CLINICAL PRIORITIES ADVISORY GROUP
March 2023

Agenda Item No	3.1
National Programme	Trauma
Clinical Reference Group	Specialised ophthalmology
URN	2201

Title
Ranibizumab in retinopathy of prematurity (preterm babies)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
Retinopathy of prematurity is a sight threatening condition caused by abnormal vascular development in the retina linked with vascular endothelial growth factor (VEGF) in preterm babies. The proposal is to use ranibizumab for a subset of babies who may benefit from using this drug when the current standard treatment of diode laser is not clinically suitable. For eligible babies, ranibizumab is a simpler intervention which, unlike standard laser treatment, does not require sedation with general anaesthetic and can be performed in an appropriate neonatal intensive care unit. Evidence suggests that ranibizumab is associated with a larger reduction in myopia than laser after 2 years. However, ranibizumab requires regular (weekly, twice monthly, and monthly) follow up in the first year, and annual follow up until age 5 years. By contrast, laser requires fewer follow up visits. Retreatment rates with ranibizumab are also higher than those with laser.

Clinical Panel recommendation
The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy proposition.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.

2.	The Head of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In preterm infants, what is the clinical effectiveness and safety of ranibizumab as first line drug treatment compared with standard of care for ROP?

Outcome	**Evidence statement**
Clinical Effectiveness	
Critical outcomes	
Unfavourable structural retinal outcomes **Certainty of evidence:** Low to very low	Unfavourable structural retinal outcomes include substantial temporal retinal vessel dragging causing structural features of macular ectopia; or retrolental membrane obscuring the posterior pole, posterior retinal fold, or retinal detachment involving the macula. This outcome is important for patients because they can all contribute to poor vision or blindness. In total, two RCTs, one extension study from the RAINBOW RCT and four retrospective cohort studies provided evidence relating to unfavourable structural retinal outcomes in infants with ROP for between 24 weeks and approximately three years follow-up. Results comparing ranibizumab and laser therapy were available from the two RCTs, the RCT extension study and one retrospective cohort study. Results comparing ranibizumab, laser therapy and bevacizumab were available from two retrospective cohort studies. Results comparing ranibizumab and bevacizumab were available from one retrospective cohort study. **At ≥3 years:** *Ranibizumab vs laser therapy* • One retrospective cohort study (Kang et al 2019) reported *statistically significantly fewer* cases of retinal detachment and temporal macular dragging for ranibizumab vs laser therapy at mean ± SD 36.3 ± 31.9 months follow-up. Retinal detachment occurred in 1/53 eyes (0.7%) after ranibizumab and 8/161 eyes (5.0%) after laser therapy (p=0.037). Temporal macular dragging occurred in 1/53 eyes (0.7%) after ranibizumab and 7/161 eyes (4.3%) after laser therapy (p=0.039). (**VERY LOW)** *Ranibizumab, laser therapy and bevacizumab*

Outcome	Evidence statement
	• One retrospective cohort study (Ling et al 2019) reported *no statistically significant difference* in progression to retinal detachment between ranibizumab (1/48 eyes, 2.1%), laser therapy (3/61 eyes, 4.9%) and bevacizumab (2/231 eyes, 0.9%) (p=0.2701) at mean ± SD 197.3 ± 110 weeks follow-up. (**VERY LOW)** **At 18 months to 2 years:** *Ranibizumab vs laser therapy* • One RCT extension study (Marlow et al 2021, RAINBOW) reported *no statistically significant difference* in structural abnormalities[1] present at age 20-28 months (corrected for prematurity) between two ranibizumab doses (0.2mg 1/56, 1.8%; 0.1mg 1/51, 2.0%) and laser therapy (4/44, 9.1%). The odds ratio of having no structural abnormality was 5.68 (95%CI 0.60 to 54), p=0.10 for ranibizumab 0.2mg vs laser therapy and 4.82 (95%CI 0.52 to 45), p=0.14 for ranibizumab 0.1mg vs laser therapy. **(LOW)** *Ranibizumab, laser therapy and bevacizumab* • One retrospective cohort study (Gunay et al 2017) reported no unfavourable anatomical outcomes[2] for 22 patients with ranibizumab or 55 patients with bevacizumab and one unfavourable anatomical outcome (retinal detachment) in one of 57 patients (1.8%) with laser therapy. Mean follow-up was 18.96 ± 4.79 months for ranibizumab, 20.68 ± 6.89 months for laser therapy and 19.40 ± 6.43 months for bevacizumab. No statistical comparison between groups reported. **(VERY LOW)** **At approximately 1 year:** *Ranibizumab vs laser therapy* • One RCT (Zhang et al 2017) reported no retinal detachment cases in patients who received ranibizumab (n=25) or laser therapy (n=25). Mean ± SD follow-up was 49.94 ± 14.67 weeks for ranibizumab and 54.03 ± 12.40 weeks for laser therapy. **(LOW)** *Ranibizumab vs bevacizumab* • One retrospective cohort study (Kang et al 2018) reported *no statistically significant difference* in cases of retinal detachment or temporal macular dragging between ranibizumab and bevacizumab at mean ± SD follow-up of 13.9 ± 12.5 months for ranibizumab and 30.9 ± 18.4 months for bevacizumab. Retinal detachment occurred in 0/52 eyes (0%) after ranibizumab and 1/101 eyes (1.0%) after bevacizumab (p=0.660). Temporal macular dragging occurred in 1/52 eyes (1.9%) after ranibizumab and 0/101 eyes (0%) after bevacizumab (p=0.340)[3]. (**VERY LOW)** **At 24 weeks:** *Ranibizumab vs laser therapy* • One RCT (Stahl et al 2019, RAINBOW) reported number of unfavourable structural retinal outcomes at 24 weeks follow-up for two

[1] In the RAINBOW RCT structural abnormalities included abnormalities that have potential effects on visual acuity: retrolental membrane obscuring the view of the posterior pole, substantial temporal retinal vessel dragging causing abnormal structural features or macular ectopia, posterior retinal fold involving the macula, or retinal detachment involving the macula

[2] Unfavourable anatomical outcomes were any of: dragging of the disc, localised tractional or non-tractional membranes at posterior pole or in the retinal periphery and total or partial retinal detachment

[3] There is a discrepancy in the paper about whether the one patient with temporal macular dragging received bevacizumab or ranibizumab. The result from the data table (rather than the text) is reported here

Outcome	Evidence statement
	ranibizumab doses (0.2mg 1/74, 1.4%; 0.1mg 5/77, 6.5%) and laser therapy (7/74, 9.5%). No statistical comparison between groups reported. **(LOW)** **For ranibizumab vs laser therapy: One RCT provided low certainty evidence of unfavourable structural retinal outcomes in 1% and 7% of patients who received 0.2mg and 0.1mg of ranibizumab respectively and 10% of patients who received laser therapy after 24 weeks follow-up. The groups were not statistically compared. An extension study to this RCT provided low certainty evidence of no statistically significant difference in structural abnormalities between ranibizumab and laser therapy at age 20-28 months (corrected for prematurity). A second RCT reported no cases of retinal detachment with either ranibizumab or laser therapy at approximately 12 months follow-up. One retrospective cohort study provided very low certainty evidence of statistically significantly fewer cases of retinal detachment and temporal dragging for ranibizumab compared to laser therapy at a mean of 36 months follow-up.** **For ranibizumab, laser therapy and bevacizumab: One retrospective cohort study provided very low certainty evidence of no statistically significant difference in retinal detachment between ranibizumab, laser therapy and bevacizumab at a mean of 197 weeks follow-up. A second retrospective study provided very low certainty evidence of a single unfavourable anatomical outcome (1.8%) in a patient who received laser therapy and no cases with ranibizumab or bevacizumab at 18-20 months follow-up. The groups were not statistically compared.** **For ranibizumab vs bevacizumab: One retrospective cohort study provided very low certainty evidence of no statistically significant difference in retinal detachment or temporal macular dragging between ranibizumab and bevacizumab at a mean follow-up of 14 months for ranibizumab and 31 months for bevacizumab.**
High myopia **Certainty of evidence:** Low to very low	High myopia (for example, <5 Dioptres), is important for patients because this contributes to patients being dependent on glasses. Glasses are essential to wear during the child's "critical period" of development up to 7 years. It can be difficult for many patients to wear glasses earlier than this age and non-compliance with not wearing them can lead to a "lazy eye" (amblyopia). In total, one extension study from the RAINBOW RCT and one retrospective cohort study provided evidence relating to high myopia outcomes in infants with ROP at 18 months to two years follow-up. Results comparing ranibizumab and laser therapy were available from the RCT extension study. Results comparing ranibizumab, laser therapy and bevacizumab were available from the retrospective cohort study. **At 18 months to 2 years:** *Ranibizumab vs laser therapy* • One RCT extension study (Marlow et al 2021, RAINBOW) reported *statistically significantly fewer* cases of high myopia present in at least one eye at age 20-28 months (corrected for prematurity) for 0.2mg ranibizumab (4/55, 7.3%) vs laser therapy (14/41, 34.1%) (OR 0.15 (95%CI 0.05 to 0.50) p=0.0021)[4]. The prevalence of high myopia per eye at age 20-28 months was also *statistically significantly lower* for 0.2mg ranibizumab (5/110 eyes, 4.5%) vs laser therapy (16/82 eyes,

[4] Outcome not reported for ranibizumab 0.1mg

Outcome	Evidence statement
	19.5%) (OR 0.19 (95%CI 0.05 to 0.69) p=0.012). There was *no statistically significant difference* in the prevalence of high myopia per eye at age 20-28 months between 0.1mg ranibizumab (8/98 eyes, 8.2%) and laser therapy (16/82 eyes, 19.5%) (OR 0.44 (95%CI 0.14 to 1.32) p=0.14). **(LOW)** *Ranibizumab, laser therapy and bevacizumab* • One retrospective cohort study (Gunay et al 2017) reported *no statistically significant difference* in the proportion of patients with high myopia between ranibizumab (13.6%), laser therapy (14%) and bevacizumab (12.7%) (p=0.979). Mean follow-up was 18.96 ± 4.79 months for ranibizumab, 20.68 ± 6.89 months for laser therapy and 19.40 ± 6.43 months for bevacizumab. **(VERY LOW)** **For ranibizumab vs laser therapy: One RCT extension study provided low certainty evidence of statistically significantly less high myopia for 0.2mg ranibizumab compared to laser therapy at age 20-28 months (corrected for prematurity). There was no statistically significant difference in high myopia for 0.1mg ranibizumab compared to laser therapy in this study.** **For ranibizumab, laser therapy and bevacizumab: One retrospective cohort study provided very low certainty evidence of no statistically significant difference in high myopia between ranibizumab, laser therapy and bevacizumab at approximately 18-20 months follow-up.**
Sight impairment/ severe sight impairment **Certainty of evidence:** Low to very low	Sight impairment/ severe sight impairment includes irreversible sight impairment outcomes such as amblyopia which cannot be treated. High myopia which does not lead to amblyopia would not overlap as it is treatable with glasses. This outcome is important for patients because this is a disability and may restrict many activities and occupations for the patient later in life. In total, one RCT (RAINBOW), one extension study from the RAINBOW RCT and two retrospective cohort studies provided evidence relating to sight impairment/ severe sight impairment in infants with ROP for between 24 weeks and approximately three years follow-up. Results comparing ranibizumab and laser therapy were available from the RCT, the RCT extension study and one retrospective cohort study. Results comparing ranibizumab and bevacizumab were available from one retrospective cohort study. Outcomes relating to sight impairment reported by the studies included cases of nystagmus[5], strabismus[6], abnormal fixation and abnormal pupil reaction (not further defined in the studies but may be associated with sight impairment/ severe sight impairment). **At 3 years:** *Ranibizumab vs laser therapy* • One retrospective cohort study (Kang et al 2019) reported *no statistically significant difference* in strabismus operations between ranibizumab (21/153 eyes, 13.7%) and laser therapy (26/161 eyes, 16.1%) (p=0.636) at mean ± SD 36.3 ± 31.9 months follow-up. (**VERY LOW)**

[5] Nystagmus is a rhythmical, repetitive and involuntary movement of the eyes which the patient has no control over. There is no cure for nystagmus and sight problems are common (Nystagmus | Great Ormond Street Hospital (gosh.nhs.uk)). However, it is also possible to have this condition with normal or near normal vision

[6] Strabismus is a squint, where the eyes point in different directions. If untreated in young children, lazy eye (amblyopia) can develop with poor vision in the eye with the squint (Squint (strabismus) - Moorfields Eye Hospital). However, it is also possible to have this condition with normal or near normal vision

Outcome	Evidence statement
	At 2 years: *Ranibizumab vs laser therapy* • One RCT extension study (Marlow et al 2021, RAINBOW) reported number of nystagmus cases, strabismus cases, abnormal fixation cases and abnormal pupil reaction cases at age 20-28 months (corrected for prematurity) for two ranibizumab doses and laser therapy. Nystagmus occurred in 2/55 patients (3.6%) after 0.2mg ranibizumab, 3/50 (6.0%) after 0.1mg ranibizumab and 5/41 (12.2%) after laser therapy. Strabismus occurred in 11/55 patients (20.0%) after 0.2mg ranibizumab, 12/49 (24.5%) after 0.1mg ranibizumab and 13/41 (31.7%) after laser therapy. Abnormal fixation occurred in 1/55 patients (1.8%) after 0.2mg ranibizumab, 8/52 (15.4%) after 0.1mg ranibizumab and 2/44 (14.5%) after laser therapy. Abnormal pupil reaction occurred in 0/55 patients (0%) after 0.2mg ranibizumab, 3/52 (6.0%) after 0.1mg ranibizumab and 1/42 (2.4%) after laser therapy. No statistical comparison between groups reported. **(LOW)** **At approximately 1 year[7]:** *Ranibizumab vs bevacizumab* • One retrospective cohort study (Kang et al 2018) reported *statistically significantly fewer* strabismus operations for ranibizumab (0/52 eyes, 0%) vs bevacizumab (21/101 eyes, 20.8%) ($p<0.001$) at mean ± SD follow-up of 13.9 ± 12.5 months for ranibizumab and 30.9 ± 18.4 months for bevacizumab. (**VERY LOW)** **At 24 weeks:** *Ranibizumab vs laser therapy* • One RCT (Stahl et al 2019, RAINBOW) reported number of nystagmus cases at 24 weeks follow-up for two ranibizumab doses (0.2mg 1/73, 1.4%; 0.1mg 0/76, 0%) and laser therapy (0/69, 0%). No statistical comparison between groups reported. **(LOW)** **For ranibizumab vs laser therapy: One RCT provided low certainty evidence of a single nystagmus case (1.4%) at 24 weeks follow-up for 0.2mg ranibizumab. There were no cases of nystagmus after 0.1mg ranibizumab or laser therapy. An extension study to this RCT provided low certainty evidence of outcomes at age 20-28 months (corrected for prematurity). This reported nystagmus in 3.6% and 6.0% of patients after 0.2mg and 0.1mg of ranibizumab respectively and 12.2% after laser therapy. This study also reported strabismus in 20.0% and 24.5% of patients after 0.2mg and 0.1mg of ranibizumab respectively and 31.7% after laser therapy. Abnormal fixation occurred in 1.8% and 15.4% of patients after 0.2mg and 0.1mg of ranibizumab respectively and 14.5% after laser therapy. Abnormal pupil reaction occurred in 0% and 6.0% of patients after 0.2mg and 0.1mg of ranibizumab respectively and 2.4% after laser therapy. This RCT and RCT extension study did not statistically compare the groups. One retrospective cohort study provided very low certainty evidence of no statistically significant difference in strabismus operations between ranibizumab and laser therapy at a mean of 36 months follow-up.** **For ranibizumab vs bevacizumab: One retrospective cohort study provided very low certainty evidence of statistically significantly fewer strabismus operations for ranibizumab compared to bevacizumab at a**

[7] Based on the mean follow-up for the ranibizumab group

Outcome	Evidence statement
	mean follow-up of 14 months for ranibizumab and 31 months for bevacizumab.
Important outcomes	
Treatment failure **Certainty of evidence:** Moderate to very low	Treatment failure (for example, retreatment within 24 weeks for ranibizumab or within 4 weeks for diode laser) is important for patients because they may need to come back for more treatment which can be inconvenient for the patient or put them at risk if anaesthesia is needed for the treatment. In total, two RCTs and five retrospective cohort studies provided evidence relating to treatment failure in infants with ROP for between 24 weeks and approximately three years follow-up. Results comparing ranibizumab and laser therapy were available from two RCTs and two retrospective cohort studies. Results comparing ranibizumab, laser therapy and bevacizumab were available from two cohort studies. Results comparing ranibizumab and bevacizumab were available from one retrospective cohort study. **At ≥3 years:** *Ranibizumab vs laser therapy* • One retrospective cohort study (Kang et al 2019) reported *no statistically significant difference* in treatment failure between ranibizumab (15/153 eyes, 9.8%) and laser therapy (22/161 eyes, 13.7%) (p=0.196) at mean ± SD 36.3 ± 31.9 months follow-up. Mean time to retreatment was 5.7 weeks for ranibizumab and 2.3 weeks for laser therapy. (**VERY LOW)** *Ranibizumab, laser therapy and bevacizumab* • One retrospective cohort study (Ling et al 2019) reported *no statistically significant difference* in treatment failure between ranibizumab (10/48 eyes, 20.8%), laser therapy (11/61 eyes, 18.0%) and bevacizumab (23/231 eyes, 10.0%) (p=0.0528) at mean ± SD 197.3 ± 110 weeks follow-up. In multivariable regression analysis, ranibizumab was a *statistically significant* independent risk factor for treatment failure compared to bevacizumab (OR 2.922 (95%CI 1.179 to 7.240), p=0.0205). Mean ± SD time to retreatment was 8.3 ± 1.6 weeks for ranibizumab, 3.6 ± 1.4[8] weeks for laser therapy and 8.8 ± 3.9 weeks for bevacizumab. (**VERY LOW)** **At approximately 18 months:** *Ranibizumab, laser therapy and bevacizumab* • One retrospective cohort study (Gunay et al 2017) reported *no statistically significant difference* in treatment failure between ranibizumab (3/22, 13.6%), laser therapy (0/57, 0%) and bevacizumab (3/55, 5.5%) (p=0.098) at mean ± SD follow-up of 18.96 ± 4.79 months for ranibizumab, 20.68 ± 6.89 months for laser therapy and 19.40 ± 6.43 months for bevacizumab. Mean ± SD time to retreatment was 8.7 ± 1.5 weeks for ranibizumab and 14 ± 2.65 weeks for bevacizumab. **(VERY LOW)** **At approximately 1 year:** *Ranibizumab vs laser therapy* • One RCT (Zhang et al 2017) reported treatment failure in 11/25 (44.0%) patients who received ranibizumab and 1/25 (4.0%) patients who received laser therapy at mean ± SD follow-up of 49.94 ± 14.67 weeks for ranibizumab and 54.03 ± 12.40 weeks for laser therapy. No statistical comparison between groups reported. Time to treatment

[8] The mean ± SD time to recurrence for laser therapy suggests some infants received retreatment post 4 weeks but this number is not reported

Outcome	Evidence statement
	failure ranged from 4 to 13 weeks for ranibizumab and was one week for laser therapy. **(MODERATE)** *Ranibizumab vs bevacizumab* • One retrospective cohort study (Kang et al 2018) reported that *statistically significantly more* eyes required additional anti-VEGF treatment for ranibizumab (7/52 eyes, 13.5%) vs bevacizumab (4/101 eyes, 4.0%) (p=0.037). The number of eyes requiring any additional treatment was 7/52 eyes (13.5%) for ranibizumab and 8/101 eyes (7.9%) for bevacizumab. No statistical comparison between groups reported. Mean ± SD follow-up was 13.9 ± 12.5 months for ranibizumab and 30.9 ± 18.4 months for bevacizumab. Time to retreatment not reported[9]. **(VERY LOW)** **At approximately 6 months:** *Ranibizumab vs laser therapy* • One RCT (Stahl et al 2019, RAINBOW) reported treatment failure up to 24 weeks follow-up for two ranibizumab doses (0.2mg 23/74, 31.1%; 0.1mg 24/77, 31.2%) and laser therapy (10/74, 13.5%). No statistical comparison between groups reported. Additional treatments after ranibizumab occurred between days 1 and 169 after initial treatment. Additional treatments after laser therapy occurred between days 1 and 29. **(LOW)** • One retrospective cohort study (Chmielarz-Czarnocińska et al 2021) reported treatment failure in 80/120 eyes (66.7%) with ranibizumab and 0/226 eyes with laser therapy at up to six months follow-up. No statistical comparison between groups reported. Time to first retreatment was 7.3 weeks to 25.4 weeks[10]. **(VERY LOW)** **For ranibizumab vs laser therapy: One RCT provided low certainty evidence of treatment failure in 31% of patients with two different ranibizumab doses and 14% with laser therapy at up to 24 weeks follow-up. A second RCT provided low certainty evidence of treatment failure in 44% of patients with ranibizumab and 4% with laser therapy at up to approximately 12 months follow-up. The RCT groups were not statistically compared. One retrospective cohort study provided very low certainty evidence of no statistically significant difference in treatment failure between ranibizumab and laser therapy at approximately three years follow-up. A second retrospective cohort study provided very low certainty evidence of treatment failure in 67% of patients following ranibizumab and 0% of patients after laser therapy at up to six months follow-up. The groups were not statistically compared.** **For ranibizumab, laser therapy and bevacizumab: Two retrospective cohort studies provided very low certainty evidence of no statistically significant difference in treatment failure between ranibizumab, laser therapy and bevacizumab at approximately three years and 18-20 months follow-up respectively. However, in one of these studies, treatment failure was statistically significantly higher for ranibizumab compared to bevacizumab in multivariable regression analysis.** **For ranibizumab vs bevacizumab: One retrospective cohort study provided very low certainty evidence of treatment failure requiring any**

[9] These results are presented as treatment failure due to the absence of any evidence to confirm that retreatment was required after 24 weeks

[10] The time to first retreatment range suggests some infants from the ranibizumab group may have received retreatment post 24 weeks but this number is not reported

Outcome	Evidence statement
	retreatment in 14% of patients after ranibizumab and 8% after bevacizumab at a mean follow-up of 14 months for ranibizumab and 31 months for bevacizumab. This study also reported that statistically significantly more eyes initially treated with ranibizumab required retreatment with anti-VEGF compared to eyes initially treated with bevacizumab.
Quality of life (QoL) **Certainty of evidence:** Low	Quality of life (for example, Children's Visual Function Questionnaire capturing vision-related QoL or broader standard QoL scales) is important for patients because it gives a measurement of the patient's vision-related quality of life. In total, one extension study from the RAINBOW RCT provided evidence relating to quality of life in infants with ROP at two years follow-up. This study compared ranibizumab and laser therapy. Quality of life was assessed using the Children's Visual Function Questionnaire (CVFQ)[11] and the Mullen Scales of Early Learning[12]. No evidence was identified relating to quality of life for ranibizumab vs bevacizumab. **At 2 years:** *Ranibizumab vs laser therapy* • One RCT extension study (Marlow et al 2021, RAINBOW) reported *no statistically significant difference* in quality of life assessed using the CVFQ at age 20-28 months (corrected for prematurity) between two ranibizumab doses (0.2mg n=54; 0.1mg n=50) and laser therapy (n=37). For 0.2mg ranibizumab vs laser therapy mean composite scores were 84 (95%CI 80 to 88) vs 77 (95%CI 72 to 83) (p=0.063). For 0.1mg ranibizumab vs laser therapy mean composite scores were 79 (95%CI 75 to 83) vs laser therapy (as above) (p>0.05). **(LOW)** • One RCT extension study (Marlow et al 2021, RAINBOW) reported median (IQR) T-scores for three subscales of the Mullen Scales of Early Learning at age 20-28 months (corrected for prematurity) for two ranibizumab doses (0.2mg n=56; 0.1mg n=52) and laser therapy (n=43). Visual reception T-scores were 40 (29 to 52) for 0.2mg ranibizumab, 38 (25 to 49) for 0.1mg ranibizumab and 40 (20 to 49) for laser therapy. Receptive language T-scores were 44 (36 to 50) for 0.2mg ranibizumab, 40 (27 to 49) for 0.1mg ranibizumab and 40 (27 to 50) for laser therapy. Expressive language T-scores were 36 (30 to 44) for 0.2mg ranibizumab, 30 (25 to 41) for 0.1mg ranibizumab and 33 (22 to 46) for laser therapy. No statistical comparison between groups reported. **(LOW)** **For ranibizumab vs laser therapy: One RCT extension study provided low certainty evidence of no statistically significant difference in vision-related quality of life at age 20-28 months (corrected for prematurity) between ranibizumab and laser therapy. The same study also reported similar scores for the different groups in an assessment using a scale of early learning but did not statistically compare the groups.**

[11] The CVFQ for children under 3 years of age is a validated questionnaire with 4 vision-related subscales (competence, personality, family impact and treatment effect), 2 subscales for general health and general vision and a summative composite score. Scores are derived from 5-point Likert-type scales from 1.0 (best possible outcome) to 0.0 (worst possible outcome). Subscale and summary scores are standardised to range from 0 to 100 with higher scores indicating better function/ quality of life

[12] The Mullen Scales of Early Learning assess developmental progress with 3 subscales (visual recognition, receptive language and expressive language). The mean population norm T-score is 50 (SD 10)

Outcome	Evidence statement
Retreatment **Certainty of evidence:** Very low	Retreatment (for example, post 24 weeks for ranibizumab or post 4 weeks for diode laser) is important for patients because they may need to come back for more treatment which can be inconvenient for the patient or put them at risk if anaesthesia is needed for treatment. In total, one RCT (RAINBOW), one extension study from the RAINBOW RCT and one retrospective cohort study provided evidence relating to retreatment in infants with ROP for between up to 24 weeks and up to approximately two years follow-up. These studies compared ranibizumab and laser therapy. No evidence was identified for retreatment for ranibizumab vs bevacizumab. **At up to two years:** *Ranibizumab vs laser therapy* • One RCT and RCT extension study (Marlow et al 2021, Stahl et al 2019, RAINBOW) reported that 0/56 patients in the 0.2mg ranibizumab group and 1/53 (1.9%) in the 0.1mg ranibizumab group received retreatment during the extension study, between 24 weeks and up to two years after initial treatment. In addition, 4/74 (5.4%) patients in the laser therapy group received retreatment more than four weeks after their initial treatment. No statistical comparison between groups reported. **(VERY LOW)** **At up to six months:** *Ranibizumab vs laser therapy* • One retrospective cohort study (Chmielarz-Czarnocińska et al 2021) reported that 46/226 eyes (20.4%) from the laser therapy group received retreatment between seven weeks and approximately six months after initial treatment. It is not clear if any ranibizumab group patients received retreatment more than 24 weeks after initial treatment. **(VERY LOW)** **For ranibizumab vs laser therapy: One RCT and RCT extension study provided very low certainty evidence of retreatment for a single patient (1.9%) after 0.1mg ranibizumab and 5% of patients after laser therapy. There were no retreatments after 0.2mg ranibizumab up to approximately two years follow-up. The groups were not statistically compared. A retrospective cohort study provided very low certainty evidence that 20% of eyes that initially received laser therapy had retreatment up to six months after initial treatment. It was not clear if any patients from the ranibizumab group had received retreatment in this study.**
Development of infection **Certainty of evidence:** Low to very low	Development of infection (for example, endophthalmitis) is important for patients because it may lead to permanent blindness. In total, two RCTs and one retrospective cohort study provided evidence relating to development of infection in infants with ROP for between 24 weeks and 18-20 months follow-up. Results comparing ranibizumab and laser therapy were available from the two RCTs. Results comparing ranibizumab, laser therapy and bevacizumab were available from the retrospective cohort study. **At 18 - 20 months:** *Ranibizumab, laser therapy and bevacizumab* • One retrospective cohort study (Gunay et al 2017) reported no cases of endophthalmitis for 22 patients after ranibizumab, 55 patients after laser therapy or 57 patients after bevacizumab. Mean follow-up was 18.96 ± 4.79 months for ranibizumab, 20.68 ± 6.89 months for laser therapy and 19.40 ± 6.43 months for bevacizumab. **(VERY LOW)**

Outcome	Evidence statement
	At approximately 1 year: *Ranibizumab vs laser therapy* • One RCT (Zhang et al 2017) reported no cases of endophthalmitis in patients who received ranibizumab (n=25) or laser therapy (n=25). Mean ± SD follow-up was 49.94 ± 14.67 weeks for ranibizumab and 54.03 ± 12.40 weeks for laser therapy. **(LOW)** **At 24 weeks:** *Ranibizumab vs laser therapy* • One RCT (Stahl et al 2019, RAINBOW) reported endophthalmitis cases at 24 weeks follow-up for two ranibizumab doses (0.2mg 0/73, 0%; 0.1mg 1/76, 1.3%) and laser therapy (0/69, 0%). No statistical comparison between groups reported. **(VERY LOW)** **For ranibizumab vs laser therapy: One RCT provided very low certainty evidence of a single case of endophthalmitis (1.3%) at 24 weeks follow-up after 0.1mg ranibizumab. There were no cases of endophthalmitis after 0.2mg ranibizumab or after laser therapy. The groups were not statistically compared. There were no cases of endophthalmitis in a second RCT comparing ranibizumab and laser therapy up to approximately 12 months follow-up.** **For ranibizumab, laser therapy and bevacizumab: There were no cases of endophthalmitis in a retrospective cohort study comparing ranibizumab, laser therapy and bevacizumab at 18-20 months follow-up.**
Safety	
Adverse events **Certainty of evidence:** Low to very low	Adverse events include those relating to VEGF treatment, cataract, treatment-related abnormal neuro-developmental outcomes, serum plasma VEGF outcomes and treatment complications. In total, two RCTs, one extension study from the RAINBOW RCT and three retrospective cohort studies provided evidence relating to adverse events in infants with ROP for between 29 days and approximately three years follow-up. Results comparing ranibizumab and laser therapy were available from the two RCTs, the RCT extension study and one retrospective cohort study. Results comparing ranibizumab, laser therapy and bevacizumab were available from one retrospective cohort study. Results comparing ranibizumab and bevacizumab were available from one retrospective cohort study. **At 3 years:** *Ranibizumab vs laser therapy* • One retrospective cohort study (Kang et al 2019) reported *no statistically significant difference* between ranibizumab and laser therapy at mean ± SD follow-up of 36.3 ± 31.9 months for the following major complications: vitreous haemorrhage; cataract, pale disc without known neurologic deficits or glaucoma. Vitreous haemorrhage occurred in 2/153 eyes (1.3%) after ranibizumab and 1/161 eyes (5.0%) after laser therapy (p=0.614). Cataract occurred in 1/153 eyes (0.7%) after ranibizumab and 1/161 eyes (0.6%) after laser therapy (p=0.738). Pale disc without known neurologic deficits occurred in 8/153 eyes (5.2%) after ranibizumab and 5/161 eyes (3.1%) after laser therapy (p=0.404). Glaucoma occurred in 0/153 eyes (0%) after ranibizumab and 2/161 eyes (1.2%) after laser therapy (p=0.499). **(VERY LOW)**

Outcome	Evidence statement
	• Kang et al (2019) also reported no deaths, major systemic complications or adverse neurodevelopmental outcomes at last follow-up with either ranibizumab or laser therapy. **(VERY LOW)** **At 18 months to 2 years:** *Ranibizumab vs laser therapy* • One RCT extension study (Marlow et al 2021, RAINBOW) reported number of adverse ocular events from enrolment in the original 24-week RANIBOW trial up to age 20-28 months (corrected for prematurity) for two ranibizumab doses (0.2mg: 2 (n=74); 0.1mg: 6[13] (n=77)) and laser therapy: 3 (n=74). Number of patients experiencing an adverse event not reported. The most common adverse event was conjunctivitis. No statistical comparison between groups reported. **(LOW)** • Marlow et al (2021) also reported no non-ocular serious adverse events related to the study intervention at last follow-up with either ranibizumab or laser therapy. **(VERY LOW)** *Ranibizumab, laser therapy and bevacizumab* • One retrospective cohort study (Gunay et al 2017) reported no major ocular complications, including iatrogenic cataract or intraocular haemorrhage, after ranibizumab (n=22), laser therapy (n=57) or bevacizumab (n=55). Mean follow-up was 18.96 ± 4.79 months for ranibizumab, 20.68 ± 6.89 months for laser therapy and 19.40 ± 6.43 months for bevacizumab. **(VERY LOW)** **At approximately 1 year:** *Ranibizumab vs laser therapy* • One RCT (Zhang et al 2017) reported no cases of anterior segment ischemia, pupillary membrane, lens opacity or vitreous haemorrhage after ranibizumab (n=25) or laser therapy (n=25). Mean ± SD follow-up was 49.94 ± 14.67 weeks for ranibizumab and 54.03 ± 12.40 weeks for laser therapy. **(LOW)** *Ranibizumab vs bevacizumab* • One retrospective cohort study (Kang et al 2018) reported *no statistically significant difference* between ranibizumab and bevacizumab at mean ± SD follow-up of 13.9 ± 12.5 months for ranibizumab and 30.9 ± 18.4 months for bevacizumab for number of cases of the following major complications: vitreous haemorrhage; cataract or pale disc without known neurologic deficits. Vitreous haemorrhage occurred in 1/52 eyes (1.9%) after ranibizumab and 1/101 eyes (1.0%) after bevacizumab (p=0.566). Cataract occurred in 0/52 eyes (0%) after ranibizumab and 1/101 eyes (1.0%) after bevacizumab (p=0.660). Pale disc without known neurologic deficits occurred in 4/52 eyes (7.7%) after ranibizumab and 4/101 eyes (4.0%) after bevacizumab (p=0.445). **(VERY LOW)** • Kang et al (2018) also reported no deaths, major systemic complications or glaucoma cases at last follow-up with either ranibizumab or bevacizumab. **(VERY LOW)** **At up to 24 weeks:** *Ranibizumab vs laser therapy* • One RCT (Stahl et al 2019, RAINBOW) reported number of deaths at 24 weeks follow-up for two ranibizumab doses (0.2mg 4/74, 5.4%;

[13] This includes 2 cases of retinal detachment which may have also been included under the structural abnormalities outcome for this study

Outcome	Evidence statement
	0.1mg 4/77, 5.2%) and laser therapy (4/74, 5.4%). No statistical comparison between groups reported. **(LOW)** • One RCT (Stahl et al 2019, RAINBOW) reported number of serious ocular adverse events and number of any ocular adverse events at 24 weeks follow-up for two ranibizumab doses and laser therapy. For serious ocular adverse events this was 4/73 (5.5%) for 0.2mg ranibizumab; 1/76 (1.3%) for 0.1mg ranibizumab; and 4/69 (5.8%) for laser therapy. Serious ocular adverse events were ROP (n=6), cataract (n=1), nystagmus[14] (n=1), conjunctivitis (n=1), endophthalmitis (n=1)[15], eye disorder (n=1)) and orbital infection (n=1). For any ocular adverse events this was 22/73 (30.1%) for 0.2mg ranibizumab; 31/76 (40.8%) for 0.1mg ranibizumab; and 23/69 (33.3%) for laser therapy. No statistical comparison between groups reported. **(LOW)** • One RCT (Stahl et al 2019, RAINBOW) reported number of serious non-ocular adverse events and number of any non-ocular adverse events at 24 weeks follow-up for two ranibizumab doses and laser therapy. For serious non-ocular adverse events this was 24/73 (32.9%) for 0.2mg ranibizumab; 24/76 (31.6%) for 0.1mg ranibizumab; and 22/69 (31.9%) for laser therapy. The most common serious non-ocular adverse events (n>5) were pneumonia, bronchiolitis and bronchopulmonary dysplasia. For any non-ocular adverse events this was 62/73 (84.9%) for 0.2mg ranibizumab; 2/76 (81.6%) for 0.1mg ranibizumab; and 53/69 (76.8%) for laser therapy. No statistical comparison between groups reported. **(LOW)** • One RCT (Stahl et al 2019, RAINBOW) reported plasma VEGF up to 29 days follow-up for two ranibizumab doses and laser therapy. In all three groups, levels reduced from day 1 to day 15 and then increased to day 29. Overall, change from day 1 to day 29 was -47 pg/mL for 0.2mg ranibizumab, +10 pg/mL for 0.1mg ranibizumab and -13 pg/mL for laser therapy. No statistical comparison between groups or over time reported. **(LOW)** • One RCT (Stahl et al 2019, RAINBOW) reported serum ranibizumab up to 29 days follow-up for two ranibizumab doses. This outcome was not applicable for laser therapy. For ranibizumab 0.2mg and 0.1mg, levels reduced from day 1 (7,820 and 4,350 pg/mL) to day 15 (4,440 and 3,400 pg/mL) and then reduced further to day 29 (1,070 and 1,060). No statistical comparison over time reported. **(LOW)** **For ranibizumab vs laser therapy: One RCT provided low certainty evidence of serious ocular adverse events in 1% of patients after 0.1mg ranibizumab and 6% after 0.2mg ranibizumab or laser therapy after 24 weeks follow-up. Serious non-ocular adverse events occurred in 32% to 33% of patients for all three groups. Rates of any ocular adverse event were 41% after 0.1mg ranibizumab and 30% and 34% after 0.2mg ranibizumab or laser therapy respectively. Rates of any non-ocular adverse event were 85% for 0.2mg ranibizumab, 82% for 0.1mg ranibizumab and 77% for laser therapy. The groups were not statistically compared. This RCT also reported plasma VEGF up to 29 days follow-up for two ranibizumab doses and laser therapy. In all three groups, levels reduced from day 1 to day 15 and then increased to day 29. The groups were not statistically compared. For the ranibizumab groups, serum ranibizumab levels reduced from day 1 to day 15 and then further reduced to day 29 (to approximately 1,000 pg/mL in both**

[14] This is also reported under the sight impairment/ severe sight impairment outcome

[15] This is also reported under the development of infection outcome

Outcome	Evidence statement
	groups). An extension study to this RCT provided very low certainty evidence of no serious non-ocular adverse events related to the study intervention at last follow-up when patients were approximately two years old (low certainty). A second RCT provided low certainty evidence of no cases of specified ocular adverse events with ranibizumab or laser therapy up to approximately 12 months follow-up. One retrospective cohort study provided very low certainty evidence of no statistically significant difference between ranibizumab and laser therapy for specified major complications up to approximately three years follow-up, with no deaths, major systemic complications or adverse neurodevelopmental outcomes at last follow-up. **For ranibizumab, laser therapy and bevacizumab: One retrospective cohort study provided very low certainty evidence of no major ocular complications with ranibizumab, laser therapy or bevacizumab at 18-20 months follow-up.** **For ranibizumab vs bevacizumab: One retrospective cohort study provided very low certainty evidence of no statistically significant differences between ranibizumab and bevacizumab for specified major complications at a mean follow-up of 14 months for ranibizumab and 31 months for bevacizumab, with no deaths, major systemic complications or glaucoma cases at last follow-up.**
Abbreviations CI: Confidence intervals; CVFQ; Children's Visual Function Questionnaire; g: Grams; IQR: Inter quartile range; kg: Kilogram; mg: Milligram; ml: Millilitres; OR: Odds ratio; pg/mL: Picogram/millilitre; RCT: Randomised controlled trial; ROP: Retinopathy of prematurity; SD: Standard deviation; VEGF: Vascular endothelial growth factor	

In preterm infants, what is the cost effectiveness of ranibizumab as first line drug treatment compared with standard of care for ROP?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified for cost effectiveness.**

From the evidence selected, are there any subgroups of preterm infants that may benefit more from ranibizumab as first line drug treatment than the wider population of interest?

Outcome	Evidence statement
Subgroups	Analysis by disease stage was reported for the critical outcome of high myopia and the important outcomes of treatment failure and safety, with some studies also reporting analysis by patient characteristics. **High Myopia** • One retrospective cohort study (Gunay et al 2017) reported presence of high myopia in a *statistically significantly lower* proportion of patients with Zone I ROP (n=42) who received ranibizumab (14.3%) or bevacizumab (23.8%) compared to laser therapy (71.4%) (p=0.019). There was *no statistically significant difference* in the presence of high myopia in patients with Zone II ROP (n=92) who received ranibizumab (12.5%), laser therapy (6%) or bevacizumab (5.9%) (p=0.773). Mean ± SD follow-up was 18.96 ± 4.79 months for ranibizumab, 20.68 ± 6.89 months for laser therapy and 19.40 ± 6.43 months for bevacizumab.

	Treatment failure
	• A post-hoc analysis from the RAINBOW RCT (Fleck et al 2022) reported number of eyes receiving additional treatment up to age 20-28 months (corrected for prematurity) by disease stage at baseline. For patients who received 0.2mg ranibizumab this was 8/35 (22.9%) for Zone I, 23/93 (24.7%) for Zone II and 9/20 (45.0%) for AP ROP with a median (range) time to first retreatment of 48.5 days (4 to 111). For patients who received 0.1mg ranibizumab this was 14/39 (35.9%) for Zone I, 12/93 (12.9%) for Zone II and 16/20 (80.0%) for AP ROP with a median (range) time to first retreatment of 48 days (7 to 128). For patients who received laser therapy this was 11/38 (28.9%) for Zone I, 17/90 (18.9%) for Zone II and 6/20 (30.0%) for AP ROP with a median (range) time to first retreatment of 16 days (7 to 141). No statistical comparison between groups or between disease stages reported.
	• A retrospective cohort study (Ling et al 2019) with a mean ± SD of 197.3 ± 110 weeks follow-up reported that in multivariable logistic regression analysis, the following were *statistically significant independent risk factors* for treatment failure:
	  • Zone I ROP vs Zone II ROP OR 4.444 (95%CI 1.872 to 10.552), p=0.0007
	  • Early postmenstrual age at initial treatment OR 0.816 (95%CI 0.692 to 0.963), p=0.0160
	  • Low Apgar score OR 0.832 (95%CI 0.705 to 0.982), p=0.0297
	  • Multiple births OR 2.285 (95%CI 1.071 to 4.788), p=0.0285
	• Ling et al (2019) also reported that in the ranibizumab group, higher risk of recurrent ROP was *statistically significantly* associated with:
	  • Early postmenstrual age at initial treatment OR 0.494 (95%CI 0.285 to 0.857), p=0.0121
	  • Pneumonia OR 23.582 (95%CI 1.532 to 362.908), p=0.0235
	  • Multiple birth OR 17.282 (95%CI 1.171 to 254.963), p=0.0380.
	
	Safety
	• A retrospective cohort study (Kang et al 2019) with a mean ± SD follow-up of 36.3 ± 31.9 months reported that in multivariate regression analysis, an initial ROP stage of 3 was associated with a *statistically significantly higher* incidence of major complications (retinal detachment, optic atrophy, cataract) than an initial ROP stage of 2 (OR 11.222 (95%CI 1.883 to 66.788), p=0.008)[16]
	• Kang et al (2019) also reported that gestational age and postmenstrual age at initial treatment were *not statistically significantly* associated with the incidence of major complications
	• A retrospective cohort study (Kang et al 2018) with a mean ± SD follow-up of 13.9 ± 12.5 months for ranibizumab and 30.9 ± 18.4 months for bevacizumab reported that in univariable analysis, an initial ROP stage of 3 was associated with a *statistically significant higher* incidence of major complications (retinal detachment, optic atrophy, cataract surgery) than an initial ROP stage of 2 (OR 9.046 (95%CI 1.635 to 50.061), p=0.012)
	  • Kang et al (2018) also reported that there was *no statistically significant association* between major complications and sex, birth weight, gestational age at birth or postmenstrual age at initial treatment.
	
	One retrospective cohort study reported high myopia in statistically significantly fewer patients with Zone I ROP after ranibizumab or

[16] Birth weight was also described as being statistically significantly associated with the incidence of major complications but the reporting and direction of this result was unclear

	bevacizumab compared to laser therapy. There was no statistically significant difference between treatment groups for patients with Zone II ROP. A post-hoc analysis from an RCT reported lower cases of treatment failure for patients who received ranibizumab and had Zone I or Zone II ROP than for patients with aggressive posterior ROP. For patients who received laser therapy, treatment failure cases were lower for Zone II ROP but appeared similar for Zone I and aggressive posterior ROP. However, neither the treatment groups nor disease groups were statistically compared. In a retrospective cohort study, significant independent risk factors for treatment failure included Zone I ROP, early postmenstrual age at initial treatment, low Apgar score, pneumonia and multiple births. In two retrospective cohort studies, an initial ROP stage of 3 was associated with a statistically significant higher incidence of major complications than an initial ROP stage of 2.
Abbreviations: AP: Aggressive posterior; CI: Confidence intervals; OR: Odds ratio; RCT: Randomised controlled trial; ROP: Retinopathy of prematurity; SD: Standard deviation	

From the evidence selected, what are the criteria used by the research studies to define those preterm infants diagnosed with ROP who are eligible to receive first line drug treatment with ranibizumab?

Outcome	Evidence statement
Criteria for treatment commencement with ranibizumab	The RAINBOW RCT (Fleck et al 2022, Marlow et al 2021, Stahl et al 2019) included preterm infants (birth weight <1,500g) with bilateral ROP Zone I stage 1+, 2+ 3 or 3+ or Zone II stage 3+ or AP ROP[17]. This RCT excluded infants with ROP in Zone II, stage 2+; ocular and neurological comorbidities that might result in confounding visual impairment and active ocular infection within five days before investigational treatment. The RCT by Zhang et al (2017) screened preterm infants (birth weight <2,000g or birth weight ≥2,000g but with severe systemic disorders) for ROP. Infants with binocular Zone II treatment-requiring ROP (i.e. ROP with Stage 2+ or 3+ in Zone II) were eligible for inclusion. This RCT excluded preterm infants with ROP in Zone I, Stage 4 or Stage 5 ROP and AP ROP in either eye. The retrospective cohort study by Chmielarz-Czarnocińska et al (2021) screened preterm infants (gestational age ≤33 weeks and birth weight <1,800g or high risk as determined by a neonatologist) for ROP. Treatment criteria were based on the ETROP[18] study with some cases also receiving treatment after the acute-phase treatment criteria defined by ETROP at the discretion of the examining ophthalmologist. In this study the authors stated that treatment was determined by the treating ophthalmologist depending on the severity of the disease with ranibizumab preferred for infants with Zone I ROP with plus disease, Zone I ROP stage 3 without plus disease and for AP ROP.

[17] In ROP, the three zones refer to specific locations of the eye centred around the optic nerve. Zone I is the innermost area and Zone III the outermost. There are five stages of ROP which relate to the severity of the condition from Stage 1 (mild) to Stage 5 (total retinal detachment). Retinopathy of prematurity - RNIB - See differently. Severe ROP is associated with dilation and tortuosity of the retinal vessels, termed plus disease (International Classification of Retinopathy of Prematurity, Third Edition - Ophthalmology (aaojournal.org))

[18] Early Treatment for Retinopathy Of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: Results of the early treatment for retinopathy of prematurity randomized trial. Arch. Ophthalmol. 2003;121, 1684–1694

	In their retrospective cohort study, Gunay et al (2017) stated that decisions to treat infants were made according to the indications established in the ETROP study[25]. This study excluded infants with stage 4 or 5 ROP and infants who received supplemental treatment with intravitreal injections following failed laser therapy. The retrospective cohort studies by Kang et al (2019) and Kang et al (2018) both screened preterm infants (gestational age <32 weeks and birth weight <1,500g or unstable clinical course as determined by the primary neonatologist) for ROP. Infants meeting the treatment criteria had type 1 ROP as defined in the ETROP study[19] with some cases receiving earlier treatment at the discretion of the primary ophthalmologist. In Kang et al (2018) the authors stated that there was a gradual change in preference from bevacizumab to ranibizumab over the study period due to reports of safer systemic profiles for ranibizumab. • In their retrospective cohort study, Ling et al (2020) stated that indications for treatment were infants whose retinopathy met the criteria of Type I ROP in the BEAT-ROP study[20].
Abbreviations: AP: Aggressive posterior; BEAT-ROP: Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity; ETROP: Early Treatment for Retinopathy of Prematurity; g: Grams; RCT: randomised controlled trial; ROP: retinopathy of prematurity; VEGF	

Patient Impact Summary
If untreated, severe retinopathy of prematurity (ROP) can lead to blindness which has the following impacts on the patient's everyday life: • **mobility:** Patients have severe problems in walking about • **ability to provide self-care:** Patients have moderate problems in washing or dressing • **undertaking usual activities:** Patients have severe problems in doing their usual activities • **experience of pain/discomfort:** Patients usually have no pain or discomfort • **experience of anxiety/depression:** Patients are severely anxious or depressed
Further details of impact upon patients: Blindness from severe ROP is a critical outcome for a patient's ability to function which would likely have long-term wide-ranging impacts on the patient's mental and physical health. There are more than 320 cases of severe ROP in the UK per year. Almost 50% of cases with untreated severe ROP can develop partial or complete retinal detachment, resulting in severe visual impairment or complete blindness. Severe visual impairment or vision loss in early childhood can lead to delayed motor, language, emotional, social and cognitive development, with lifelong

[19] Good WV; Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. Trans Am Ophthalmol Soc 2004;102:233-48

[20] The reference for the BEAT-ROP study given by the study authors is the same as the reference for the ETROP study provided by Chmielarz-Czarnocińska et al (2021) and Gunay et al 2017

consequences. School-age children with vision impairment can also experience lower levels of educational achievement.

This impact follows patients into adulthood. Adults with vision loss often experience lower rates of employment and productivity and struggle with their mental wellbeing as a direct result.

Further details of impact upon carers:
Blindness from severe retinopathy of prematurity would likely have impacts on parents and carers mental health. Parents and carers may struggle to come to terms with the diagnosis, and may experience a range of emotions including anger, fear, anxiety and stress. Looking after a child with severe visual impairment or vision loss may be associated with an enhanced need for caring support throughout the patient's whole life, special schooling requirements, and potential financial impacts for the household.

Considerations from review by Rare Disease Advisory Group

Overall RDAG was supportive of the policy. One RDAG member who is an ophthalmologist was supportive of the policy but highlighted that the difference in safety profile between ranibizumab and laser (specifically the rare risk of endophthalmitis with the drug) needs to be better explained and that shared decision making and clear discussions with parents/carers on risk benefit ratios were essential at every stage.

It was also highlighted that future evidence on the relative effectiveness of ranibizumab and laser therapy for different subgroups, combination therapy of laser and ranibizumab for aggressive/non-responsive cases and cost effectiveness analysis of laser therapy vs ranibizumab would help inform future clinical and commissioning protocols.

The PWG acknowledged that there is a difference in safety between laser and ranibizumab. However, the policy proposition is restricted to babies who cannot have laser therapy. This has been stated more clearly in the policy proposition. The proposition also states the need for shared decision making between parents/carers and treating clinicians.

Pharmaceutical considerations

This clinical commissioning policy proposition recommends ranibizumab for the treatment of babies with zone I ROP (stage 1+, 2+, 3 or 3+), zone II ROP (stage 3+) AP-ROP (aggressive posterior ROP); use of ranibizumab for these indications is in line with the marketing authorisation of the originator product (Lucentis). The policy proposition also recommends ranibizumab to treat patients with A-ROP (aggressive ROP beyond the posterior retina) disease; use of ranibizumab for this indication is not within the marketing authorisation (for Lucentis or biosimilar products) so use would be off-label. Ranibizumab is excluded from tariff.

Considerations from review by National Programme of Care

The proposal received the full support of the Trauma PoC on the 8th of February 2023.