National Institute for Health and Care Excellence

SingleTechnology Appraisal (STA)

Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Allergan Ltd.	Yes	Thank you for your comment. No action required.
	Bayer plc	Appropriate	Thank you for your comment. No action required.
	CSAS	The topic is appropriate for consideration.	Thank you for your comment. No action required.
	NHS Worcestershire on behalf of West Mercia PCT Cluster	The topic is appropriate for consideration.	Thank you for your comment. No action required.
	The Royal College of Pathologists	Entirely appropriate and timely	Thank you for your comment. No action required.
Wording	Allergan Ltd.	Yes	Thank you for your comment. No action required.

Section	Consultees	Comments	Action
Wording (cont.)	Bayer plc	Appropriate	Thank you for your comment. No action required.
	CSAS	The wording of the draft scope is appropriate.	Thank you for your comment. No action required.
	NHS Worcestershire on behalf of West Mercia PCT Cluster	The wording of the draft scope is appropriate.	Thank you for your comment. No action required.
	Novartis Pharmaceuticals UK Ltd	The wording of the remit is not consistent with the population in the scope ('visual impairment' is missing from the remit)	Thank you for your comment. The wording of the draft remit has been amended to include 'visual impairment'.
	The Royal College of Pathologists	Yes	Thank you for your comment. No action required.
Timing Issues	Allergan Ltd.	N/A	No action required.
	Bayer plc	Appropriate	Thank you for your comment. No action required.
Timing Issues (cont.)	CSAS	The timing is appropriate. Ranibizumab (a comparator outlined in the draft scope) is currently undergoing NICE appraisal for this indication with a completion date TBA. The preliminary recommendation in the ACD for this technology (Nov 2011) indicates that ranibizumab is not recommended for the treatment of visual impairment caused by macular oedema secondary to central or branch retinal vein occlusion.	Thank you for your comment. The scope has been updated to reflect the guidance on ranibizumab in NICE technology appraisal no. 283.

Section	Consultees	Comments	Action
Timing Issues (cont.)	NHS Worcestershire on behalf of West Mercia PCT Cluster	The timing is appropriate. Ranibizumab (a comparator outlined in the draft scope) is currently undergoing NICE appraisal for this indication with a completion date TBA. The preliminary recommendation in the ACD for this technology (Nov 2011) indicates that ranibizumab is not recommended for the treatment of visual impairment caused by macular oedema secondary to central or branch retinal vein occlusion.	Thank you for your comment. The scope has been updated to reflect the guidance on ranibizumab in NICE technology appraisal no. 283.
	The Royal College of Pathologists	Moderate	Thank you for your comment. No action required.
Additional	Bayer plc	NA	No action required.

Section	Consultees	Comments	Action
comments on the draft remit	CSAS	The comparators may need to be reviewed if the FAD for ranibizumab agrees with the Nov 2011 ACD	Thank you for your comment. The scope has been updated to reflect the guidance on ranibizumab in NICE technology appraisal no. 283.
Additional comments on the draft remit (cont.)	NHS Worcestershire on behalf of West Mercia PCT Cluster	The comparators may need to be reviewed if the FAD for ranibizumab agrees with the Nov 2011 ACD	Thank you for your comment. The scope has been updated to reflect the guidance on ranibizumab in NICE technology appraisal no. 283.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Allergan Ltd.	Accurate and balanced	Thank you for your comment. No action required.
	Bayer plc	The Royal College of Ophthalmologists, in their interim guidance for the Management of Retinal Vein Occlusion (RVO), December 2010 (1), cite 80 new cases of central retinal vein occlusion (CRVO) per million of the population. Reference: 1. The Royal College of Ophthalmologists. Interim guidelines for the management of retinal vein occlusion. December 2010.	Thank you for your comment. The epidemiology of the disease in the scope should relate to populations within the UK. The figure referred to in this comment is derived from pooled analysis of data from a range of different countries. No action required.
	CSAS	The background information provided is appropriate.	Thank you for your comment. No action required.
	NHS Worcestershire on behalf of West Mercia PCT Cluster	The background information provided is appropriate.	Thank you for your comment. No action required.
	Novartis Pharmaceuticals UK Ltd	The evidence is equivocal as to whether there is an increased risk of vascular death associated with RVO	Thank you for your comment. The clinician at the scoping workshop indicated that stroke and other thrombotic events are associated with RVO. No action required.
	The Royal College of Pathologists	Generally clear and comprehensive. I thought the wording relating to ranibizumab was potentially confusing given that it is approved by NICE for AMD	Thank you for your comment. The scope has been updated to reflect the guidance on

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			ranibizumab in NICE technology appraisal no. 283..
The technology/ intervention	Allergan Ltd.	N/A to Allergan	No action required.
	Bayer plc	No comment	No action required.
	CSAS	The description of the intervention is accurate.	Thank you for your comment. No action required.
	NHS Worcestershire on behalf of West Mercia PCT Cluster	The description of the intervention is accurate.	Thank you for your comment. No action required.
	The Royal College of Pathologists	Yes. It might be worth elaborating on the mechanism(s) of action of aflibercept.	Thank you for your comment. The scope is intended to provide a brief summary of the disease, prognosis associated with the condition, and the new technology compared with alternative treatments currently used in the NHS. A more detailed description of the technology and mechanism of action may be included in the submissions.
Population	Allergan Ltd.	Yes, defined appropriately	Thank you for your comment. No action required.
	Bayer plc	No comment	No action required.
	CSAS	The population as defined in the draft scope states treatment is for 'adults with visual impairment caused by central retinal vein occlusion (CRVO)'. How 'visual impairment' is defined is not clear. Consider defining the level of visual impairment for which the treatment is being considered.	Thank you for your comment. The clinician at the scoping workshop confirmed that the populations recruited in the

Section	Consultees	Comments	Action
Population (cont.)	CSAS (cont.)	The draft scope describes two sub-categories of CRVO: ischaemic and non-ischaemic. It states: "non-ischaemic CRVO may resolve completely without any complications or may progress to the ischaemic type". It is not clear if the intention is to consider the therapy for all types of CRVO or only ischaemic and non-resolved non-ischaemic CRVO. Consider defining the population to describe which subgroups will be included.	clinical trials for aflibercept reflect people with visual impairment caused by central retinal vein occlusion as defined in routine clinical practice, that is, people with mean central retinal thickness greater than or equal to 250 µm on optical coherence tomography and best-corrected visual acuity of 20/40 to 20/230 in the affected eye using Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart. The manufacturer indicated at the scoping workshop that, other factors being the same, the efficacy of aflibercept in clinical trials did not vary with the type of underlying CRVO (ischaemic and non-ischaemic). Aflibercept would therefore be considered for macular oedema caused by any type of CRVO subject to the marketing authorisation. No action required.
	NHS Worcestershire on behalf of	The population as defined in the draft scope states treatment is for 'adults with visual impairment caused by central retinal vein occlusion (CRVO)'. How 'visual impairment' is defined is not clear. Consider defining the level of visual	Thank you for your comment. The clinician at the scoping

Section	Consultees	Comments	Action
Population (cont.)	West Mercia PCT Cluster NHS Worcestershire on behalf of West Mercia PCT Cluster (cont.)	impairment for which the treatment is being considered. The draft scope describes two sub-categories of CRVO: ischaemic and non-ischaemic. It states: "non-ischaemic CRVO may resolve completely without any complications or may progress to the ischaemic type". It is not clear if the intention is to consider the therapy for all types of CRVO or only ischaemic and non-resolved non-ischaemic CRVO. Consider defining the population to describe which subgroups will be included.	workshop confirmed that the populations recruited in the clinical trials for aflibercept reflect people with visual impairment caused by central retinal vein occlusion as defined in routine clinical practice, that is, people with mean central retinal thickness greater than or equal to 250 µm on optical coherence tomography and best-corrected visual acuity of 20/40 to 20/230 in the affected eye using Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart. The manufacturer indicated at the scoping workshop that, other factors being the same, the efficacy of aflibercept in clinical trials did not vary with the type of underlying CRVO (ischaemic and non-ischaemic). Aflibercept would therefore be considered for macular oedema caused by any type of CRVO subject to the marketing authorisation. No action required.
	The Royal	Yes	Thank you for your comment.

Section	Consultees	Comments	Action
	College of Pathologists		No action required.
Comparators Comparators (cont.)	Allergan Ltd. Allergan Ltd. (cont.)	Ozurdex must be considered as the standard of care as per NICE recommendation. Bevacizumab is not licensed for RVO.	Thank you for your comment. Relevant comparator technologies may include those that do not have a marketing authorisation for the indication defined in the scope but that are used routinely for the indication in the NHS. Consultees indicated at the scoping workshop that bevacizumab is currently used in the NHS to treat macular oedema caused by CRVO; therefore, bevacizumab should remain a comparator in the scope.
	Bayer plc Bayer plc (cont.)	Dexamethasone intravitreal implant, ranibizumab (subject to on-going NICE appraisal) and best supportive care (for ischaemic CRVO only) are appropriate comparators. Dexamethasone intravitreal implant is currently considered routine and best practice in the NHS (including existing NICE guidance) for the first-line treatment of macular oedema secondary to CRVO. Dexamethasone is recommended by both The Royal College of Ophthalmologists for the management of CRVO (1) and is recommended by NICE (TA229)(2) for the treatment of macular oedema secondary to CRVO. With regard to best supportive care, panretinal photocoagulation (PRP) is relevant for ischaemic CRVO, rather than laser anastomosis. The updated NICE guide to the methods of technology appraisal (June 2008)	Thank you for your comment. Best supportive care (including laser anastomosis for ischaemic CRVO only) has been removed from the scope. The clinician at the scoping workshop indicated that pan-retinal photocoagulation would typically be used when CRVO causes complications (glaucoma secondary to neovascularisation) and therefore is not a relevant comparator. It was agreed to

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Comparators (cont.)	Bayer plc (cont.)	(3) defines relevant comparator technologies with specific consideration given to routine and best practice in the NHS (including existing NICE guidance), including technologies that do not have a marketing authorisation for the indication defined in the scope but that are used routinely for the indication in the NHS. Bevacizumab cannot be appropriately considered routine and best practice in the NHS (including existing NICE guidance) for the first-line treatment of CRVO for the following reasons: • There is no existing NICE guidance on bevacizumab for CRVO. A NICE workshop in July 2010 (published December 2010) (4) on the potential appraisal of bevacizumab for eye conditions was held, where clinical experts, industry and academia were represented. Despite the workshop, in a recent parliamentary questions, [70741], Mr Simon Burns stated there are no immediate plans to refer this topic to NICE for appraisal, but will keep this position under review. Moreover, the manufacturer has indicated that it does not intend to apply for a license for bevacizumab in eye conditions. • In the absence of any referral of bevacizumab to NICE for appraisal, the inclusion of bevacizumab as a comparator in the draft scope for aflibercept solution for injection is likely to be considered by stakeholders as a substitute for a NICE appraisal of bevacizumab. However, this contradicts the report from the NICE workshop that indicates provisions for safety are necessary for any appraisal of bevacizumab: "*There is support for an appraisal of intravitreal bevacizumab for eye conditions. Stakeholders agreed that an appraisal would need to be conditional on, or incorporate the assessment of, the safety and quality of intravitreal bevacizumab by a regulatory body or through the involvement of regulatory expertise. It was suggested that options for commissioning the relevant skills and expertise for this purpose be explored. Arrangements for safety monitoring / pharmacovigilance will need to be explored*". Existing studies in CRVO are insufficiently powered to assess bevacizumab safety.	add 'clinical observation' as a comparator for people with ischaemic CRVO given that there is no established treatment for this subpopulation. Relevant comparator technologies may include those that do not have a marketing authorisation for the indication defined in the scope but that are used routinely for the indication in the NHS. Consultees indicated at the scoping workshop that bevacizumab is currently used in the NHS to treat macular oedema caused by CRVO; therefore, bevacizumab should remain a comparator in the scope.

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Comparators (cont.)	Bayer plc (cont.)	• The MHRA (Medicines and Healthcare products Regulatory Agency) clarified in August 2011 (5) that the preparation of bevacizumab for intravitreal use involves manipulation of an authorised medicine to produce multiple aliquots. The MHRA considers that this process results in the creation of an unlicensed medicine. The MHRA advises healthcare professionals – in line with General Medical Council (GMC) guidance – that they need to be satisfied before prescribing an unlicensed medicine that an alternative, licensed medicine would not meet the patient's needs It is also of concern that the bevacizumab Summary of Product Characteristics (SmPC) states within the section 4.4 (6) "Special warnings and precautions for use" under the subheading 'Eye disorders' that adverse reactions have been reported from unapproved intravitreal use. The listed reactions are: infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. The SmPC states that some of these appeared as serious adverse reactions. No frequency of these side effects is given within the SmPC as the unlicensed use of bevacizumab in "Eye disorders" is not subject to pharmacovigilance. The Royal College of Ophthalmologist guidelines for RVO (1) refer to GMC guidelines on the use of unlicensed medicines. GMC guidance from 2008 (7) on the use of unlicensed and medicines indicates that bevacizumab is not an appropriate comparator clinically as there are now licensed alternatives for CRVO "*18. You can prescribe unlicensed medicines but, if you decide to do so, you must:* *a. Be satisfied that an alternative, licensed medicine would not meet the patient's needs* *b. Be satisfied that there is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy* *c. Take responsibility for prescribing the unlicensed medicine and for*	

Section	Consultees	Comments	Action
Comparators (cont.)	Bayer plc (cont.)	*overseeing the patient's care, including monitoring and any follow up treatment (see also paragraphs 25-27 on prescribing for hospital outpatients)* *d. Record the medicine prescribed and, where you are not following common practice, the reasons for choosing this medicine in the patient's notes."* For wAMD where, similarly to CRVO, a licensed NICE-recommended alternative exists, the Royal College of Ophthalmologists recommends bevacizumab as part of research rather than routine and best practice in the NHS. In a statement issued on 4th May 2011, the College clarified that *"the College is fully aware of the current NHS funding issues but remains committed to maintaining professional standards and patient safety. It would be inappropriate for the College to compromise on safety and urges caution in the interpretation of the CATT Study. Until the safety concerns are properly addressed, ranibizumab remains the recommended treatment for wet AMD. The College however continues to support use of bevacizumab as part of research. Where informed consent has been taken to use a drug outside of its licensed product indication, the responsibility for its use lies with the clinician".* The cost effectiveness of aflibercept solution for injection compared with bevacizumab cannot be evaluated using NICE methods for technology appraisal given the variable and highly uncertain cost for intravitreal bevacizumab and the absence of routine or best practice guidelines. •The NICE methods state that the list price of a technology should be used in the base-case of any technology appraisal (section 5.5.2) and that if the acquisition price paid differs from the public list price, prices are required to be transparent, consistently available across the NHS and the period for which the specified price is available is guaranteed (see section 5.5.2). • The price paid for the intravitreal bevacizumab used in the treatment of CRVO is not transparent, consistent across the NHS, and defined for a specific period of time, as deemed necessary by NICE methods. Intravitreal bevacizumab is currently manufactured by independent centres from the	

Section	Consultees	Comments	Action
Comparators (cont.)	Bayer plc (cont.)	concentrate for intravenous infusion that is licensed in the UK for the treatment of metastatic colorectal cancer and listed in the BNF (8) at a list net price of £242.66 for a 4-ml (100mg) vial. These centres charge variable prices and may have limited capacity to supply the NHS. In future, other centres may start to manufacturer bevacizumab at different prices. • The Southampton Assessment Group report (9) for the NICE workshop on bevacizumab for eye conditions also indicated that *"…there are no dose escalating/ranging studies of intravitreal bevacizumab and the optimum dose and dose-frequency are unknown…Safety concerns have also been raised as bevacizumab was not designed, manufactured or approved for intraocular use..."*. There has been an absence of appropriate efficacy and adequately powered safety studies to establish best practice bevacizumab for CRVO. This has been demonstrated in the NICE guidance for dexamethasone (TA229) where any definitive conclusion on comparative efficacy, safety and cost effectiveness versus bevacizumab was impossible. The absence of a license has also led to variations in the bevacizumab intravitreal injection product. Counterfeit bevacizumab in the US has been arriving through UK sources (10). In addition, there were 21 sterile endophthalmitis cases based on product issued at Moorfields Pharmaceuticals leading to withdrawal of batches of bevacizumab (11) and subsequent led to a temporarily suspension of compounding of bevacizumab by Moorfields Pharmaceuticals (http://www.rcophth.ac.uk/news.asp?section=24&sectionTitle=News&itemid=752) Legal action against the Southampton, Hampshire, Isle of Wight and Portsmouth (SHIP) group of PCTs was initiated by Novartis regarding their recommendation to use bevacizumab for wAMD. The board of management of SHIP acknowledged a number of reasons for their withdrawal of their bevacizumab policy (12). The outcome of this action, which resulted in this guidance being withdrawn, and any similar repetition of the Moorfields incident	

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Comparators (cont.)		elsewhere, may impact on the future availability of intravitreal bevacizumab for eye conditions in other local areas. References: 1. The Royal College of Ophthalmologists. Interim guidelines for the management of retinal vein occlusion. December 2010. 2. NICE. Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion (TA229). August 2010. 3. NICE. Guide to the methods of technology appraisal. June 2008. 4. NICE. Eye conditions - bevacizumab (Avastin): report of findings from a workshop held at NICE on 13 July 2010. December 2010. 5. MHRA. Off-label or unlicensed use of medicines: prescribers' responsibilities. Drug safety update, Volume 2, Issue 9 April 2009 (available at http://www.mhra.gov.uk/Safetyinformation/ DrugSafetyUpdate/CON087990 – accessed July 2012). 6. Bevacizumab Summary Product Characteristics (SmPC) (available at http://www.medicines.org.uk/EMC/medicine/15748/SPC/-Avastin+25mg+ml+concentrate+for+solution+for+infusion/ - accessed August 2012). 7. GMC. Good practice in prescribing medicines - guidance for doctors. September 2008 (available at http://www.gmc-uk.org/guidance/ethical_guidance/prescriptions_faqs.asp - accessed July 2012).	

Section	Consultees	Comments	Action
Comparators (cont.)		8. British National Formulary (BNF) 63. March 2013. 9. Southampton Health Technology Assessment Group. Bevacizumab for age-related macular degeneration and other eye conditions: an assessment of published evidence and ongoing trials (Avastin report). July 2010 (available at http://www.nice.org.uk/ourguidance/niceguidancebytype/-technologyappraisals/proposedappraisals/-bevacizumabineyeconditions.jsp – accessed July 2012). 10. Food and Drugs Administration (FDA). Statement: Counterfeit Version of Avastin in U.S. Distribution. July 2012 (available at http://www.fda.gov/drugs/drugsafety/ucm291960.htm - accessed August 2012). 11. The Royal College of Ophthalmologists. Potential bevacizumab-related sterile endophthalmitis cases. March 2012 (available at http://www.rcophth.ac.uk/news.asp?section=24&section-Title=News&itemid=752 – accessed July 2012). 12. Novartis launches legal challenge against PCT cluster. Health Services Journal. April 2012 (available at http://www.hsj.co.uk/news/pharmaceuticals/novartis-launches-legal-challenge-against-pct-cluster/5044067.article – accessed July 2012).	

Section	Consultees	Comments	Action
Comparators (cont.)	CSAS	The National Horizon Scanning Centre idetified that current treatment options for CRVO with macular oedema include triamcinolone acetonide (intravitreal corticosteroid) and pegaptanib (intravitreal VEGF inhibitor). Both are used off-label for this indication. Consider either adding these treatments as comparators or explaining why they are not included.	Thank you for your comment. The triamcinolone acetonide formulation available in the UK is contraindicated for ocular use; pegaptanib is not available in the UK. Therefore, these are not relevant comparators. No action required.
	NHS Worcestershire on behalf of West Mercia PCT Cluster	The National Horizon Scanning Centre idetified that current treatment options for CRVO with macular oedema include triamcinolone acetonide (intravitreal corticosteroid) and pegaptanib (intravitreal VEGF inhibitor). Both are used off-label for this indication. Consider either adding these treatments as comparators or explaining why they are not included.	Thank you for your comment. The triamcinolone acetonide formulation available in the UK is contraindicated for ocular use; pegaptanib is not available in the UK. Therefore, these are not relevant comparators. No action required.
	Novartis Pharmaceuticals UK Ltd	The need for the caveat for ranibizumab to be included as a comparator 'subject to on-going NICE appraisal' is unclear, in the context of the inclusion of unlicensed bevacizumab as a comparator which is not subject to NICE appraisal.	Thank you for your comment. Ranibizumab is included in the scope subject to on-going NICE appraisal because the Committee would normally consider comparator interventions in accordance with their respective NICE guidance (if available). Relevant comparator technologies may include those that do not have a

Section	Consultees	Comments	Action
	Novartis Pharmaceuticals UK Ltd (cont.)		marketing authorisation for the indication defined in the scope but that are used routinely for the indication in the NHS. Consultees indicated at the scoping workshop that bevacizumab is currently used in the NHS to treat macular oedema caused by CRVO; therefore, bevacizumab should remain a comparator in the scope.
	The Royal College of Pathologists	I would defer to ophthalmology colleagues but I believe the comparators are appropriate	Thank you for your comment. No action required.
Outcomes	Allergan Ltd.	Yes	Thank you for your comment. No action required.

Section	Consultees	Comments	Action
Outcomes (cont.)	Bayer plc	Visual acuity in the study eye is the most relevant outcome for the measure of clinical effectiveness. Clinical outcomes measured in the COPERNICUS/GALILEO (13, 14) clinical trials of aflibercept solution for injection relate to the study eye only. References: 13. Boyer et al. Vascular Endothelial Growth Factor Trap-Eye for Macular Edema Secondary to Central Retinal Vein Occlusion. Six-Month Results of the Phase 3 COPERNICUS Study. Ophthalmology, 2012 May;119(5):1024-32. Epub 2012 Mar 21. 14. Bayer press release. Bayer and Regeneron Report Positive Results for VEGF Trap-Eye in Second Phase 3 Study in Central Retinal Vein Occlusion. April 2011 (available at http://www.investor.bayer.de/en/news/archive/investor-news-2011/investor-news-2011/showNewsItem/1271/1303934280/5215501c2d/ - accessed August 2012).	Thank you for your comment. The Committee would normally consider the appropriateness of outcome measures during the course of the appraisal. No action required.
	CSAS	'Progression resulting from neovascularisation requiring pan-retinal photocoagulation' was used as a secondary outcome in one of the identified phase III trials (GALILEO). Consider adding need for photocoagulation as an additional outcome.	Thank you for your comment. The scope has been amended to include 'need for pan-retinal photocoagulation' as an outcome.
	NHS Worcestershire on behalf of West Mercia PCT Cluster	'Progression resulting from neovascularisation requiring pan-retinal photocoagulation' was used as a secondary outcome in one of the identified phase III trials (GALILEO). Consider adding need for photocoagulation as an additional outcome.	Thank you for your comment. The scope has been amended to include 'need for pan-retinal photocoagulation' as an outcome.

Section	Consultees	Comments	Action
	The Royal College of Pathologists	Yes. I think retinal thickness (readily assessed by OCT) would be a logical parameter to follow	Thank you for your comment. It was agreed at the scoping workshop that it would be relevant to consider subgroups by central macular thickness rather than consider retinal thickness as an outcome measure. The scope has been amended to reflect this.
Economic analysis	Allergan Ltd.	No further comments	No action required.
	Bayer plc	No comment	No action required.
	CSAS	The time horizon is appropriate.	Thank you for your comment. No action required.
	NHS Worcestershire on behalf of West Mercia PCT Cluster	The time horizon is appropriate.	Thank you for your comment. No action required.
	The Royal College of Pathologists	Failure to control disease can lead to progressive visual failure. Life-long time horizon should be considered. Some attempt needs to be made to estimate how long treatment might be required and allowance made for potential long-term side-effects.	Thank you for your comment. The Committee would normally consider issues relating to the economic evaluation of a technology during the course of the appraisal. No action required.
Equality and Diversity	Allergan Ltd.	No issues identified	Thank you for your comment. No action required.
	Bayer plc	No comment	No action required.

Section	Consultees	Comments	Action
	CSAS	There were no equality issues identified.	Thank you for your comment. No action required.
	NHS Worcestershire on behalf of West Mercia PCT Cluster	There were no equality issues identified.	Thank you for your comment. No action required.
	The Royal College of Pathologists	No concerns	Thank you for your comment. No action required.
Innovation	Allergan Ltd.	No further comments.	No action required.

Section	Consultees	Comments	Action
Innovation (cont.)	Bayer plc	Aflibercept tightly binds to all forms of VEGF and PlGF known to contribute to angiogenesis in the eye. In comparison ranibizumab is a recombinant, humanized, monoclonal antibody Fab fragment against VEGF-A. Thus, aflibercept binds tighter to VEGF than the natural receptors and currently available treatments (15). Aflibercept has been studied in two phase III trials, COPERNICUS and GALILEO (13, 14), of similar design. In both trials, aflibercept achieved its primary endpoints of proportion of participants achieving at least 15 letters of vision from baseline compared to patients receiving sham injections. Thus, it has been shown that aflibercept has the potential to make a significant and substantial impact on health-related benefits through improved vision. References: 13. Boyer et al. Vascular Endothelial Growth Factor Trap-Eye for Macular Edema Secondary to Central Retinal Vein Occlusion. Six-Month Results of the Phase 3 COPERNICUS Study. Ophthalmology, 2012 May;119(5):1024-32. Epub 2012 Mar 21. 14. Bayer press release. Bayer and Regeneron Report Positive Results for VEGF Trap-Eye in Second Phase 3 Study in Central Retinal Vein Occlusion. April 2011 (available at http://www.investor.bayer.de/en/news/archive/investor-news-2011/investor-news-2011/showNewsItem/1271/1303934280/5215501c2d/ - accessed August 2012). 15. Papadopoulos et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. Angiogenesis (2012) 15:171–185.	Thank you for your comment. The Committee would normally consider the innovative aspect of a technology during the course of the appraisal. No action required.

Section	Consultees	Comments	Action
	CSAS	No additional comments	No action required.
	NHS Worcestershire on behalf of West Mercia PCT Cluster	No additional comments	No action required.
	The Royal College of Pathologists	- Certainly treatment for CRVO remains unsatisfactory. The comparison between 'pure' VEGF inhibitors and aflibercept will be of interest. A successful new treatment for macular oedema would represent a therapeutic 'step - change'.	Thank you for your comment. The Committee would normally consider the innovative aspect of a technology during the course of the appraisal. No action required.
Other considerations	Allergan Ltd.	N/A	No action required.
	Bayer plc	Any analysis of the suggested subgroups will be limited by the evidence available.	Thank you for your comment. No action required.
	CSAS	No additional comments	No action required.
	NHS Worcestershire on behalf of West Mercia PCT Cluster	No additional comments	No action required.

Section	Consultees	Comments	Action
Other considerations (cont.)	The Royal College of Pathologists	It might be worth considering whether or not the patient has diabetic retinopathy	Thank you for your comment. The manufacturer indicated at the scoping workshop that people with comorbid diabetes have been excluded from the clinical trials for aflibercept. The evidence would therefore not allow a separate consideration of people with and without diabetic retinopathy. No action required.
Questions for consultation	Bayer plc	*Have the most appropriate comparators for aflibercept for the treatment of macular oedema caused by CRVO been included in the scope?* See comments under the 'comparators' section. • *Should grid laser photocoagulation also be considered?* No. It is not an appropriate comparator for CRVO. • *Are the comparators listed routinely used in clinical practice?* See comments under the 'comparators' section. • *Should aflibercept be compared with any combination treatment?* Only in the context of best supportive care for ischaemic CRVO. See comments under the 'comparators' section.	Thank you for your responses. The clinician at the scoping workshop indicated that best supportive care (including laser anastomosis for ischaemic CRVO only) is not an appropriate comparator and therefore it has been removed from the scope. It was agreed to add 'clinical observation' as a comparator instead given that there is no established treatment for people with ischaemic CRVO. The Committee would normally consider issues relating to the economic evaluation of a technology during the course of the

Section	Consultees	Comments	Action
Questions for consultation (cont.)	Bayer plc (cont.)	• *How should 'best supportive care' be defined?* See comments under the 'comparators' section. *Have the most appropriate outcome measures been included in the scope? Should other outcome measures be considered?* No. Relevant outcomes are considered. *Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?* See comments in 'other considerations' section. No other subgroups are appropriate. *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* As experienced in previous appraisals at NICE of new treatments for eye conditions, there are limitations in the way that currently available health-related quality of life instruments are able to capture the benefits of improved visual acuity and including benefit that in QALY estimates. *NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process.* This is appropriate	appraisal. No action required.

Section	Consultees	Comments	Action
Questions for consultation (cont.)	CSAS	No additional comments	No action required.
	NHS Worcestershire on behalf of West Mercia PCT Cluster	No additional comments	No action required.
	The Royal College of Pathologists	Duration of macular oedema is considered. If data are available duration between onset of CRVO and treatment may be of importance.	Thank you for your response. The clinician at the scoping workshop indicated that CRVO may be asymptomatic in its early stages and therefore it would be difficult to establish onset of CRVO. No action required.
Additional comments on the draft scope.	CSAS	No additional comments	No action required.
	NHS Worcestershire on behalf of West Mercia PCT Cluster	No additional comments	No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

British Ophthalmic Anaesthesia Society (BOAS)
Macular Disease Society
Medicines and Healthcare products Regulatory Agency
The Department of Health
The Royal College of Nursing

There were no comments received on the provisional matrix