[redacted],

Thank you for the opportunity to provide my comments on the ACD for the appraisal of ranibizumab for the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion.

It is disappointing that the use of ranibizumab is not recommended for this condition based on this ACD.
I have noted my comments under 3 of your suggested headings below:

Has all of the relevant evidence been taken into account?

Mortality
I refer the Committee to the NHS Evidence Review in 2010, which summarises the published evidence for an excess mortality risk associated with RVO. This review notes that 'the body of evidence from observational studies on this subject are conflicting'. Whilst there is some evidence suggesting an increased risk of cerebrovascular mortality, there are other studies suggesting no increased risk. It is of concern that the Tsaloumas study has been selected, whilst the wider body of evidence has been ignored. In addition this study suggests an increased risk of myocardial infarction rather than overall mortality; as may have been interpreted in this appraisal.

All the evidence regarding overall mortality in RVO patients must be taken into account in order to reach a balanced view. Based on all the published evidence, it is not reasonable to conclude that there is an increased overall mortality risk for these patients.

Furthermore cardiovascular assessment and management of cardiovascular risk factors, as recommended by the Royal College of Ophthalmologists, is likely to have improved the risk of mortality in patients with RVO since the Tsaloumas study, which begun in the 1980s.

10 letter changes in BCVA
As my clinical colleagues and I confirmed at the Committee Meeting, a change in BCVA of at least 10 letters is considered clinically meaningful. This level of improvement can be of significant benefit to patients, even when vision in the other eye is unaffected.

Using the Brazier utilities presented in the ERG's report (page 108) would not capture these important benefits to patients of 10 letter change in BCVA. These suggest that patients with 20/80 (6/30) BCVA and 20/400 (6/120) BCVA have the same utility value applied. This difference is equivalent to 35 letters, whereas our comments to the Committee were that much smaller changes in vision are of benefit to patients. To set this in context, 6/30 snellen metres is moderately impaired vision, whereas 6/120 is likely to be a blind eye. Therefore, I do not feel that the evidence about a clinically meaningful difference of 10 letters has been taken into account.

Utilities for worse-seeing eye
The evidence for the 0.1 estimate of overall utility gain in the worse-seeing eye is not clear. I am aware of the study by Brown and colleagues in which a difference of around 0.1 was suggested for patients with good bilateral vision and good vision in only one eye; the second eye having vision less than 6/12. This implies that more than 0.1 could be derived from improving vision in a worse seeing eye that has very poor vision or is blind. The Brown study was a small sample of patients, which means it should be interpreted cautiously, but it is noteworthy that some patients with unilateral visual impairment had utility values as low as 0.33.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Patients with Ischaemia
The ACD implies that the evidence for ranibizumab cannot be applied to patients with any degree of ischaemia. I would like to clarify that brisk afferent pupillary defect is clinical sign of irreversible

ischaemic vision loss and is equivalent to severe retinal ischaemia. Therefore, RCO guidelines do not recommend any treatment for this group of patients. Patients with less severe forms of ischaemia are likely to benefit from treatment, including with ranibizumab. It is important to ensure the summary of clinical effectiveness is clear on this point, to avoid an unnecessary restriction of treatment in patients who could benefit. As it stands, the ACD is slightly misleading on this issue.

Assumptions about the effectiveness of laser
The Committee notes that the unpooled estimates for the sham group in BRVO during months 7-12 were higher than the pooled estimates. It is important to remember that the BRAVO study introduced ranibizumab to the sham arm from month 7. Therefore the outcomes in the sham arm from month 7 are actually representative of patients treated with ranibizumab for the first time, not sham injections. It seems to me to be quite unreasonable to conclude that ranibizumab is not cost-effective compared to laser, when it is actually being compared to ranibizumab.

Bevacizumab
There are very few evidence based studies on bevacizumab for RVO and Novartis presented data from observational studies in wet AMD that suggest systemic safety concerns might be associated with bevacizumab in the eye. Due to these reasons and given that bevacizumab is not routinely used in the NHS for eye conditions, it is prudent that provision to monitor and review its safety when used in the eye is established in the NHS.

Dexamethasone implant
The Committee has concluded that all the ICERs for ranibizumab compared to dexamethasone are underestimated. However, the summary of cost effectiveness evidence does not take account of the increased frequency of retreatments in clinical practice, compared to the frequency studied in GENEVA. As noted in the NICE appraisal of dexamethasone implant, it is likely that patients would be treated every 4 months (rather than every 6 months) and this would increase the number of clinic visits as well as the cost of drug. Importantly, there is also uncertainty about the adverse events of treatment – both in relation to an increased retreatment regimen than studied in the trials and in relation to the long term efficacy beyond the 12 month data currently available.

I also note that an increased mortality rate for RVO was not applied during the dexamethasone appraisal.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

For the reasons set out above, I do not believe that the provisional recommendations can be considered are appropriate guidance. I am confident that further review of the evidence will ensure that a sound decision is reached.

Thank you for your consideration of my comments. I would be happy to attend another meeting of the Appraisal Committee to clarify any of these issues if that would be helpful.

Yours sincerely

Sobha Sivaprasad
Clinical Expert