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Dear [redacted]

NHS Wiltshire regards eye disease and chronic long term conditions as an important area for commissioning and therefore values innovative interventions for this disease which are proven to be cost effective and affordable in their implementation. NHS Wiltshire welcomes the publication of the Appraisal Committee's recommendations.

Whilst we welcome the fact that the proposed patient access scheme would not impose an excessive administrative burden on the NHS, we question the effect such a scheme has on the ability of NHS commissioners to implement NICE Guidance. Such schemes may influence commissioners in such a way that services and technologies are commissioned inequitably.

**The clinical trials that assessed the effectiveness of ranibizumab are not fully generalisable to NHS clinical practice**

The scope for this technology appraisal included people with or without retinal ischaemia. However both the BRAVO trial, which had assessed ranibizumab for macular oedema following BRVO and the CRUISE trial which had assessed ranibizumab for macular oedema following CRVO excluded people with brisk afferent pupillary defect which is severe retinal ischaemia. There is therefore a lack of evidence for the effectiveness of ranibizumab for treatment of RVO in patients with severe ischaemia. Both trials had compared ranibizumab to sham injection rather than treatments used in current clinical practice (bevacizumab and dexamethasone invitreal implants). Although there were differences in the study populations of a study that had assessed dexamethasone (GENEVA), such as time to treatment after emergence of oedema, it was determined that indirect comparisons could be made.

Comments from clinical specialists were that ranibizumab had approximately equal effectiveness to bevacizumab but no head to head clinical trials comparing these two treatments against each other are yet available.

**The outcomes in the trial of ranibizumab for branch retinal vein occlusion were confounded.**
In the BRAVO trial, patients were treated with monthly ranibizumab or sham injections for six months however, after three months the patients could receive grid laser photocoagulation for rescue treatment. This was used in 57.6% of patients in the sham injection group and 21.4% of the ranibizumab group in the first six months. It was noted that the treatment period of the BRAVO trial was insufficient to capture any benefits of grid laser photocoagulation on patient outcomes, which may last longer than three years. Clinical advice to the ERG suggested that concomitant use of ranibizumab and grid laser photocoagulation does not reflect how ranibizumab would be used in clinical practice. Data from the BRAVO trial was treated with caution. Laser photocoagulation is not indicated for people with CRVO.

**People with macular oedema secondary to RVO will be treated in their 'worse seeing eye'**
The manufacturer's model had assumed that people would be treated in their better seeing eye. This was considered inappropriate. Clinical specialists confirmed that RVO is a unilateral disease in most patients and therefore the proportions of people treated in the 'worse seeing eye' in the BRAVO and CRUISE trials better reflect clinical practice. Over 90% in the patients in the BRAVO and CRUISE trials were treated in their worse seeing eye.

**Retinal vein occlusion and a decrease risk in visual acuity both are associated with increased mortality.**
Data was presented from studies other than the BRAVO and CRUISE trials that suggested that there was an increased risk of mortality both with RVO and with vision impairment as a consequence of RVO.

**Innovativeness of the technology.**
In some cases NICE will take into consideration how innovative an intervention is. For ranibizumab the Committee concluded that ranibizumab is one of a group of innovative anti-VEGF treatments, and does not stand alone in this therapeutic area and its benefits are appropriately captured in the QALY calculation**.**

As NHS Commissioners, we welcome the support of NICE in providing the slides, templates, and advice on the implementation of this guidance.

Yours sincerely

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**Director of Public Health and Public Protection**