
1310

Final Decision
Analytic Protocol
(DAP) to guide the
assessment of optical
coherence
tomography for
assessment of central
retinal thickness in
the presence of
macular oedema
secondary to central
retinal vein occlusion

January 2013

Table of Contents

Purpose of this document	2
Purpose of application	3
Background	3
Current arrangements for public reimbursement	3
Regulatory status	5
Intervention	6
Description	6
Delivery of the intervention.....	9
Prerequisites.....	11
Co-administered and associated interventions.....	13
Listing proposed and options for MSAC consideration	13
Proposed MBS listing	13
Clinical place for proposed intervention	16
Comparator	19
Outcomes for safety and effectiveness evaluation	20
Effectiveness.....	21
Safety	Error! Bookmark not defined.
Summary of PICO to be used for assessment of evidence (systematic review)	22
Clinical claim	24
Outcomes and health care resources affected by introduction of proposed intervention	26
Outcomes for economic evaluation.....	26
Health care resources.....	26
Proposed structure of economic evaluation (decision-analytic)	28

MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Australian Government Health Minister to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

This document is a decision analytic protocol (DAP) that will be used to guide the assessment of optical coherence tomography (OCT) for:

1. identification of patients with macular oedema secondary to central retinal vein occlusion (CRVO) who are eligible for treatment with aflibercept¹;
2. monitoring these patients to determine their ongoing eligibility for aflibercept, as well as the clinical effectiveness of this treatment.

The draft protocol was only finalised after inviting relevant stakeholders to provide input. This final protocol will provide the basis for the assessment of the intervention.

The protocol guiding the assessment of the health intervention has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

Patients – specification of the characteristics of the patients or population in whom the intervention is to be considered for use;

Intervention – specification of the proposed intervention;

¹ The applicant proposed that pending availability of aflibercept through the Pharmaceutical Benefits Scheme (PBS), a mean baseline retinal thickness measurement of ≥ 250 μm would be an acceptable cut-off for patient eligibility to receive treatment. See section "Proposed MBS listing", third paragraph.

Comparator – specification of the therapy most likely to be replaced by the proposed intervention; and

Otcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention.

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of optical coherence tomography (OCT) for the identification of patients with central retinal vein occlusion (CRVO) and monitoring of treatment was received from Bayer Australia Ltd by the Department of Health and Ageing in May 2012. The proposed listing of OCT is to identify patients who would benefit from treatment with aflibercept (pending approval of this drug on the TGA and PBS for this particular indication), and secondly to monitor the treatment regimen.² The proposed use of OCT to monitor treatment rests on the premise that the treating clinician can thereby optimise drug administration. The applicant claims that this avoids the unnecessary costs due to dosing too frequently and the risk of compromise to patient health outcomes as a result of dosing too infrequently.

Adelaide Health Technology Assessment, School of Population Health, University of Adelaide, as part of its contract with the Department of Health and Ageing, drafted this decision analytic protocol in order to guide the development of an application for MBS funding that will address MSAC's decision-making concerns regarding public funding of the intervention.

Background

Current arrangements for public reimbursement

No clinical indications for OCT are currently included for reimbursement under the MBS. A previous assessment of OCT for the diagnosis and monitoring of macular disease and glaucoma was considered by MSAC in November 2008 (application 1116), however the application for funding of OCT with respect to these indications was rejected on the grounds of insufficient evidence to support the clinical claims of the applicant. The proposed indications for the current application are narrower than for those considered in the previous MSAC assessment.

² However, in addition to aflibercept as a potential treatment regimen for CRVO, there are alternatives such as ranibizumab (TGA-approved) and bevacizumab (off-label use). See RCO (2010). *Interim guidelines for management of retinal vein occlusion* [Internet]. The Royal College of Ophthalmologists. Available from: <http://www.rcophth.ac.uk/news.asp?section=24&itemid=374&search=> [Accessed 21 June 2012].

The applicant claims that OCT is offered to patients as an out-of-pocket expense and that a number of patients elect to have this service in the context of symptoms and history suggestive of CRVO³. Based on the applicant's own internal research, the cost of the service is claimed to be \$200-250 with no subsidies from private health insurance currently available. These claims of a scenario involving self-funded access to OCT are reasonable given the place of OCT as an established technology⁴; however, CRVO/macular oedema can be managed without the use of OCT under current publicly funded arrangements. The supplementary information which was provided by Bayer Australia indicated that the main services used in the diagnosis and monitoring of CRVO/macular oedema are fundus fluorescein angiography (FFA), retinal photography with intravenous dye injection and electroretinography. The relevant item numbers for these services are 11204, 11205, 11210, 11215, and 11218, however advice from the MESP is that electroretinography and electrooculography (items 11204, 11205 and 11210) have no role in the diagnosis of CRVO. These services may occasionally be performed in some centres to determine the presence of retinal ischaemia, which may indicate treatment with laser photocoagulation. Items 11215 and 11218, however, are commonly used in the diagnosis of CRVO and may be used during follow-up to monitor progression to retinal ischaemia, which indicates treatment with pan-retinal laser photocoagulation (PRP)⁵. A number of standard tests such as slit lamp examination, visual acuity testing and intraocular pressure testing may also be performed as part of the diagnostic process, and these would be included in the MBS fee structure for professional attendance (comprehensive consultation) by an ophthalmologist.

Following a clinical diagnosis of macular oedema secondary to CRVO, a number of treatments have been recommended internationally. These include intravitreal injection of steroids such as triamcinolone⁶, anti-angiogenic drugs (e.g. bevacizumab and ranibizumab⁷), and intravitreal implants containing the steroid dexamethasone. However, none of these are PBS listed for treatment of macular oedema secondary to CRVO, and only ranibizumab is approved by the Therapeutic Goods Administration (TGA) for this indication⁸. The applicant proposes that OCT be listed as a reimbursed service to determine patient eligibility for

³ Sudden or gradual onset of visual loss and a history of any of the following: hypertension, diabetes mellitus, cardiovascular disorders, coagulopathies, vasculitis, autoimmune disorders, use of oral contraceptives, closed head trauma, alcoholism and primary open-angle or angle-closure glaucoma.

⁴ The applicant quotes page 26 of MSAC application 1116 to further substantiate this claim. The passage referred to reads: "It is the expert opinion of the Advisory Panel that OCT machines are located in every Australian state capital city and in the Australian Capital Territory. Machines are also located in some major population centres outside capital cities. Wide dissemination of the technology has occurred across Australia, and as such it is not possible to accurately describe the number of machines around the country."

⁵ MBS item number 42809.

⁶ The RCO 2010 Guidelines, however, no longer recommend triamcinolone.

⁷ Bevacizumab and ranibizumab act by inhibition of vascular endothelial growth factor (VEGF).

⁸ Treatment of macular oedema secondary to RVO, which includes CRVO.

treatment with aflibercept, the VEGF inhibitor for which PBS listing will be concurrently sought. As such, the current application for the use of OCT in the context of CRVO/macular oedema as defined in this protocol will require assessment as a co-dependent technology.

The proposed use of OCT in the applicant's documentation is specifically for a patient population who have a confirmed diagnosis of CRVO using the currently reimbursed tests identified above (retinal photography with intravenous dye injection; MBS item numbers 11215, and 11218). Accordingly, the proposed OCT services will be complementary to these diagnostic tests for CRVO; however MESP have expressed the opinion that this is unlikely to result in an increase in the use of items 11215 and 11218 in the event that aflibercept becomes available on the PBS. Usage of other item numbers identified by the applicant (i.e. 11204, 11205, and 11210) is also unlikely to change for the reasons previously noted above. A total of 30,792 services were billed under these item numbers during the 2010-2011 financial year, representing a cost to the MBS of \$4.14 million. Usage of these item numbers over the last five years is summarised in Table 1 (DHA 2012). Both these services declined over this period, however the usage of item 11218 which is for retinal photography involving multiple exposures of *both* eyes with intravenous dye injection has been utilised substantially more than item 11215 which is the same service performed for *one eye* only. While CRVO is rarely observed to occur simultaneously in two eyes (Jonas et al 2010; Laouri et al 2011; Mitchell et al 1996), it should be noted that these services are used to diagnose a variety of retinal conditions in which bilateral investigations may be required. Therefore, the large difference in usage between these items is not necessarily a reflection of practice patterns involving the routine examination of both eyes to reduce the likelihood of missing rare cases of bilateral CRVO. Introduction of OCT under the proposed indication would be an additional cost to the MBS on top of costs for services billed under items for retinal photography.

Regulatory status

The use of OCT for retinal and macular imaging is currently listed on the Australian Register of Therapeutic Goods (ARTG number 194817). The Therapeutic Goods Administration (TGA) approved OCT for these indications in February 2012.

The proposed co-dependent drug, aflibercept, was approved by the TGA for the treatment of neovascular (wet) age-related macular degeneration in March 2012⁹. Aflibercept, marketed by Bayer Australia Ltd as Eyelea, is not currently on the ARTG for the proposed treatment of macular oedema secondary to CRVO. Bayer Australia has noted that an application for TGA approval of the new clinical indication is currently being prepared.

⁹ ARTG 180859 (intravitreal injection, vial) and ARTG 180860 (intravitreal injection, pre-filled syringe).

Table 1 MBS item usage for retinal photography with intravenous dye injection for the period 2006-2011

Year	Item number	
	11215	11218
2006-07	2,838	36,507
2007-08	2,214	35,626
2008-09	1,716	33,620
2009-10	1,282	31,810
2010-11	1,134	29,658
Total	9,184	167,221

Intervention

Description

Optical coherence tomography has been proposed as a technology to improve the management of patients with macular oedema secondary to CRVO. This section will summarise the clinical aspects and pathogenesis of CRVO, describe the specific application of managing macular oedema/CRVO using OCT, which is not intended to replace current diagnostic methods but rather provide additional information to inform treatment, and thirdly provide a layman's summary of how OCT works.

The disease processes underlying retinal vein occlusion (RVO) are only partly understood at the present time. It is believed that an external compression of the vein wall at the level of the lamina cribosa or arteriovenous crossing obstructs the normal flow of blood in the retinal vascular system, but a variety of other factors, including changes in the vessel walls and thrombotic tendencies may contribute to development of RVO. The disease can be differentiated into two main types. Central retinal vein occlusion, which involves the whole of the central venous system, is characterised by superficial and deep intraretinal haemorrhages in all four quadrants of the retina associated with variable degrees of venous engorgement and tortuosity, optic disc swelling¹⁰, cotton wool spots and cystoid macular oedema. Branch retinal vein occlusion (BRVO) differs from CRVO in that venous engorgement is limited to branches of the retinal venous system and haemorrhages are found only within a sector of the retina. The complications of BRVO and CRVO can overlap and both conditions are further classified into ischaemic and non-ischaemic types, however

¹⁰ The optic disc, also known as the optic nerve head, is the location where nerve cell axons exit the eye to form the optic nerve.

treatment of BRVO and its prognosis differ from CRVO and further discussion of BRVO is beyond the scope of this document (Jonas et al 2010; Kiire & Chong 2012; McAllister 2012).

Within CRVO, classification of the disease into non-ischaemic and ischaemic forms depends on the degree of capillary non-perfusion (CNP) as shown by fluorescein angiography findings. For this reason, the non-ischaemic form of the condition is also referred to as perfused CRVO while ischaemic disease is denoted as non-perfused. Based on the Central Vein Occlusion Study (CVOS), CRVO which shows more than 10 disc areas¹¹ of CNP by fluorescein angiography is considered to be ischaemic. Differentiation between ischaemic and non-ischaemic disease has important implications for treatment and prognosis. The prognosis for ischaemic disease has generally found to be poorer than non-ischaemic disease for which macular oedema may be self-resolving in up to 30 per cent of eyes. Serious complications, such as neovascular glaucoma, are rarely observed in this context. When neovascularisation in the context of ischaemic CRVO does occur, both the anterior segment of the eye (iris and angle) and the posterior segment (retina and optic disc) may be affected. The resulting complications can contribute to a loss of visual acuity which is usually in addition to the loss already sustained from the macular oedema component of CRVO. In eyes where macular oedema is persistent (not spontaneously resolving) earlier commencement of treatment has been associated with better visual outcome. Visual acuity at presentation is also believed to be an important prognostic indicator (Coscas et al 2011; Kiire & Chong 2012; McAllister 2012).

Examination with OCT has diffused into clinical practice and is reported to have widespread applications including the detection of macular and retinal disease (Jonas et al 2010). Under the applicant's proposal, the claimed utility of this technology is for assessing macular oedema secondary to CRVO in order to identify patients who would benefit most from treatment with aflibercept. In this capacity, it is not intended as a technology that can replace the ophthalmological testing which enables diagnosis of CRVO. Tests such as fluorescein angiography, indispensable to the diagnostic process, assess the area and extent of retinal haemorrhage, and the extent of capillary non-perfusion (Coscas et al 2011). Conversely, OCT is claimed to offer the added benefit of quantitatively measuring the extent of macular oedema based on central retinal thickness (CRT). This is potentially useful as a baseline measure to identify patients for treatment with aflibercept, and also to monitor patients at regular intervals following commencement of the treatment. It is suggested that this will permit the tailoring of dosing regimens to obtain maximum benefit without the excess cost and potential risks involved with over-treatment.

¹¹ That is, the area equivalent to the surface area of the optic disc multiplied by ten.

Optical coherence tomography can be considered as the optical analogue of ultrasound. In OCT, cross-sectional image acquisition is based on mapping the depth-wise reflection of light from the subject tissue. The use of light instead of sound permits the acquisition of images at higher resolution than ultrasound without the need for contact with the patient's eye. However, reflected light cannot be measured directly by the echo time delay principle as in ultrasound, and therefore OCT relies on the optical technique known as low coherence interferometry. During a retinal scan, an OCT machine generates an imaging beam which is split into two. One beam is projected at the retina and the other onto a mirror, which reflects the incident light to produce a reference beam. This technique allows the light returning from the retina to interfere with the reference light beam that has travelled a known path length. The signals generated by this interference are detected by an interferometer and correspond to optical interfaces within the retina. Scans of the retina at a single point known as A-scans, are repeated at different points to generate two dimensional B-scans, which may in turn be combined to produce three dimensional images. The images are displayed on a computer monitor either in grey scale or false colour in order to differentiate intra-retinal microstructures. Use of false colour enhances visualisation of these structures, as the human eye only has limited ability to differentiate levels of grey (Drexler & Fujimoto 2008; Marschall et al 2011; MSAC 2009; Sakata et al 2009; van Velthoven et al 2007).

In clinical practice, two main types of OCT systems are available. First generation OCT systems are based on A-scans which are acquired in the time domain, whereas second generation systems acquire A-scans in the spectral frequency domain. Time domain technology (e.g. Zeiss Stratus OCT) uses light at wavelength of 820 nm to achieve a maximum of 512 A-scans per B-scan at a rate of 400 A-scans per second. Axial and transverse retinal image resolutions of 10 and 20 μm , respectively, are achieved. The more recent spectral domain systems can acquire 4,000 to 8,000 A-scans per B-scan at a rate of 18,000 to 40,000 A-scans per second with superior resolution in the axial (5-7 μm) and transverse (10-20 μm) planes, when compared to time domain OCT. Second generation OCT also permits imaging in three dimensions via reconstruction of the two-dimensional A-scan and B-scan data (Marschall et al 2011; MSAC 2009).

The submission does not specify any trademarked technology for the provision of OCT procedures for the management of CRVO/macular oedema. Clinical trials of aflibercept cited by the applicant have employed Zeiss Stratus OCT imaging software, and the Royal College of Ophthalmologists (UK) have recommended equipment with specifications corresponding to the Zeiss Stratus OCT system as a minimum (RCO 2010). However, it is understood that other OCT equipment is made by a number of manufacturers is available in Australia, and the proposal is for a generic intervention to monitor macular oedema in patients with CRVO.

Aflibercept, the anti-angiogenic drug which is to be used in the treatment regimen informed by OCT, is registered under the trading name Eyelea.

OCT is currently TGA approved for imaging of the retina and macula for diagnostic purposes¹², and the proposed MBS item descriptor, though yet to be finalised, is currently in line with the TGA approved indications. Aflibercept, however, is only listed on the ARTG for the treatment of neovascular age-related macular degeneration, and so TGA approval of the proposed new indication as treatment of CRVO will be required prior to, or parallel to, determination of eligibility for listing on the PBS.

Delivery of the intervention

Clinical trials of aflibercept referred to in the application¹³ followed a protocol in which the drug was injected every month for the first six months and as needed thereafter, i.e. pro re nata dosing. The application mentions that during the pro re nata phase from week 24 to week 52 in the "Galileo" trial, the mean number of aflibercept injections was 2.5, but in adhering to the research protocol, OCT was performed every four weeks without regard to whether or not further injections were required. The application maintains that such a rigorous schedule is unlikely to be required in clinical practice and instead would follow response-based criteria. However, if practice were to accord with trial protocols, the annual use per patient would be in the range of six to twelve OCT procedures. In light of using response-based criteria for continuing aflibercept therapy as proposed in the application, the number of OCT procedures required for each patient in the monitoring of CRVO/macular oedema would vary and would be restricted by the definition of treatment response. No further OCT would be required for patients who respond inadequately to aflibercept. The applicant has stated that clinician input will be sought to further inform estimates of annual utilisation on a per patient basis.

To estimate the *number of patients* who would utilise OCT for the proposed indications within a yearly time-frame, prevalence and incidence rates of CRVO in Australia are required. The Blue Mountains Eye Study (Mitchell et al 1996), a population-based survey of 3654 individuals representative of the Australian population for income and socioeconomic status, provides prevalence data for retinal vein occlusion (RVO) as shown in Table 2. According to Mitchell and colleagues, CRVO represents approximately a quarter of all CRVO

¹² Searching www.ebs.tga.gov.au identified the following listing of OCT specifically for retinal/macular imaging: Retinal optical coherence tomography system (ARTG 194817), Emergo Asia Pacific Pty Ltd.

¹³ These trials referred to as "Galileo" and "Copernicus" are listed on the website of the US National Institutes of Health registry of clinical trials as having been completed. The details are accessible at www.clinicaltrials.gov.

cases, and the prevalence of CRVO is thus calculated by multiplying the prevalence of RVO in each age group by 0.25 (25%).

Table 2 Prevalence rates of CRVO in Australia (Mitchell et al 1996)

Age group	Reported prevalence of RVO (%)	Proportion of CRVO in RVO (%)	Calculated prevalence of CRVO (%)
<60 years	0.70	25	0.18
60-69 years	1.20		0.30
70-79 years	2.10		0.53
≥80 years	4.65		1.16

Abbreviations: RVO, retinal vein occlusion; CRVO, central retinal vein occlusion.

Based on these estimates, it is then possible using population data from the Australian Bureau of Statistics to estimate prevalent cases of CRVO from the present up until 2016, as shown in Table 3. A limitation of this method of estimation is that it assumes the prevalence of CRVO will remain constant over four years, and to this end the number of cases is expected to grow as per the population growth.

Table 3 Estimated prevalence of CRVO in Australia: 2012-2016 (ABS 2008).

Year	2012	2013	2014	2015	2016
Population projection by age, n					
Age, years					
50-59	2,896,524	2,944,896	2,989,980	3,020,428	3,040,548
60-69	2,276,029	2,355,677	2,418,143	2,478,740	2,539,717
70-79	1,338,525	1,381,862	1,441,080	1,504,636	1,569,522
≥80	888,517	908,012	926,691	946,430	970,356
Total	7,399,595	7,590,447	7,775,894	7,950,234	8,120,143
Prevalence of CRVO, %					
50-59	0.18				
60-69	0.30				
70-79	0.53				
≥80	1.16				
Estimated CRVO cases					
50-59	5,069	5,154	5,232	5,286	5,321
60-69	6,828	7,067	7,254	7,436	7,619
70-79	7,027	7,255	7,566	7,899	8,240
≥80	10,329	10,556	10,773	11,002	11,280
Total	29,253	30,031	30,825	31,624	32,460

A more recent paper published as part of the Blue Mountains Eye Study (Cugati et al 2006) estimated the ten-year cumulative incidence of CRVO to be 0.4 per cent (95% CI [0.1-0.7%]). While prevalence is an important consideration for the monitoring of CRVO,

incidence is important when considering diagnosis. No data from the Australian Institute of Health and Welfare (AIHW) on the incidence of CRVO are currently available.

As with any technology, it is not expected that uptake of OCT for identification and monitoring of CRVO/macular oedema will be 100 per cent. However, growth in the utilisation of OCT for the proposed application would be expected over time, particularly if aflibercept or another treatment (e.g. ranibizumab) becomes available on the PBS.

Prerequisites

The proposed OCT service is suggested as being co-dependent with the PBS listing of aflibercept which will require consideration by the TGA and the PBAC. Given that aflibercept is administered by intravitreal injection, OCT services in the management of CRVO related macular oedema would be most appropriately provided by ophthalmologists in a consultation room setting. Although optometrists are able to, and do use OCT for a variety of indications, the subsequent medical management in the context of CRVO would require the clinical expertise of an ophthalmologist, as optometrists can only obtain accreditation to prescribe *topical* medications in Australia (OBA 2010). Therefore the listing proposed in the application seeks to restrict the service to ophthalmologists. An optometrist or GP is the first point of contact for a patient experiencing visual impairment, with referral to an ophthalmologist where clinically indicated.

No formal training or accreditation is required in order for a practitioner to carry out OCT, and it is understood that instructions from the manufacturers of OCT equipment are provided in adequate detail for safe operation by the appropriate medical professional. In the context of CRVO management, the clinician in charge of care would be an ophthalmologist. It is not expected that introduction of OCT for the publicly reimbursed management of CRVO/macular oedema will have implications for staffing numbers, training or skill set, as OCT has already diffused widely in the current practice of ophthalmology. The applicant cites this as reasoning for the unlikelihood of any notable access issues. However, given the proposed restriction of the service to ophthalmologists and that the vast majority of ophthalmologists practice in major urban centres, there is likely to be only limited access to specialist care of CRVO (OCT monitoring and any intravitreal treatment) in outer regional, remote and very remote areas (AIHW 2009).

Eligible populations for OCT and aflibercept treatment are provided by two trials registered on <http://www.clinicaltrials.gov/> (Table 4), of which only one ("Copernicus") was published at the time of preparing this document (Boyer et al 2012). Also shown are the criteria for continuing treatment with aflibercept.

Table 4 Patient eligibility criteria for the Galileo and Copernicus trials of aflibercept

Trial	Inclusion criteria	Exclusion criteria	Retreatment criteria for deterioration and improvement
Copernicus	<p>Subjects at least 18 years of age with centre-involved macular oedema secondary to CRVO with mean CRT ≥ 250 μm on OCT</p> <p>ETDRS BCVA of 20/40-20/320 in the study eye</p>	<p>Previous treatment with anti-angiogenic drugs in the study eye (pegaptanib sodium, anecorvate acetate, bevacizumab, ranibizumab, etc)</p> <p>Prior panretinal laser photocoagulation or macular laser photocoagulation in study eye</p> <p>CRVO duration >9 months from diagnosis date</p> <p>History of intraocular corticosteroid use in the study eye or periocular corticosteroids in the study eye within 3 months of commencing aflibercept</p> <p>Iris neovascularisation, vitreous haemorrhage, traction retinal detachment, or pre-retinal fibrosis involving the macular in either study or fellow eye</p>	<p>Deterioration^a: >50 μm increase in CRT compared to lowest previous measurement; new or persistent cystic retinal changes or sub-retinal fluid on OCT; persistent diffuse oedema >250 μm in central subfield on OCT; loss of 5 or more ETDRS chart letters from best previous measurement in conjunction with increase in CRT</p> <p>Improvement: Rapid^b and substantial improvement of visual acuity (≥ 5 letters) since last visit, plus absence of retinal oedema in central subfield</p>
Galileo	<p>Centre-involved macular oedema secondary to CRVO for no longer than 9 months with mean CRT (subfield) ≥ 250 μm on OCT</p> <p>Subjects ≥ 18 years</p> <p>ETDRS BCVA of 20/40-20/320 in the study eye</p>	<p>Any prior treatment with anti-VEGF agents in the study eye (pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc) or previous treatment with systemic anti-angiogenic medications</p> <p>Prior panretinal laser photocoagulation or macular laser photocoagulation in the study eye</p> <p>CRVO disease duration >9 months from date of diagnosis</p> <p>Previous use of intraocular corticosteroids in the study eye within 3 months prior to commencement of aflibercept treatment</p> <p>Iris neovascularisation, vitreous haemorrhage, traction retinal detachment, or pre-retinal fibrosis involving the macular in either study or fellow eye</p>	As per Copernicus

Abbreviations: CRVO, central retinal vein occlusion; CRT, central retinal thickness; ETDRS, early treatment diabetic retinopathy study; BCVA, best corrected visual acuity; VEGF, vascular endothelial growth factor.

^aThe publication by Boyer et al (2012) indicates that retreatment was provided if either improvement or deterioration criteria were met, but that if none of these criteria were met, sham injection was administered. The applicant maintains that retreatment could include either aflibercept or sham injection, as per responses to the treatments allocated at baseline. Release dates for Galileo are unavailable at this time.

^bRapid improvement appears to refer to the improvement of ≥ 5 letters having occurred during the period between the current and most recent visit for OCT (Boyer et al 2012).

Co-administered and associated interventions

The applicant notes that OCT systems are stand-alone mobile equipment with no specific complementary services required. While in general terms this is correct, several prior tests are required before OCT is performed. To briefly summarise, a patient typically presenting with sudden painless visual loss where CRVO is the cause will in the first instance require a medical history check to identify key risk factors for CRVO. A range of baseline ophthalmic assessments would be followed by fundus photography and/or fundus fluorescein angiography (FFA) in order to confirm a diagnosis of CRVO and the extent of damage to the macula/retina. Fundus photography permits the clinician to identify the area of retinal thickening and haemorrhage, whereas FFA identifies the presence and area of fluorescein leakage and capillary non-perfusion. These tests also determine the presence or absence of macular oedema. Finally, OCT then measures retinal thickness, providing a quantitative assessment of the severity of macular oedema (Blodi et al 2010; Ip et al 2009; Kiire & Chong 2012; McAllister 2012; Ossewaarde-Van Norel et al 2012; RCO 2010; Wong & Scott 2010). The applicant stresses that each test provides information about different aspects of the pathophysiological features of CRVO/macular oedema. Under the proposed listing, the patient's eligibility for treatment with aflibercept would then be determined. Under existing arrangements, aflibercept is TGA approved only for the treatment of wet (neovascular) age-related macular degeneration.

Listing proposed and options for MSAC consideration

Proposed MBS listing

The proposed wording of the MBS items is shown in Table 5, and reflects the wording contained in the proposed DAP provided by the applicant and rewording informed by feedback from the Department of Health and Ageing. Bayer Australia has provided costing data based on running costs within a typical ophthalmological practice as the basis for a fee structure for the proposed item, and suggest the service is claimed to be between \$200 and \$250. The fees in Table 5 are therefore conservatively nominated as being the upper end of the range provided. The fee structure will be ultimately determined at the discretion of the Department of Health and Ageing in the event that the application for OCT services is successful.

Since the listing proposes that OCT would be used in conjunction with aflibercept, which is administered as an intravitreal injection, the application suggests that this procedure can be appropriately billed in the majority of cases under the existing item number 42738, and in some instances under 42739 or 42740, as shown in Table 6.

Table 5 Proposed MBS item descriptors for OCT for the measurement of CRVO for determining the eligibility of aflibercept and monitoring aflibercept *Item number to be assigned by department if MBS listed*

Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS	
xxxx	Optical coherence tomography for the assessment of central retinal thickness to determine the eligibility for PBS-subsidised aflibercept of a patient with macular oedema secondary to central retinal vein occlusion. Fee: ██████ Benefit: 75% = \$187.50 85% = \$212.50
xxxx	Optical coherence tomography for the assessment of central retinal thickness to determine whether to modify therapy with PBS-subsidised aflibercept in a patient with macular oedema secondary to central retinal vein occlusion. Fee: ██████ Benefit: 75% = \$187.50 85% = \$212.50
Explanatory notes Diagnosis of macular oedema secondary to central retinal vein occlusion by professional attendance of an ophthalmologist is required. Diagnosis will involve the use of standard assessments, including but not limited to retinal photography with intravenous dye injection (items 11215 and 11218). Determination of aflibercept eligibility requires both baseline and ongoing assessment using optical coherence tomography	

The medical condition specifying the eligible patient population is macular oedema secondary to CRVO. The applicant proposed that, pending availability of aflibercept through the PBS, a mean baseline retinal thickness measurement of $\geq 250 \mu\text{m}$ using OCT would be an acceptable cut-off to determine patient eligibility for aflibercept treatment with reimbursement from the PBS. This figure is based on clinical trials (Galileo and Copernicus, see <http://www.clinicaltrials.gov>) suggesting that this patient population can be appropriately targeted for effective treatment with aflibercept¹⁴. Treatment continuation criteria, which depend on follow-up monitoring with OCT, have also been investigated in these trials. Details are summarised in Table 4, however at this stage it is anticipated that the criteria are likely to require further refinement in consultation with expert clinical advice, PBAC and MSAC.

¹⁴ PASC have requested that further justification of this cut-off is provided.

Table 6 Current MBS item descriptors under which it is proposed intravitreal injections with aflibercept will be provided.

Category 3 – THERAPEUTIC PROCEDURES
<p>42738</p> <p>PARACENTESIS OF ANTERIOR CHAMBER OR VITREOUS CAVITY, or both, for the injection of therapeutic substances, or the removal of aqueous or vitreous humours for diagnostic purposes or therapeutic purposes, 1 or more of, as an independent procedure.</p> <p>Fee: \$295.15 Benefit: 75% = \$221.40 85% = \$250.90</p>
<p>42739</p> <p>PARACENTESIS OF ANTERIOR CHAMBER OR VITREOUS CAVITY, or both, for the injection of therapeutic substances, or the removal of aqueous or vitreous humours for diagnostic purposes or therapeutic purposes, 1 or more of, as an independent procedure, for a patient requiring anaesthetic services.</p> <p>Fee: \$295.15 Benefit: 75% = \$221.40 85% = \$250.90</p>
<p>42740</p> <p>INTRAVITREAL INJECTION OF THERAPEUTIC SUBSTANCES, or the removal of vitreous humour for diagnostic purposes, 1 or more of, as a procedure associated with other intraocular surgery.</p> <p>Fee: \$295.15 Benefit: 75% = \$221.40 85% = \$250.90</p>
<p>Associated Notes</p> <p>Items 42738 and 42739 provide for paracentesis for the injection of therapeutic substances and/or the removal of aqueous or vitreous, when undertaken as an independent procedure. That is, not in conjunction with other intraocular surgery.</p> <p>Item 42739 should be claimed for patients requiring anaesthetic services for the procedure. Advice from the Royal Australian and New Zealand College of Ophthalmologists is that independent injections require only topical anaesthesia, with or without subconjunctival anaesthesia, except in specific circumstances as outlined below where additional anaesthetic services may be indicated:</p> <ul style="list-style-type: none"> • nystagmus or eye movement disorder; • cognitive impairment precluding safe intravitreal injection without sedation; • a patient under the age of 18 years; • a patient unable to tolerate intravitreal injection under local anaesthetic without sedation; or • endophthalmitis or other inflammation requiring more extensive anaesthesia (eg peribulbar). <p>Practitioners billing item 42739 must keep clinical notes outlining the basis for the use of anaesthetic.</p> <p>Item 42740 provides for intravitreal injection of therapeutic substances and/or the removal of vitreous for diagnostic purposes when performed in conjunction with other intraocular surgery including with a service to which Item 42809 (retinal photocoagulation) applies.</p>

Limitations to the use of OCT in CRVO management have been partly considered in the funding proposal. The applicant has proposed that the listing completely depends on aflibercept becoming available on the PBS. Advice from the Department is that the claimed utility of OCT to inform treatment with anti-VEGF drugs cannot be assumed. The requirement to formally assess the dependency of aflibercept treatment on OCT has been suggested following a submission to the PBAC for ranibizumab in patients with retinal vein

occlusion (RVO). The ranibizumab submission specifically indicates that OCT is *not* necessary for either diagnosis or monitoring of treatment effectiveness, based on information from the applicant's expert advisory panel. Accordingly, there would be no requirement for OCT to determine patient eligibility criteria in the context of CRVO/RVO¹⁵. This suggests that the additional diagnostic information provided by OCT may not necessarily provide additional benefit in terms of final patient outcomes. For this reason PASC have requested that the clinical effectiveness, safety and cost-effectiveness of aflibercept *without* the use of OCT are included as part of the final assessment, in addition to the scenarios involving aflibercept plus OCT, and standard medical management. This is discussed in further detail under the "Comparator" section of this document.

The applicant has indicated that the proposed MBS listing of OCT provides for the following:

1. OCT alone cannot be used to diagnose macular oedema for CRVO. Diagnosis of CRVO and the identification of macular oedema require the services described in MBS item numbers 11215, and 11218 and clinical examination (*prior* to any use of OCT under the requested listing);
2. the listing is specific to OCT for determining a patient's eligibility/non-eligibility (baseline) to receive PBS-funded treatment with aflibercept, in turn subject to ongoing eligibility criteria which will be based on measurement of CRT and a response-based continuation rule¹⁶; and
3. that only patients with macular oedema secondary to CRVO will be eligible.

Clinical place for proposed intervention

Listing of the proposed intervention will represent a complementary publicly funded service to the current clinical management of macular oedema secondary to OCT, as shown in the management algorithm depicted by Figure 1. The applicant claims that OCT enables the measurement of central retinal thickness (CRT), which is not possible using other current diagnostic methods, and therefore provides additional information whereby patients who are most likely to benefit from aflibercept treatment are targeted. The suggested cut-off for which a patient cannot receive publicly reimbursed treatment with aflibercept is a CRT measurement of less than 250 microns (not shown in Figure 1). To receive continuing

¹⁵ As previously discussed, CRVO is included within the broader disease designation of RVO.

¹⁶ The proposal provides that ongoing treatment will only attract a subsidisation for patient's showing sufficient response, with a response criterion yet to be finalised. The proposed listing of OCT will therefore be subject to the same continuation rule.

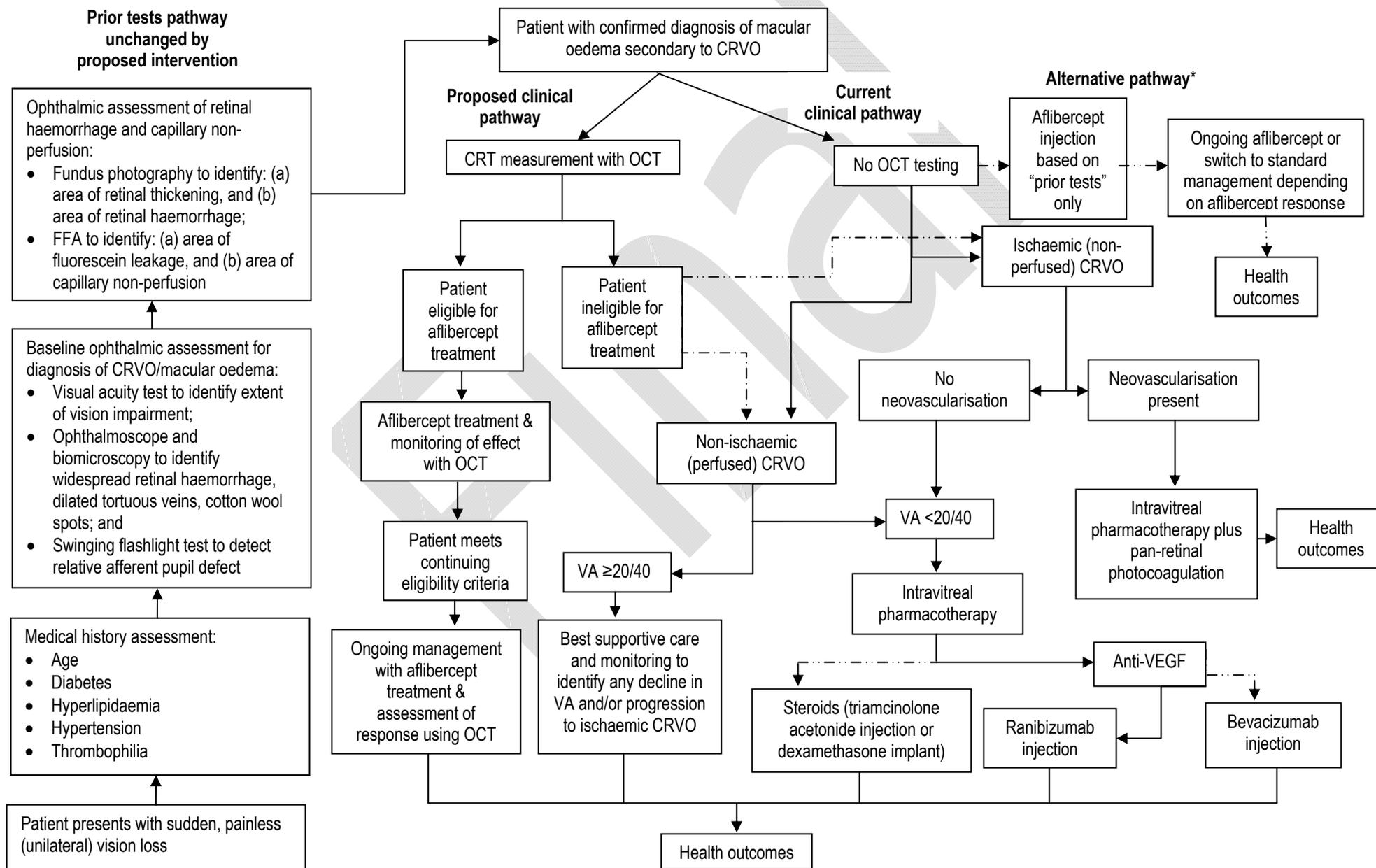
treatment with aflibercept, patients would also have to meet treatment response criteria, as determined by OCT monitoring, but these are yet to be finalised.

At the present time, publicly funded treatments for patients with CRVO are limited. While pan-retinal photocoagulation (PRP) is a publicly funded treatment which may be appropriate for some patients with CRVO, it is not specifically a treatment for macular oedema. Rather, treatment with PRP is recommended only in cases of ischaemic CRVO where neovascularisation is present (RCO 2010). The Members of the Expert Standing Panel (MESP) have clarified that PRP acts to down regulate VEGF, but not to the level required to effect any change in macular oedema, and thus it is reserved as a measure to prevent secondary neovascularisation due to increased VEGF levels. In this clinical context, the treatment regimen may involve *both* photocoagulation and pharmacotherapy to treat the neovascularisation and macular oedema components of CRVO, respectively. However, under current arrangements in Australia, no pharmacotherapy is PBS-listed for the treatment of macular oedema, and only ranibizumab is TGA approved for this indication. Therefore, pharmacotherapy options are available only on a self-funded basis. As shown in the algorithm, visual acuity outcomes at initial clinical examination have been considered important in determining the course of treatment under the current clinical pathway¹⁷. Links to treatments which are not currently TGA approved for use in Australia¹⁸ are shown by the use of dotted lines in the management algorithm, as is the proposed pathway for patients who fail aflibercept treatment to be managed under the current provisions, and the alternative pathway in which aflibercept is provided without OCT, based on standard diagnosis alone.

¹⁷ While no guidelines or formal criteria exist, the MESP have expressed the opinion that selection of visual acuity thresholds shown in the management algorithm (as per the Galileo and Copernicus trials) are clinically sensible. MESP also indicated that these criteria for the decision between clinical observation (in anticipation of spontaneous resolution of macular oedema) and medical management do align with actual clinical practice in Australia (correspondence, 30 August 2012).

¹⁸ MESP have indicated that in practice, bevacizumab is used off-label.

Figure 1 Clinical management algorithm for patients with confirmed diagnosis of macular oedema secondary to CRVO. Note that OCT is proposed as an additional service which will not change use of prior diagnostic tests which are relevant to both current and proposed pathways. Abbreviations: CRVO, central retinal vein occlusion; FFA, fundus fluorescein angiography; CRT, central retinal thickness; OCT, ocular coherence tomography; VA, visual acuity; VEGF, vascular endothelial growth factor. *As requested by PASC.



Comparator

As shown in the management algorithm at Figure 1, the most appropriate comparator involves standard diagnostic testing *without* the additional information provided by OCT. Therapeutic intervention for macular oedema based on diagnostic testing alone involves intravitreal pharmacotherapy and pan-retinal photocoagulation (PRP), as per the evidence from available guidelines. The Royal College of Ophthalmologists (UK) recommend pan-retinal photocoagulation (A grade evidence, i.e. minimum RCT level evidence) when iris new vessels or angle new vessels are visible. In other words, PRP is a treatment specifically for neovascularisation as opposed to macular oedema¹⁹. Treatment of macular oedema with ranibizumab (or other anti-VEGF drugs), and combination treatment of concurrent macular oedema and neovascularisation with VEGF *and* PRP are supported by lower level evidence.

While no publicly funded pharmacotherapy is available for treatment of macular oedema secondary to CRVO in Australia²⁰, ranibizumab is TGA approved for this indication. Retinal photocoagulation is MBS listed (item 42809) without restriction, but this treatment targets the neovascularisation component of CRVO, not macular oedema. Therefore the most appropriate comparator for the integrated submission would be ranibizumab alone, at the exclusion of combination treatment with ranibizumab and pan-retinal photocoagulation. It is the opinion of the Members of the Expert Standing Panel (MESP), who have agreed to provide clinical advice in the production of this document, that pan-retinal photocoagulation alone is not used in clinical practice to treat macular oedema. The MESP have informed that photocoagulation acts to down regulate VEGF, but not to the level required to effect any change in macular oedema, and thus it is reserved as a measure to prevent secondary neovascularisation due to increased VEGF. In other words, photocoagulation is indicated in the late sequelae of CRVO where neovascularisation is present, whereas ranibizumab alone is appropriate in the absence of neovascularisation (RCO 2010). Accordingly, it is deemed inappropriate to compare a treatment that is aimed solely at the neovascularisation component of CRVO with a treatment that specifically targets macular oedema, and therefore the comparator for aflibercept will be ranibizumab (as part of standard medical management which involves prior diagnostic tests, but not OCT).

This choice of this comparator is supported by PBAC Guidelines²¹ for determining a main comparator. The guidelines state:

¹⁹ See “Clinical place for proposed intervention” (p.20).

²⁰ A variety of drugs for intravitreal injection are recommended in clinical guidelines of the RCO (UK). However, only ranibizumab has TGA approval in Australia for macular oedema secondary to CRVO.

²¹ Version 4.3, 2008.

“The main comparator is defined as the therapy that prescribers would most replace with the proposed drug in practice if the PBS subsidises the proposed drug as requested. PBAC does not and has no power to recommend that prescribers substitute the proposed drug for any particular comparator. Therefore, PBAC bases its judgment about the main comparator on what would be *likely* to happen, rather than what *should* happen, in keeping with the above definition of the main comparator.”

“...If no currently PBS-listed drug is available, the main comparator would usually be standard medical management (this could include a nonlisted drug, a surgical procedure or conservative management). When this situation arises, the main comparator should be clearly and consistently defined both in the submission and in the direct randomised trials.”

In addition to ranibizumab, a second comparator involving the use of aflibercept informed only by currently funded diagnostic tests, i.e. without the use of OCT, has been requested by PASC, as this comparison is suggested to be the most relevant for the purposes of MSAC. The rationale provided is that the claimed utility of OCT to inform aflibercept treatment needs to be part of the assessment for MSAC/PBAC consideration, rather than an assumption from the outset. In other words, a scenario considering the clinical effectiveness, safety and cost-effectiveness of aflibercept without the use of OCT will be required.

Outcomes for safety and effectiveness evaluation

Health outcomes will be measured in order to assess the safety and effectiveness of the proposed interventions and appropriate comparators. In terms of a direct evidence comparison (e.g. OCT plus aflibercept versus standard medical management (e.g. ophthalmic assessment without OCT plus ranibizumab)), the relevant effectiveness outcomes would be stabilisation or regression of macular oedema, as measured by the patient relevant measures such as visual acuity or by the surrogate outcome of central retinal thickness(CRT). However, the validity of CRT as a surrogate outcome for visual acuity will need to be assessed, particularly with reference to the nominated 250 µm threshold of CRT used to determine eligibility for treatment, and the magnitude of change specified for subsequent treatment decisions.

In terms of a linked evidence comparison, the applicant has proposed that OCT represents a gold standard technique to measure CRT, and on this basis reasons that selection of another reference standard is difficult. While it is recognised that OCT provides the unique ability to provide measurements of CRT, current clinical practice in the absence of access to OCT relies on clinical examination, including but not limited to fundus photography with

intravenous dye injection. Given the lack of another reference standard for measurement of CRT, a direct evidence approach is the only option. Thus, the health outcomes of patients treated with aflibercept as a result of eligibility determined by OCT,²² following a clinical confirmation of CRVO, should be compared to the health outcomes of patients who have undergone standard medical management of CRVO. Additionally, as mentioned previously, a third scenario involving the use of aflibercept without OCT has been requested by PASC. This will be necessary to determine the clinical effectiveness and safety of aflibercept alone, relative to: (a) aflibercept informed by OCT, and (b) standard medical management. The health outcomes to be measured in the assessment are:

Effectiveness

Primary effectiveness outcomes include improvement in visual acuity, function/activities of daily living, and quality of life.

OCT is proposed to measure CRT to determine treatment eligibility, and to monitor response to guide the use of ongoing treatment as a surrogate outcome for visual acuity. PASC therefore advised that an assessment of the evidence should include evidence to demonstrate:

- baseline CRT predicts a material variation in aflibercept's treatment effect on visual acuity, with reference to the nominated $\geq 250 \mu\text{m}$ threshold of CRT for determining eligibility for aflibercept;
- the association between change in CRT and improvement in visual acuity
- the reliability of OCT measurement of CRT; and
- the proposed response criteria can detect true inter-individual variation in treatment effects to confirm OCT's value as a monitoring test.

Relevant methodology for assessing the value of treatment monitoring has been previously described elsewhere (Bell et al 2009). Establishing the value of treatment monitoring lies in effective demonstration that the observed variation in response to therapy (aflibercept) *between* individuals (treatment-related variation) on the surrogate outcome (CRT) exceeds the variation observed *within* individuals upon repeated measurement (measurement-related variation). Conversely, a finding that inter-individual variation in treatment effects on CRT is small in comparison to intra-individual variation would show that the former is not clinically relevant and suggests that treatment monitoring should be avoided. The example provided

²² A CRT measurement $\geq 250 \mu\text{m}$ is proposed as a baseline cut-off, with ongoing eligibility criteria to be finalised for incorporation into the final DAP.

by Bell and colleagues (Bell et al 2009) demonstrated this principle using a large RCT which compared the treatment effects of alendronate (for low bone mineral density) and placebo in 6459 post-menopausal women. Their finding that treatment-related variation in bone mineral density was small compared to intra-individual variation led to the conclusion that monitoring of bone mineral density in this population is unnecessary.

Bell and colleagues have provided a checklist for determining whether a treatment response/continuation rule is appropriate within the context of monitoring a surrogate outcome (Bell et al 2010)(Table 7).

Table 7 Checklist for deciding when a response rule may be appropriate (Bell et al 2010)

<p>1. Has the surrogate outcome been shown to predict risk of the clinically relevant outcome?^a</p> <ul style="list-style-type: none"> • Is there meta-analytic evidence demonstrating a relationship between treatment effect on the surrogate and treatment effect on risk of clinically relevant outcome?
<p>2. Is the proposed target for the surrogate outcome associated with a clinically important decrease in the risk of adverse clinical outcome?^b</p>
<p>3. Is systematic measurement error in the surrogate outcome small?^c</p> <ul style="list-style-type: none"> • What is the potential for systematic under/over-estimation of the surrogate outcome?
<p>4. Is the response rule likely to detect true between person variation in treatment effects on the surrogate outcome?^d</p> <ul style="list-style-type: none"> • What is the inter-individual variation in treatment effects on the surrogate outcome? • What is the intra-individual variation in the surrogate outcome? • What is the ratio of inter-individual variation in treatment effects to intra-individual variation?

Note: It is suggested (Bell et al 2010) that decision makers start with the item for which information is most easily available. If the response rule fails any of the checklist items, then it is unlikely to be useful and further appraisal is not required.

^aA surrogate outcome should only be considered for treatment monitoring if it is *known* to predict the effect of treatment on risk of the clinical outcome(s). The preferred evidentiary standard is meta-analyses of RCTs where the change in surrogate outcome is related to change in risk of a clinically relevant outcome(s) for patients treated with the intervention relative to those on control. If this level of evidence is lacking because the treatment is recently developed, then meta-analyses of RCTs of other therapies for the *same disease* may be acceptable evidence. Otherwise, observational data demonstrating that the surrogate predicts the clinically relevant outcome may be admissible.

^bAs per the criteria for the first item in the checklist, meta-analyses of RCT evidence are preferred.

^cSystematic error occurs when true values for the surrogate outcome is under- or over-estimated due to bias. Where possible, choosing a surrogate for which there is less room for interpretation should minimise this type of error. At the very least, especially where only one surrogate can be pragmatically chosen, standardised methods of measurement and reporting should be used.

^dIf there are insufficient data to estimate the inter-individual variation in treatment effects, the largest probable variation may still be estimated (see Bell et al 2010). Random intra-individual variation occurs due to biological fluctuations as well as technical error. This can be minimised by standardising how measurements are taken (technique and time) and using the mean of multiple measurements (before and after treatment). The ratio of inter-individual variation in treatment effects to the random intra-individual variation enables quantification of the likelihood of detecting true inter-individual variation in treatment effects. The larger the ratio, the more likely that the true inter-individual variation will be detected by a response rule.

Safety

Safety outcomes include any adverse events related to testing and any subsequently indicated treatment(s). These could include:

- intraocular inflammation;
- cataract;
- raised intra-ocular pressure (IOP);

- exacerbation of pre-existing neovascular glaucoma;
- endophthalmitis, and;
- retinal detachment (Hahn & Fekrat 2012; RCO 2010).

A subgroup analysis comparing outcomes of different OCT systems, e.g. time domain versus spectral domain may be appropriate, depending on the availability of evidence.

Summary of PICO to be used for assessment of evidence (systematic review)

Table 8 provides a summary of the PICO used to:

- (1) define the question for public funding;
- (2) select the evidence to assess the safety and effectiveness of
 - a. OCT for the identification of CRVO patients eligible for aflibercept treatment,
 - b. OCT for the continued treatment monitoring of eligible patients, and
 - c. treatment with aflibercept;
- (3) provide the evidence-based inputs for any decision-analytical modelling to determine the cost-effectiveness of the interventions in the population with macular oedema secondary to CRVO.

Question 1 in Table 8 is of main relevance for MSAC purposes, whereas question 2 is of relevant for the integrated submission. As part of the integrated submission, a further comparison of aflibercept without prior OCT versus standard medical management is expected.

Table 8 Summary of PICO to define research questions that assessment will investigate

Patients	Prior tests	Intervention	Direct evidence comparator	Reference standard/ evidentiary standard	Outcomes to be assessed
<p>Eligible for OCT Patients diagnosed with macular oedema secondary to CRVO</p> <p>Eligible for aflibercept CRT $\geq 250 \mu\text{m}$ on initial OCT with treatment response criteria for continued treatment to be finalised (suggested criteria based on trial data are shown at Table 4)</p>	<p>At least one of the following as part of the ophthalmological investigation: visual acuity testing, ophthalmoscope findings, biomicroscopy, swinging-flashlight test, fundus photography and FFA</p>	<p>Aflibercept in conjunction with OCT for the assessment of CRT following "prior tests"</p>	<p>Aflibercept without OCT ("prior tests" only)</p> <p>Standard medical management* (+ placebo, where relevant)</p> <p>*SMM = "prior tests" with no OCT and followed by treatment with ranibizumab or clinical observation where indicated by findings of the "prior tests"</p>	<p><i>Not applicable</i></p>	<p>Safety Adverse events associated with testing and treatment</p> <p>Assessment of test performance for intended purposes See text for details</p> <p>Effectiveness Visual acuity, function/activities of daily living, quality of life</p> <p>Cost-effectiveness Gain in QALYs</p>
<p>Questions</p> <ol style="list-style-type: none"> 1. What is the safety, effectiveness, and cost-effectiveness of OCT for the identification and monitoring of patients diagnosed with macular oedema secondary to CRVO for baseline (CRT $\geq 250 \mu\text{m}$ on initial OCT) and ongoing aflibercept eligibility compared to aflibercept initiation and reinjection of aflibercept without OCT assessment of CRT? 2. What is the safety, effectiveness, and cost-effectiveness of OCT for the identification and monitoring of patients diagnosed with macular oedema secondary to CRVO for baseline (CRT $\geq 250 \mu\text{m}$ on initial OCT) and ongoing aflibercept eligibility compared to standard medical management? 					

Abbreviations: OCT, optical coherence tomography; CRVO, central retinal vein occlusion; SMM, standard medical management; FFA, fundus fluorescein angiography; CRT, central retinal thickness; QALYs, quality-adjusted life-years.

Clinical claim

The application indicates that OCT for the identification and monitoring of CRVO/macular oedema does not directly produce a clinical outcome. However, given the currently proposed co-dependency, the outcomes of aflibercept treatment cannot be determined without prior OCT and thus the clinical outcomes associated with OCT-monitored aflibercept treatment are relevant.

The clinical claim is that adding OCT at the eligibility stage would have the potential to reinforce the diagnosis of CRVO and to exclude patients with less severe CRVO as

manifested by a lower CRT and thus less macular oedema. Also, with this measurement as a baseline, adding OCT at the monitoring stage would have the potential to avoid unnecessarily early re-injections. It would also be less invasive than repeated fundus fluorescein angiography for monitoring purposes.

The application indicates that OCT is currently the only modality to provide measurements of CRT, but no information regarding the accuracy of OCT have been supplied. Performance of OCT will therefore need to be based on test-re-test reliability of CRT measurements, and a comparison of intra-individual versus inter-individual variability to provide evidence of validity of the proposed response rules for monitoring treatment (Bell et al 2010).

A cost-effectiveness analysis (CEA) or cost-utility analysis (CUA) to assess the outcomes of aflibercept treatment, following the use of OCT or administered after standard testing without OCT, would be appropriate in the event that aflibercept with or without OCT is found to be superior to standard medical management. If the non-inferiority of aflibercept is demonstrated relative to standard medical management, the type of economic evaluation required would be a CEA, CUA or cost-minimisation analysis as shown in Table 9. Should demonstration of superiority in health outcomes fail due to a lack of evidence and the combined cost of OCT and aflibercept, or aflibercept alone, is found to be higher than the suggested comparator, an economic evaluation would not be required.

Table 9 Classification of an intervention for determination of economic evaluation to be presented

		Comparative effectiveness versus comparator								
		Superior		Non-inferior		Inferior				
Comparative safety versus comparator	Superior	CEA/CUA		CEA/CUA		Net clinical benefit	CEA/CUA			
						Neutral benefit	CEA/CUA*			
						Net harms	None [^]			
	Non-inferior	CEA/CUA		CEA/CUA*		None [^]				
						Inferior	Net clinical benefit	CEA/CUA	None [^]	
							Neutral benefit	CEA/CUA*		
Net harms	None [^]									

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

*May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

[^]No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Outcomes and health care resources affected by introduction of proposed intervention

Outcomes for economic evaluation

The application suggests that the main treatment goal for aflibercept treatment guided by OCT is to improve visual acuity and associated *quality of life* (QoL). Gain in quality-adjusted life-years (QALYs) would therefore be an appropriate health outcome for the economic evaluation. The applicant did not provide details of potentially relevant adverse events associated with either OCT or aflibercept. However, adverse events should be modelled if they differ to those associated with standard medical management.

Health care resources

The list of resources to be considered in the economic analyses are outlined in Table 10. Information regarding the frequency and duration of OCT testing after the initial injection will need to be provided in the submission of evidence.

Table 10 List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
Resources provided to identify eligible population										
Baseline OCT	Ophthalmologist	Consulting rooms	100% of patients with diagnosed CRVO	1						
Resources provided to deliver proposed intervention										
Aflibercept administration	Ophthalmologist, MBS	Consulting rooms	Patients with baseline CRT $\geq 250 \mu\text{m}$	1 per eye, with 2 required in the rare event of bilateral disease. Trial data suggest each unit delivered monthly in first 6 months and then	Item number 42738 \$295.15 \$221.40 (75%) \$250.90 (85%) Item number 42739 \$295.15					

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost						
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost	
				pro re nata (typically 2-3 injections during months 6-12)	\$221.40 (75%) \$250.90 (85%) Item number 42740 \$295.15 \$221.40 (75%) \$250.90 (85%)						
Aflibercept drug acquisition	Ophthalmologist, PBS	Consulting rooms	Patients with baseline CRT $\geq 250 \mu\text{m}$								
Resources provided in association with proposed intervention											
OCT monitoring	Ophthalmologist	Consulting rooms	Patients with baseline CRT $\geq 250 \mu\text{m}$	Monthly for the first 6 months, then as needed	\$250						
Resources provided to deliver standard medical management											
Ranibizumab alone, drug acquisition	Ophthalmologist	Consulting room	TBD	TBD							
Ranibizumab alone, drug administration	Ophthalmologist, MBS	Consulting rooms	TBD	TBD	Item number 42738 \$295.15 \$221.40 (75%) \$250.90 (85%) Item number 42739 \$295.15 \$221.40 (75%) \$250.90 (85%)						

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
					Item number 42740 \$295.15					
					\$221.40 (75%) \$250.90 (85%)					

Abbreviations: OCT, optical coherence tomography; CRVO, central retinal vein occlusion; CRT, central retinal thickness; TBD, to be disclosed

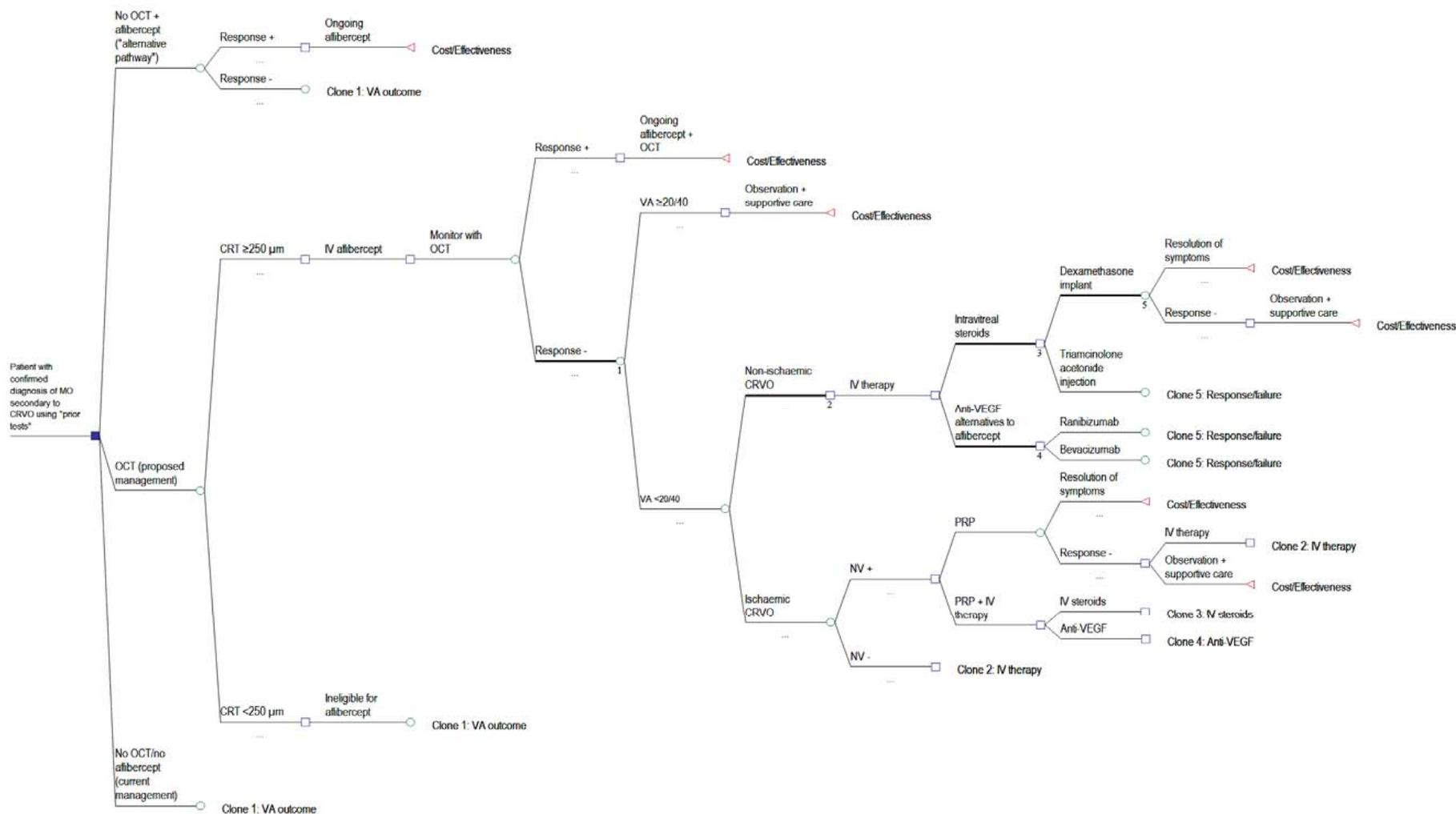
* Include costs relating to both the standard and extended safety net.

Proposed structure of economic evaluation (decision-analytic)

The decision analytic shown below (Figure 2) makes provision for determination of differences in patient outcomes between aflibercept treatment predicated on the results of OCT testing following an initial diagnosis of CRVO, or standard diagnostic tests alone (no OCT) and the outcomes of an alternative treatment algorithm predicated on the results of standard medical management. Under the proposed listing of OCT on the MBS and aflibercept on the PBS, the baseline tests used to diagnose CRVO/macular oedema will be universally applied to all patients with suspected CRVO as the underlying cause of macular oedema, with no differences in cost incurred as a result. All patients therefore enter the pathway having obtained a diagnosis using "prior tests" otherwise referred to as standard medical management, consistent with Table 8. Note that key findings of the prior clinical examination process (e.g. visual acuity, presence/absence of neovascularisation) have been included at the relevant nodes within the decision analytic as these outcomes are required for appropriate differential management of the relevant population sub-groups.

The definition of response to treatment (which determines subsequent treatment options) will need to be clearly specified in the submission of evidence.

Figure 2 Decision tree showing scenarios in which OCT and aflibercept are either available/unavailable for the clinical management of macular oedema secondary to CRVO.
 Note that all patients enter the pathway with “prior testing” as detailed in Figure 1 (see also text on decision analytic).
 Abbreviations: MO, macular oedema; CRVO, central retinal vein occlusion; OCT, optical coherence tomography; VA, visual acuity; IV, intravitreal; NV, neovascularisation; VEGF, vascular endothelial growth factor; PRP, pan-retinal photocoagulation



References

- ABS (2008). *Population projections, Australia (Series B). Cat. no. 3222.0* [Internet]. Australian Bureau of Statistics. Available from: <http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3222.02006%20to%202101> [Accessed 21 June 2012].
- AIHW (2009). *Eye health labour force in Australia. Cat. No PHE 116* [Internet]. Australian Institute of Health and Welfare. Available from: <http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=6442459946> [Accessed 21 June 2012].
- Bell, K. J., Hayen, A. et al (2009). 'Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data', *BMJ*, 338, b2266.
- Bell, K. J., Irwig, L. et al (2010). 'Should response rules be used to decide continued subsidy of very expensive drugs? A checklist for decision makers', *Pharmacoepidemiol Drug Saf*, 19 (1), 99-105.
- Blodi, B. A., Domalpally, A. et al (2010). 'Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) Study system for evaluation of stereoscopic color fundus photographs and fluorescein angiograms: SCORE Study Report 9', *Arch Ophthalmol*, 128 (9), 1140-1145.
- Boyer, D., Heier, J. et al (2012). '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*, 119 (5), 1024-1032.
- Coscas, G., Loewenstein, A. et al (2011). 'Management of retinal vein occlusion--consensus document', *Ophthalmologica*, 226 (1), 4-28.
- Cugati, S., Wang, J. J. et al (2006). 'Ten-year incidence of retinal vein occlusion in an older population: the Blue Mountains Eye Study', *Arch Ophthalmol*, 124 (5), 726-732.
- DHA (2012). *Medicare item reports* [Internet]. Department of Health and Ageing. Available from: https://www.medicareaustralia.gov.au/statistics/mbs_item.shtml [Accessed 21 June 2012].
- Drexler, W. & Fujimoto, J. G. (2008). 'State-of-the-art retinal optical coherence tomography', *Prog Retin Eye Res*, 27 (1), 45-88.
- Hahn, P. & Fekrat, S. (2012). 'Best practices for treatment of retinal vein occlusion', *Curr Opin Ophthalmol*, 23 (3), 175-181.
- Ip, M. S., Oden, N. L. et al (2009). 'SCORE Study report 3: study design and baseline characteristics', *Ophthalmology*, 116 (9), 1770-1777 e1771.
- Jonas, J., Paques, M. et al (2010). 'Retinal vein occlusions', *Dev Ophthalmol*, 47, 111-135.
- Kiire, C. A. & Chong, N. V. (2012). 'Managing retinal vein occlusion', *BMJ*, 344, e499.
- Laouri, M., Chen, E. et al (2011). 'The burden of disease of retinal vein occlusion: review of the literature', *Eye (Lond)*, 25 (8), 981-988.
- Marschall, S., Sander, B. et al (2011). 'Optical coherence tomography-current technology and applications in clinical and biomedical research', *Anal Bioanal Chem*, 400 (9), 2699-2720.
- McAllister, I. L. (2012). 'Central retinal vein occlusion: a review', *Clin Experiment Ophthalmol*, 40 (1), 48-58.
- Mitchell, P., Smith, W. & Chang, A. (1996). 'Prevalence and associations of retinal vein occlusion in Australia. The Blue Mountains Eye Study', *Arch Ophthalmol*, 114 (10), 1243-1247.
- MSAC (2009). *Optical Coherence Tomography: MSAC Application 1116*, Commonwealth of Australia, Canberra.
- OBA (2010). *Endorsement for scheduled medicines registration standard* [Internet]. Optometry Board of Australia. Available from: www.optometryboard.gov.au/documents/default.aspx?record=WD10%2f158&dbid=AP&chksum=uA2c3Oie3cwpQqUMXLHfKg%3d%3d [Accessed 23 May 2012].
- Ossewaarde-Van Norel, J., Camfferman, L. P. & Rothova, A. (2012). 'Discrepancies between Fluorescein Angiography and Optical Coherence Tomography in Macular Edema in Uveitis', *Am J Ophthalmol*.
- RCO (2010). *Interim guidelines for management of retinal vein occlusion* [Internet]. The Royal College of Ophthalmologists. Available from: <http://www.rcophth.ac.uk/news.asp?section=24&itemid=374&search=> [Accessed 21 June 2012].
- Sakata, L. M., Deleon-Ortega, J. et al (2009). 'Optical coherence tomography of the retina and optic nerve - a review', *Clin Experiment Ophthalmol*, 37 (1), 90-99.

van Velthoven, M. E., Faber, D. J. et al (2007). 'Recent developments in optical coherence tomography for imaging the retina', *Prog Retin Eye Res*, 26 (1), 57-77.
Wong, T. Y. & Scott, I. U. (2010). 'Clinical practice. Retinal-vein occlusion', *N Engl J Med*, 363 (22), 2135-2144.

Final