGF agents were associated with more additional treatments (risk ratio 2.16), a longer time from treatment to retreatment or recurrence (weighted mean difference 6.43 weeks), fewer surgical interventions (risk ratio 0.45), less astigmatism (weighted mean difference -0.25 D), and fewer ametropic eyes (risk ratio = 0.51).[68] Table 2 compares Laser and anti-VEGF treatment.

The risks and benefits of alternative treatments must be discussed and agreed with parents. The view of the GDG was that the evidence for improved efficacy of anti-VEGF treatment for Zone I ROP outweighs other considerations. In addition, as the boundary between Zone I and Zone II is an artificial construct, posterior Zone II as defined by ICROP3 may also be treated in the same way as Zone I disease. Anti-VEGF's must not be administered if there are any signs of conjunctival infection.

Regarding Zone II ROP, anti-VEGF treatment is preferred in systemically unstable infants who might not tolerate laser treatment; and in infants in whom the view of the fundus is poor due to small pupil, tunica vasculosa lentis, or media haze due to haemorrhage or other cause, providing no signs of conjunctival infection are present.

However, the GDG were of the view that laser may remain the preferred treatment modality for most infants. Discussion with parents of the risks and benefits of alternative treatments should also include potential systemic morbidity.

Table 2: Comparison of Laser and Anti-VEGF treatment

	Laser	Anti-VEGF
Efficacy – structure % unfavourable	7/74 (9%) infants (RAINBOW)[6] 19/146 (26%) eyes (BEAT-ROP)[5] 9% prethreshold eyes in ETROP (randomised one eye per infant), at 6 years[69]	1/74 (1%) infants (RAINBOW in the 0.2mg ranibizumab group)[6] 2/140 (3%) eyes (BEAT-ROP)[5]
Efficacy – function	ETROP at 6 years Type 1 eyes 20/200 or worse in 25% eyes (randomised one eye per infant)[69]	RAINBOW 2 years Visual function questionnaire, ranibizumab and laser gave similar results (trend towards ranibizumab slightly better results)[28]
Retreatment rate	19% infants (RAINBOW)[6] 32/146 (22%) eyes (BEAT-ROP)[5]	31% infants (RAINBOW)[6] 4% infants (BEAT-ROP)[5] 8% infants following bevacizumab[70] 11.8% following aflibercept[71]
Adverse effects, acute		
Cataract	1.9% eyes (ETROP)[21] 0.3% eyes (G-ROP)[20]	1% infants (RAINBOW)[6]
Endophthalmitis	0	1% infants (RAINBOW)[6]
Conjunctival haemorrhage	3% infants (RAINBOW)[6]	8% infants (RAINBOW)[6]
Corneal opacity	2% infants (RAINBOW)[6] 0.6% eyes (G-ROP)[20]	0% (RAINBOW)[6]
Hyphaema	1.6% eyes (G-ROP)[20]	
Retinal haemorrhage	10% infants (RAINBOW)[6]	8% infants (RAINBOW)[6]
Retinal surface fibrosis	Transient, usually mild fibrosis changes may occur overlying stage 3 ROP following laser, especially when laser has been applied late[72]	Occasional cases of retinal "crunch" have been reported following bevacizumab, with fibrosis overlying the arcade vessels and progressive traction retinal detachment[73,74]
Vitreous haemorrhage	5.4% eyes (G-ROP)[20] 0% (RAINBOW)[6]	0% (RAINBOW 0.2mg group) (but 5% infants in RAINBOW, 0.1mg group)[6] 0.11% eyes following bevacizumab[22]

Table 2: Comparison of Laser and Anti-VEGF treatment continued...

	Laser	Anti-VEGF
Adverse effects, long term		
Myopia > 5 Dioptres	42% eyes (BEAT-ROP)[67] 32% eyes (ETROP)[75] 20% eyes (RAINBOW)[28] Myopia has been associated with the extent of laser treatment[76]	3% eyes (BEAT-ROP[69]) 5% eyes 0.2mg ranibizumab (RAINBOW[29])
Raised IOP	1.67% eyes (ETROP)[77]	
Visual Field	2.3% – 7.5% reduction (ETROP)[78]	
Systemic effects		Ranibizumab (RAINBOW)[6] no difference vs. laser to 2 years[28] Bevacizumab[26,27] Possible differences in neurodevelopmental outcomes compared to laser, but baseline bias in cohort studies.

4.6 Post-treatment: When should infants treated for ROP be reviewed and what are the indications for retreatment of ROP?

Post-treatment review is important to detect and treat adverse events, monitor disease regression, detect disease reactivation and determine if retreatment is necessary.

Laser

The first examination should take place 5-9 days after treatment and should initially continue weekly for signs of regression. From 7-14 days start to consider re-treatment with laser if disease regression is inadequate and untreated retinal areas are identified. Rescue treatment with an anti-VEGF agent should be considered from 14 days if disease regression is inadequate and laser treatment has been optimal.

Anti-VEGF

The first examinations should take place 1-2 days and 5-7 days after treatment to detect adverse effects of treatment. Following partial or complete disease regression, regular examinations must be maintained to detect disease reactivation: weekly for 4 weeks, 2 weekly for a further 12 weeks and then 4-weekly for a further 8 weeks (total of 24 weeks) and up to 32 weeks in eyes treated for A-ROP with bevacizumab after treatment.

Disease reactivation in the form of Plus disease and / or extraretinal new vessels should be treated with transpupillary laser, to produce near-confluent ablation of the entire avascular retina.

Anti-VEGF agents may be used for retreatment but require more intensive follow-up and carry a higher rate of further disease reactivation, requiring further retreatment. Anti-VEGF agents differ. The above follow- up schedule was used in the RAINBOW trial of ranibizumab.[6] Longer follow-up may be needed following bevacizumab (follow-up to 65 weeks PMA has been recommended)[79].

EUA following Anti-VEGF

Following initial Anti-VEGF treatment consider EUA / Examination under sedation with possible transpupillary laser to produce near-confluent ablation of the entire avascular retina IF the retina has not fully vascularised (or this is uncertain) AND:

- Regular follow-up is becoming unsustainable for social and / or geographic reasons.
- The growing child's limited cooperation precludes adequate examination of the peripheral retina.
- There is uncertainty about the presence of signs of disease reactivation.

OR:

- During longer term follow-up a significant area of Persistent Avascular Retina is seen or suspected.

Note: Fluorescein angiography can be helpful, if available.

Post-treatment systemic recovery

Infants treated for ROP, especially those treated with laser, may become unstable during treatment. In the UK national study, three (0.9%) infants suffered significant respiratory distress during or immediately after treatment, all 3 infants had laser (one also had anti-VEGF therapy)[54]. The possible need for admission to an intensive care setting should be considered when planning treatment.

Post-treatment eye drops

Due to the increased risk of complications such as hyphaema, posterior synechiae and transient cataract in very immature infants following laser, the GDG felt that the prophylactic use of steroid and mydriatic eye drops may be justified for up to 7 days in these infants and longer if problems develop, but prophylactic antibiotics are not required.

As a risk of endophthalmitis exists with anti-VEGF agents, prophylactic topical antibiotics may be appropriate following anti-VEGF treatment.

Post-treatment examination

Post-treatment review is important to detect and treat adverse events, monitor disease regression, detect disease reactivation and determine if retreatment is necessary. The optimal timing for review has not been studied, but trial protocols and trial results are of some value in determining appropriate follow up schedules.[5,6]

The nature and timing of post-treatment examinations are different for laser and anti-VEGF treatment, and are summarised in Tables 3 and 4. Additional examinations will be required if abnormal findings are present.

Review following Laser

Early examinations are required to detect anterior segment adverse effects such as iritis, posterior synechiae and hyphaema. A first examination at 1 week is appropriate, providing prophylactic mydriatic and steroid eye drops are routinely used post-treatment.

The second examination at 2 weeks, preferably performed with wide angle photography, is used to observe disease regression and determine whether "top up" treatment for untreated "skip" areas of retina is required. 11/74 (15%) laser treated infants in the RAINBOW study received "top up" laser to skip areas within 10 days of baseline.[6] The laser re-treatment rate in the ETROP trial was 13.9% for prethreshold treatment.[15] In the experience of the GDG, if re-treatment is required, it is usually undertaken between
10-14 days after initial treatment.

Failure of disease regression after two weeks in the presence of optimal laser cover of avascular retina should prompt consideration of rescue treatment with an anti-VEGF. In the RAINBOW trial, 9/74 (12%) infants treated with laser at baseline received rescue treatment with ranibizumab within the first 4 weeks post-laser.[6] Anti-VEGF rescue treatment following primary laser treatment requires initial follow-up as for primary anti-VEGF treatment.

Providing disease has been well controlled by acute management during the first four weeks, it is highly unusual for active disease to recur following laser treatment. Relatively infrequent follow-up examinations are required (see Table 3).

Table 3: Follow-up after Laser

Following laser treatment, review at:	Specifics to consider during review:
1 week ± 2 days	• Examine conjunctiva, cornea, AC, lens, vitreous and retina for **adverse effects** and **disease regression.**
2 weeks	• Detailed examination of whole retina, preferably with wide-angle photography. • Expect regression of plus disease if initially present. • Careful assessment of extent of laser: **consider top-up treatment if any gaps in laser cover of avascular retina in the presence of plus disease.** • **If laser treatment cover is complete, consider rescue treatment with anti-VEGF if continued or worsening ROP is present from this timepoint onwards.**
3-4 weeks	• Expect complete regression of plus disease. • If normal anterior segment, clear media, and no plus disease or stage 3 ROP at this timepoint, **extremely unlikely** that further treatment will be needed.
3 months	• Careful examination of retina.
6 months	

1 year (postnatal)	• Assess:
	  • Visual function
	  • Strabismus assessment
	  • Cycloplegic refraction
	  • Retinal evaluation
	• Discharge to community services at 5 years if stable.

18 months	
2 years	
3 years	
4 years	
5 years	

Review following Anti-VEGF treatments

Follow-up examinations are required more frequently and for a more prolonged period following anti-VEGF treatment (Table 4). In addition to early examinations to detect and treat adverse effects including endophthalmitis, and to monitor disease regression, a prolonged period of follow-up is required to detect and treat disease reactivation. Prophylactic laser, before discharge, after bevacizumab treatment for ROP has been shown to reduce the number of outpatient ROP screening examinations.[80]

The first examinations at 1-2 days and at 1 week are to detect and treat anterior segment adverse effects and endophthalmitis. While ideally all the examinations should be performed by an ophthalmologist, in exceptional circumstances where this proves very difficult to arrange, the pupils should be dilated and red reflex examination performed by a neonatologist or trained neonatal nurse, using a direct ophthalmoscope. A local protocol may need to be agreed to facilitate this.

Disease regression appears to be more rapid following anti-VEGF than laser.[81] If ROP is unchanged or worse 1 week after treatment AND it is considered possible that the drug was not correctly delivered, consider re-injection. If plus disease has not improved or is worsening after 1-2 weeks, rescue treatment with laser should be considered.

In the RAINBOW trial, 7/74 (9%) infants treated with ranibizumab 0.2mg at baseline received rescue laser treatment within the first 4 weeks.[6]

Unlike laser, the absence of active ROP disease after four weeks does NOT indicate that treatment is complete. Disease reactivation may occur, and retreatment may be needed. A schedule, based on the protocol of the RAINBOW trial, is shown in Table 4. Additional examinations may be required, dependent on disease activity such as persistent pre-plus or increasing stage of ROP. The timing of disease reactivation may vary with different anti-VEGF agents and follow-up may be needed for longer following bevacizumab than following ranibizumab. Follow-up to 65 weeks PMA has been advised following bevacizumab.[6,70,79] Regular follow-up beyond 24 weeks may be needed for a longer period if significant persistent avascular retina (PAR) is present.

Partial or complete regression followed by later disease reactivation is a relatively frequent occurrence following primary anti-VEGF treatment. Retreatment was required in 8% infants treated with bevacizumab in the case series of infants that included the population of the BEAT-ROP study,[70] and 31% infants treated with ranibizumab 0.2mg in the RAINBOW study required additional treatment.[6] Small case series and trials in a range of clinical settings, using a range of disease reactivation criteria have reported a reactivation rate of 6.8% – 14.4% for bevacizumab[82,83,84,85] and 18.75% – 64% for ranibizumab.[84,86,87,88,89,90] The most frequently reported clinical criteria for retreatment are reactivation of plus disease and/or stage 3 ROP. Tortuous retinal vessels can occasionally persist for reasons other than active ROP. Disease reactivation is more likely to occur in eyes with initial severe posterior disease, especially AP-ROP.[70] In the UK national surveillance study of treated ROP at one year follow-up (only 51.4% of the original cohort), 11% of those treated with laser and 35.7% of those treated with anti-VEGF had been retreated.[23]

The half-life of ranibizumab in the eye (5.6 days) is shorter than that of bevacizumab[34] and disease reactivation appears to occur earlier with ranibizumab. The median (range) interval from injection to retreatment in each infant was 8 (4-16) weeks for ranibizumab[6] and 15 (12-31) weeks for bevacizumab.[70] 90% of infants retreated with bevacizumab required retreatment between 13 and 25 weeks after injection (at adjusted age 45-55 weeks). The schedule of review examinations should reflect the likely timing of reactivation. The schedule given in Table 4 is based on the RAINBOW trial protocol (examinations 1 and 3 days after treatment, then at 1, 2, 3, 4, 6, 8, 12, 16, 20, 24 weeks after treatment). Based on a median time to reactivation of 8 weeks, additional examinations at 10 and 14 weeks are recommended. A similar schedule may be used for bevacizumab, with the recognition that disease reactivation is less common following bevacizumab treatment and occurs later. Follow-up to 65 weeks PMA has been recommended for bevacizumab.[79]

Treatment of disease reactivation following initial Anti-VEGF treatment

Following primary anti-VEGF treatment, disease reactivation may be treated using repeat anti-VEGF injection, or laser therapy. Either approach appears to be effective.[6] However, potential difficulties with further, frequent follow-up, the risk of a requirement for a further repeat injection, and the risk of persistent avascular retina (PAR) following anti-VEGF mean that in the view of the GDG, laser is the preferred approach. One infant in the CARE-ROP trial retreated twice with ranibizumab was found to have bilateral retinal detachment 23 weeks after the second retreatment, at PMA 75 weeks.[91] In addition, anti-VEGF treatment should be avoided if there are any signs of fibrosis present.[92] We suggest the criteria of plus disease and / or extraretinal new vessels for retreatment for reactivation. However, these criteria have not been subjected to a clinical trial and retreatments have been performed in other circumstances. Failure of progression of normal vascularisation is NOT an indication for retreatment with an anti-VEGF agent – indeed the situation may have been caused by anti-VEGF effects.

Table 4: Follow-up after Anti-VEGF treatment

Following first anti-VEGF treatment, review at:	Specifics to consider during review:
1-2 days	• Examine anterior segment and red reflex for treatment complications and signs of endophthalmitis. When it is logistically difficult to arrange examination by an ophthalmologist, the pupils should be dilated and red reflex examination performed by a neonatologist or trained neonatal nurse, using a direct ophthalmoscope. • A suggested approach to treatment of preterm neonatal endophthalmitis is given in Appendix 1.
1 week	• Examine anterior segment, media and retina. • Plus disease should have started to regress. • If ROP is unchanged or worse after treatment (failure of TVL (tunica vasculosa lentis) to regress, pupil dilation to improve and plus disease to lessen in the first 1-2 days post injection) AND it is considered possible that the drug was not correctly delivered, consider re-injection.
2 weeks	• If continued or worsening ROP, consider **rescue laser treatment** from this timepoint onwards.
3 weeks	
4 weeks	• Reactivation of ROP in the form of plus disease and / or New Vessels may be treated with **laser or** repeat anti-VEGF (from 4 weeks of initial injection). In general, laser is more definitive. However, anti-VEGF retreatment may be appropriate in certain circumstances (e.g., the disease remains very posterior).
6 weeks	
8 weeks	
10 weeks	
12 weeks	
14 weeks	
16 weeks	
20 weeks	
24 weeks	

1 year	• Assess:
	  • Visual function
	  • Strabismus assessment
	  • Cycloplegic refraction
	  • Retinal evaluation
	• Discharge to community services at 5 years if stable.

18 months	
2 years	
3 years	
4 years	
5 years	

Follow-up for Persistent Avascular Retina (PAR)

The current recommendations in American Academy of Pediatrics (AAP) ROP treatment guideline is for follow-up until the peripheral retina has fully vascularised.[79] However, PAR may occur following bevacizumab or ranibizumab treatment, and there is controversy as to how it should be managed (see below). Sahin et al. reported a mean time to full retinal vascularisation of 24 weeks following bevacizumab 0.625 mg, with faster vascularisation (14 weeks) following treatment with bevacizumab 0.0625mg.[93] Chang et al reported that vascularisation reached zone III in eyes treated with bevacizumab at a mean of 54.5 weeks post menstrual age compared with 47 weeks in in control eyes.[94] Fluorescein angiography at age 4 years following intravitreal bevacizumab treatment showed some peripheral vascular abnormalities (vascular leakage, and shunts) in all of 20 eyes studied.[95] PAR also occurs following treatment with ranibizumab. A case series of 43 infants treated with ranibizumab found PAR beyond 24 weeks post treatment in 12% infants.[90] 17 of 83 (20%) infants followed for 90 weeks following intravitreal ranibizumab had PAR extending more than 2-disc diameters posterior to the ora serrata and all of these had abnormal fluorescein angiography findings.[96] In the RAINBOW study 38% of infants had full retinal vascularisation 24 weeks after treatment with ranibizumab 0.2mg.[6] No adverse effects to 2 years were evident in the RAINBOW trial, but longer-term data are not yet available. It should be noted that PAR also occurs in some untreated Type 2 ROP eyes.[97]

Examination under anaesthetic (EUA), fundus fluorescein angiography (FFA) and laser

Extended follow-up after anti-VEGF treatment may result in practical difficulties: it becomes increasingly difficult to assess an active young child with indirect ophthalmoscopy, and social and geographical factors may make regular clinic visits challenging for families. When there is persisting pre-plus, uncertainty about disease reactivation, evidence of PAR, or simply difficulty in regularly obtaining a good view of the peripheral retina, it may become necessary to schedule an examination under anaesthetic. In some circumstances more conservative outpatient investigation using oral fluorescein (dosage of 7.5mg/kg using 20% fluorescein diluted in juice) followed by ultra-wide field imaging may be possible.[98] Fluorescein angiography (dose 7.7 mg/kg body weight with intravenous 10% fluorescein: accessdata.fda.gov/drugsatfda_docs/label/2006/021980s000lbl.pdf under anaesthetic may be used to delineate the extent of avascular retina and the presence of any blood vessel abnormalities more accurately. Fluorescein angioscopy using a binocular indirect ophthalmoscope with a blue filter may be used if more formal angiography imaging is not available. Laser may then be applied if widespread areas of abnormality are present. The management of PAR is controversial. Both conservative and prophylactic laser management have been advocated,[99] but no trials have been performed. We suggest that following anti-VEGF treatment, uncomplicated PAR in Zone III does not normally require treatment. However, eyes with PAR that extends into Zone II, especially with co-existing blood vessel abnormalities, may be at increased risk of haemorrhage or retinal detachment and prophylactic laser to all avascular retina should be considered as a non-urgent treatment from corrected age 12-18 months approximately. While evidence of the benefit of this course of action is unclear at present, centres that provide anti-VEGF treatment should have the necessary expertise and equipment to manage disease reactivation and PAR. The ophthalmologist must have a robust pathway to be able to re-admit such infants for investigation and management as they are likely to require intensive care monitoring post-procedure.

4.7 What are the indications for vitreo-retinal surgery?

Evidence Grade B

As soon as any significant peripheral retinal traction is detected, the case should be discussed with a specialist paediatric VR surgery centre, with a view to possible transfer for early vitreoretinal surgery.

Treatment of stage 4 and stage 5 ROP

While the visual outcome of retinal detachment surgery for stage 4 and stage 5 ROP is poor in many eyes, some limited but useful functional vision can be achieved in some stage 4a and stage 4b eyes. The visual outcomes of surgery for stage 5 ROP are poor.[100] The emphasis of ROP services must be on effective screening and prompt treatment of acute ROP in order to minimise the number of infants that require vitrectomy surgery.[100]

Lens sparing vitrectomy (LSV) is the preferred technique in specialist paediatric retina referral centres. Scleral buckling surgery has a limited role.[101] Vitrectomy with lensectomy (LV) may be needed when anterior fibrotic traction is present. Simultaneous bilateral surgery is safe and reduces anaesthetic exposure.[102] 20% infants will require more than one procedure.[103] Stage 4a ROP may progress rapidly to stage 4b and then stage 5, so LSV is usually performed early, at a mean PMA of 40 weeks.[104,105] Prompt referral is essential. Better anatomical and functional results are obtained for stage 4a ROP. Following LSV, lens opacity severe enough to require lensectomy is unusual.[103] Of all eyes in this series, 5.9% required lensectomy because of lens opacity.

There is a high risk for glaucoma in eyes rendered aphakic or which had stage 5 ROP[106,107]. Late re-detachment occurs more frequently following surgery for stage 5 ROP than stage 4b ROP[108].

International centres with specialist surgical expertise report limited successful outcomes. The expectations of surgery, if it is recommended, must be modest. Retinal reattachment rates following the first surgical procedure have been reported as 82% – 89% in stage 4a eyes,[109,110] 63% – 73% in stage 4b eyes,[103,109,110,111] and 42% – 43% in stage 5 eyes.[103,109] Anatomical success has been reported in 8/14 (57%) eyes with the subgroup of stage 5A eyes (open funnel).[112] The only UK published series reported retinal reattachment in 16/22 (73%) eyes with stage 4 ROP, and 0% for seven stage 5 eyes.[100] Anatomical success in 36 eyes following endoscopic surgery was 95% for stage 4A, 88% for stage 4B and 33% for stage 5 ROP.[113]

Even with successful retinal reattachment, visual outcomes are in general limited, especially for stage 4b and stage 5 eyes. For stage 4a ROP, 8/19 eyes were reported to achieve a visual acuity of 6/60 or better[109] and 12/23 eyes achieved 20/400 or better.[105] However, 5/19 eyes[109] and 4/23 eyes[105] only had light perception (LP) or no light perception (NPL) vision. For stage 4b, 7/38 eyes had 20/400 or better,[109] 24/56 eyes[111] and 3/9 eyes[105] had 20/800 or better. Vision outcomes following surgery for stage 5 ROP are poor. In one series[109] 18/31 eyes had LP or NPL and only 11/31 eyes had any measurable vision with a range of 20/2000 – 20/20000. 9/14 (64%) could fix and follow light at 1 year in the subgroup of stage 5A eyes (open funnel), but longer term results are not yet available.[112] It has been advised that eyes with stage 5C ROP (corneal opacity present) should not be subjected to surgery.[112] In the UK series, 13/22 (59%) stage 4 eyes obtained vision better than PL and 5/22 (23%) had 6/60 or better.[100] No vision better than PL was obtained in stage 5 eyes.[100]

4.8 What long-term follow-up should be offered to infants treated for ROP?

As per Tables 3 and 4, following the management of acute ROP, continued annual follow-up to age 5 years is recommended.

A long-term follow-up study of 411 Swedish infants of less than 27 weeks' gestational age examined at 30 months of age found that 20% had been treated for ROP.[114] 3.1% of the cohort were visually impaired, and 1% were blind. Visual impairment was caused by retinal and / or cerebral abnormalities. Visual impairment was associated with having been treated for ROP and with cognitive impairment. Eye and vision problems including refractive error, strabismus and visual impairment were found in 69% of those who had required ROP treatment. The UK national surveillance study of treated ROP at one year follow-up reported 3.8% were severely sight impaired and 8.4% were sight impaired.[23] Neurological or development impairment was reported in 12%.

Refractive error

The proportion of eyes with high myopia (-5.00 dioptres or worse) at 2 years was 32.4% in the early treatment arm of the ETROP trial (compared to 13.3% of untreated eyes in the conventional management arm).75 Of interest, the degree of myopia was stable over time and was not progressive.[115] 47/77 (61%) of children who had been treated for ROP in a Swedish cohort had a refractive error, defined as myopia worse than – 3 dioptres, hypermetropia greater than + 3 dioptres, astigmatism of 2 dioptres or more and/ or anisometropia of 2 dioptres or more.[114] In the UK national study,[23] at one year after treatment, 20.5% of children had been prescribed glasses. High myopia defined as 5 dioptres or more occurred in 8.33% and myopia of -0.25 dioptres or more in 36.4% of children. A lower prevalence of both high myopia (defined as -5 dioptres or more) and myopia has been reported in children aged two years who had been treated with IVB only (10%) compared to IVB and laser (29.4%) and IVB and vitrectomy (100%).[116] This was not related to differences in axial lengths but thought to be associated with abnormalities in anterior segment development. High myopia (-8.00 dioptres or worse) was less frequent following bevacizumab (2.7%) than following laser treatment (41.6%) in the BEAT-ROP trial,[67] and in the RAINBOW trial at 2 years 5% eyes treated with ranibizumab 0.2mg and 20% eyes treated with laser had myopia of -5 dioptres or worse.[28]

Strabismus

In the UK national study 14.3% of treated children at age one year had strabismus and 7.7% had nystagmus.[23] A German study of 4–10-year-old children found strabismus was more frequent following preterm birth (15%), and even more so if ROP occurred (26%).[117]

Glaucoma

Glaucoma is most often related to a shallow anterior chamber, in the presence of stage 4 or stage 5 ROP but can occur in a range of settings.[101,106,118,119,120] Eyes treated with laser for ROP have a long-term risk of development of angle closure glaucoma and this may also be the case following anti-VEGF treatment – long term follow-up is not yet available.[120] This form of glaucoma may be related to abnormal anterior segment development,[120] with a shallow anterior chamber and is associated with myopia. A range of treatments have been described, including peripheral iridectomy or lensectomy.[119,120] The ETROP study reported that 1.67% of children had glaucoma by six years.[77] 11 of the 12 eyes had received laser treatment and one, in the conventional arm of the trial, had received no treatment. Eight of the eyes had undergone treatment for retinal detachment. Seven of the 12 eyes had glaucoma with a shallow anterior chamber. Inflammation was suggested as a possible cause in eyes without a shallow anterior chamber. The presence of glaucoma was associated with a poor visual outcome.[77]

4.9 Organisation of Services

A recent review of severe visual impairment due to ROP in Sweden concluded that 65% of cases had been potentially preventable, and that organisational failures were a leading cause of poor outcomes[121].

Networks for peripheral screening and centralised treatment

All arrangements for ROP screening and treatment must be robust, including cover for sickness and leave.[122] While ROP screening is an essential component of all neonatal units managing preterm infants, within networks ROP treatment has become centralised. This approach requires careful planning and excellent communication. The use of widefield digital retinal imaging (WFDRI) enables screeners to more easily make decisions on treatment and judgements on disease regression/reactivation in liaison with treaters. Establishing ROP MDTs can be of considerable benefit (Appendix E).

Communication

When an infant is referred for treatment, the peripheral screener should provide documentation of previous ROP screenings (copy of previous screening sheets or imaging). An example of a referral form is in Appendix C. When an infant is transferred away from the treating ophthalmologist, clear written information (and where appropriate verbal communication) on follow-up requirements must be provided to the receiving neonatal unit (timing of next eye review) and the receiving follow-up ophthalmologist (treatment details and a clear plan of follow-up). WFDRI images, where available, will assist the ophthalmology handover process.

Ophthalmologists' work commitment

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.

4.10 What skills and training are required for those who treat ROP?

Evidence Grade C

> Any ophthalmologist undertaking treatment or making treatment decisions must be skilled in examining premature retinae to identify the type of ROP and which treatment modality is most appropriate for the patient. Ophthalmologists in treating centres must have experience in undertaking both laser and anti-VEGF injection in preterm infants so they can offer the most appropriate treatment for each patient. Some local ophthalmologists may be competent in anti-VEGF injections but will refer for laser therapy. When this expertise is not available within the local unit, formal network arrangements must be in place with good communications for prompt transfer to the treating centre.

The availability of retinal imaging may assist the sharing of information between screeners and treaters.

In the 12 month UK national study performed in 2014, 55 units reported treating infants for ROP.[8] 10 units reported treating 1 infant only and one unit reported treating the maximum of 26 infants. 29 units treated 5 or less infants. Only 11 units reported treating 10 or more infants. Any ophthalmologist undertaking treatment of infants with ROP must ensure that their skills are current and maintained. Whilst it is not possible to mandate numbers it is unlikely that an ophthalmologist only undertaking one ROP treatment or less a year will be able to maintain and demonstrate treatment proficiency.

Any ophthalmologist undertaking treatment or making treatment decisions must be skilled in examining premature retinae to identify the type of ROP and which modality is best suited for the patient. Before undertaking ROP treatment independently they should be competent in both laser and anti-VEGF injection treatment. However, some local ophthalmologists may be competent in anti-VEGF injections and will refer for laser therapy. ROP treatment may be undertaken by paediatric ophthalmologists or by retinal specialists.

In the UK, trainee ophthalmologists must have participated in ROP screening before completion of surgical training. There is no requirement to have been involved in treatment for ROP. Opportunities to assist in these procedures should be facilitated where possible. Experience in performing ROP treatment is gained at fellowship level either in paediatric ophthalmology or vitreo-retinal surgery. Retinal fellowship training in the UK is often of longer duration than paediatric ophthalmology fellowship training. Unsurprisingly most fellows report not feeling confident in ROP evaluation at the start of their fellowship, but this improves significantly with training and participation in treatment.[123,124] Experience can also be gained at consultant level by appropriate training and supervision.

Because of lack of experience prior to fellowship training, fellows should be directly supervised during their ROP training. Before undertaking ROP laser it would be anticipated that the trainee / fellow would be confident in undertaking indirect laser, including the use of indentation. Most trainees will have experience in undertaking intravitreal injections in adults, but the technique for intravitreal anti-VEGF injection in an infant is different and the eye considerably smaller, with a relatively bulky crystalline lens.

It is not possible to mandate the number of treatments a fellow should participate in before feeling competent, but it has been reported that paediatric ophthalmology fellows who participated in six or more laser treatments during training felt this was adequate.[124] Fellows in training may find difficulty in adequately lasering the retina superiorly and inferiorly, and digital imaging to demonstrate skip areas can be helpful in educating trainees.[125] As the number of infants in the UK who require treatment is low compared to the number screened, treatment will only take place in a small number of units. To provide training in ROP treatment during what may only be a one-year fellowship program, there will need to be adequate exposure to treatment opportunities.

4.11 What facilities are required at treatment sites?

In a unit undertaking ROP treatment there must be neonatal medical, nursing, and managerial support for the ophthalmological team. The treating neonatal unit will need to be able to accept at short notice infants from other units who require treatment. Increasingly as infants are discharged home earlier from neonatal units there may need to be provision for dealing with readmission of outpatients. Re-admission and treatment should occur within 48 hours to prevent sight loss. This will require negotiation and cooperation to provide the best treatment for the infant. Nurses attached to the ophthalmological team to support ROP screening and treatment are an invaluable asset.

In a unit undertaking regular ROP treatments, wide field digital retinal imaging (WFDRI) should be available. This is helpful in providing educational backup for trainees and information for parents and is important for documentary purposes.

Any centre undertaking ROP treatment should be able to offer both laser and anti-VEGF therapy. Cryotherapy is now virtually never used so does not need to be available to the ophthalmic team. The recent UK study reported that 90% of treatments were undertaken with the 810nm diode laser.[8] Results reported with the frequency doubled YAG at 532 nm have been comparable to those of the 810

nm diode laser.[59,60] Any laser that is used for ROP treatment should be serviced regularly. An indirect ophthalmoscope and appropriate lenses should be available. All laser treatments should be performed in an approved laser- safe environment that has been risk assessed.

A centre providing regular ROP treatment must have prompt access to anti-VEGF drugs. Appropriate equipment for intravitreal injections should be kept available, preferably pre-packed.

A screening and treatment co-ordinator for ROP, usually a senior neonatal nurse, should be available in all treatment units. Appendix E gives details of this role.

5. Implementation

5.1 What are the facilitators to implementation of this guideline?

The 2008 ROP screening and treatment guideline is universally used in neonatal units and ophthalmic units. This guideline update will be received with interest.

Local protocol and staffing arrangements for ROP management are already in place. The updated guideline recommendations require updating but not wholesale change of these.

Training in screening and treatment of ROP is already incorporated in ophthalmology Retina and Paediatric ophthalmology fellowship programmes. Some modifications and updating will be required to ensure adequate training and experience in updated techniques.

A national service for ROP vitreoretinal surgery treatment of stage 4a or worse ROP is currently in development and the updated guideline will assist this process.

5.2 What are the barriers to implementation of this guideline?

Availability of cots in treating units – both physical space and neonatal nursing resource.

Ability to re-admit infants from home to a suitable environment – both physical space and nursing resource.

Inadequate availability of trained ophthalmologists.

Lack of awareness of the urgency and importance of ROP treatment.

Anti-VEGF drug costs are currently unknown but are likely to increase drug costs of treatment.

Increased need for follow-up appointments with more use of anti-VEGF therapy.

Increased admissions for retreatment with more use of anti-VEGF therapy.

There is not currently a resourced national service for ROP Vitreoretinal surgery.

Lack of widespread availability of wide field retinal imaging. This technology allows screeners to transfer images to treaters for advice on whether or not to transfer an infant for treatment and for an opinion on disease regression / reactivation after treatment. This reduces the need to transfer infants unnecessarily. Appendix E gives a further example of the use of imaging to undertake ROP MDT meetings.

Families may have difficulty adhering to follow-up (particularly where there are barriers to communication/ distance to treatment centre etc.). The use of anti-VEGF agents therefore places additional demands on families.

5.3 Training tools for the implementation of these guidelines

A range of teaching seminars and publications will disseminate knowledge of the new guidelines. On line training tools are available eg. portal.e-lfh.org.uk/MyElearning, American Academy of Ophthalmology Retinopathy of Prematurity: Case based training). (www.aao.org/interactive-tool/retinopathy-of-prematurity-case-based-training).

5.4 New protocols and processes for the implementation of these guidelines

Clinical appendices A, B, C, and E of this guideline provide protocols and templates to help implement the guideline. Departmental protocols should be updated in line with this updated guideline.

5.5 Resource implications of these guidelines

Anti-VEGF drug costs are currently unknown but are likely to increase drug costs of treatment.

ROP screening and treatment is already standard in the care of neonates in the UK. The recommended use of ant-VEGF drugs in certain circumstances is already in place in many units. The number of babies currently treated in this way each year is small (currently less than 100 in UK) and while the drug costs for ROP treatment are currently unknown, NICE has previously reported the costs of these drugs when used in the very large numbers of adults undergoing anti-VEGF therapy for retinal diseases.

Delivery costs should be considered in the context of likely reduced incidence life-long blindness.

Increased need for follow-up appointments with more use of anti-VEGF therapy.

Increased admissions for retreatment with more use of anti-VEGF therapy. There is not currently a resourced national service for ROP Vitreoretinal surgery.

5.6 How should ROP treatment be audited?

All departments engaged in ROP work should audit their activity, using the following minimum dataset:

- Number of infants treated each year.
- The gestational age and birth weight of the treated infants.
- Method of treatment used. Short term outcome of treatment (was re-treatment needed and if so when).
- Treatment outcome at 1 year (retinal structure) – treaters should ask the ophthalmologist undertaking follow-up to provide feedback on outcome).

Using the collected information to establish a national UK treatment database and participate in the EU-ROP European database would allow long term information of treatment and outcomes to be identified.

5.7 Suggested audit standards

1. Percentage of infants needing ROP treatment for their ROP who are treated within 72 hours of the decision to treat being made (48 hours for A-ROP and Zone I ROP).
2. Outcome of treatment (retinal structure). Retinal structure at 1 year follow-up. It is acknowledged that case mix may influence outcomes.

5.8 Research recommendations

Follow-up of infants treated both with laser and anti-VEGF agents

Setting up of a national registry of infants treated for ROP

Participate in European registry of infants treated for ROP

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7. Clinical Appendices

Appendix A: Suggested treatment of preterm neonatal endophthalmitis

Infection following anti-VEGF injection has been reported in the literature as single case reports.[126,127,128] Once the diagnosis has been made treatment should be given as soon as possible as delay in starting treatment will adversely affect outcome. Involvement of neonatal and microbiology colleagues will be required.

The adult intravitreous dose of both vancomycin and ceftazidime is 2mg.[129] The paediatric dose is 1mg. The volume of a premature infant eye at the age around when anti-VEGF is given is 1/3 of adults'.[130,131] So, the correct dose is 0.67mg. For dexamethasone, dosing is less critical, the adult dose is 0.4mg. If reduced in the same way as for antibiotics the correct dose for a premature infant is 0.133mg.

Considering volume, injecting 0.025 ml fluid into a premature eye puts the IOP up to an average of 40mm Hg initially, recovering over 10-15 minutes.[63] 0.02ml volume per injection, with a gap of a few minutes between injections is necessary. Paracentesis of a preterm eye without a microscope would be very hazardous.

The antibiotic vials are 1g. Dilute in 10ml normal saline, discard 6.7ml, top up the remaining 3.3ml to 10ml again, mix well and draw up 0.02ml; for each antibiotic.

For dexamethasone, make up 4mg in 1ml normal saline, and draw up 0.02ml (for a dose of 0.08mg).

Vancomycin	0.67mg in 0.02 ml
Ceftazidime	0.67mg in 0.02ml
Dexamethasone	0.08mg in 0.02ml

Topical antibiotics and steroid, and oral or intravenous (IV) antibiotics will also be required. Publications reported the use of intravenous meropenem, vancomycin or amikacin. In the UK, IV or oral ciprofloxacin and clindamycin +/- rifampicin can be used. The appropriate dosages should be checked with neonatal colleagues (as a guide ciprofloxacin IV 10m/kg bd and orally 15mg/kg bd, clindamycin 37.5mg tds orally, rifampicin IV or orally 10mg/kg bd). Topical quinolones e.g., levofloxacin or moxifloxacin drops should be used hourly and dexamethasone 0.1% qid.

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Appendix B: ROP tractional retinal detachment referral to GOSH-Oxford ROP retinal detachment surgical service

If there is potential concern about retinal traction or detachment, if possible, prior to macula dragging and displacement, a referral can be made to the de facto national ROP Retinal Detachment (RD) service. Please contact the surgical teams at Great Ormond Street Hospital for Children (Mr Chien Wong,
Mr Rob Henderson, Mr CK Patel) or Oxford University Hospitals NHS Trust (Mr CK Patel).

Indications for referral

1. Tractional RD (stage 4A, 4B or 5).
2. Peripheral retinal traction, e.g. temporal peripheral vessel straightening prior to macula or disc dragging.

A phone or email discussion with the GOSH-Oxford Paediatric VR team should be urgently initiated. Upon acceptance of referral, the following should be emailed to the team to include:

1. The neonatal discharge summary (e.g., from Badger.net).
2. Funding authorisation for referrals outside NHS jurisdiction.
3. Retinal images, where they exist.
4. Confirmation of local bed reserved for immediate post-operative repatriation.
5. Include telephone numbers/email address of parents and responsible neonatologists.

Surgery
Surgery is primarily carried out at GOSH, with Oxford as a second site. Patients will usually be admitted 1 day prior to surgery, and discharged back to the local unit 24 hours post-operatively. It is expected that the local team will have a bed available for timely repatriation.

Postoperative care
Joint postoperative ophthalmic care between the local and GOSH teams in the short and long-term. Annual review will be required long term, usually at GOSH.

Appendix C: Referral form for ROP treatment/ possible treatment

Referral form on the following page

Referral form for (possible) ROP treatment

Referring Ophthalmologist:

Contact details for Ophthalmologist:

Hospital of referral:

NHS number:

Hospital number:

Date and time of referral:

Accepting ophthalmologist:

Patient information

Name of infant:

Date of birth:

Gestation:

Current gestational age:

Birth weight (Kg):

Current weight (Kg):

Referral from Home: Y/N

Date discharged from hospital:

Infection status:

Respiratory status

Receiving respiratory support? Y/N

Has parent /carer been informed of transfer? Y/N

If Yes please give details:

Telephone details for parent:

Additional information/ patient history (if required): e.g. interpreter required/social concerns:

PLEASE EMAIL COPY OF BADGER.NET OR OTHER ELECTRONIC SUMMARY TO NICU

Ophthalmology

Reason for referral:

A) Second opinion Y/N

B) Intervention (treatment) required? Y/N

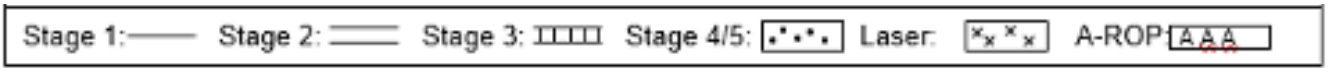
Date of last review:

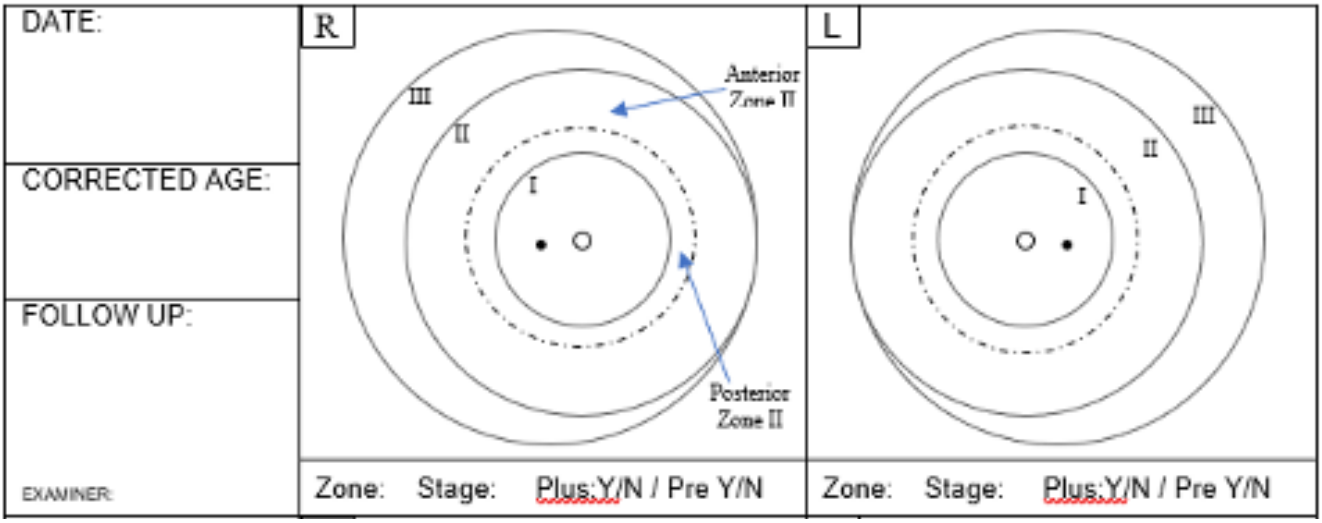
	Right		Left	
Stage		Stage		
Zone		Zone		
Preplus	Y/N	Preplus	Y/N	
Plus	Y/N	Plus	Y/N	

Images/documentation of last review to be sent to referrer with this form: Y/N

If no images please record last findings below:

Response to drops if known:





Appendix D: Information leaflet for parents on treatment of ROP

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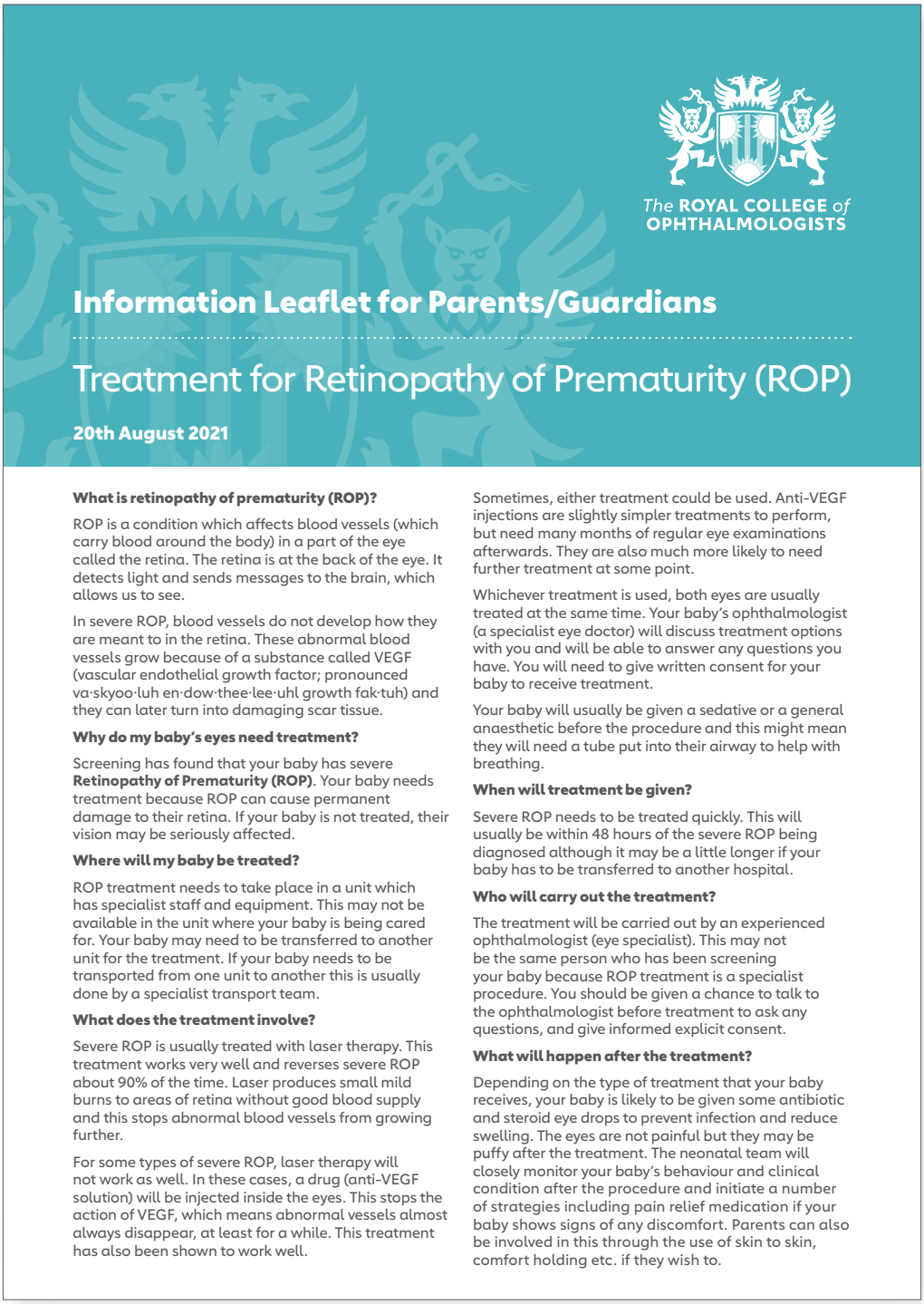

The ROYAL COLLEGE of OPHTHALMOLOGISTS

Information Leaflet for Parents/Guardians

Treatment for Retinopathy of Prematurity (ROP)

20th August 2021

What is retinopathy of prematurity (ROP)?

ROP is a condition which affects blood vessels (which carry blood around the body) in a part of the eye called the retina. The retina is at the back of the eye. It detects light and sends messages to the brain, which allows us to see.

In severe ROP, blood vessels do not develop how they are meant to in the retina. These abnormal blood vessels grow because of a substance called VEGF (vascular endothelial growth factor; pronounced va·skyoo·luh en·dow·thee·lee·uhl growth fak·tuh) and they can later turn into damaging scar tissue.

Why do my baby's eyes need treatment?

Screening has found that your baby has severe **Retinopathy of Prematurity (ROP)**. Your baby needs treatment because ROP can cause permanent damage to their retina. If your baby is not treated, their vision may be seriously affected.

Where will my baby be treated?

ROP treatment needs to take place in a unit which has specialist staff and equipment. This may not be available in the unit where your baby is being cared for. Your baby may need to be transferred to another unit for the treatment. If your baby needs to be transported from one unit to another this is usually done by a specialist transport team.

What does the treatment involve?

Severe ROP is usually treated with laser therapy. This treatment works very well and reverses severe ROP about 90% of the time. Laser produces small mild burns to areas of retina without good blood supply and this stops abnormal blood vessels from growing further.

For some types of severe ROP, laser therapy will not work as well. In these cases, a drug (anti-VEGF solution) will be injected inside the eyes. This stops the action of VEGF, which means abnormal vessels almost always disappear, at least for a while. This treatment has also been shown to work well.

Sometimes, either treatment could be used. Anti-VEGF injections are slightly simpler treatments to perform, but need many months of regular eye examinations afterwards. They are also much more likely to need further treatment at some point.

Whichever treatment is used, both eyes are usually treated at the same time. Your baby's ophthalmologist (a specialist eye doctor) will discuss treatment options with you and will be able to answer any questions you have. You will need to give written consent for your baby to receive treatment.

Your baby will usually be given a sedative or a general anaesthetic before the procedure and this might mean they will need a tube put into their airway to help with breathing.

When will treatment be given?

Severe ROP needs to be treated quickly. This will usually be within 48 hours of the severe ROP being diagnosed although it may be a little longer if your baby has to be transferred to another hospital.

Who will carry out the treatment?

The treatment will be carried out by an experienced ophthalmologist (eye specialist). This may not be the same person who has been screening your baby because ROP treatment is a specialist procedure. You should be given a chance to talk to the ophthalmologist before treatment to ask any questions, and give informed explicit consent.

What will happen after the treatment?

Depending on the type of treatment that your baby receives, your baby is likely to be given some antibiotic and steroid eye drops to prevent infection and reduce swelling. The eyes are not painful but they may be puffy after the treatment. The neonatal team will closely monitor your baby's behaviour and clinical condition after the procedure and initiate a number of strategies including pain relief medication if your baby shows signs of any discomfort. Parents can also be involved in this through the use of skin to skin, comfort holding etc. if they wish to.

Appendix E: Models of ROP network services ROP Screening and treatment service coordination

The role of the ROP Co-ordinator and deputies

The overall aim is to ensure that ROP services are fully coordinated.

The screening and treatment of infants for ROP requires close communication between neonatologists, ophthalmologists, nursing staff and parents/carers.

A dedicated role needs to be funded to ensure that no aspects of ROP screening, treatment and follow-up are overlooked, including communication with the parents/carers.

This role is usually carried out by a lead nurse with designated deputies to ensure the service is covered throughout the year.

The extent of the role will depend upon the number of infants eligible for ROP screening, the number of neonatal units covered and whether the units are also treatment centres.

Role Summary

- Responsible for the coordination of the ROP service delivered to all eligible infants including supervision of designated deputy/deputies.
- Oversight of day-to-day management of ROP screening and treatment in accordance with the national ROP guidelines.

Principle Duties and Responsibilities

(Duties and Responsibilities related to ROP Screening are given in the RCPCH Screening Guideline.)

Clinical – treatments performed within the Neonatal Unit

- Coordinate arrangements for each infant as required.
- Obtain information from the screening ophthalmologist on the modality of treatment required and the necessary timescale for treatment.
- Schedule the treatment in liaison with the treating ophthalmologist and the neonatal team.
- Ensure parents/carers are informed of the arrangements and informed consent has been obtained.
- Ensure all required drugs and equipment are in place on the day of the treatment.
- Ensure mydriatic drops are prescribed and available on the day of the treatment.
- Communicate with the treating ophthalmologist to confirm the timing and place of the treatment.
- Ensure all post-treatment aftercare is in place, and that ophthalmology follow-up has been scheduled.
- Ensure parents/carers are informed that the treatment has been carried out, and of aftercare and follow-up arrangements.
- In liaison with the treating ophthalmologist, ensure that any prognostic information given to the parents/carers is clear, accurate and documented.

Clinical – transfers for treatment outside unit

- Coordinate arrangements for the transfer of each infant requiring treatment.
- Obtain information from the screening ophthalmologist on the modality of treatment required and the necessary timescale for treatment.
- Liaise with the treating ophthalmologist, the receiving neonatal team and the transport service.
- Ensure parents/carers are informed of the arrangements and informed consent obtained.
- When receiving the infant back from the treating unit, ensure all post-treatment aftercare is in place, and that ophthalmology follow-up is scheduled.
- Ensure parents/carers are informed of aftercare and follow-up arrangements.
- In liaison with the treating ophthalmologist, ensure that any prognostic information given to the parents/carers is clear, accurate and documented.

Follow-up after treatment

- Liaise with the treating ophthalmologist to prepare a follow-up regimen in line with the treatment modality (e.g. laser 7-10 days approx. after treatment, and anti-VEGF 2-3 days approx. after treatment and then 2-4 weekly for 6 months).

Communication

- Act as clinical specialist advisor in relation to the ROP service.
- Promote and maintain interdepartmental communication between neonatal staff, ophthalmologists and community services.
- Ensure mandatory assessments and audits are completed on time.
- Ensure parents/carers are informed about all stages of ROP screening including the possible need for outpatient appointments.

Training, development and research

- Identify learning needs and contribute to the training of deputy/deputies.
- Support other staff in developing their learning experience related to ROP.
- Contribute to clinical governance agenda within the ROP service by participating in audit and research and thereby support the development of evidence-based practice.

ROP Screening and Treatment MDT meeting

Establishing a weekly ROP MDT (multi-disciplinary team) meeting of ROP screeners, treaters, nurses and ROP coordinator allows discussion of cases and decision making between screeners and treaters. The meeting would take place virtually rather than in person. The availability of fundal imaging enhances these meetings. Such meetings allow for collective decision making and ensures that no infant is transferred without the need for treatment having been confirmed.

Ideally such meetings would follow on from screening that took place early in the week to allow for discussion and treatments to be undertaken mid-week.

8. Methodology Appendices

Appendix F: Scope of the Guideline

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). In 1996 the guidelines were revised and extended to cover treatment, parent information and counselling, and the management of end-stage ROP. In 2008 the Royal College of Paediatrics & Child Health (RCPCH) in collaboration with the RCOphth, BAPM and Bliss reviewed the 1996 guideline and applied advances in the methodology of guideline development and new research into ROP to develop evidence-based recommendations for health professionals caring for infants who are at risk of developing ROP. When considering the most appropriate approach to revision of the 2008 ROP screening and treatment guideline, the RCPCH and the RCOphth decided to develop two companion guidelines. The Screening guideline has been developed by the RCPCH, and the Treatment guideline by RCOphth. There has been close collaboration between the two colleges, and with BAPM and Bliss. The two guidelines are complementary. Where screening and treatment processes overlap, some material has been duplicated.

Clinical need for updating the guideline

Evidence that the 2008 guideline required updating came from several sources. Clinical studies of the criteria for ROP screening, and developments in telemedicine have prompted the need to review ROP screening arrangements, which then impact arrangements for treatment. Major changes in the treatment of ROP occurred following the publication of the Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity (BEAT-ROP) trial in 2011, and the RAnibizumab Compared With Laser Therapy for the Treatment of INfants BOrn Prematurely With Retinopathy of Prematurity (RAINBOW) trial in 2019.While these trials demonstrated anti-Vascular Endothelial Growth Factor (VEGF) agents are effective in the treatment of ROP, they raised questions on the systemic safety of the agents and of patterns of disease regression and reactivation following the use of these agents. The recent publication of the third iteration of the international classification of ROP (ICROP 3), along with the two anti-VEGF trials necessitate a fresh approach to clinical practice, using an updated guideline.

Guideline objectives

The aims of the guideline are:

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

Guideline Scope

The guideline covers all aspects of the treatment of ROP. Management of acute tractional retinal detachment (Stage 4 and Stage 5 ROP) has been included for the first time. Although the guideline aims to cover most situations where ROP requires treatment, it does not cover rare, complex or unusual cases.

Population covered
The target population is all infants in UK with treatment-requiring ROP identified by screening. This population is drawn from the population of infants who require to be screened for sight threatening ROP. All infants born at less than 31 weeks gestation OR less than 1501g birth weight, irrespective of sex or comorbidities. The age range is the at-risk period for development of treatment-requiring ROP, PMA 30-50 weeks.

Target audience
The guideline is primarily aimed at neonatal and ophthalmic teams but also provides a resource for all healthcare professionals involved in the treatment of sight threatening ROP, including anaesthetic teams, managers, and commissioners. The guideline has been developed for use within the UK healthcare environment. Infants developing ROP in developing countries are significantly different from those in more developed countries, as aggressive forms of ROP may occur in infants of later gestation and greater birth weight. Although the guideline will not be directly aimed at parents of infants with ROP, their needs have been considered both within the guideline and in the parent information leaflet.

Healthcare setting and services
Secondary and tertiary healthcare settings in which the screening and diagnosis of infants at risk of ROP takes place.

Key areas of management
The guideline will contain a background section which will include the epidemiology of treatment-requiring ROP and the history of treatment modalities for ROP. This section is for reference and will not include evidence-based recommendations.

The evidence-based guidance will include the following key areas of management:

a) Treatment

Recommendations in this section will consider the following areas:

- ROP treatment Facilities and training
- ROP treatment modalities
- Post treatment follow-up
- Longer term follow-up
- Management of asymmetric ROP
- Retinal reattachment surgery
- Management of the disorganised anterior segment

b) Information for Parents

Throughout the guideline the issues around communicating with parents will be considered. If it seems appropriate a separate section in the main guideline on how the healthcare team should communicate with parents may be included to address the process of providing information to parents regarding screening and diagnosis. Information will also be included on parental consent, parental information, and support and counselling, and screening outcomes.

c) Recommendations for further research

The guideline will also include suggestions for further research.

Clinical management – areas that will not be covered

- Screening for ROP (this area is excluded from this scope as the review of ROP treatment is being led by the RCPCH – with close collaboration with the RCOphth).
- Health economist assessment including the cost effectiveness of ROP screening and treatment in the guideline (this area was also outside the scope for the current 2008 guideline).
- Evidence for organisational issues will not be reviewed directly, however recommendations may be developed where appropriate (this area was also outside the scope for the current 2008 guideline).

Audit support within the guidance

The guidance aims to review existing key criteria for audit, which will enable objective measurements to be made of the extent and nature of local implementation of this guidance. Key recommendations for implementation will be highlighted and tools for implementation of the guideline may also be included.

References

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Gilbert C. Retinopathy of prematurity: A global perspective of the epidemics, population of babies at risk and implications for control. Early Hum Dev. 2008;84(2):77–82.

Mora JS, Waite C, Gilbert CE, Breidenstein B, Sloper JJ, Mora JS. A worldwide survey of retinopathy of prematurity screening. Br J Ophthalmol. 2018;102(1):9–13

Appendix G: Methodology of the Guideline

Guideline methodology

The guideline update has been developed according to the RCOphth Guideline Process Manual March 2020 V1.2. The guideline update followed standard guideline developmental stages. After agreeing the scope, a Guideline Development Group (GDG) was appointed to oversee the development of the guideline. The process included the development of clinical questions, a systematic search of the literature to answer these questions, grading and selection of the evidence according to pre- arranged inclusion criteria, and critical appraisal of the included papers. The RCOphth used the SIGN 50 grading hierarchy. Where there was no strong evidence, the GDG agreed good practice points (GPP) by consensus, and the assistance of the UK Special Interest Group for ROP forum (ROP-SIG).

ROP-SIG is a secure internet forum used by all ROP screeners and treaters in the UK. ROP-SIG was consulted by the GDG in all aspects of guideline development.

The following were ROP-SIG members at the time of the guideline development.

Joseph Abbott, Wagih Aclimandos, Gill Adams, Louise Allen, Dania Al-Nuaimi, Muhammed Aman Ullah, Luis Amaya, Jane Ashworth, Philip Banerjee, Jonathan Barnes, Victoria Barrett, John Sebastian Barry, Adam Bates, Richard Best, Susmito Biswas, Andrew Blaikie, Kate Bolton, Howard Bunting, Mike Burdon, Jeremy Butcher, Anne Cees Houtman, Chris Child, Jessy Choi, Vivi Choleva, Luke Clifford, Ahmad Dabbagh, Annegret Dahlmann-Noor, Arun Dev Borman, Luna Dhir, Leticia Dujardin, Anthony Evans, Kevin Falzon, Alan Fenton, Brian Fleck, Eva Gajdosova, Vernon Geh, Nick George, Sonia George, AJ Ghauri, Lawrence Gnanaraj, Raina Goyal, Paul Haigh, Chris Hammond, Hassan Hashmi, Dominic Heath, Rob Henderson, Roxane Hillier, Melanie Hingorani, Saurabh Jain, Sunila Jain, Rohit Jolly, David Jones, Lav Joshi, Namir Kafil-Hussain, Simon Kelly, Nihal Kenawy, Ayman Khaier, Tina Kipioti, Archana Kulkarni, Tim Lavy, Joanna Lawson, Jane Leitch, Adam Lewis, Vernon Long, Mary Macrae, Usman Mahmood, Aeesha Malik, Qasim Mansoor, Richard Markham, Jane Marr, Kristina May, Eibhlin McLoone, Eoghan Millar, Murad Moosa, Ali Mount, Wisam Muen, Alan Mulvihill, Vineeta Munshi, Mahi Muqit, Narendran Nair, William Newman, Rory Nicholson, Una O'Colmain, Michael O'Gallagher, Sally Painter, C.K. Patel, Himanshu Patel, Rachel Pilling, Marcus Posner, Narman Puvanachandra, Dinesh Rathod, Ashwin Reddy, Aravind Reddy, Ailsa Ritchi, Alison Rowlands, Conrad Schmoll, Stephen Scotcher, Christopher Scott, Rajnish Sekhri, Eulee Seow, Ayad Shafiq, Katherine Shirley, Tamsin Sleep, Shona Sutherland, Katya Tambe, Jonathan Tan, Anamika Tandon, Alison Tappin, Robert Taylor, Maria Theodorou, Shery Thomas, Peter Tiffin, Maria Tsimpida, Patrick Watts, Stephanie West, Louisa Wickham, Cathy Williams, Chien Wong, Siobhan Wren, Damien Yeo, Rahila Zakir.

Developing the clinical questions

The GDG reviewed and updated the clinical questions from the 2008 guideline. The review questions were developed from a framework which identified population, intervention, comparison and outcome as areas on which the guideline should focus on. The full list of clinical questions is included in the Participants Intervention Comparator Outcome (PICO) chart below.

1. Background and epidemiology

a. What is the UK incidence of ROP

b. What are the demographic and clinical features of patients with ROP

c. What are the aetiological feature and the risk factors for treatment with ROP.

Population	Intervention	Comparison	Outcome
Patient referred for treatment with ROP in the UK			
Retinopathy of Prematurity Treatment Cryotherapy Laser therapy Anti-VEGF therapy		Ethnicity Birth weight Gestation age	

2. Required site facilities and training for those who treat ROP

a. What training and experience should be gained prior to starting treating for ROP?

b. What training and experience should be gained prior for the continuation of screening/treating?

c. What facilities should exist at a centre treating for ROP?

Population	Intervention	Comparison	Outcome
UK paediatric ophthalmologists Hospital Eye units	Training Experience Facilities		
Retinopathy of Prematurity Treatment Cryotherapy Laser therapy Anti-VEGF therapy Education training	Cryotherapy Laser therapy Anti-VEGF therapy Imaging Communication	Trials, surveys, guidelines, policy documents and professional reports	

3. Treatment:

Ophthalmic indications for treatment

a. What indication warrant treatment for ROP

Population	Intervention	Comparison	Outcome
Patient referred for treatment with ROP in the UK	Screening and referral		Treatment warranted
Retinopathy of Prematurity Treatment Cryotherapy Laser therapy Anti-VEGF therapy	ROP Zone ROP plus disease		

Timing of treatment

a. How soon after screening should treatment be administered?

Population	Intervention	Comparison	Outcome
Patient referred for treatment with ROP in the UK	ROP Treatment	Time	Visual, retinal, refractive
Retinopathy of Prematurity Treatment Cryotherapy Laser therapy Anti-VEGF therapy	Cryotherapy Laser therapy Anti-VEGF therapy		Visual, retinal, refractive

Treatment techniques available for treating ROP

a. What area of the eye should be treated?

b. Is cryotherapy more effective at treating infants with ROP than other treatment modalities?

c. Is laser therapy more effective at treating infants with ROP than other treatment modalities?

d. Is anti-VEGF therapy more effective at treating infants with ROP than other treatment modalities?

Population	Intervention	Comparison	Outcome
Patient referred for treatment with ROP in the UK	ROP Treatment	Other treatment modalities	Visual, retinal, refractive
Retinopathy of Prematurity Treatment Cryotherapy Laser therapy Anti-VEGF therapy	Cryotherapy Laser therapy Anti-VEGF therapy	Systematic reviews, trials	Visual, retinal, refractive

Adverse events

a. What are the adverse effects and complications (inc. perioperative outcomes) for the different treatment modalities on active ROP?

b. What are the side-effects/adverse reaction related to ROP treatment, including anaesthetics?

Population	Intervention	Comparison	Outcome
Patient referred for treatment with ROP in the UK	ROP Treatment	Other treatment modalities	Adverse events Complications Side effects Adverse reations
Retinopathy of Prematurity Treatment Cryotherapy Laser therapy Anti-VEGF therapy	Cryotherapy Laser therapy Anti-VEGF therapy	Systematic reviews, trials, population studies	

4. Post-operative Review and re-treatment

a. How soon after treatment should the patient be reviewed?

b. How often after treatment should the patient be reviewed?

Population	Intervention	Comparison	Outcome
Patient referred for treatment with ROP in the UK	Post-operative review		
Retinopathy of Prematurity Treatment Cryotherapy Laser therapy Anti-VEGF therapy		Trials, population studies	Time Number of reviews

a. What should be included in a post-operative review?

Population	Intervention	Comparison	Outcome
Patient referred for treatment with ROP in the UK	Post-operative review Imaging Communication between hospitals Communication with Patient families	No imaging	Re-treatment rates Number of reviews patient
Retinopathy of Prematurity Treatment Cryotherapy Laser therapy Anti-VEGF therapy		Trials, population studies	Time Number of reviews

a. What indications warrant re-treatment for ROP

Population	Intervention	Comparison	Outcome
Patient referred for treatment with ROP in the UK	Screening and referral		Treatment warranted
Retinopathy of Prematurity Treatment Cryotherapy Laser therapy Anti-VEGF therapy	ROP Zone ROP plus disease		

a. How soon after treatment should re-treatment be administered?

Population	Intervention	Comparison	Outcome
Patient referred for treatment with ROP in the UK	ROP Treatment	Time	Visual, retinal, refractive
Retinopathy of Prematurity Treatment Cryotherapy Laser therapy Anti-VEGF therapy	Cryotherapy Laser therapy Anti-VEGF therapy		Visual, retinal, refractive

a. What are the most effective re-treatment modalities?

Population	Intervention	Comparison	Outcome
Patient referred for treatment with ROP in the UK	ROP Treatment	Other treatment modalities	Visual, retinal, refractive
Retinopathy of Prematurity Treatment Cryotherapy Laser therapy Anti-VEGF therapy	Cryotherapy Laser therapy Anti-VEGF therapy	Systematic reviews, trials	Visual, retinal, refractive

a. When do ophthalmologists stop offering re-treatment

Population	Intervention	Comparison	Outcome
Patient referred for treatment with ROP in the UK	ROP Treatment		Visual, retinal, refractive
Retinopathy of Prematurity Treatment Cryotherapy Laser therapy Anti-VEGF therapy	Cryotherapy Laser therapy Anti-VEGF therapy	Systematic reviews, trials, population studies	Visual, retinal, refractive

5. Long-term follow-up and review

c. How long after treatment should the patient be followed-up?

d. How often after treatment should the patient be followed-up

e. What should be included in a follow-up appointment?

Population	Intervention	Comparison	Outcome
Patient referred for treatment with ROP in the UK	Post operative review		
Retinopathy of Prematurity Treatment Cryotherapy Laser therapy Anti-VEGF therapy	Follow-up Review Long-term	Trials, population studies	Time Number of reviews

6. Treatment of asymmetric ROP

Population	Intervention	Comparison	Outcome
Retinopathy of Prematurity Treatment Cryotherapy Laser therapy Anti-VEG therapy	Treatment to one or both eyes	Bilateral or unilateral treatment	Visual, retinal, refractive

7. Retinal surgery re-attachment

Population	Intervention	Comparison	Outcome
Patient treated with ROP in the UK who develop stage 4 or stage 5 ROP	Vitreoretinal surgery	Trials, case series	Visual, retinal, refractive

8. Treating disorganised anterior segment

Population	Intervention	Comparison	Outcome
Patient treated with ROP in the UK who develop long term sequelae of ROP	Anterior segment surgery	Trials, case series	Visual, retinal, refractive, ocular structure and ocular appearance

9. What information should be provided for parents and when should this information be provided

Population	Intervention	Comparison	Outcome
Parents of Patients treated with ROP in the UK	Written and verbal communication, surgical consent	Communication on surgical procedure strategies qualitative and quantitative research	Parent satisfaction scores

Identifying the evidence

The review questions formed the starting point for systematic searches of the relevant evidence (Appendix H).

Reviewing and synthesising the evidence

Evidence relating to the review questions was initially identified by the RCOphth staff team by screening the titles and abstracts of publications against the inclusion criteria, with disagreements settled by a member of the GDG. Full text articles were then obtained directly from the publisher, the British Library or as freely available online. At full text review each publication was screened by either two GDG members or one GDG and one member of the RCOphth staff team and the relevant information extracted.

Full text articles were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review questions in the appropriate population and reported outcomes of interest. Publications were critically appraised using checklists developed by the SIGN checklists for different study types (i.e. randomised controlled trials (RCT), case-control, and cohort studies) and key information about the study's population, methods and results were extracted using a proforma.

Extracted data were placed into evidence tables and used by the GDG members to develop recommendations which were reviewed and agreed by the GDG (Evidence Tables in Appendix I). Where the research evidence is discussed, the terminology employed is that used in the original research studies.

Developing recommendations

GDG virtual meetings were held to discuss the identified evidence. To formulate recommendations, summaries of the evidence were presented, and updated recommendations linked to new evidence developed. The proposed recommendations were presented to the group for discussion at virtual meetings where they were refined before being agreed. Members of the ROP Special Interest Group (SIG) secure internet forum provided feedback and suggestions on wording of the draft recommendations, based on draft summaries of the evidence, following an iterative process.

Evidence based recommendations were developed taking into consideration findings from the evidence review and were graded according to the strength of the evidence based on the grading system. The formulation of recommendations followed the SIGN grading hierarchy used in the 2008 Guideline. Each recommendation indicates the corresponding level of evidence and recommendation grading. Where there was no strong evidence, of low quality or non-existent, those recommendations were agreed by

the GDG as good practice points (GPP) thorough informal consensus process. Each recommendation is presented stating the level of evidence and grading of the recommendation. For evidence-based recommendations, the strength of the recommendation is presented with action verbs or 'should' for strong recommendation and 'consider' or 'may' for moderate recommendations. For good practice points where no strong evidence was identified, the wording of the recommendation has been presented as that decided by the GDG during an informal consensus process and identified clearly as a GPP in brackets.

The GDG also identified areas where there was a lack of evidence and suggested recommendations for future research.

Levels of Evidence (SIGN 50)

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

Type of evidence	Description
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 low 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 (for example, case reports, case series)
4	Expert opinion, formal consensus

Guideline consultation

The scope was sent for consultation to stakeholders and relevant specialty groups, including the SIG-ROP forum from August 2021 to November 2021, and comments were received.

The draft guideline consultation took place between October 2021 and November 2021. During this time stakeholders were given the opportunity to comment on the guideline. All comments were reviewed by GDG members for consideration and discussion.

Stakeholder Involvement

A number of organisations were invited to be involved in the development of the Guideline. From some key stakeholders, identified representatives were invited to become members of the GDG. The organisations were formally invited at the beginning of the development, involved in the consultation on the scope and draft of the guideline, and were informed on the progress at different stages during the development. A full list of organisations is included in the main guideline.

Parent, carer lay member participation

The Guideline sought to involve parents and carers from the outset. The GDG included two parents with children who had undergone treatment for ROP. They were able to feed into every aspect of the development process and were closely involved during the update of the parent information leaflet. Discussions were centred on the content, format, and best language to present the information needed for families to consent to ROP treatment. The GDG and stakeholder representatives also included parent, carer, and patient information charities.

Conflicts of Interest

Conflict of Interest statements of members of the Guideline Development Group, ROP-SIG, and reviewers assisting with the critical appraisal of the literature for this guideline are given in Appendix J.

Updating the Guideline

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

Guideline Dissemination

The Guideline content is presented in four formats:

- The full Guideline report can be downloaded from the RCOphth and RCPCH websites.
- The executive summary highlighting the key recommendations for implementation is available as a separate document.
- A parent information leaflet.
- A peer-reviewed article with a summary of the guideline and its recommendations will be submitted to relevant journals for wider dissemination.

References

RCOphth Guideline Process Manual March 2020 V1.2 available from RCOphth.

Scottish Intercollegiate Guidelines Network. A guideline developer's handbook. Edinburgh: SIGN; 2019. *(SIGN publication no. 50)*. November 2019.

Appendix H: Search Strategy and Selection Criteria

The review questions formed the starting point for systematic searches of the relevant evidence. All literature searches were conducted on core databases MEDLINE and EMBASE.

The initial searches were performed on the period from 01 Jan 2007 until 21 November 2019 and were followed by a follow-up search until 23 August 2021.

Inclusion criteria applied to all papers were:

- Studies reporting primary data on children with sight-threatening ROP.
- English language.
- 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 hdr.undp.org/en/content/latest-human-development-index-ranking).
- A small number of high-quality studies from Turkey, Iran, Mexico, India and China were also included.
- Studies of good methodological quality assessed using the SIGN standardised check list.
- Studies classifying stages and severity of ROP according to ICROP criteria.
- Papers published since the date of publication of the existing RCPCH/RCOphth guidelines (2008).

Exclusion criteria applied to all papers were:

- There was no searching of grey literature, nor was hand searching of journals undertaken.
- Studies conducted out with the top 30 countries on the United Nations Human Development Index hdr.undp.org/en/content/latest-human-development-index-ranking) were excluded, except for a small number of high-quality studies from Turkey, Iran, Mexico, India and China.

Infants developing ROP in developing countries are significantly different from those in more developed countries, as aggressive forms of ROP may occur in infants of later gestation and greater birth weight. The evidence reviewed for the guideline was mainly restricted to studies undertaken in the top 30 countries in the United Nations Human Development Index to be consistent with this finding (found at hdr.undp.org/en/content/latest-human-development-index-ranking). However, we were aware that ROP is much more common in "middle income" countries than in "developed countries" and that much high-quality research is performed in academic institutions in countries that fall outside the UN HDI top 30 countries. For this reason, we critically reviewed and have judiciously included a small number of key, good quality studies from Turkey, Iran, Mexico, India and China.

References

Gilbert C. Retinopathy of prematurity: A global perspective of the epidemics, population of babies at risk and implications for control. Early Hum Dev. 2008;84(2):77–82.

Mora JS, Waite C, Gilbert CE, Breidenstein B, Sloper JJ, Mora JS. A worldwide survey of retinopathy of prematurity screening. Br J Ophthalmol. 2018;102(1):9–13.

Databases used

EMBASE and MEDLINE databases were used, for the time period 2007 – 2021

Search Strategy for ROP treatment guideline

Q2 Required site facilities and training for those who treat ROP

a. What training and experience should be gained prior to starting treating for ROP?
b. What training and experience should be gained prior for the continuation of screening/ treating?
c. What facilities should exist at a centre treating for ROP?

MEDLINE

1. "Retinopathy of Prematurity"/
2. (retinopath$ adj3 prematur$).tw.
3. (retrolental adj2 (fibroplas$ or fibrosis)).tw.
4. ROP.tw. 5. or/1-4
6. Computer User Training/
7. Computer Simulation/
8. Computer-Assisted Instruction/
9. (train$ or education$ or tutorial).tw.
10. (virtual$ or simulat$).tw.
11. Telemedicine/
12. (telemedicine or tele-educat$).tw.
13. exp Education, Medical/
14. Teaching/
15. Inservice Training/
16. Physician's Practice Patterns/
17. Professional Practice/
18. Professional Competence/
19. Clinical Competence/
20. "Surveys and Questionnaires"/
21. (skill$ or competenc$).tw.
22. (residenc$ or resident$ or curriculum).tw.
23. Ophthalmologists/ec, ed, og, st, sn, sd, td [Economics, Education, Organization & Administration, Standards, Statistics & Numerical Data, Supply & Distribution, Trends]
24. Ophthalmology/ec, ed, mt, og, st, sn, sd, td [Economics, Education, Methods, Organization & Administration, Standards, Statistics & Numerical Data, Supply & Distribution, Trends]
25. (facilities or equipment).tw.
26. or/6-25
27. 5 and 26

Embase

1. retrolental fibroplasia/
2. (retinopath$ adj3 prematur$).tw.
3. (retrolental adj2 (fibroplas$ or fibrosis)).tw.
4. ROP.tw.
5. or/1-4
6. computer simulation/
7. (virtual$ or simulat$).tw.
8. (train$ or education$ or tutorial).tw.
9. Telemedicine/

10. (telemedicine or tele-educat$).tw.
11. medical education/
12. Teaching/
13. In service Training/
14. clinical practice/
15. professional practice/
16. professional competence/
17. clinical competence/
18. questionnaire/
19. (residenc$ or resident$ or curriculum$).tw.
20. (skill$ or competenc$).tw.
21. (facilities or equipment).tw.
22. or/6-21
23. 5 and 22

Q3 Treatment techniques available for treating ROP

1. "Retinopathy of Prematurity"/
2. (retinopath$ adj3 prematur$).tw.
3. (retrolental adj2 (fibroplas$ or fibrosis)).tw.
4. ROP.tw.
5. infant, low birth weight/ or infant, very low birth weight/ or infant, extremely low birth weight/ or infant, premature/ or infant, extremely premature/
6. ((low or extremely) adj2 birth weight$).tw.
7. ((late or moderate or very or extrem$) adj2 preterm$).tw.
8. (LBW or VLBW or ELBW or VPT or EPT).tw.
9. or/1-8
10. exp cryotherapy/
11. exp cryosurgery/
12. (cryotherap$ or cryosurg$).tw.
13. or/10-12
14. exp light coagulation/
15. (photocoagulat$ or photoablat$).tw.
16. Laser Therapy/
17. lasers, semiconductor/
18. ablation techniques/
19. (laser or lasers).tw.
20. (argon or diode).tw.
21. or/14-20
22. exp angiogenesis inhibitors/
23. angiogenesis inducing agents/
24. endothelial growth factors/
25. exp vascular endothelial growth factors/
26. (anti adj2 VEGF$).tw.
27. (endothelial adj2 growth adj2 factor$).tw.
28. (anti adj1 angiogen$).tw.
29. (macugen$ or pegaptanib$ or lucentis$ or rhufab$ or ranibizumab$ or bevacizumab$ or avastin or aflibercept$ or conbercept$ or OPT 302 or Opthea$ or RTH258 or Brolucizumab$ or abicipar pegol).tw.

30. VEGF TRAP$.tw.
31. or/22-30
32. 9 and 13 and 21
33. 9 and 13 and 31
34. 9 and 21 and 31 35. or/32-34
36. exp case reports/
37. (case$ adj3 (report$ or series)).tw.
38. or/36-37
39. 32 not 38

Embase

1. retrolental fibroplasia/
2. (retinopath$ adj3 prematur$).tw.
3. (retrolental adj2 (fibroplas$ or fibrosis)).tw.
4. ROP.tw.
5. prematurity/
6. exp low birth weight/
7. ((low or extremely) adj2 birth weight$).tw.
8. ((late or moderate or very or extrem$) adj2 preterm$).tw.
9. (LBW or VLBW or ELBW or VPT or EPT).tw.
10. or/1-9
11. exp cryotherapy/
12. (cryotherap$ or cryosurg$).tw.
13. or/11-12
14. exp laser surgery/
15. (photocoagulat$ or photoablat$).tw.
16. (laser or lasers).tw.
17. (argon or diode).tw.
18. or/14-17
19. angiogenesis/
20. exp angiogenesis inhibitors/
21. angiogenic factor/
22. endothelial cell growth factor/
23. monoclonal antibody/
24. vasculotropin/
25. (anti adj2 VEGF$).tw.
26. (endothelial adj2 growth adj2 factor$).tw.
27. (anti adj1 angiogen$).tw.
28. (macugen$ or pegaptanib$ or lucentis$ or rhufab$ or ranibizumab$ or bevacizumab$ or avastin or aflibercept$ or conbercept$ or OPT 302 or Opthea$ or RTH258 or Brolucizumab$ or abicipar pegol).tw.
29. VEGF TRAP$.tw.
30. or/19-29
31. 10 and 13 and 18
32. 10 and 13 and 30
33. 10 and 18 and 30
34. or/31-33
35. exp case report/

36. (case$ adj3 (report$ or series)).tw.
37. or/35-36
38. 34 not 37

Q3 Ophthalmic indications for treatment

a. What indication warrant treatment for ROP Timing of treatment
a. How soon after screening should treatment be administered?

MEDLINE

1. "Retinopathy of Prematurity"/
2. (retinopath$ adj3 prematur$).tw.
3. (retrolental adj2 (fibroplas$ or fibrosis)).tw.
4. ROP.tw.
5. or/1-4
6. Neonatal Screening/
7. mass screening/
8. screen$.tw.
9. tomography, Optical Coherence/
10. Retcam.tw.
11. Ophthalmoscopy/
12. "Referral and Consultation"/
13. (referral$ or referred).tw.
14. (stage adj1 (three or four or five)).tw.
15. (stage adj1 (III or IV or V)).tw.
16. (zone adj1 (one or two or three)).tw.
17. (zone adj1 (I or II or III)).tw.
18. (plus disease or pre plus disease).tw.
19. (ROP adj2 zone$).tw.
20. or/6-19
21. 5 and 19
22. or/6-18
23. 5 and 22

Embase

1. retrolental fibroplasia/
2. (retinopath$ adj3 prematur$).tw.
3. (retrolental adj2 (fibroplas$ or fibrosis)).tw.
4. ROP.tw.
5. or/1-4
6. prenatal screening/ or newborn screening/
7. screening/
8. screen$.tw.
9. optical coherence tomography/
10. Retcam.tw.
11. Ophthalmoscopy/
12. patient referral/
13. (referral$ or referred).tw.
14. (stage adj1 (three or four or five)).tw.

15. (stage adj1 (III or IV or V)).tw.
16. (zone adj1 (one or two or three)).tw.
17. (zone adj1 (I or II or III)).tw.
18. (plus disease or pre plus disease).tw.
19. (ROP adj2 zone$).tw.
20. or/6-19
21. 5 and 20

Q3 Adverse events

1. What are the adverse effects and complications (inc perioperative outcomes) for the different treatment modalities on active ROP?
2. What are the side-effects/adverse reaction related to ROP treatment, including anaesthetics?

MEDLINE

1. "Retinopathy of Prematurity"/
2. (retinopath$ adj3 prematur$).tw.
3. (retrolental adj2 (fibroplas$ or fibrosis)).tw.
4. ROP.tw.
5. or/1-4
6. Anesthesia/ae, mt [Adverse Effects, Methods]
7. ((anesthe$ or anaesthe$) adj3 (method$ or manage$ or adverse or safety)).tw.
8. vitreous hemorrhage/
9. Retinal Hemorrhage/
10. Choroid Hemorrhage/
11. ((vitreous or vitreal or retina$ or subretina$ or choroidal or suprachoroidal) adj2 (hemorrhag$ or haemorrhag$)).tw.
12. (iatrogenic adj3 (break$ or tear$)).tw.
13. Lens, Crystalline/in [Injuries]
14. (lens$ adj2 (injur$ or damage$)).tw.
15. (laser$ adj3 (injur$ or damage$)).tw.
16. or/6-15
17. 5 and 16

Embase

1. retrolental fibroplasia/
2. (retinopath$ adj3 prematur$).tw.
3. (retrolental adj2 (fibroplas$ or fibrosis)).tw.
4. ROP.tw.
5. or/1-4
6. anesthesia complication/
7. anesthesia/ae [Adverse Drug Reaction]
8. ((anesthe$ or anaesthe$) adj3 (method$ or manage$ or adverse or safety)).tw.
9. vitreous hemorrhage/
10. Retinal Hemorrhage/
11. Choroid Hemorrhage/
12. ((vitreous or vitreal or retina$ or subretina$ or choroidal or suprachoroidal) adj2 (hemorrhag$ or haemorrhag$)).tw.

13. (iatrogenic adj3 (break$ or tear$)).tw.
14. (lens$ adj2 (injur$ or damage$)).tw.
15. (laser$ adj3 (injur$ or damage$)).tw.
16. or/6-15
17. 5 and 16

Q4 Post-operative Review and re-treatment

MEDLINE

1. "Retinopathy of Prematurity"/
2. (retinopath$ adj3 prematur$).tw.
3. (retrolental adj2 (fibroplas$ or fibrosis)).tw.
4. ROP.tw.
5. or/1-4
6. (post-operat$ adj3 (examin$ or review$)).tw.
7. (postoperat$ adj3 (examin$ or review$)).tw.
8. (treat$ adj3 review$).tw.
9. or/6-8
10. 5 and 9

Embase

1. retrolental fibroplasia/
2. (retinopath$ adj3 prematur$).tw.
3. (retrolental adj2 (fibroplas$ or fibrosis)).tw.
4. ROP.tw.
5. or/1-4
6. (post-operat$ adj3 (examin$ or review$)).tw.
7. (postoperat$ adj3 (examin$ or review$)).tw.
8. (treat$ adj3 review$).tw.
9. or/6-8
10. 5 and 9

Q4

a. What indications warrant re-treatment for ROP
a. How soon after treatment should re-treatment be administered?
a. What are the most effective re-treatment modalities?
a. When do ophthalmologists stop offering re-treatment?

MEDLINE

1. "Retinopathy of Prematurity"/
2. (retinopath$ adj3 prematur$).tw.
3. (retrolental adj2 (fibroplas$ or fibrosis)).tw.
4. ROP.tw.
5. or/1-4
6. Retreatment/
7. treatment failure/
8. (retreat$ or re-treat$).tw.

9. ((repeat$ or further or additonal or frequen$) adj3 treat$).tw.
10. ((repeat$ or further or additonal or frequen$) adj3 intervention$).tw.
11. ((repeat$ or further or additonal or frequen$) adj3 therap$).tw.
12. or/6-11
13. 5 and 12

Embase

1. "Retinopathy of Prematurity"/
2. (retinopath$ adj3 prematur$).tw.
3. (retrolental adj2 (fibroplas$ or fibrosis)).tw.
4. ROP.tw.
5. or/1-4
6. Retreatment/
7. treatment failure/
8. (retreat$ or re-treat$).tw.
9. ((repeat$ or further or additonal or frequen$) adj3 treat$).tw.
10. ((repeat$ or further or additonal or frequen$) adj3 intervention$).tw.
11. ((repeat$ or further or additonal or frequen$) adj3 therap$).tw.
12. or/6-11
13. 5 and 12

Q5 Long-term follow-up and review

c. How long after treatment should the patient be followed-up?
d. How often after treatment should the patient be followed-up
e. What should be included in a follow-up appointment?

MEDLINE

1. "Retinopathy of Prematurity"/
2. (retinopath$ adj3 prematur$).tw.
3. (retrolental adj2 (fibroplas$ or fibrosis)).tw.
4. ROP.tw.
5. or/1-4
6. (followup adj5 (month$ or year$)).tw.
7. (follow-up adj5 (month$ or year$)).tw.
8. or/6-7
9. 5 and 8

Embase

1. retrolental fibroplasia/
2. (retinopath$ adj3 prematur$).tw.
3. (retrolental adj2 (fibroplas$ or fibrosis)).tw.
4. ROP.tw.
5. or/1-4
6. (followup adj5 (month$ or year$)).tw.
7. (follow-up adj5 (month$ or year$)).tw.
8. or/6-7
9. 5 and 8

Q6 Treatment of asymmetric ROP

Search strategy used for both MEDLINE and Embase.

1. (asymmet$ adj20 ROP).tw.
2. (asymmet$ adj20 retinopath$ adj2 prematur$).tw.
3. (asymmet$ adj20 retrolental adj2 fibroplasi$).tw. 4. or/1-3

Q7 Retinal surgery re-attachment

MEDLINE

1. "Retinopathy of Prematurity"/
2. (retinopath$ adj3 prematur$).tw.
3. (retrolental adj2 (fibroplas$ or fibrosis)).tw.
4. ROP.tw.
5. or/1-4
6. retinal detachment/
7. retinal perforation/
8. vitreous detachment/
9. (retina$ adj2 break$).tw.
10. (retina$ adj2 tear$).tw.
11. (retina$ adj2 detach$).tw.
12. (retina$ adj2 perforat$).tw.
13. exp vitrectomy/
14. vitrectom$.tw.
15. PPV$.tw.
16. Scleral Buckling/
17. (scleral adj2 buckl$).tw.
18. (scleral adj2 encircl$).tw.
19. encircling band.tw.
20. or/6-19
21. 5 and 20

Embase

1. retrolental fibroplasia/
2. (retinopath$ adj3 prematur$).tw.
3. (retrolental adj2 (fibroplas$ or fibrosis)).tw.
4. ROP.tw.
5. or/1-4
6. exp retina tear/
7. exp retina detachment/
8. (retina$ adj2 break$).tw.
9. (retina$ adj2 tear$).tw.
10. (retina$ adj2 detach$).tw.
11. (retina$ adj2 perforat$).tw.
12. exp vitrectomy/
13. vitrectom$.tw.
14. PPV$.tw.
15. exp sclera buckling procedure/
16. (scleral adj2 buckl$).tw.

17. (scleral adj2 encircl$).tw.
18. encircling band.tw.
19. or/6-18
20. 5 and 19

Q8 Treating disorganised anterior segment

Search strategy used for both MEDLINE and Embase.

1. (disorganised adj2 anterior adj2 segment).tw.

Q9 What information should be provided for parents MEDLINE

1. "Retinopathy of Prematurity"/
2. (retinopath$ adj3 prematur$).tw.
3. (retrolental adj2 (fibroplas$ or fibrosis)).tw.
4. ROP.tw.
5. or/1-4
6. exp Health Education/
7. exp Patient Education as Topic/
8. exp "Patient Acceptance of Health Care"/
9. exp Patient Satisfaction/
10. patient education handout/
11. (patient$ adj4 (leaflet$ or booklet$ or pamphlet$ or video$ or website$ or social media)).tw.
12. (parent$ adj4 (leaflet$ or booklet$ or pamphlet$ or video$ or website$ or social media)).tw.
13. (patient$ adj4 (information or advice or advise$ or support$ or discuss$ or guidance or knowledge)).tw
14. (parent$ adj4 (information or advice or advise$ or support$ or discuss$ or guidance or knowledge)).tw.
15. (patient$ adj4 (experience$ or expectation$ or need$ or preference$ or perspective$ or attitude$ or view$ or opinion$ or choice$)).tw.
16. (parent$ adj4 (experience$ or expectation$ or need$ or preference$ or perspective$ or attitude$ or view$ or opinion$ or choice$)).tw.
17. or/6-16
18. 5 and 17

Embase

1. retrolental fibroplasia/
2. (retinopath$ adj3 prematur$).tw.
3. (retrolental adj2 (fibroplas$ or fibrosis)).tw.
4. ROP.tw.
5. or/1-4
6. exp patient information/
7. health education/
8. patient education/
9. doctor patient relation/
10. patient satisfaction/
11. (patient$ adj4 (leaflet$ or booklet$ or pamphlet$ or video$ or website$ or social media)).tw.
12. (parent$ adj4 (leaflet$ or booklet$ or pamphlet$ or video$ or website$ or social media)).tw.
13. (patient$ adj4 (information or advice or advise$ or support$ or discuss$ or guidance or knowledge)).tw.

14. (parent$ adj4 (information or advice or advise$ or support$ or discuss$ or guidance or knowledge)).tw.
15. (patient$ adj4 (experience$ or expectation$ or need$ or preference$ or perspective$ or attitude$ or view$ or opinion$ or choice$)).tw.
16. (parent$ adj4 (experience$ or expectation$ or need$ or preference$ or perspective$ or attitude$ or view$ or opinion$ or choice$)).tw.
17. or/6-16
18. 5 and 17

Appendix I: Tables of evidence

Background and epidemiology

Author	Year	Country	Title	Study type	Evidence level
Adams	2017	UK	Treatment trends for retinopathy of prematurity in the UK: Active surveillance study of infants at risk.	Prospective cohort	2++
Haines	2005	UK	UK population based study of severe retinopathy of prematurity: screening, treatment, and outcome.	Prospective cohort	2++
Palmer	1991	USA	Incidence and early course of retinopathy of prematurity. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. Ophthalmology.	Prospective cohort	2++
Kim	2018	USA	Retinopathy of prematurity: a review of risk factors and their clinical significance.	Review	1+
Hartnett	2015	USA	Pathophysiology and mechanisms of severe retinopathy of prematurity.	Review	1+
Chiang	2021	International	International Classification of Retinopathy of Prematurity, Third Edition	Review and guideline	2++

Required site facilities and training for those who treat ROP

Author	Year	Country	Title	Study type	Evidence level
Adams	2017	UK	Treatment trends for retinopathy of prematurity in the UK: Active surveillance study of infants at risk.	Prospective cohort	2++
Bradley	2012	USA	Pediatric ophthalmology fellowship training in laser ablation for retinopathy of prematurity.	Survey	3
Chan	2015	USA	The Global Education Network for Retinopathy of Prematurity (Gen-Rop): Development, Implementation, and Evaluation of A Novel Tele-Education System	Training event	3
Chen	2007	UK	Variation in anaesthesia for the laser treatment of retinopathy of prematurity – A survey of ophthalmologists in the UK.	Survey	3
Kang	2013	USA	The use of digital imaging in the identification of skip areas after laser treatment for retinopathy of prematurity and its implications for education and patient care.	Retrospective case series	3
Kemper	2008	USA	Retinopathy of prematurity care: patterns of care and workforce analysis	Survey	3
Novitskaya	2020	UK	Retinopathy of prematurity treatment in the UK: trends in neonatal anaesthetic support and location of treatment from a national surveillance study.	Survey	3
Sanghi	2010	India	Frequency-doubled Nd:YAG (532 nm green) versus diode laser (810 nm) in treatment of retinopathy of prematurity.	Retrospective case series	3
Wong	2012	USA	Training fellows for retinopathy of prematurity care: A Web-based survey.	Survey	3

Treatment

Author	Year	Country	Title	Study type	Evidence level
Ophthalmic indications for treatment					
Cryotherapy for Retinopathy of Prematurity Cooperative Group	1988	USA	Multicenter trial of cryotherapy for retinopathy of prematurity. Preliminary results.	RCT	1++
Early Treatment for Retinopathy of Prematurity Cooperative Group	2003	Global	Revised Indications for the Treatment of Retinopathy of Prematurity: Results of the Early Treatment for Retinopathy of Prematurity Randomized Trial.	RCT	1++
Timing of treatment					
Schaffer	1993	USA	Prognostic factors in the natural course of retinopathy of prematurity. The Cryotherapy for Retinopathy of Prematurity Cooperative Group.	RCT	1++
Fukushima	2020	Japan	Characterization of the Progression Pattern in Retinopathy of Prematurity Subtypes.	Retrospective case series	2+
Bellsmith	2020	USA	Aggressive Posterior Retinopathy of Prematurity: Clinical and Quantitative Imaging Features in a Large North American Cohort.	Retrospective case series	2+
Treatment techniques available for treating ROP					
Palmer	2005	USA	15-Year Outcomes Following Threshold Retinopathy of Prematurity: Final Results From the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity.	RCT	1++
Cryotherapy for Retinopathy of Prematurity Cooperative Group	2001	USA	Multicenter Trial of Cryotherapy for Retinopathy of Prematurity: ophthalmological outcomes at 10 years.	RCT	1++
Good	2004	USA	Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial.	RCT	1++
Good	2006	USA	The early treatment for retinopathy of prematurity study: Structural findings at age 2 years.	RCT	1++
Mintz-hittner	2011	USA	Efficacy of Intravitreal Bevacizumab for Stage 3+ Retinopathy of Prematurity.	RCT	1++
Stahl	2019	Global	Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial.	RCT	1++

Treatment continued...

Author	Year	Country	Title	Study type	Evidence level
Adverse events					
Stahl	2019	Global	Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial.	RCT	1++
Good	2004	USA	Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial.	RCT	1++
Morrison	2018	USA	Ocular complications following treatment in the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study	Retrospective case series	2+
Davitt	2013	USA	Incidence of cataract development by 6 months' corrected age in the Early Treatment for Retinopathy of Prematurity study.	RCT	1++
Adams	2018	UK	Retinopathy of prematurity in the United Kingdom: retreatment rates, visual and structural 1-year outcomes.	Cohort study	2++
Tsai	2020	Global	Neurodevelopmental Outcomes After Bevacizumab Treatment for Retinopathy of Prematurity–A Meta- Analysis.	Meta analysis	1-
Kaushal	2020	Global	Neurodevelopmental outcomes following bevacizumab treatment for retinopathy of prematurity: a systematic review and meta-analysis.	Meta analysis	1-
Kennedy	2018	USA	Medical and developmental outcomes of bevacizumab versus laser for retinopathy of prematurity.	RCT	1-
Tinning	2016		Vascular endothelial growth factor signalling is necessary for expansion of medullary micro vessels during postnatal kidney development.	Laboratory model	4
Woik	2015		Regulation of lung development and regeneration by the vascular system.	Review of basic science	4
Rosenstein	2010		VEGF in the nervous system.	Review of basic science	4
Kong	2015		Pharmacokinetics of bevacizumab and its effects on serum vegf and igf-1 in infants with retinopathy of prematurity.	Prospective cohort	2++
Chen	2019		Serum vascular endothelial growth factor levels before and after intravitreous ranibizumab injection for retinopathy of prematurity.	Prospective cohort	2++
Fidler	2020		Ranibizumab population pharmacokinetics and free vegf pharmacodynamics in preterm infants with retinopathy of prematurity in the rainbow trial.	RCT	1++
Novitskaya	2020	UK	Retinopathy of prematurity treatment in the UK: trends in neonatal anaesthetic support and location of treatment from a national surveillance study.	Survey	3
Chen	2007	UK	Variation in anaesthesia for the laser treatment of retinopathy of prematurity – A survey of ophthalmologists in the UK.	Survey	3

Post-operative Review and re-treatment

Author	Year	Country	Title	Study type	Evidence level
Mintz-hittner	2011	USA	Efficacy of Intravitreal Bevacizumab for Stage 3+ Retinopathy of Prematurity.	RCT	1++
Stahl	2019	Global	Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial.	RCT	1++
Good	2004	USA	Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial.	RCT	1++
Adams	2018	UK	Retinopathy of prematurity in the United Kingdom: retreatment rates, visual and structural 1-year outcomes.	Prospective Cohort study	2++
Fidler	2020	Global	Ranibizumab population pharmacokinetics and free vegf pharmacodynamics in preterm infants with retinopathy of prematurity in the rainbow trial.	RCT	1++
Mueller	2017	Germany	Treatment of type I ROP with intravitreal bevacizumab or laser photocoagulation according to retinal zone.	Retrospective comparitive case series	2+
Mintz-hittner	2016	USA	Clinical Management of Recurrent Retinopathy of Prematurity after Intravitreal Bevacizumab Monotherapy.	Retrospective case series	2+
Karkhaneh	2016	Iran	Efficacy of intravitreal bevacizumab for zone-II retinopathy of prematurity.	RCT	1-
Roohipoor	2019	Iran	Comparison of intravitreal bevacizumab injection and laser photocoagulation for type 1 zone II retinopathy of prematurity.	RCT	1+
Ling	2020	Taiwan	Rates and Risk Factors for Recurrence of Retinopathy of Prematurity After Laser or Intravitreal Anti- Vascular Endothelial Growth Factor Monotherapy.	Retrospective comparitive case series	2+
Martínez-Castellanos	2020	Mexico	A proposal of an algorithm for the diagnosis and treatment of recurrence or treatment failure of retinopathy of prematurity after anti-VEGF therapy based on a large case series.	Retrospective case series	3
Zhang	2017	China	Comparison of Intravitreal Injection of Ranibizumab Versus Laser Therapy for Zone Ii Treatment-Requiring Retinopathy of Prematurity.	RCT	1+
Lyu	2017	China	Recurrence of retinopathy of prematurity after intravitreal ranibizumab monotherapy: Timing and risk factors.	Retrospective case series	3
Huang	2017	China	Ranibizumab Injection as Primary Treatment in Patients with Retinopathy of Prematurity: Anatomic Outcomes and Influencing Factors.	Retrospective case series	3
Hu	2017	China	Recurrence of Retinopathy of Prematurity in Zone II Stage 3+ after Ranibizumab Treatment:	Retrospective case series	3
Arámbulo	2018	Venezuela	Analysis of the Recurrence of Plus Disease after Intravitreal Ranibizumab as a Primary Monotherapy for Severe Retinopathy of Prematurity.	Retrospective case series	3

Post-operative Review and re-treatment continued...

Author	Year	Country	Title	Study type	Evidence level
Stahl	2021	Germany	Ranibizumab in retinopathy of prematurity – one- year follow-up of ophthalmic outcomes and two-year follow-up of neurodevelopmental outcomes from the CARE-ROP study.	RCT	1+
Honda	2008	Japan	Acute contraction of the proliferative membrane after an intravitreal injection of bevacizumab for advanced retinopathy of prematurity.	Single case report	3
Fierson	2018	USA	Screening examination of premature infants for retinopathy of prematurity.	Opinion	4
Sahin	2018	Turkey	Ultra-low dose of intravitreal bevacizumab in retinopathy of prematurity.	Retrospective case series	2+
Lepore	2017	Italy	Follow-up to Age 4 Years of Treatment of Type 1 Retinopathy of Prematurity Intravitreal Bevacizumab Injection versus Laser: Fluorescein Angiographic Findings.	RCT	1+
Cheng	2019	China	Fluorescein angiography of retinal vascular involution after intravitreal injection of ranibizumab for retinopathy of prematurity.	Retrospective case series	3
Al-Taie	2019	New Zealand	Persistent avascular retina in infants with a history of type 2 retinopathy of prematurity: To treat or not to treat?	Prospective cohort	2++
Garcia Gonzalez	2018	USA	Prophylactic peripheral laser and fluorescein angiography after bevacizumab for retinopathy of prematurity.	Retrospective case series	3

Long-term follow-up and review

Author	Year	Country	Title	Study type	Evidence level
Adams	2018	UK	Retinopathy of prematurity in the United Kingdom: retreatment rates, visual and structural 1-year outcomes.	Prospective Cohort study	2++
Fidler	2020		Ranibizumab population pharmacokinetics and free VEGF pharmacodynamics in preterm infants with retinopathy of prematurity in the rainbow trial.	RCT	1++
Mueller	2017	Germany	Treatment of type I ROP with intravitreal bevacizumab or laser photocoagulation according to retinal zone.	Retrospective comparitive case series	2+
Mintz-hittner	2016	USA	Clinical Management of Recurrent Retinopathy of Prematurity after Intravitreal Bevacizumab Monotherapy.	Retrospective case series	2+
Karkhaneh	2016	Iran	Efficacy of intravitreal bevacizumab for zone-II retinopathy of prematurity.	RCT	1-
Roohipoor	2019	Iran	Comparison of intravitreal bevacizumab injection and laser photocoagulation for type 1 zone II retinopathy of prematurity.	RCT	1+
Ling	2020	Taiwan	Rates and Risk Factors for Recurrence of Retinopathy of Prematurity After Laser or Intravitreal Anti- Vascular Endothelial Growth Factor Monotherapy.	Retrospective comparative case series	2+
Martínez-Castellanos	2020	Mexico	A proposal of an algorithm for the diagnosis and treatment of recurrence or treatment failure of retinopathy of prematurity after anti-VEGF therapy based on a large case series.	Retrospective case series	3
Zhang	2017	China	Comparison of Intravitreal Injection of Ranibizumab Versus Laser Therapy for Zone Ii Treatment-Requiring Retinopathy of Prematurity	RCT	1+
Lyu	2017	China	Recurrence of retinopathy of prematurity after intravitreal ranibizumab monotherapy: Timing and risk factors.	Retrospective case series	3
Huang	2017	China	Ranibizumab Injection as Primary Treatment in Patients with Retinopathy of Prematurity: Anatomic Outcomes and Influencing Factors.	Retrospective case series	3
Hu	2017	China	Recurrence of Retinopathy of Prematurity in Zone II Stage 3+ after Ranibizumab Treatment: A Retrospective Study.	Retrospective case series	3
Arámbulo	2018	Venezuela	Analysis of the Recurrence of Plus Disease after Intravitreal Ranibizumab as a Primary Monotherapy for Severe Retinopathy of Prematurity.	Retrospective case series	3
Stahl	2021	Germany	Ranibizumab in retinopathy of prematurity – one- year follow-up of ophthalmic outcomes and two-year follow-up of neurodevelopmental outcomes from the CARE-ROP study.	RCT	1+
Honda	2008	Japan	Acute contraction of the proliferative membrane after an intravitreal injection of bevacizumab for advanced retinopathy of prematurity.	Single case report	3
Fierson	2018	USA	Screening examination of premature infants for retinopathy of prematurity.	Opinion	4
Sahin	2018	Turkey	Ultra-low dose of intravitreal bevacizumab in retinopathy of prematurity.	Retrospective case series	2+

Long-term follow-up and review continued...

Author	Year	Country	Title	Study type	Evidence level
Lepore	2017	Italy	Follow-up to Age 4 Years of Treatment of Type 1 Retinopathy of Prematurity Intravitreal Bevacizumab Injection versus Laser: Fluorescein Angiographic Findings.	RCT	1+
Cheng	2019	China	Fluorescein angiography of retinal vascular involution after intravitreal injection of ranibizumab for retinopathy of prematurity.	Retrospective case series	3
Al-Taie	2019	New Zealand	Persistent avascular retina in infants with a history of type 2 retinopathy of prematurity: To treat or not to treat?	Prospective cohort	2++
Garcia Gonzalez	2018	USA	Prophylactic peripheral laser and fluorescein angiography after bevacizumab for retinopathy of prematurity.	Retrospective case series	3

Treatment of asymmetric ROP

Author	Year	Country	Title	Study type	Evidence level
Azad R	2010	India	Profile of asymmetrical retinopathy of prematurity in twins.	Retrospective Cohort	2+
Quinn GE	1995	USA	Correlation of Retinopathy of Prematurity in Fellow Eyes in the Cryotherapy for Retinopathy of Prematurity Study.	Prospective Cohort	2++

Retinal reattachment surgery

Author	Year	Country	Title	Study type	Evidence level
Hansen ED	2019	USA	A review of treatment for retinopathy of prematurity.	Expert opinion	4
Yonekawa Y	2016	International	Immediate Sequential Bilateral Pediatric Vitreoretinal Surgery: An International Multicenter Study.	Retrospective case series	3
Nudleman E	2015	USA	Long term outcome on lens clarity after lens sparing vitrectomy for Retinopathy of Prematurity.	Retrospective case series	3
Aoyama K	2010	Japan	Anesthesia protocols for early vitrectomy in former preterm infants diagnosed with aggressive posterior retinopathy of prematurity.	Retrospective case series	3
Singh R	2012	USA	Long-term visual outcomes following lens sparing vitrectomy for Retinopathy of Prematurity.	Retrospective case review	3
Nudleman E	2018	USA	Glaucoma after Lens-Sparing Vitrectomy for Advanced Retinopathy of Prematurity.	Retrospective case series	3
Iwahasmi-Shima C	2012	Japan	Intraocular pressure elevation is a delayed-onset complication after successful vitrectomy for stages 4 and 5 retinopathy of prematurity.	Retrospective case series	3
Karacorlu M	2017	Turkey	Long-term functional results following vitrectomy for advanced retinopathy of prematurity.	Retrospective case review	3
Ozsaygili C	2019	Turkey	Parameters affecting postoperative success of surgery for stage 4A/4B ROP.	Retrospective case series	3
El Reyes	2008	Egypt	Three year anatomic and visual outcomes after vitrectomy for stage 4B Retinopathy of prematurity.	Retrospective case series	3
Ozsaygili C	2021	Turkey	Pre-operative anatomical features associated with improved surgical outcomes for stage 5 ROP.	Retrospective case series	3
Patel CK	2021	UK	Evolution of outcomes of surgery for retinal detachment in retinopathy of prematurity.	Retrospective case series	3

Treating disorganised anterior segment

Author	Year	Country	Title	Study type	Evidence level
Hansen	2019	USA	A review of treatment for retinopathy of prematurity.	Review	4
Ozsaygili	2021	Turkey	Preoperative Anatomical Features Associated With Improved Surgical Outcomes for Stage 5 ROP.	Case series	3
Nudleman	2018	USA	Glaucoma after Lens-Sparing Vitrectomy for Advanced Retinopathy of Prematurity.	Case series	2+
Senthil	2020	India	Management outcomes of secondary glaucoma due to retinopathy of prematurity: A 19-year prospective study at a tertiary eye care Institute.	Prospective case series	2+
Lee	2020	USA	The role of lens extraction and goniosynechialysis.	Case series	3
Trigler	2005	USA	Case series of angle-closure glaucoma after laser treatment for retinopathy of prematurity.	Case series	3

What information should be provided for parents and when should this information be provided

Author	Year	Country	Title	Study type	Evidence level
Flanagan	2017	UK	Involving the parents of preterm infants.	Expert opinion	4
Eneriz-Wiemer	2018	USA	Parents' Knowledge and Education of Retinopathy of Prematurity in Four California Neonatal Intensive Care Units.	Cross-sectional study	3

Appendix J: Conflict of interest statements

GGW Adams	Institutional grant support from Bayer
L Allen	NIHR institutional grant, equity holder Neocam, Cambridge Medical Innovations, inventor Neocam, Digivis, Kidseyez
F Ashworth	Honorarium from Bayer ,Biomarin MPS, Tamid Biotech
S Biswas	Unpaid member of clinical advisory board to Phoenix Technology Group; honorarium from Santen and Recordati Rare Diseases
B W Fleck	Unpaid consultant to Novartis as a member of the RAINBOW Trial committee
R Henderson	Honorarium received from Novartis and Medscape
A C Houtman	Wellcome Institutional Strategic Support Fund (ISSF) Feasibility Award
M O'Gallagher	Expenses and honorarium from Thea Pharmaceuticals, Santen, PAssPACES
L Wickham	Payment for talks by B+L and Alcon
S Wren	Honorarium from Alcon

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