Australian Government

Department of Health

MEDICAL SERVICES ADVISORY COMMITTEE

1377

Optical coherence tomography (OCT) for retinal assessment in the presence of diabetic macular oedema (DMO) with vision impairment for access to treatment with dexamethasone posterior segment drug delivery system (dexamethasone PS DDS)

Protocol

June/2014

1) Title of Application

Optical coherence tomography (OCT) for retinal assessment in the presence of diabetic macular oedema (DMO) with vision impairment for access to treatment with dexamethasone posterior segment drug delivery system (dexamethasone PS DDS)

2) Purpose of application

Please indicate the rationale for the application and provide one abstract or systematic review that will provide background.

The purpose of this document is to guide the assessment of OCT for:

1. identification of patients with DMO with vision impairment who may benefit from treatment with dexamethasone PS DDS

2. monitoring these patients to determine their ongoing eligibility for retreatment with dexamethasone PS DDS.

The assessment will investigate whether the use of OCT is of benefit to clinicians for the purpose of identifying patients who should be treated and/or for monitoring outcomes of treatment. It will investigate whether the intervention leads to the avoidance of unnecessary costs due to dosing too frequently and the risk of compromise to patient health outcomes as a result of dosing too infrequently.

An overview of DMO, use of OCT and current treatments of DMO can be found in The Royal Collage of Ophthalmologists (2012) and Ford et al. (2013). Furthermore, Pelosini et al. (2011) discusses how OCT, which provides information on central macular thickness and volume of retinal tissue in oedema, are good predictors of visual acuity (VA) in DMO.

3) Population and medical condition eligible for the proposed medical services

Provide a description of the medical condition (or disease) relevant to the service.

The proposed population is patients with vision impairment due to DMO. Diabetes mellitus (DM) is a serious disease associated with significant morbidity, a high burden of disease management, and a negative impact on quality of life. It is a chronic disease of hyperglycaemia. It is caused when either the pancreas produces insufficient insulin to enable glucose uptake by cells (type 1 DM), or the cells and tissues of the body do not respond fully to the insulin that is produced (type 2 DM). Chronic hyperglycaemia damages blood vessels and can lead to the development of macro-vascular complications (e.g. ischemic heart disease, stroke) and micro-vascular complications (e.g. diabetic retinopathy).

Diabetic retinopathy (DR) is the most common micro-vascular complication of DM. Almost all type 1 DM patients and more than 60% of type 2 DM patients develop retinopathy within 15-20 years of diagnosis (Williams et al. 2004). In developed countries, DR is the most common cause of acquired blindness among persons of working age, and a person with DM is 25 times more likely to sustain severe loss of vision than a person in the general

population (Ciulla et al. 2003, Williams et al. 2004). DR results from damage to retinal blood vessels associated with chronic hyperglycaemia, hyperlipidaemia, and hypertension; all of these are common features of poorly controlled DM (Ding et al. 2012).

DMO is a serious complication of DR and can develop at any stage of DR. Macular oedema refers to the swelling and thickening of the macula, the central part of retina responsible for central vision. Retinal thickening and hard exudates are characteristic features of DMO. A healthy retina is shown in Figure 1; hard exudates are shown in Figure 2. DMO is the principal cause of vision loss in individuals with DR and a leading cause of visual impairment, including blindness, among patients with DM (Mohamed et al. 2007).

Figure 1 Fundoscopy image of a healthy retina

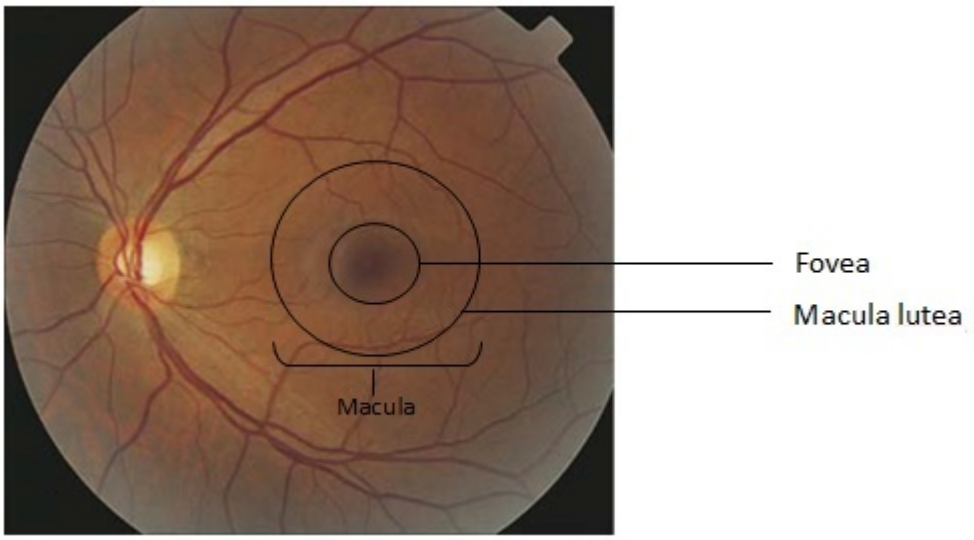
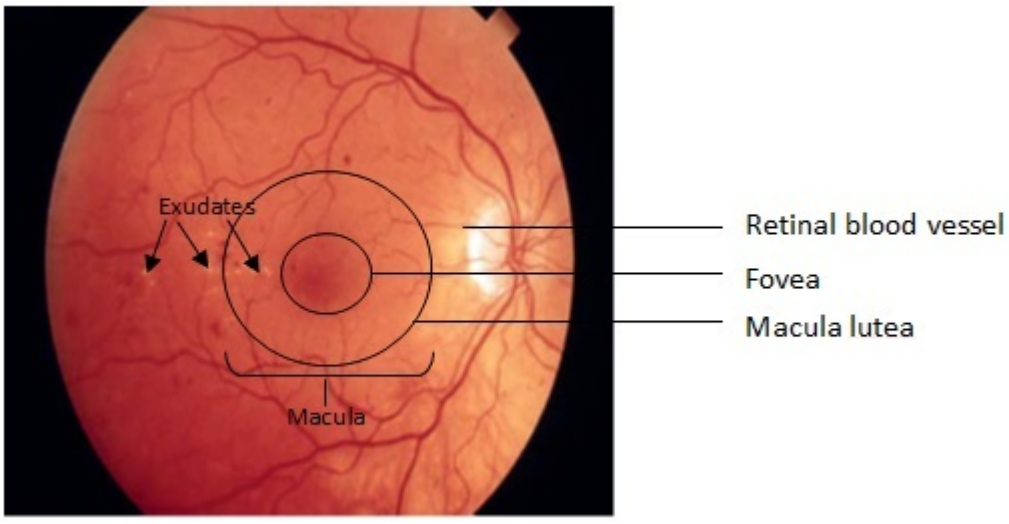


Figure 2 Fundoscopy image of hard exudates



Classification

DMO can be classified into subtypes based on the location, severity, and distribution of the oedema. Sub-classification is presented in Table 1.

DMO may be classified as centre involving or non-centre involving DMO. DMO may be asymptomatic, as oedema has not yet spread to affect the fovea and central vision, and retinal thickening is minimal (Diabetic Retinopathy Clinical Research Network et al. 2012). DMO patients only become aware of deterioration in vision when the fovea is affected (Kollias et al. 2010). Studies have identified an incidence of progression from non-centre involving DMO to centre involving DMO of 31-35% over 14-19 months (Browning et al. 2008, Bhavsar et al. 2011). It is important to differentiate between non-centre involving DMO and centre involving DMO; clinical treatment guidelines recommend that all patients with centre involving DMO should be considered for treatment (Ciulla et al. 2003, Romero-Aroca et al. 2010, American Academy of Ophthalmology Retina Panel 2012).

DMO also may be classified as focal or diffuse depending on the distribution of oedema. The distinction between focal and diffuse DMO is important in order to decide whether focal laser photocoagulation treatment is appropriate. However, these two terms have not been defined consistently in the literature (Browning et al. 2008).

In this co-dependent submission, the proposed PBS listing of dexamethasone PS DDS comprise patients with centre involving DMO whose vision is impaired.

Table 1 Classification of DMO

DMO Subclassification	Description
DMO present	Retinal thickening or hard exudates present in the posterior pole of the macula
Non-centre involving	Absence of foveal centre oedema
Centre involving	At least one of the following conditions met: • Retinal thickening within 500μm of the centre of the macula • Hard exudates within 500μm of the centre of the macula • A zone of retinal thickening one disc area in size, provided some part is within one disc diameter of the centre of the macula
Mild	Retinal thickening or hard exudates distant from the centre of the macula
Moderate	

Retinal thickening or hard exudates approach but do not involve the centre of the macula

Severe

Retinal thickening or hard exudates involve the centre of the macula

Focal

Leakage from micro-aneurysms in a defined area of the macula, with less macular thickening; laser photocoagulation is historic standard of care

Diffuse

Extensive capillary leakage in a more widespread area of the posterior retinal capillary bed, with poorly demarcated and extensive macular thickening; unsuited to focal laser photocoagulation – more commonly treated with grid photocoagulation (see Section 5.4.2.1)

References: American Academy of Ophthalmology Retina Panel 2012; ETDRS Study report number 1, 1985; Diabetic Retinopathy Clinical Research Network et al. 2012; Giuliari et al. 2012, ICER 2012, Royal college of Ophthalmologists 2012.

Pathophysiology

The pathophysiology of DMO is complex and multifactorial. DMO arises primarily as a result of disruption of the blood–retinal barrier (BRB), which leads to increased accumulation of fluid within the intra-retinal layers of the macula (Ciulla et al. 2003, Rangasamy et al. 2012).

Hyper-glycaemia activates three important pathogenic mechanisms in the retinal capillary endothelial cells. These are:

- enhanced activation of advanced glycation end products (AGE)
- increased production of diacylglycerol (DAG)
- increased oxidative stress.

These three pathogenic mechanisms are responsible for an increase in protein kinase C within retinal capillary endothelial cells. This increase is associated with dysfunction of retinal endothelial cells and the loss of retinal pericyte (Ciulla et al. 2003, Rangasamy et al. 2012). Pericytes are involved in the regulation of capillary blood flow in the retina and maintain the integrity of the BRB. Damage to pericytes in diabetes leads to altered haemodynamics and abnormal regulation of retinal perfusion.

Inflammation

Inflammation is a significant component of DMO. Enhanced activation of AGE, increased DAG, and oxidative stress drive the release of pro-inflammatory factors:

- a direct result of hypoxia
- a direct result of oxidation stress
- binding by AGE to some receptors, initiating cellular activation and oxidative inflammatory events
- recruitment and activation of leukocytes.

Key inflammatory processes cause the breakdown of the BRB and increase vascular permeability leading to the development of macula oedema and the transition from DR to DMO (Ciulla et al. 2003, Romero-Aroca et al. 2010, Rangasamy et al. 2012). These include:

- increased vascular endothelial growth factor (VEGF) levels
- endothelial dysfunction
- leukocyte adhesion
- decreased pigment epithelium-derived factor levels
- increased protein kinase C production.

Vitreous levels of numerous pro-inflammatory factors have been reported to be significantly higher in patients with DMO. A key factor associated with the development and progression of DMO is VEGF. Following the disruption of micro-capillaries leading to retinal ischemia, VEGF is up-regulated. This protein is known to increase vascular permeability and to directly disrupt the BRB, triggering retinal neovascularisation (Ciulla et al. 2003, Romero-Aroca et al. 2010, Rangasamy et al. 2012). It is important to note that current anti-VEGF agents used to treat DMO primarily inhibit VEGF overexpression. This is in contrast to corticosteroids, which broadly target all of the pro-inflammatory factors associated with the development of DMO.

Quality of life

Patients with DM suffer a wide range of health-related quality of life problems in physical functioning, role functioning, and mental health (Rubin et al. 1999). Vision loss due to DMO exacerbates this burden by limiting a patient's ability to perform everyday activities, such as driving, shopping, preparing meals, and using the telephone. This may in turn lead to feelings of frustration and loss of independence. Additionally, the ability to monitor blood sugar level and control diabetes through the appropriate dose of anti-diabetic medication is dependent on good vision.

Summary

In summary, DMO is a complication of poorly controlled DM. Persistent oedema in the macula due to DMO can result in photoreceptor damage and loss of central vision, ultimately leading to a loss of vision.

Define the proposed patient population that would benefit from the use of this service. This could include issues such as patient characteristics and /or specific circumstances that patients would have to satisfy in order to access the service.

The assessment will investigate the value of OCT for diagnosis and monitoring of DMO in a specialist ophthalmologic setting. The proposed population is patients with centre involving DMO and vision impairment. Patients would be eligible for retreatment if evidence of residual DMO is present.

4) Diagnosis of DMO with vision impairment

People with diabetes present to a variety of examiners, including general practitioners, general physicians, endocrinologists, optometrists and ophthalmologists (NHMRC 2008). All are potentially able to screen for DR. A patient typically presents with painless visual loss,

however, symptoms of DMO include blurred vision, double vision, loss of contrast and floaters (patches of vision loss), which may appear as small black dots or lines 'floating' across the front of the eye. In the first instance, patients require a medical history check to identify key risk factors for DMO. This would be followed by a clinical examination comprising VA and examination of the retina, often via a dilated pupil. Baseline ophthalmic assessments are then performed in order to confirm a diagnosis of DMO and the extent of damage to the macula/retina. Baseline ophthalmic assessments include fundus photography, slit-lamp bio-microscopy, ophthalmoscopy, fluorescein angiography and OCT. OCT measures retinal thickness, providing a quantitative assessment of the macular oedema. A diagram of the process of diagnosing DMO with vision impairment is provided in Figure 5.

Visual acuity

Visual acuity tests measure the ability to see fine detail (central vision). Visual acuity is determined by measuring the smallest size print that a person can read, most commonly on the Snellen eye chart. Both distance and near acuities are measured. The chart uses capital letters of different sizes to test vision in literate adults. The test is conducted at six metres. The test result is given as a fraction that indicates the distance in metres at which that row of the chart can be read by a normal eye. The top number of the fraction indicates the test distance (how far you are standing from the chart). It is usually six metres in Australia. The bottom number represents the size of the letter seen. The larger the bottom number the larger the letter on the chart (e.g. 6/48 indicates a bigger letter than 6/12). Normal visual acuity is recorded as 6/6.

Fluorescein angiography

Intravenous fluorescein angiography (FA) is a technique for examining the circulation of the retina and choroid using a fluorescent dye and a specialised camera. It involves intravenous injection of sodium fluorescein into the systemic circulation, and then an angiogram is obtained by photographing the fluorescence emitted after illumination of the retina with blue light at a wavelength of 490nm. The test uses the dye tracing method. Sodium fluorescein is well tolerated by most patients, but angiography is an invasive procedure with an associated risk of complication or adverse reaction.

FA is commonly performed as part of the clinical assessments for the initial diagnosis of DMO. Unlike OCT, which provides a structural assessment, FA provides an assessment of the function of the retina. FA is generally not performed for repeat assessments of DMO.

Fundus examination

Dilated fundus examination (DFE) is a diagnostic procedure that employs the use of mydriatic eye drops (such as tropicamide) to dilate or enlarge the pupil in order to obtain a better view of the fundus of the eye. Once the pupil is dilated, an ophthalmoscope or fundus camera is used to view the inner surfaces of the eye. DFE has been found to be a more effective method for evaluation of internal ocular health than non-dilated examination.

- Ophthalmoscopy

The scanning laser ophthalmoscope (SLO) was first introduced into clinical practice in the early 1980s as a technique for imaging the optic nerve head (Bartsch et al. 2006). The

scanner focuses a laser beam on the retina, with reflects light being focussed onto a photo-detector and is recorded on either video tape or a computer (Sharp et al. 2004). The laser beam scans across the retina one line at a time at high speed; between 20 and 30 frames per second are captured by the SLO, with between 256 and 1,536 lines per frame.

- Fundus photography

Fundus photography is the creation of a photograph of the interior surface of the eye, including the retina, optic disc, macula, and posterior pole. Compared to ophthalmoscopy, fundus photography generally needs a considerably larger instrument. Modern fundus photographs generally recreate considerably larger areas of the fundus than what can be seen at any one time with handheld ophthalmoscopes.

Slit-lamp bio-microscopy

The slit-lamp is one of the most fundamental examination tools in ophthalmology, and it has been in use in various forms for over a century. It utilises an illuminator, which projects a thin slit of light into the eye, and a binocular microscope through which the examiner observes light reflected from ocular structures (James et al. 2007). The illuminator can be adjusted in terms of the intensity, height, width, angle and colour of the slit-beam.

5) Treatment and monitoring of DMO with vision impairment

The benchmark treatment for DMO has traditionally been laser photocoagulation. However, as laser treatment does not always improve vision or even prevent further loss in many cases, several new pharmacotherapies that are injected into the vitreous for DMO have been successfully trialled over the past decade. The two major classes of these drugs are vascular endothelial growth factor (VEGF) antagonists and steroids.

Laser photocoagulation

The underlying process of laser photocoagulation is the closure of leaking micro-aneurysms by thermal coagulation. In current practice, laser photocoagulation is predominantly used in patients without vision loss and with non-centre involving DMO. A small proportion of patients with vision loss will be treated with laser photocoagulation (Expert opinion 2014; refer to Figure 6). These are patients where the source of oedema lies outside the macula, but the 'leakage' into the macula causes vision impairment. Laser photocoagulation can in those cases be applied outside of the macula to treat the microvascular leakage causing the macula oedema. OCT is commonly used for reassessment of disease and retreatment every three to six months on an ongoing basis. Laser photocoagulation is not used in the central macula region (fovea) as laser burns to this region will severely impair vision and can lead to blindness.

Intravitreal anti-VEGFs

Current evidence shows that anti-VEGF therapies reverse visual impairment, in addition to stabilising and preventing future vision loss (Mitchell and Wong 2013) and are the most commonly used treatment for centre involving DMO in Australia. Globally, four anti-VEGF therapies are currently used for ophthalmic conditions: ranibizumab, bevacizumab (off-label), aflibercept, and pegaptanib. In Australia, ranibizumab and bevacizumab (off-label) are the most commonly used anti-VEGF treatment for vision loss due to centre involving DMO (Expert Opinion 2014). Ranibizumab is currently the only anti-VEGF treatment indicated for DMO in Australia. None of the anti-VEGF therapies are currently PBS-listed for treatment of DMO.

Ranibizumab is administered monthly until maximum VA is reached (Lucentis® Product Information). Thereafter, patients are monitored monthly and treatment is resumed when vision loss in indicated. This treatment regimen requires monthly monitoring of the disease, which incorporates OCT assessments as standard practice in Australia (Expert Opinion 2014). Similarly, bevacizumab is administered 6-weekly for treatment of vision loss due to centre involving DMO (Rajendram et al. 2012). This treatment regimen requires 6-weekly monitoring of the disease, which also incorporates OCT assessments as standard practice in Australia (Expert Opinion 2014). Furthermore, the Mitchell and Wong (2013) guideline recommends monthly anti-VEGF injections given for at least three consecutive months ('loading' dose) followed by monthly assessment visits.

Intravitreal corticosteroids

Given the role of inflammation in the pathogenesis of DMO, the use of intravitreal corticosteroids are an alternative treatment due to their potent anti-inflammatory, anti-vascular endothelial growth factor, and anti-proliferative effects. The development of intravitreal implants has enabled the development of a sustained release formulation of dexamethasone implant to be introduced recently. It is not yet registered for treatment of DMO in Australia.

Indicate if there is evidence for the population who would benefit from this service i.e. international evidence including inclusion / exclusion criteria. If appropriate provide a table summarising the population considered in the evidence.

A systematic review of the evidence to support the use of OCT for identifying suitable candidates and for monitoring outcomes of treatment with dexamethasone PS DDS has not, to date, been conducted by Allergan. It will be conducted as part of the assessment.

Previous MSAC assessments, 1116 and 1310, conducted systematic reviews of the evidence for use of OCT. Allergan acknowledges the absence of direct evidence for the effectiveness of OCT. No RCTs have been identified which compares diagnosis or a monitoring strategy involving OCT to a strategy *without* OCT in patients with treated or untreated macular disease.

In the absence of this direct evidence, the MSAC Assessment Report of aflibercept for retinal vein occlusion (MSAC 2009; Application 1116) reported an evaluation of the effectiveness of OCT using a linked evidence approach. Results of evidence for accuracy, change in management, and the expected benefit of changes in treatment on health outcomes were addressed.

The MSAC Assessment Report stated that the accuracy of the OCT results is uncertain due to the lack of an appropriate reference standard. In the absence of conclusions regarding accuracy, MSAC stated that it was not possible to draw conclusions regarding the clinical significance or impact of OCT on health outcomes using a linked evidence approach.

Provide details on the expected utilisation, if the service is to be publicly funded.

Diabetes mellitus is a global epidemic with significant morbidity (Mitchell and Wong 2013, International Diabetes Federation 2013). Although DR affects one in three people with DM, the leading cause of vision loss in this population is DMO (Klein et al. 1984, Harris et al. 1998). DMO is a growing public health concern. If left untreated, it can eventually lead to blindness.

A recent report by the Meta-Analysis for Eye Disease group (Yau et al. 2012) pooled the results of 35 studies in order to assess the incidence of DR and DMO in patients with DM, producing a cohort of over 22,000 patients. The authors concluded that, on a global scale, approximately 35% of individuals with DM have DR, and 7.5% have DMO. Applying this to the number of Australians with DM estimated for 2011-2012, 999,000 (http://www.aihw.gov.au/diabetes/ accessed Feb 2014), the prevalence of DMO in Australia is estimated at 75,000 people.

According to Petrella et al. (2012), approximately 63% of people with DMO have associated vision impairment (<20/40 in Snellen foot or <6/12 Snellen metric equivalent). This would equate to 47,000 people in Australia being eligible for treatment of DMO with a pharmaceutical. Further details of expected utilisation will be provided in the MSAC and PBAC submissions.

6) Intervention – proposed medical service

Provide a description of the proposed medical service.

OCT is a non-invasive ophthalmic imaging technique, considered to be a safe procedure (MSAC 2009). It 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.

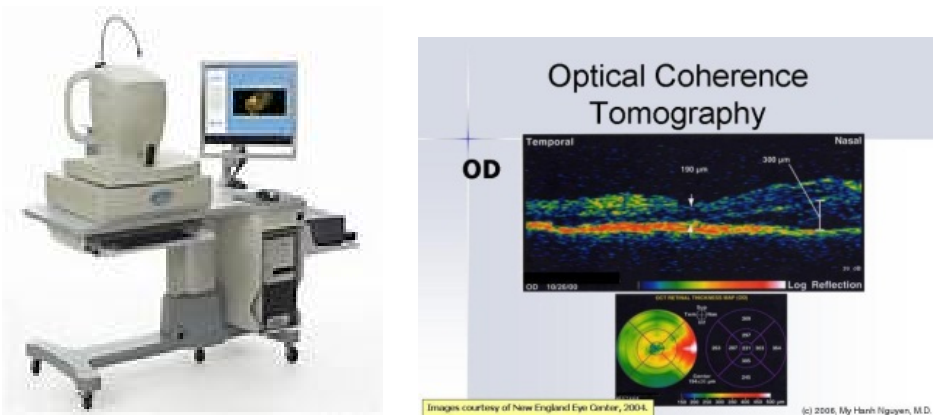
One beam is projected at the retina and the other onto a mirror, which reflects the incident light to produce a reference beam. This technique allows the light returning from the retina to interfere with the reference light beam that has travelled a known path length. The signals generated by this interference 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 (Drexler and 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 820nm 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 20μm, 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 (5-7μm) and transverse (10-20μm) 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 use of OCT for retinal and macular imaging is currently listed on the Australian Register Of Therapeutic Goods (ARTG number 194817; approved February 2012). A picture of an OCT machine and a cross-sectional OCT image are presented in Figure 3.

Figure 3 Images of a) an OCT machine and b) a cross-sectional OCT image of the retina

a) b)



If the service is for investigative purposes, describe the technical specification of the health technology and any reference or “evidentiary” standard that has been established.

OCT equipment is made by a number of manufacturers and different specifications are available in Australia. The proposal is for a generic intervention to diagnose and monitor patients with DMO.

Indicate whether the service includes a registered trademark with characteristics that distinguish it from any other similar health technology.

This submission will not specify any trademarked technology for the provision of OCT procedures for the management of DMO. The proposal is for a generic intervention to diagnose and monitor patients with DMO.

Clinical trials of dexamethasone PS DDS have employed both time domain and spectral domain OCT imaging. It is understood that spectral-domain OCT is now most commonly used in Australia.

Indicate the proposed setting in which the proposed medical service will be delivered and include detail for each of the following as relevant: inpatient private hospital, inpatient public hospital, outpatient clinic, emergency department, consulting rooms, day surgery centre, residential aged care facility, patient's home, laboratory. Where the proposed medical service will be provided in more than one setting, describe the rationale related to each.

Given that dexamethasone PS DDS is administered by intravitreal injection, OCT services in the management of DMO with vision impairment would be most appropriately provided by ophthalmologists in a private consulting room or public outpatient clinic setting.

Although optometrists are able to, and do use OCT for a variety of indications, the subsequent medical management in the context of DMO 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.

Describe how the service is delivered in the clinical setting. This could include details such as frequency of use (per year), duration of use, limitations or restrictions on the medical service or provider, referral arrangements, professional experience required (e.g.: qualifications, training, accreditation etc.), healthcare resources, access issues (e.g.: demographics, facilities, equipment, location etc.).

In many practices, the technical component of performing the scan is done by trained ancillary staff such as orthoptists. In smaller practices the scans may be performed by ophthalmologists themselves. No formal training or accreditation is required in order for a practitioner to carry out OCT, and it is understood that instructions and training from the manufacturers of OCT equipment are provided in adequate detail for safe operation by the appropriate medical professional.

Dilation of the pupil is undertaken prior to OCT scanning to optimise image quality. The patient is positioned in front of the OCT machine, and height adjustments are made to maximise the comfort of the patient. The scan is then performed, with the possibility of additional repeated scans if initial scans are of suboptimal quality. OCT takes approximately three to five minutes to perform per eye by a trained operator.

As with many other diagnostic imaging modalities, there is technical expertise required to perform the scan, but the critical element is the interpretation. Ophthalmologists receive a minimum of 5 years' supervised training in the interpretation of OCT scans as part of the

Royal Australian and New Zealand College of Ophthalmologists (RANZCO) accredited training. In fact, OCT is a mandatory requirement for accreditation of ophthalmology training posts.

As OCT is already established as a diagnostic and management tool in most ophthalmic practices, it is likely that OCT would continue to be used as part of the diagnosis of DMO, and subsequently every three to six months to monitor the disease and applicability for retreatment with dexamethasone PS DDS (source: MEAD trials). The use of OCT for evaluating retreatment of dexamethasone PS DDS may result in considerably less frequent monitoring (and treatment injections) compared with other current anti-VEGF treatments (e.g. ranibizumab) which require monthly monitoring on an ongoing basis.

In the MEAD randomised controlled trials (RCTs), OCT was performed using time domain technology. Scans were executed in both eyes at the qualification/baseline visit, and in the study eye only every three months. The mean retinal thickness in the 1 mm central subfield was captured. OCT images were collected and submitted for evaluation to a central reading centre using standardised procedures by graders. Retinal thickness of ≥ 300µm by OCT in the 1mm central macular subfield of the study eye at qualification/baseline was a criterion for entry into the trial. Patients were eligible for retreatment if retinal thickness in the 1mm central macular subfield by OCT was > 175µm or upon investigator interpretation of the OCT for any evidence of residual retinal oedema consisting of intraretinal cysts or any regions of increased retinal thickening (within or outside of the centre subfield). Dexamethasone PS DDS was administered PRN with a minimum six-month interval. Further analyses of OCT usage patterns in the MEAD RCTs will be presented in the MSAC submission. The schedule of assessments in the MEAD trials is provided in Appendix 2.

[Redacted]

It is proposed that in clinical practice dexamethasone will be administered as a fixed dose every 5-6 months and OCT will be performed every 3-6 months to assess whether the treatment is having positive effects, resulting in a reduction in CRT.

There is evidence that conditions such as DM, which increase the risk of developing macular diseases, affect lower socioeconomic groups (AIHW 2008). Accordingly, the proposed MBS listing would ensure equitable access to OCT examinations, which are important in the management of DMO.

Patients with DM are under the care of GPs and endocrinologists specialising in DM. The GP or endocrinologist may monitor the patient's vision, however optometrists or GPs are often the first point of contact for a patient experiencing visual impairment, with referral to an ophthalmologist where clinically indicated.

Due to the above mentioned practice, access issues are assumed to be minimal, but 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 some limited access to specialist care of DMO in outer regional, remote and very remote areas (AIHW 2009). However, the availability of PBS-listed dexamethasone PS DDS could minimise the treatment burden and any access issues for rural patients.

7) Co-dependent information (if not a co-dependent application go to Section 6)

Please provide detail of the co-dependent nature of this service as applicable

This application is likely to be a co-dependent application. It should be noted that OCT is already established in ophthalmology practice; however, its use is not reimbursed.

The proposed co-dependent therapy is dexamethasone PS DDS. An application to the PBAC for PBS-listing of dexamethasone PS DDS is being prepared. It is expected that the PBAC and MSAC submissions will be two stand-alone, co-ordinated submissions.

Dexamethasone PS DDS is a novel, injectable biodegradable intravitreal implant containing 700µg dexamethasone in the NOVADUR® solid polymer drug delivery system (DDS), which delivers dexamethasone to the posterior segment of the eye (Allergan 2013). Images of dexamethasone PS DDS are provided in

Figure **4**.

Dexamethasone is a potent corticosteroid that has been shown to be effective in the reduction of macular oedema due to a number of causes (Kuppermann et al. 2007, Haller et al. 2010). Bolus intravitreal administration of corticosteroids has been associated with suboptimal durability, due to their short half-life; approximately three hours (Herrero-Vanrell et al. 2011). The innovative dexamethasone PS DDS intravitreal implant was developed to provide and sustain dexamethasone levels in the vitreous well beyond the half-life and elimination of free dexamethasone compounded for the eye and intravitreally injected. The device contains a co-polymer, poly (lactic-co-glycolic) acid, a material similar to that used in dissolvable sutures, which dissolves and degrades into carbon dioxide and water over time, so surgical removal is not necessary (Allergan 2013).

Dexamethasone PS DDS is preloaded into a specially designed applicator with a 22-gauge needle and is injected into the posterior segment of the eye via the pars plana. Dexamethasone PS DDS is characterised by dual-phase pharmacokinetics; the biodegradable implant initially releases a burst of dexamethasone to rapidly achieve a therapeutic concentration. A consistent release of therapeutic doses over time reduces the need for frequent intravitreal injections and allows for sustained and long-lasting drug levels to the target areas despite a low daily dose (Allergan 2013, Chang-Lin et al. 2011).

Today, anti-VEGF therapies are most commonly used and these therapies target DMO through a single mechanism of action. However, corticosteroids, such as dexamethasone, also inhibit other mediators of inflammation in addition to VEGF. Inhibition of pro-inflammatory factors decreases oedema and capillary leakage, stabilising the BRB, thereby achieving long-term vision improvement.

Clinical evidence for dexamethasone PS DDS comes from two identically designed Phase III RCTs, the MEAD trials. The Clinical Study Reports for these trials will be available to MSAC for consideration. Publication of trial data is expected in 2014.

The long-term benefit of dexamethasone PS DDS was demonstrated in the MEAD Phase III studies of patients with DMO using a number of clinically relevant and complimentary endpoints. There was a clinically meaningful improvement of 15 or more letters BCVA from baseline with dexamethasone PS DDS compared to sham at the final visit. Following retreatment, patients achieved clinically relevant and statistically significant increases in VA. This was supported by rapid and sustained anatomical improvement as measured by OCT.

Dexamethasone PS DDS was shown to have an early onset of action, with a long duration of effect after injection. Thus, good VA is maintained over long periods of time, requiring a low frequency of repeat injections. Given specific retreatment criteria, therapy can be customised based on individual patient needs and response. Retreatment criteria may include assessment of VA, central retinal thickness (CRT) or physician's interpretation for any evidence of residual retinal oedema.

Dexamethasone PS DDS was well tolerated with up to seven treatments over three years. There was no evidence of incremental systemic adverse events (AEs) associated with dexamethasone PS DDS in this older diabetic population, and there was no increased risk of arterial thromboembolic events following repeat treatment. Ocular AEs were consistent with ophthalmic steroid therapy, and the overall safety profiles were similar between the 700µg and 350µg doses. Patients with DMO are likely to develop cataracts during their lifetime and the predicted development or progression of cataracts as well as intraocular pressure (IOP) elevation can be managed with readily available, safe, and effective interventions.

There was no cumulative effect of dexamethasone PS DDS on increased IOP. Vision improvements were observed in the majority of patients except during the time between cataract AEs reporting and cataract extraction. The benefit on reduction of oedema as measured by OCT was consistently demonstrated across the whole study duration, regardless of the lens status. There were no reports of delayed wound healing.

Overall, the benefit-risk profile of dexamethasone PS DDS is favourable. Clinically relevant treatment benefits have been observed as measured by improvements in vision and retinal anatomy. The higher 700µg dose generally showed a greater and more consistent response than the 350µg dose, which in the absence of dose-dependent clinically relevant side effects, suggests the use of dexamethasone PS DDS (700µg) in this population to maximise the treatment benefit. Thus, the overall benefit-risk profile supports the use of dexamethasone PS DDS in patients with DMO.

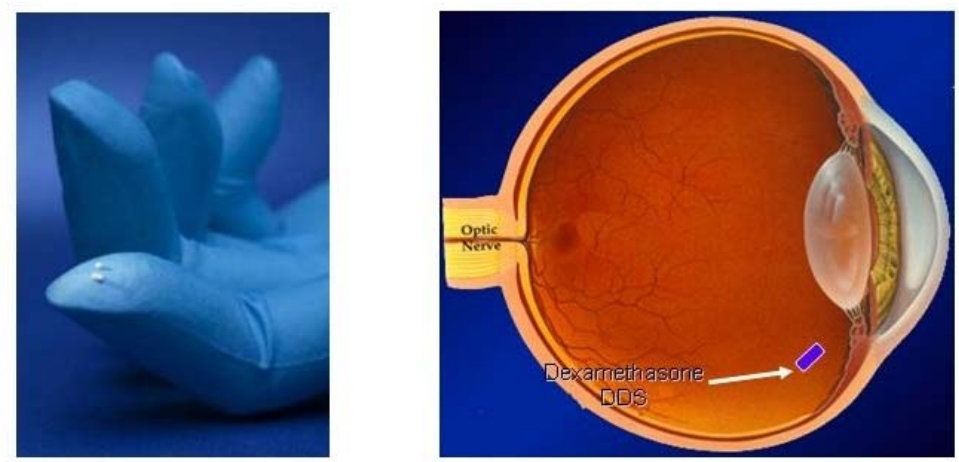
[Redacted]

OCT is proposed to be used in conjunction with dexamethasone PS DDS, which is administered as an intravitreal injection. This intravitreal injection procedure can be appropriately billed in the majority of cases under the existing MBS item numbers 42738, 42739 or 42740. It is unlikely to result in an increase in the use of items 42738, 42739 or 42740 in the event that dexamethasone PS DDS becomes available on the PBS since patients would instead have been injected with alternate therapies, such as anti-VEGF therapies.

Furthermore, the proposed use of OCT is specifically for a patient population with centre involving DMO determined using the currently reimbursed tests (e.g. Retinal photography; MBS item numbers 11215 and 11218). Accordingly, the proposed OCT services will be complementary to these diagnostic tests for DMO; however, it is unlikely to result in an increase in the use of items 11215 and 11218 in the event that dexamethasone PS DDS becomes available on the PBS.

Figure 4 a) Image of dexamethasone PS DDS implant and b) a cross-sectional image of the retina with dexamethasone PS DDS implanted

a) b)



8) Comparator – clinical claim for the proposed medical service

Please provide details of how the proposed service is expected to be used, for example is it to replace or substitute a current practice; in addition to, or to augment current practice.

Diagnosis of DMO with vision impairment

OCT augments other ophthalmic assessments in the diagnosis of DMO and the identification of patients with centre involving DMO for pharmacological treatment. It also provides information on the extent of DMO.

The proposed comparison for diagnosis of DMO is:

Standard diagnostic tests incl. OCT versus standard diagnostic tests excl. OCT

Clinical examination, VA and ophthalmic assessments all form part of the assessment of macular disease. OCT represents an additional ophthalmic assessment. It serves to augment, rather than replace the other ophthalmic assessments.

Monitoring of DMO with vision impairment for treatment with dexamethasone PS DDS

The proposed comparison for monitoring of DMO is:

Standard monitoring tests incl. OCT + dexamethasone PS DDS versus standard monitoring tests excl. OCT + dexamethasone PS DDS

Comparator to be addressed in the PBAC submission

It is proposed that the co-dependent PBAC application will assess the value of standard management of DMO versus the management with the introduction of dexamethasone PS DDS.

Standard monitoring tests incl. OCT + dexamethasone PS DDS versus standard monitoring tests excl. OCT + standard treatment

9) Expected health outcomes relating to the medical service

Identify the expected patient-relevant health outcomes if the service is recommended for public funding, including primary effectiveness (improvement in function, relief of pain) and secondary effectiveness (length of hospital stays, time to return to daily activities).

Health outcomes will be measured in order to assess the safety and effectiveness of the proposed interventions and appropriate comparators.

The use of OCT for the identification and monitoring of DMO does not directly produce a clinical outcome. However, OCT is currently the only modality which provides measurements of CRT and macular pathology relevant to DMO. To our knowledge, no information regarding the accuracy of OCT technology is available in the published literature due to the lack of a reference standard for measurement of CRT (MSAC Application 1116 Assessment Report).

Health outcomes measures for diagnosis of DMO

Together with the other ophthalmic assessments, OCT will provide additional information on DMO including CRT, tissue integrity, macular volume and cystoid space size.

Allergan acknowledges that STEP was engaged by MSAC earlier this year to investigate the accuracy and value of OCT.

Health outcomes measures for monitoring of DMO

The purpose of monitoring patients with DMO is to appropriately identify their ongoing eligibility for dexamethasone PS DDS retreatment. The primary effectiveness outcome

measure is improvement in VA. An improvement in VA positively impacts the patient's daily activities and quality of life.

Health outcomes measures in PBAC submission

The PBAC submission will compare OCT and dexamethasone PS DDS with standard of care. The patient-relevant health outcome to be measured and compared is BCVA. Results from the MEAD **[Redacted]** RCTs will be applied.

The proposed use (and current practice) of OCT to diagnose and monitor treatment may optimise drug administration. Using OCT may avoid the unnecessary costs and treatment burden due to dosing too frequently.

MBS reimbursement of OCT will also remove any patient 'out-of-pocket' expenses related to OCT. This is particularly important in relation to DMO since this disease often affects lower socio-economic groups (AIHW 2008). People in lower socio-economic groups are less able to pay for OCT examinations and would greatly benefit from reimbursement of OCT.

Reimbursement of OCT and dexamethasone PS DDS may also lead to increased compliance and improvement in disease management in diabetic patients with a high burden of disease management. People with DM experience a high burden of disease management that includes primary care, endocrinology, and other specialist visits, and may need numerous medications to manage the condition. DMO increases an already significant burden of disease management for DM patients.

OCT has already become an essential part of the standard of care, and so apparent is its utility to specialists and patients that it has rapidly become the 'gold standard' tool for anatomic macular examination. An indication of the fundamental role that OCT now plays is apparent. For instance, recent guidelines for managing age-related macular degeneration (RCO 2013) state that OCT is essential to treat this disease. Moreover, many clinical trials of treatments of macular diseases are now designed with OCT measurements as the primary outcome measure. Detecting and managing macular problems without OCT is now obsolete.

To date, trials of treatments for DMO which included OCT have not been analysed to assess whether adopting OCT improves patient outcomes compared to not adopting OCT, and as such, OCT is not yet a Government funded procedure (MSAC 2013c). Previous assessments of OCT for the diagnosis and monitoring of macular disease, glaucoma and macular oedema secondary to central retinal vein occlusion were considered by MSAC (applications 1116 and 1310). However, these applications were rejected on the grounds of insufficient evidence to support the clinical claims of the applicant.

Collaboration between industry, patient support groups and Government is continuing in order to resolve the concern of reimbursement of OCT in a timely manner. Allergan is willing to investigate re-analysing the MEAD patient level trial data to assist in providing further information about the performance of OCT in guiding therapy. Any such additional re-analyses would remain commercial in confidence.

Describe any potential risks to the patient.

OCT is a non-invasive imaging tool and is considered a safe procedure. No studies were identified which reported any AEs with the use of OCT (MSAC Application 1116 Assessment Report). Safety outcomes included any AEs related to testing and any subsequently indicated treatment(s). It is proposed that a review is conducted to identify any safety concerns from the use of OCT and/or dexamethasone PS DDS. Findings could include AEs of:

- Intraocular inflammation
- Cataract
- Raised intra-ocular pressure (IOP)
- Exacerbation of pre-existing neovascular glaucoma
- Endophthalmitis
- Retinal detachment.

Specify the type of economic evaluation.

Details of costs associated with OCT are outlined in Table 4. The relevant economic evaluation would incorporate the comparative safety and effectiveness of the potential co-dependent therapy, dexamethasone PS DDS, versus standard of care for DMO. It is proposed that the comparative safety and effectiveness of dexamethasone PS DDS treatment for DMO for this application be assessed by PBAC. Allergan also proposes that the economic evaluation be carried out by PBAC.

At present, the type of economic evaluation is uncertain. If ranibizumab is PBS-listed for DMO, the economic evaluation will most likely be a cost-minimisation analysis between ranibizumab and dexamethasone PS DDS. In the event that ranibizumab is not PBS-listed for DMO, the economic analysis will most likely be an economic analysis of one or more commonly used off-label therapies versus dexamethasone PS DDS.

10) Fee for the proposed medical service

Explain the type of funding proposed for this service.

There are currently no specific MBS item numbers that cover OCT for the diagnosis and/or monitoring of macular diseases.

It is proposed that OCT for retinal assessment in the presence of DMO for access to treatment with dexamethasone PS DDS is listed on the MBS. The proposal is for inclusion into Category 2 (Diagnostic Procedures and Investigations).

Table 2 Proposed MBS item descriptors for OCT for retinal assessment in the presence of DMO for access to treatment with dexamethasone PS DDS

CATEGORY 2: DIAGNOSTIC PROCEDURES AND INVESTIGATIONS
xxxx Optical coherence tomography (OCT) for retinal assessment to determine the eligibility for PBS-subsidised dexamethasone PS DDS in patients with diabetic macular oedema. Fee: 75% benefit: 85% benefit:
xxxx Optical coherence tomography (OCT) for retinal assessment to determine whether to continue PBS-subsidised dexamethasone PS DDS in patients with diabetic macular oedema. Fee: 75% benefit: 85% benefit:
Explanatory notes Diagnosis of diabetic macular oedema by professional attendance of an ophthalmologist is required. Diagnosis will involve the use of standard assessments.

Note: xxxx=Item number to be assigned by Department if MBS listed.

Please indicate the direct cost of any equipment or resources that are used with the service relevant to this application, as appropriate.

It is not expected that reimbursement of OCT for retinal assessment in the presence of DMO for access to treatment with dexamethasone PS DDS will have implications on equipment costs, staffing numbers, training or skill set, since OCT has already diffused widely in the current practice of ophthalmology.

Provide details of the proposed fee.

It is proposed that the fee for OCT be aligned with that of the Department of Veterans' Affairs reimbursement; approximately $91.75.

Based on the MSAC OCT stakeholder forum (MSAC 2013c), the average charge for OCT across Australia is approximately $80, varying from $50 - $120. The current Department of Veterans' Affairs reimbursement for OCT is $91.75 (Item MT12).

11) Clinical Management Algorithm - clinical place for the proposed intervention

Provide a clinical management algorithm (e.g.: flowchart) explaining the current approach (see (6) Comparator section) to management and any downstream services (aftercare) of the eligible population/s in the absence of public funding for the service proposed preferably with reference to existing clinical practice guidelines.

Please refer to Figure 5 and Figure 6 in the Appendix 1.

- Figure 5 outlines the current (and proposed) clinical management algorithm of diagnosis of centre involving DMO with vision loss.

- Figure 6 outlines the current clinical management algorithm of treatment, repeat assessments and retreatments of DMO with vision loss.

References: Giuliari (2012), Mitchell and Wong (2012), The Royal College of Ophthalmologists (2012), Ford et al. (2013), Australian expert opinion (2014).

Provide a clinical management algorithm (e.g.: flowchart) explaining the expected management and any downstream services (aftercare) of the eligible population/s if public funding is recommended for the service proposed.

Please refer to Figure 5 and Figure 7 in the Appendix 1.

- Figure 5 outlines the proposed clinical management algorithm of diagnosis of centre involving DMO.
    - No change is proposed to the clinical management algorithm of diagnosis of DMO An expert panel consisting of 10 Australian ophthalmologists has confirmed that OCT is already routine clinical practice even in the absence of MBS reimbursement. With MBS funding, some patients may experience less out-of-pocket costs
    -
- Figure 7 outlines the proposed clinical management algorithm of treatment, repeat assessments and retreatments of DMO.
    - Inclusion of dexamethasone PS DDS as a treatment option
    - Repeat assessments and retreatments may be less frequent with dexamethasone PS DDS compared with anti-VEGF treatment for DMO.

12) Regulatory Information

Please provide details of the regulatory status. Noting that regulatory listing must be finalised before MSAC consideration.

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 therapy, dexamethasone PS DDS, is not currently listed on the ARTG. An application for treatment of DMO was submitted to the TGA **[Redacted]**.

13) Decision analytic

Provide a summary of the PICO as well as the health care resource of the comparison/s that will be assessed, define the research questions and inform the analysis of evidence for consideration by MSAC (as outlined in Table 3).

Please refer to Table 3 below.

14) Healthcare resources

Using tables 2 and 3, provide a list of the health care resources whose utilisation is likely to be impacted should the proposed intervention be made available as requested whether the utilisation of the resource will be impacted due to differences in outcomes or due to availability of the proposed intervention itself.

Please refer to Table 4 below. The template 'Table 3' has not been completed. It is proposed that the Health State information will be addressed in the PBAC application.

15) Questions for public funding

Please list questions relating to the safety, effectiveness and cost-effectiveness of the service / intervention relevant to this application, for example:

- Which health / medical professionals provide the service
- Are there training and qualification requirements
- Are there accreditation requirements

Allergan acknowledges the absence of direct evidence for the effectiveness of OCT. No RCTs have been identified which compares diagnosis or a monitoring strategy involving OCT to a strategy *without* OCT in patients with treated or untreated macular disease.

In the absence of this direct evidence, the MSAC Assessment Report of aflibercept for retinal vein occlusion (MSAC 2009; Application 1116) reported an evaluation of the effectiveness of OCT using a linked evidence approach. Results of evidence for accuracy, change in management, and the expected benefit of changes in treatment on health outcomes were addressed.

The MSAC Assessment Report stated that the accuracy of the OCT results is uncertain due to the lack of an appropriate reference standard. In the absence of conclusions regarding accuracy, MSAC stated that it was not possible to draw conclusions regarding the clinical significance or impact of OCT on health outcomes using a linked evidence approach.

However, the MSAC Assessment Report included clinical advice from its expert advisory panel that the *'introduction of OCT examination of the macula has revolutionised diagnosis and management of retinal disease by ophthalmic specialists, through giving a qualitative and quantitative measure of cross-sectional anatomical change in the macula. OCT has become an essential part of the standard of care, and so apparent is its utility to specialists*

and patients that it has rapidly become the 'gold standard' tool for anatomic macular examination.

Despite the widespread diffusion of this technology into retinal ophthalmology at every level, establishing the utility of OCT for macular disease in the MSAC report has been difficult due to a lack of published evidence in the literature with an appropriate comparator.'

Furthermore, Allergan would also like to acknowledge the advice given in the MSAC minutes for application 1310 (MSAC 2013a) where MSAC agreed with the advice of Protocol Advisory Sub-Committee (PASC) that different types of evidence addressing four main questions would be needed to consider the performance of OCT at baseline in predicting variation in the effectiveness of dexamethasone PS DDS and the performance of changes in OCT for monitoring response to dexamethasone PS DSS. Requests for information to address the following data gaps were highlighted):

1. baseline CRT predicts a material variation in dexamethasone PS DDS treatment effect on visual acuity, with reference to the nominated ≥ 300μm threshold of CRT for determining eligibility for dexamethasone PS DDS
2. the association between change in CRT and improvement in visual acuity
3. the reliability of OCT measurement of CRT
4. the proposed response criteria can detect true inter-individual variation in treatment effects to confirm OCT's value as a monitoring test.

The MSAC assessment will include evidence to address the above questions. MSAC has previously endorsed the advice of PASC, with reference to Bell et al. (2010).

Allergan is willing to investigate re-analysing the MEAD patient level trial data to assist in providing further information about key questions from MSAC on OCT in guiding therapy. The analyses would predominantly be of correlations from the MEAD trial to address questions 1 and 2 above. These analyses would remain commercial in confidence.

Table 3: Summary of PICO to define research question

PICO	MSAC Comments
Patients	Eligibility for OCT Patients presenting with symptoms of DMO with vision impairment as per clinical management algorithms (Figure 5 and Figure 7). Eligibility for dexamethasone PD DDS Patients diagnosed with vision loss due to centre involving DMO as per clinical management algorithm (Figure 7) and the MEAD [Redacted] RCTs.
Intervention	Diagnosis of DMO: Standard diagnostic tests plus OCT Monitoring of DMO: Dexamethasone PS DDS with OCT
Comparator	Diagnosis of DMO: Standard diagnostic tests without OCT ('prior tests' only) Monitoring of DMO: Dexamethasone PS DDS without OCT ('prior tests' only) PBAC: Standard medical management (Standard monitoring tests ('prior tests') plus standard treatment, e.g. ranibizumab)
Outcomes	Safety • Adverse events associated with OCT and dexamethasone PS DDS Assessment of OCT performance • Evidence of accuracy of OCT in the published literature Effectiveness • VA • OCT provided additional information on CRT, tissue integrity, macular volume and cystoid space size. Cost-effectiveness of the use of dexamethasone PS DDS to treat DMO including the cost of OCT OR cost-minimisation.
For investigative services	
Prior tests	Prior tests include at least one of the following: VA testing, ophthalmoscopy, slit-lamp bio-microscopy, fluorescein angiography, and fundus photography.
Reference standard	Not applicable

Table 4: 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 government budget	Private health insurer	Patient	Total cost
Resources provided to identify eligible population										
Baseline OCT	Ophthalmologists MBS	Private consulting room OR Public outpatient clinic	100% of patients with suspected or diagnosed DMO	1	To be determined Approx. $91.75					
Resources provided to deliver proposed intervention										
OCT monitoring	Ophthalmologist MBS	Private consulting room OR Public outpatient	Patients with diagnosed DMO	Trial data suggests every 3-6 months	To be determined Approx. $91.75					

	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 government budget	Private health insurer	Patient	Total cost
		clinic								
Resources provided in association with proposed intervention										
Dexamethasone PS DDS administration	Ophthalmologists, MBS	Private consulting room OR Public outpatient clinic	Patients with diagnosed DMO	1 per eye, with 2 required in the event of bilateral disease. Trial data suggest each unit delivered every 5-6 months	**Item number 42738, 42739, 42740:** $300.75 $225.60 (75%) $255.65 (85%)					
Dexamethasone PS DDS acquisition	Ophthalmologists, PBAC	Private consulting room	Patients with diagnosed DMO	1 per eye, with 2 required in the			To be determined			

	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 government budget	Private health insurer	Patient	Total cost
		OR Public outpatient clinic		rare event of bilateral disease. Trial data suggest each unit delivered every 6 months						
Resources provided to deliver comparator 1										
N/A										
Resources used to manage patients successfully treated with the proposed intervention										
NA										
Resources used to manage patients who are unsuccessfully treated with the proposed intervention										
Cataract removal surgery	Cataract surgeon MBS	Day surgery	Based on MEAD trial		If removal and insertion in separate operations:					

<table>
<tr><th></th><th>Provider of resource</th><th>Setting in which resource is provided</th><th>Proportion of patients receiving resource</th><th>Number of units of resource per relevant time horizon per patient receiving resource</th><th colspan="2">Disaggregated unit cost</th></tr>
<tr><th></th><th></th><th></th><th></th><th></th><th>MBS</th><th>Safety nets*</th><th>Other government budget</th><th>Private health insurer</th><th>Patient</th><th>Total cost</th></tr>
<tr><td></td><td></td><td>centre and outpatient clinics</td><td>data. Rates will be dependent on the patient population in the PBAC submission.</td><td></td><td>Item number | Fee
42698 (removal) | $594.75
42701 (insertion) | $331.70
51318 (assistance) | $179.75

If removal and insertion in one operation:
Item number | Fee
42702 or 42707 | $760.65 or $797.10</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

	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 government budget	Private health insurer	Patient	Total cost
					51318 (assistance)	$179.75					
Resources used to manage patients successfully treated with comparator 1											
NA											
Resources used to manage patients who are unsuccessfully treated with comparator 1											
NA											

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

APPENDIX 1: Clinical Management Algorithms

Figure 5 Current and proposed clinical management algorithm: Diagnosis of centre involving DMO with vision impairment

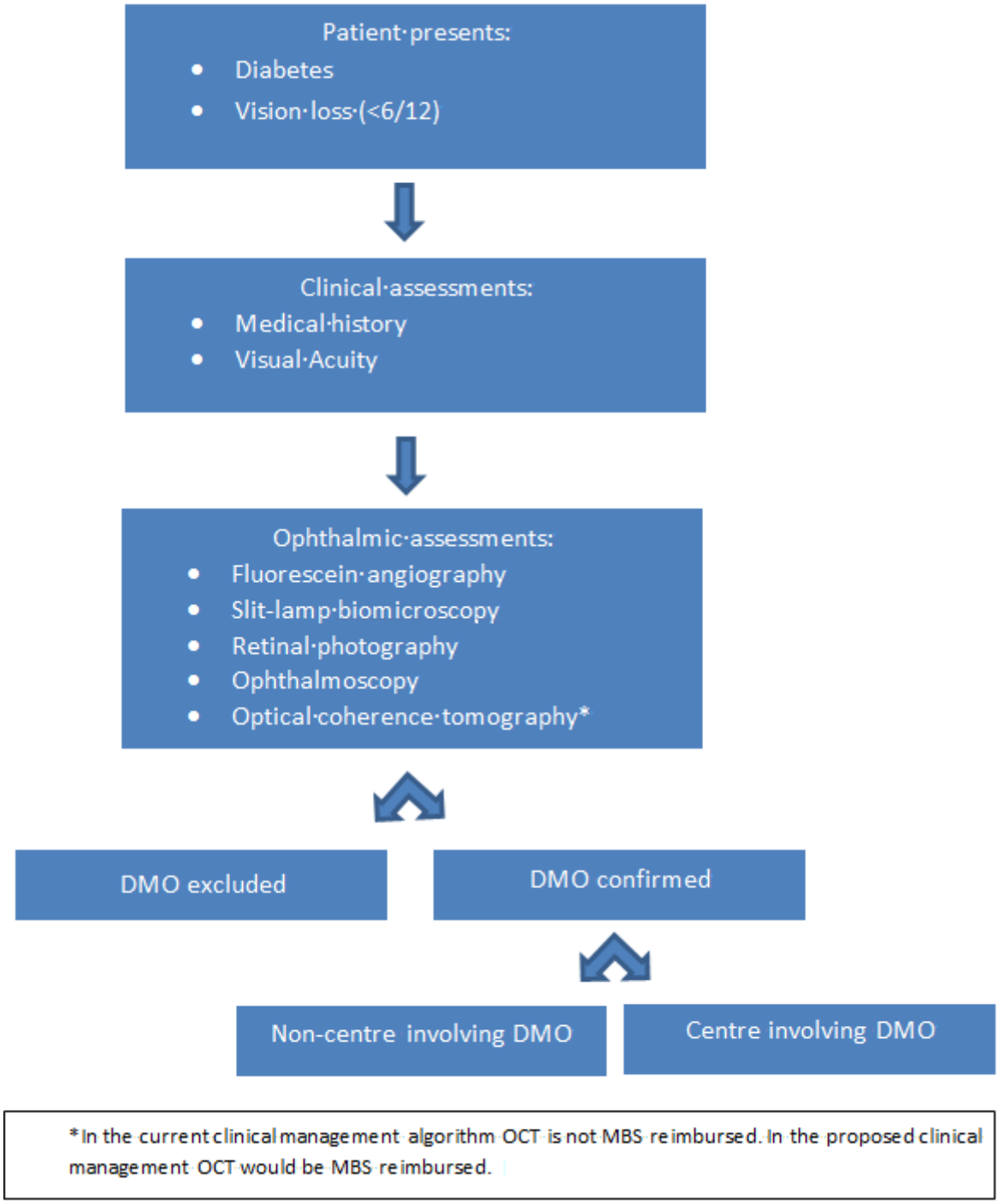


Figure 6 Current clinical management algorithm: Pharmacological treatment, repeat assessment and retreatment of centre involving DMO with vision impairment

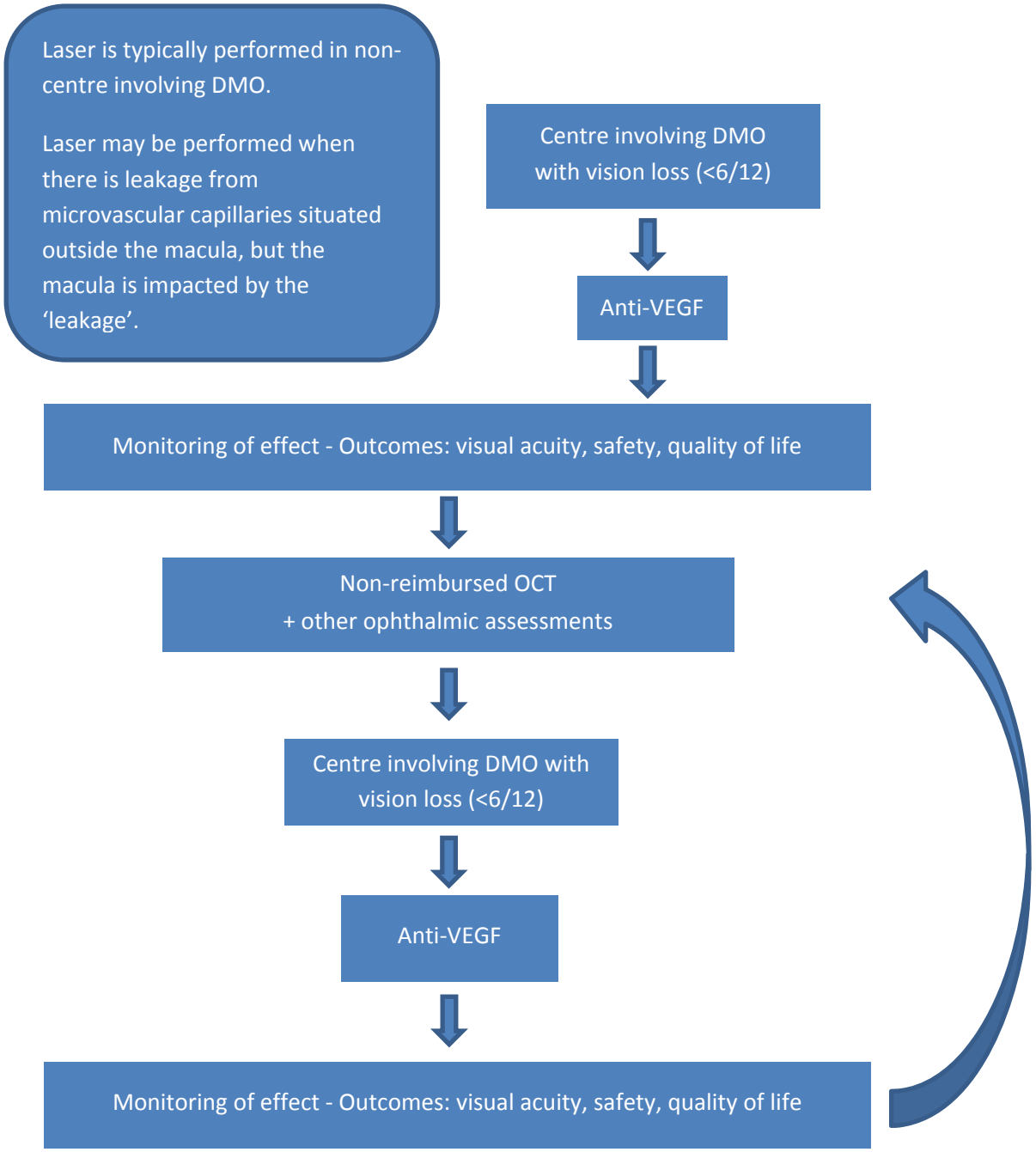
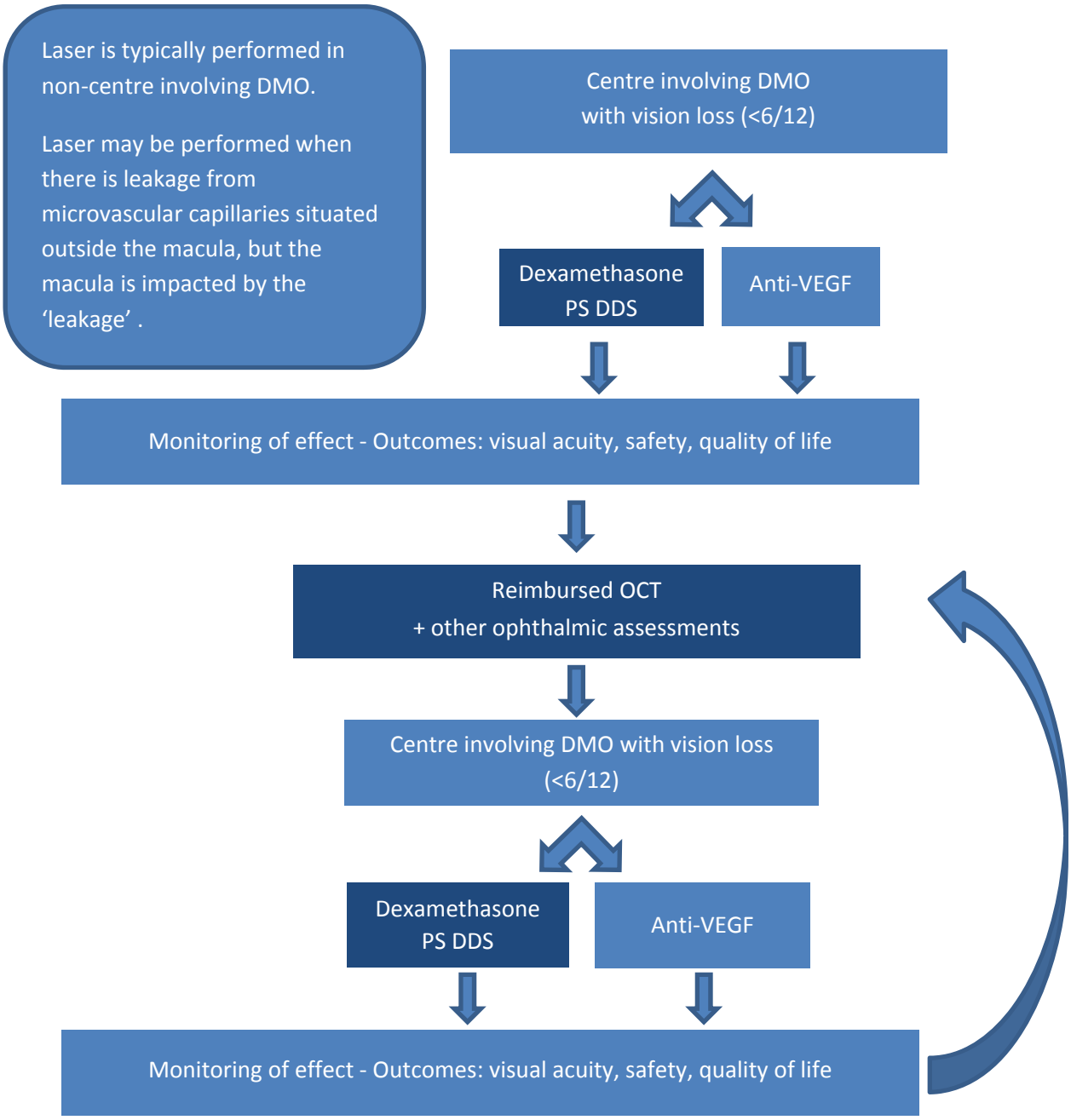
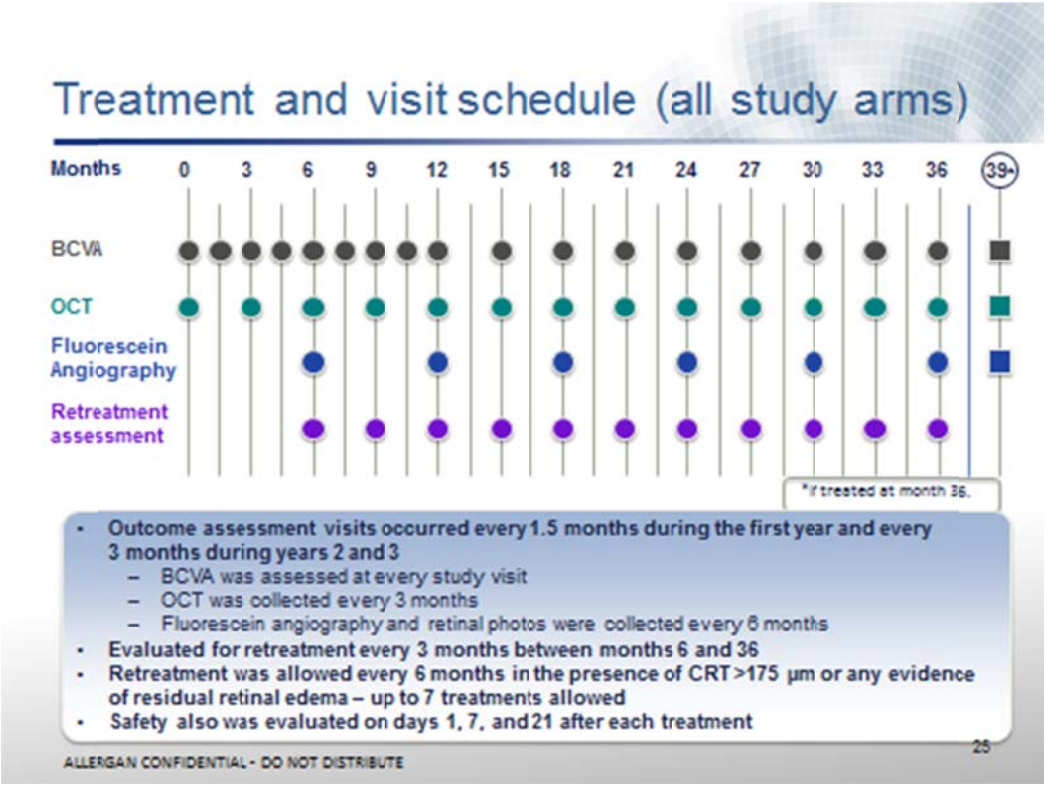


Figure 7 Proposed clinical management algorithm: Treatment, repeat assessment and retreatment of centre involving DMO with vision impairment



APPENDIX 2: Schedule of assessments in trials

Figure 8 Schedule of assessments in MEAD trials



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