Health Technology Assessment Programme

National Institute for Health Research

NETSCC, HTA
27 November 2014

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Draft Protocol for Technology Assessment Short Report HTA 14/151/02

13/11/2014 Updated version

Title of the project: The use of fundus-autofluorescence imaging for retinal conditions: a systematic review

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1. Plain English Summary

Retinal conditions are diseases associated with the retina of the eye- the part of the eye which collects light and converts it into signals to the brain to create an image. These conditions can be chronic and can lead to an increasing risk of vision loss. Some of the relatively common retinal conditions include age-related macular degeneration, geographic atrophy, inherited retinal dystrophies, retinitis pigmentosa, cone-rod dystrophy, central serous chorioretinopathy, diabetic retinopathy and retinal vein occlusion. These conditions are most commonly found in older adults, although some of the genetically inherited conditions occur in children and young adults. The conditions can affect quality of life due to potential loss of vision, time-consuming monitoring and unpleasant treatment procedures.

Fundus auto-fluorescence imaging is a potential technique to diagnose some of the retinal conditions. In this diagnostic technique images of the retina are obtained non-invasively which is preferable to patients. Research indicates that advances in technology have led to this technique becoming clinically relevant only recently.

The aim of this project is to systematically review the available evidence on the use of fundus autofluorescence imaging for the diagnosis and or monitoring of retinal conditions, including the use of FAF imaging in monitoring disease management. Along with providing a comprehensive and up-to-date synthesis of the best quality evidence for the diagnostic use of the technique in current clinical practice, this research will also aim to identify needs for future research in the area.

2. Decision problem

2.1 Research aim and objectives

The aim of this project is to assess the use of fundus autofluorescence (FAF) imaging using confocal scanning laser ophthalmoscopy (cSLO) for the diagnosis and monitoring of retinal conditions. Specific research objectives are:

- For each retinal condition, to determine the diagnostic and monitoring performance of FAF imaging (using cSLO), including monitoring of disease management.
- To identify future research needs and develop research recommendations.

2.2 Background

Retinal conditions are chronic progressive, potentially sight-threatening diseases. They include various conditions such as age-related macular degeneration (AMD), central serous chorioretinopathy (CSC), inherited retinal dystrophies (IRD), diabetic retinopathy (DR), retinal vein occlusion (RVO), and cystoid macular oedema (CMO). Age-related macular degeneration includes dry AMD which develops slowly, geographic atrophy, which can develop from dry AMD, and wet AMD which can develop very quickly. Inherited retinal dystrophies include retinitis pigmentosa, cone and cone-rod dystrophies and Stargardt's disease, which affects children and young adults.

In the UK, AMD affects around 600,000 people,[1] and 250,000 older adults suffer from blindness due to this condition.[2] Each year in England and Wales there are around 5000 to 7500 new cases of classic subfoveal choroidal neovascularisation associated with wet AMD.[3] Hereditary retinal dystrophies are a broad (and growing) group of hereditary disorders affecting the retina. About 150 children and 250 adults of working age in the UK are registered as blind or partially sighted as a result of these conditions.[4] The estimated prevalence of retinitis pigmentosa is approximately 16,000, Stargardt's disease is 6,000 and cone-rod diseases is 1/40,000 (i.e. about 1600 in the UK). [5;6] Among people who have had diabetes for 20 years, virtually everyone with type 1 and 80% of people with type 2 will have early clinical signs of diabetic retinopathy.[7] Proliferative retinopathy may occur in up to 50% of patients with type 1 diabetes and about 10% of patients with type 2 diabetes who have had the disease for 15 years.[7] There are an estimated 520 new cases of retinal vein occlusion per million people annually (i.e. approximately 35,000 in the UK).[8] Cystoid macular oedema is a less common retinal

condition which can occur especially following complicated cataract surgery.[9] The incidence of other causes of CMO varies according to the specific pathology. In people with untreated diabetes, there is a 25-30% chance of developing clinically significant macular oedema (CSMO), compared with 12% in treated patients.[9]

Age related macular degeneration (AMD)

AMD is a condition that results in a person's central vision becoming increasingly blurred, which can lead to difficulties reading and recognising people's faces, or colours appearing less vibrant.[10] It develops from ineffective functioning of the macula of the eye. Although AMD usually affects both eyes, it does not result in complete blindness as the peripheral vision is not affected. AMD can be sub-divided into two main types, dry AMD and wet AMD.

Dry AMD

Dry AMD affects about 85% of patients with AMD,[11] and develops as a result of damage to cells of the macula due to a build-up of waste products (lipofucsin) into deposits called drusen.[10] There is no effect on vision in the earliest stage when drusen are small and few. However, in the later stages, patients suffer from deterioration of sharpness in their central vision due to enlargement of the drusen. This results in the need for more light to undertake normal daily activities.[11] Symptoms of dry AMD include need for brighter light while reading, difficulty in reading and recognising people's faces, appearance of colours as being less vibrant, and hazy vision. Patients with this condition lose their vision gradually over many years,[10] and in some cases the disease progresses to the more severe geographic atrophy or wet AMD due to genetic, environmental or other risk factors. This condition usually affects both eyes of the patients.[11]

Wet AMD

Wet AMD, also known as neovascular or exudative AMD, has a rapid onset and it is likely to result in rapid deterioration in vision.[12] Choroidal neovascularisation (CNV: the development of new blood vessels in the choroid, between the white of the eye and Bruch's membrane) is characteristic of wet AMD.[13] CNV includes classic and occult forms, according to appearance on investigation by fluorescein angiography. The classic form is associated with more rapid progression than the occult form, in which there is fluid leakage but no new vessels.[3] New vessels can also form in the macular retina.[13] Blood and serum leak from the vessels causing Bruch's membrane, the retinal pigment epithelium (RPE), and the retina to separate from each other.[13] Fluid also gathers in the retina which makes it thicken.[13] Photoreceptors then become misaligned, resulting in cell loss, fibrosis and eventual scarring.[13]

Symptoms include central visual blurring, distortion and straight lines appearing crooked or wavy, though patients do not always notice this in the first eye affected.[13] Patients may suddenly become unable to read, drive, and see fine detail such as facial expressions and features due to a central dark patch in the visual field.[13]

Diagnosis is based on slit-lamp biomicroscopy. If CNV is suspected, fluorescein angiography is used to assess the composition, size and location of CNV, and guide management and assessment of prognosis.[14]

Geographic atrophy secondary to AMD

The advanced stage of dry AMD where degeneration of the deepest cells of the retinal pigment epithelium (RPE) occurs is known as geographic atrophy (GA).[11;15] Although the global prevalence of GA is very small with 0.66% in all age groups, the prevalence is highest in those aged 90 years and above at 22%. Increasing age, genetic factors and smoking are reported as the most consistent factors leading to GA.[15]

The evolution process of GA from progression of large drusen to hypopigmentation to the death of RPE cells can exceed 6 years. Although less frequent, patients with GA could experience a drusenoid RPE detachment or a RPE rupture.

Inherited retinal dystrophies

Stargardt's disease

Stargardt's disease, also known as juvenile macular dystrophy, fundus flavimaculatus and Stargardt's macular dystrophy (SMD), is a genetic condition affecting the macula, the small area near the centre of the retina which is responsible for central vision.[16] This condition initially affects children and young adults aged up to 20 years,[17] with the symptoms appearing in late childhood to early adulthood and deteriorating over time.[16] In most of the cases, this condition leads to progressive loss of vision and blindness.[18]

The first symptoms of the condition include problems in reading as blind spots can occur. Although initially the blind spots are small in size, in the later stages these spots may increase in size and colour vision might be affected. Similar to AMD, people with the condition experience decreased central vision while the peripheral vision usually remains normal. The symptoms as well as the rate of disease progression can vary from person to person.[19]

Retinitis pigmentosa

Retinitis pigmentosa (RP) is a group of disorders in which abnormalities in photoreceptors (rods and cones) or the RPE lead to progressive visual loss. Mutations in more than 50 different genes are known to cause non-syndromic RP. Symptoms appear between childhood and the age of 30.[20] Retinitis pigmentosa causes “night blindness," followed by gradual reduction of peripheral vision and eventual loss of central vision.[21] The speed of sight loss varies with different genetic forms of RP. Diagnosis relies on documenting progressive loss in photoreceptor function using electroretinography (ERG) and visual field testing.

Cone-rod dystrophy

Cone or cone-rod dystrophy, sometimes called inverse or central retinitis pigmentosa, is a group of disorders characterized by bilateral and symmetric loss of cone function and reduced rod function. [21] Cone-rod dystrophies are characterized by retinal pigment deposits visible on fundus examination, predominantly localized to the macular region.[6] Loss of central visual acuity, light aversion, and colour vision defects appear before peripheral visual loss and defective dark adaptation. The fundus changes may be similar to those of RP. Cone-rod dystrophies tend to demonstrate early onset and are often found in syndromes such as Alström syndrome, Bardet-Beidl syndrome, the neuronal ceroid lipofuscinoses, and Joubert syndrome and related disorders.[21]

The distinction between Cone-rod dystrophies (CRDs) and Rod-cone dystrophies (RCDs)

Typical retinitis pigmentosa (RP) are also called rod-cone dystrophies (RCDs), because they result from vision loss in rod photoreceptors first, followed by the secondary loss in cone photoreceptors. In cone-rod dystrophies (CRDs) cones are affected first, followed by rods. Rods are concentrated in the outer walls of the retina, while cones are concentrated in the centre of the retina.[20] CRDs are usually more severe and develop more rapidly than RCDs.[6]

Other retinal dystrophies include X-linked retinoschisis, Leber congenital amaurosis, Pattern dystrophy, Best disease, Maternal inherited diabetes and deafness, and Choroideremia.[22]

Central serous chorioretinopathy

CSC is caused by detachment of the neurosensory retina resulting from leakage of fluids from the choroidal circulation beneath the retina.[23;24] This condition affects the macula of the eye. Symptoms include blurry vision, a grey blind spot in the central vision or unexplained flashes of light. Stress and steroid medications are believed to be linked with the condition, although the exact cause is unknown. Both younger and older men and women can be diagnosed with CSC, although it is most common in men aged between 25 and 45 years. Unlike other retinal conditions, people with this disorder can experience spontaneous visual recovery. Patients may or may not experience symptoms in the other

eye. It is also possible that new detachments may develop- although the timing can range from weeks to even years.[24]

Diabetic retinopathy

Diabetic retinopathy (DR) occurs when abnormal new blood vessels result in intraocular haemorrhage and possible retinal detachment, or the macula or fovea is damaged.[25] DR is a complication of diabetes, with early clinical signs including micro-aneurysms in retinal capillaries and dot intra-retinal haemorrhages. As DR progresses, patients develop proliferative retinopathy, characterised by the development of new retinal blood vessels, an increase in the number and size of intra-retinal haemorrhages, and 'cotton-wool' spots, often resulting in significant irreversible vision loss.[26] New vessels can grow into the vitreous cavity, between the retina and the lens of the eye, and haemorrhage in the vitreous cavity, causing visual loss and retinal detachments.[7]

Symptoms of DR include blurred, hazy and distorted vision, seeing black lines and dots, fluctuating vision, periods of temporary 'blackness' due to retinal haemorrhage, difficulty distinguishing colours, poor peripheral vision and poor depth perception.[26]

Diabetic macular oedema (DMO), which can occur at any stage of DR, commonly causes irreversible loss of central vision.[26] In DMO the retina swells due to accumulating fluid and proteins in the macula following the breakdown of the blood-retina barrier and an increase in vascular permeability. The most common symptom of DMO is blurred vision. Other symptoms include distorted visual images, floaters, loss of contrast sensitivity, intolerance to light, changes in colour vision and scotomas (where part of the visual field is missing).[27]

Cystoid macular oedema

As mentioned above, macular oedema is the accumulation of fluid between the layers of the central retina (the macula) and the RPE due to leakage from dilated capillaries. Acute oedema, of less than four months duration, often resolves spontaneously.[28] Chronic oedema, which persists for four months or more, may lead to the formation of cystic honeycomb-like spaces in the retina called cystoid macular oedema (CMO).[29]

CMO known as Irvine-Gass syndrome is the commonest cause of poor visual outcome following cataract surgery, although the cause is unclear.[28] CMO can also occur in central (and occasionally) branch retinal vein occlusions and retinal dystrophies (e.g. retinitis pigmentosa).[9] Other conditions in which CMO can occur include inflammatory diseases (uveitis, scleritis, birdshot chorioretinopathy, toxoplasmosis), various types of retinal vascular disease (idiopathic retinal telangiectasia, radiation retinopathy), or may be drug-induced (such as can occur with topical adrenaline 2%, particularly in

patients without a lens). It can also occur following injury to the eye and in association with choroidal tumours.[9]

Clinically important CMO is characterised by reduced visual acuity and accounts for 0.1% to 12 % of cases. Diagnosis of CMO is made using slit lamp biomicroscopic examination of the macula and with the aid of fundus fluorescein angiography (FFA) or ocular coherence tomography (OCT).[29]

Retinal vein occlusion

Retinal vein occlusion (RVO) occurs when blood clots or fat deposits block blood vessels, and occurs particularly in people with cardiovascular conditions,[30] who are over 50.[31] An obstruction can occur causing central retinal vein occlusion (CRVO), branches of the central retinal vein occlusion (BRVO) or a trunk of the central retinal vein occlusion (hemi-RVO).[32] RVO can lead to fluid from capillaries draining into the obstructed vein, caused in part by secretion of vascular endothelial growth factor (VEGF) and interleukin-6, and resulting in thickening of the retina through oedema.[33]

CRVO can be ischaemic (I-CRVO) or non-ischaemic (NI-CRVO), and about 8% of those with NI-CRVO can develop I-CRVO.[34] CRVO most commonly affects one eye but in around 10% of patients the disease affects both eyes.[31] The main causes of visual problems and complications of CRVO are macular oedema, vitreous haemorrhage, development of new blood vessels (neovascularization), and neovascular glaucoma.[35] Some people with CRVO do not need treatment and macular oedema resolves in about a third of patients with non-ischaemic CRVO.[31]

BRVO results from blockages in one of the four vessels that drain blood from the retina, and involves the local area around blocked venules (tiny vessels that return blood from capillaries to veins).[30] BRVO often occurs at arteriovenous crossings, where the artery and vein share a common outer sheath.[36] The effects of BRVO vary between people, but include localized retinal oedema, superficial and deep retinal haemorrhages, intra-retinal microvascular abnormalities or anastomotic vessels (the development of new connections between vessels), and venous dilation or sheathing (coating around the vessels) in part of the retina near the obstructed vein.[8] Symptoms of BRVO include decreased visual acuity, peripheral visual loss, distortion of vision, or 'blind spots'. In some cases spontaneous improvement in vision can occur as macular oedema (which follows acute occlusion of the vein) resolves.[37]

Impact of retinal conditions

Significant distress results from developing visual loss,[38] and diagnosis and monitoring can be time-consuming, and less than pleasant. For example, some patients have fluorescein angiography, which

involves intravenous injections of dye. FAF imaging is relatively easy to accomplish, requires little time and is non-invasive,[39] so may be preferred by patients, and encourage attendance.

People with retinal conditions require frequent treatments and regular monitoring of response to treatment and disease progression. With the aging population and recent treatment advances, demand is increasing.[40]

2.3 Definition of the intervention

Fundus autofluorescence in relation to retinal health

The ocular fundus refers to the portion of the interior surface at the back of the eye, opposite the lens, that can be viewed with an ophthalmoscope. The fundus includes the retina (light-sensitive layer), optic disc (where axons exit the eye to form the optic nerve), macula (a yellow spot near the centre of the retina where structures for high-acuity vision are located), fovea (the central part of the macula responsible for sharp central vision) and the posterior pole (the area of the retina between the optic disc and macula).

The fundus of the human eye has a 'natural' or 'background' level of fluorescence, which is referred to as autofluorescence. This is caused by the presence of molecules with fluorescent properties (i.e., molecules which, when exposed to light of an appropriate wavelength, absorb the incident electromagnetic energy and re-emit this as light at wavelengths longer than those of the initial source). The fluorescent molecules, known as fluorophores, are potentially of clinical value in detecting age- or disease-related processes, since their density and distribution alters with ageing of the eye and with certain pathological conditions. Notably, lipofucsin is a fluorescent pigment that accumulates in the RPE as a by-product of cell metabolism and can lead to the development of drusen. Lipofucsin deposition normally increases with age but its accumulation may also reflect cell dysfunction or metabolic abnormalities in the RPE. Excessive lipofucsin deposition in the RPE is considered pathologic and is associated with visual loss.[41] FAF imaging techniques have potential value as diagnostic tools since the presence and distribution of fluorophores may correlate with disease activity and may provide an early indication of future disease development, progression or response to treatment.

Note that the term 'autofluorescence' refers specifically to 'natural' or 'background' fluorescence of the eye, i.e. it excludes fluorescence arising from the addition of fluorescent dyes such as fluorescein.

Fundus autofluorescence imaging techniques

The intensity of light emitted during fundus autofluorescence (FAF) is relatively weak (about two orders of magnitude lower than the background of a fluorescein angiogram at peak dye transit) and so

specialist imaging techniques are required to enable FAF to be detected and mapped. FAF has been an area of interest in ophthalmic research for over 40 years but it has only recently become clinically relevant, as a result of technological advances.[41] FAF images can be obtained non-invasively through the use of a fundus camera, fundus spectrophotometry, or confocal scanning laser ophthalmoscopy (cSLO).

The fundus camera uses a single flash to image the entire retinal area instantaneously. The acquired autofluorescence image is derived from all tissues in the light beam with fluorescent properties, and light scattered anterior and posterior to the plane of interest can greatly influence the detected signal. Fundus spectrophotometry was developed to measure FAF from small retinal areas (2^o diameter). It incorporates an image intensifier diode array as a detector and beam separation in the pupil to minimise the contribution of autofluorescence from the crystalline lens.[42] In cSLO a focused low-power laser beam is swept across the fundus in a raster pattern to provide the excitatory light source for fluorophores.[43] The confocal nature of the optics reduces the detection of autofluorescence from structures anterior to the retina such as the lens and cornea. Unlike fundus spectrophotometry, cSLO allows imaging of FAF over larger retinal areas (e.g. 55^o in Heidelberg Retina Angiograph (HRA)-based systems). To reduce background noise and enhance image contrast the mean image of several FAF images is usually obtained (usually based on 4-16 frames, after adjustments to correct for eye movement). In order to block the reflected light but permit autofluorescence light to pass, cSLO have a barrier filter and it should be noted that the cut-off wavelength of the filter differs among the devices. Image contrast and brightness have also been observed to differ among cSLO devices. These differences must be taken into account when comparing the results of FAF imaging obtained using different cSLO devices.[44]

Of these methods, cSLO is the most sensitive approach for identifying autofluorescence that arises specifically from the fundus (i.e. minimising the detection of autofluorescence arising from other parts of the eye such as the lens).[44] According to clinical experts consulted during the preparation of this protocol, cSLO is the current standard method employed for obtaining FAF imaging of retinal conditions.

2.4 Place of the intervention in the treatment pathway and current service provision

Current treatment options

The aim of treatments for retinal conditions is to reduce symptoms, slow disease progression, or help people to continue their normal activities. People with vision problems may attend low vision clinics, use low vision aids (eg. glasses, practical training), receive mobility training and psychological support. Those with hereditary conditions are also likely to receive genetic counselling. Diet may help to slow disease progression, so diets rich in vitamin A, C and E, lutein, zeaxanthin and omega-3 fatty

acids may be recommended, though there is currently limited evidence that these are effective.[13] Because retinal conditions may be related to systemic disease, treatment of high blood pressure, raised cholesterol, control of diabetes, smoking cessation and diagnosis and treatment of raised pressure in the eye are considered important.[38]

Dry age-related macular degeneration (Dry AMD) and geographic atrophy

Currently treatment for dry AMD includes vision clinics, advice and mobility training. However, experimental treatments are also available which include: sub-threshold laser therapy to reduce drusen;[45] autologous transplant of RPE and choroid for pigment epithelium tears;[46] antioxidant therapy; prevention of photoreceptor and RPE loss; and treating inflammation.[47] Patients with geographic atrophy are recommended to take supplements of antioxidants plus zinc, along with behavioural changes such as ceasing smoking and controlling their BMI.[15]

Wet age-related macular degeneration (Wet AMD)

Several treatments for wet AMD are only recommended for patients with visual acuity below a certain threshold. These include eye injections of anti-VEGF drugs (ranibizumab and aflibercept), laser photocoagulation to destroy lesions away from the fovea [13] and photodynamic therapy with verteporfin for classic choroidal neovascularisation (CNV).[3;13] In end-stage disease, an artificial lens may be implanted, to magnify or deflect images to a less damaged part of retina.[13]

Emerging treatments include laser photocoagulation, macular translocation (moving the macular away from abnormal blood vessels), photodynamic therapy plus an anti-VEGF, combination PDT and triamcinolone, radiotherapy, ciliary neurotrophic growth factor, off-label anti-angiogenic drugs (anecortave acetate, bevacizumab), and triple therapy (combination PDT, anti-VEGF and steroid).[13]

Inherited retinal dystrophies

There are treatments for Retinitis pigmentosa, but they lack robust evidence. These include: vitamin A/beta-carotene, acetazolamide, lutein, and immunosuppressants. There is currently no treatment available for Stargardt's disease, though ongoing research is investigating dietary supplementation, use of sunglasses to prevent further retinal damage,[18] drug treatment (e.g. 4-methylpyrazole - fomepizole, Antizol™), and sub-retinal transplantation of stem-cell-derived RPE cells.[48] Laser treatment may be an option for those with CSC.[24]

Molecular and gene therapy research is ongoing for inherited conditions, including cone and cone-rod dystrophies,[49] as the specific genes responsible for dystrophies are identified. However, identifying whether people have a specific condition can be difficult, and genetic misdiagnosis may lead to ineffective treatment in some patients and lack of treatment in others.[50]

Central serous chorioretinopathy (idiopathic detachment of the neurosensory retina)
Treatment may be unnecessary, especially in corticosteroid-induced disease that recovers when steroid dosage is reduced.[51] Treatment is considered in recurrent chronic CSC or a single CSC episode, of greater than 3 months duration, with some signs of chronic CSC.[51] Photodynamic therapy (PDT) with verteporfin is the treatment of choice, and micropulse diode laser photocoagulation seems an effective alternative to PDT.[51] Glucocorticoid inhibitors are being evaluated in ongoing research.

Diabetic retinopathy
Treatments for retinopathy include retinal laser photocoagulation, intravitreal anti-VEGF or steroid drugs.[52] Surgery is offered when vision worsens despite laser photocoagulation or when macular oedema is severe or chronic.[27] Options include steroid-releasing implants for patients with an artificial lens, [53] or removal of vitreous humour.[27] NICE is evaluating aflibercept and dexamethasone intravitreal implants for diabetic macular oedema. [54;55] Fenofibrate, a lipid-lowering fibrate, has shown some promise.[56]

Cystoid macular oedema
Non-steroidal anti-inflammatory agents (NSAIDs) are used to treat CMO, though their effect in acute CMO remains unclear.[28] Irvine-Gass syndrome is managed with topical steroids and NSAIDs. Acetazolamide or triamcinolone injections can be used for persistent oedema. Rarely, the vitreous is removed. Anti-VEGF drugs have been used in CMO secondary to central retinal vein occlusion, though the long-term effects are unknown.[9]

Retinal vein occlusion
Laser pan-retinal photocoagulation (PRP) may be used for new blood vessels in the iris or angle of the eye.[38] Anti-VEGF injections (ranibizumab, aflibercept) are used to treat new blood vessel development and macular oedema,[57;58] followed by anti-VEGF with PRP if further vessels develop. Anti-VEGF injections can be used in BRVO if laser photocoagulation does not work or is unsuitable.[58] Low-dose corticosteroid injections have shown promise for neovascularisation and macular oedema.[59] There is limited evidence for the efficacy of surgery, for example arteriovenous sheathotomy (separating the shared outer coating where veins and arteries cross) for BRVO.[60]

2.6 Relevant comparators
According to clinical experts, the most relevant comparator for this technology assessment is fundus imaging performed using fundus fluorescein angiography (FFA). It is a technique of fundal photography which is conducted using a rapid-sequence of images after fluorescein dye is intravenously injected to the eye to examine tiny blood vessels in the eye for the diagnosis of a range

of eye conditions such as diabetic mellitus, retinal vein occlusion, age-related macular degeneration, Stargardt's disease, choroidal rupture and chorioretinitis, and CSC.[61;62] Other imaging tests that may be used in clinical practice will also be included as a comparator, where reported (e.g. fundus photography, indocyanine green angiography, optical coherence tomography, or any combination of relevant tests).

2.7 Outcomes

The key outcome measures will include: sensitivity and specificity; positive and negative likelihood ratios; positive and negative predictive values; and diagnostic odds ratios. The working definitions of each of these outcomes are: [71]

- Sensitivity: True identification of the people with the condition of interest. It is also known as true positive rate. A high sensitivity test result implies that a negative result rules out a condition.
- Specificity: Also known as the true negative rate, it indicates the true identification of people without the condition. A test with high specificity implies that a positive result confirms the condition.
- Likelihood ratios: These ratios indicate how much more likely particular test results are in people with the condition than in those without the condition. A positive likelihood ratio is the ratio of the true positive rate to the false positive rate which is expressed as: sensitivity/(1-specificity) whereas a negative likelihood ratio is the ratio of the false negative rate to the true negative rate, expressed as: (1-sensitivity)/specificity.
- Positive and negative predictive values: Positive predictive value (PPV) is the probability of the condition of interest among people with a positive test result. Negative predictive value (NPV), on the other hand, is the probability of not having the condition among people with a negative test result.
- Diagnostic odds ratio: This overall indicator of diagnostic performance is estimated as the ratio of the odds of a positive test result among those with the condition of interest to the odds of a positive test result among those without the condition of interest.

2.5 Existing evidence of clinical effectiveness

Scoping searches conducted in September 2014 identified three completed systematic reviews and one ongoing evidence synthesis of imaging technologies in people with retinal conditions. None of the published systematic reviews included FAF imaging and they are therefore unlikely to be of relevance to the proposed technology assessment. The protocol for the ongoing evidence synthesis (which was commissioned by the NIHR HTA Programme) is for optical coherence tomography in wet AMD. FAF imaging was an eligible comparator; however, as wet AMD is not the focus of the current

review the published report is unlikely to include studies of relevance, although it will be checked. The review is due to be published in November 2014.

The scoping searches for the current protocol identified over 70 primary research studies of potential relevance which would need to be assessed against the inclusion criteria. Full details of the study designs and/or the reference standards are not clear from the study abstracts but preliminary scoping suggests that many of these studies would need to be considered formally for their eligibility into the proposed review.

Need for research

FAF imaging is a promising procedure for the diagnosis of diseases of the retina.[41] The primary studies appear to be of variable methodological quality, in some cases involving small sample sizes and unclear study designs. A systematic evaluation of both the quantity and the quality of the available evidence would be useful to inform health service policy and practice in this area.

3. Report methods for synthesis of evidence

A review of the evidence for clinical-effectiveness will be undertaken systematically following the general principles outlined in Centre for Reviews and Dissemination (CRD) report 'Undertaking Systematic Reviews of Research on Effectiveness' (Third edition)[64] and the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (formally QUOROM statement),[65] taking into consideration specific aspects of methodology that are relevant to the synthesis of evidence of diagnostic test accuracy.

3.1 Search strategy

A comprehensive search strategy will be developed, tested and refined by an experienced information scientist (see Appendix 1for a draft Medline search strategy). The search strategy will aim to identify studies on the diagnosis of relevant retinal conditions using the intervention and relevant comparators (see below for the inclusion/exclusion criteria).

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

Electronic databases to be searched will include:

- General health and biomedical databases – MEDLINE (Ovid); PreMedline In-Process & Other Non-Indexed Citations; EMBASE; the Cochrane Library; Web of Science; Database of Abstracts of Reviews of Effectiveness (DARE); Health Technology Assessment database; MEDION database of diagnostic accuracy studies.
- Internet pages – American Academy of Ophthalmology (AAO), Association for Research in Vision and Ophthalmology (ARVO); Cochrane Eyes and Vision Group (CEVG); European Association for Vision and Eye Research (EVER); Royal College of Ophthalmologists.
- Grey literature and research in progress – UK Clinical Research Network Portfolio Database; World Health Organization International Clinical Trials Registry Platform (WHO ICTRP); Current Controlled Trials; Clinical Trials.gov; NIHR Clinical Research Network Portfolio.

All databases will be searched from 1990 (approximately 10 years prior to the likely publication of the earliest relevant evidence) to the present and searches will be limited to the English language.

3.2 Inclusion/Exclusion criteria:

- Population: patients of any age who are suspected to have, or have previously been diagnosed with the retinal conditions listed above (section 2.2).
- Index test: FAF imaging performed using cSLO.
- Reference standard: Fundus imaging performed using any clinically relevant method (e.g. fundus photography, fundus fluorescein angiography (FFA), indocyanine green angiography, optical coherence tomography, or any combination of relevant tests).
- Outcomes: Sensitivity and/or specificity (including any data from which these can be calculated) for the diagnosis, management or monitoring of retinal conditions. Inter- and intra-observer agreement, adverse events, test acceptability to patients and clinicians, and test interpretability will be secondary outcomes, i.e. will not themselves act as inclusion criteria but will be synthesised if reported alongside diagnostic accuracy outcomes.
- Study designs: Prospective studies will be prioritised: retrospective studies will be included in data synthesis only if no prospective studies are available for a given retinal condition. Both the intervention and comparator should have been compared in the same group of patients. Studies will be excluded if they have small sample sizes (i.e. if fewer than 10 study eyes), do not enable direct comparisons of FAF imaging against relevant reference tests, or do not clearly report their study design or methods.

3.3 Inclusion process and data extraction strategy

Studies will be selected for inclusion through a two-stage process using the predefined and explicit criteria (as specified in section 3.2). The literature search results will be screened by two reviewers to identify all citations that may meet the inclusion criteria. Full manuscripts of relevant studies will be retrieved and assessed by two reviewers using a standardised eligibility form.

Data extraction and quality assessment will be undertaken by one reviewer and checked by a second reviewer using a pre-designed and piloted data extraction form (Appendix 2) to avoid any errors. At each stage, any disagreements between reviewers will be resolved by consensus or if necessary by arbitration by a third reviewer.

3.4 Quality assessment

The methodological rigour of studies reporting diagnostic accuracy will be assessed using the Cochrane Collaboration adaptation[66] of the QUADAS tool[67] (which focuses on methodological quality rather than quality of reporting) (see Appendix 3). In addition to the modified QUADAS criteria, if necessary, we will distinguish between studies that included one or both eyes per individual so as to avoid any unit-of-analysis issues (e.g. using a sub-group analysis approach proposed by Virgili and colleagues[68]). Most diagnostic test accuracy studies in ophthalmology do not justify their sample sizes.[69] Based on published tables of sample sizes required to achieve a given level of diagnostic outcome precision,[70] we considered a minimum sample size of 10 eyes per study appropriate to exclude highly imprecise evidence.

3.5 Methods of analysis/synthesis

Studies will be synthesized through a structured narrative review with tabulation of results of included studies. Where appropriate and where suitable data are available, meta-analysis will be employed to synthesise data on test sensitivity and specificity. The appropriateness of meta-analysis will be determined by critical appraisal of the primary studies during the quality assessment step (section 3.4). To account for correlation between sensitivity and specificity, and their dependence on the prevalence of retinal conditions, any pooling of sensitivity and specificity outcomes will be based on appropriate hierarchical random effects models (using statistical software such as Winbugs or SAS). Synthesis of the findings may include summary receiver operating characteristic (sROC) curves to illustrate the trade-off between test sensitivity and specificity for different diagnostic thresholds. Critical consideration will be given to the presentation of likelihood ratios and diagnostic odds ratios which can usefully inform interpretation of diagnostic test accuracy but also have some limitations. Heterogeneity among studies and analyses of relevant subgroups will be explored and presented (e.g. using sensitivity and specificity paired forest plots). Where possible, the analysis and synthesis will

follow good practice approaches as recommended by the CRD (Chapter 2: Systematic reviews of Clinical Tests)[64] and the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.[71;72]

4. Expertise in this TAR team

SHTAC is one of nine academic research teams in the UK contracted to the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme to assess the clinical and cost effectiveness of health technologies. Our research supports several key decision making bodies within the UK, including the National Institute for Health and Care Excellence (NICE). With expertise in evidence synthesis, health economics, statistical modelling and epidemiology, SHTAC is involved in research addressing major policy questions on the use of drugs, devices, procedures, screening programmes, health promotion and public health, and other interventions. SHTAC has recently conducted research into treatments for cataract surgery, intrabeam radiotherapy for breast cancer, and educational interventions to improve quality of life in people with chronic skin diseases.

For a technology assessment short report of this nature at least two researchers with expertise in systematic review methodology (for clinical and cost effectiveness evidence) will be part of the project team. In addition, an experienced information specialist will be involved in the development and application of the search strategy, and a senior member of the SHTAC team will act as the guarantor to the project. The project will be coordinated by one researcher with experience in the project management of research of this type.

- **Advisory group**

An Advisory Group has been recruited comprising experts in ophthalmology and a service user organisation. The group has commented on a draft protocol and will comment on the draft final report. The group will also be consulted during the course of the project for advice as necessary. The current members of the group are:

- Andrew Lotery, Professor of Ophthalmology, Faculty of Medicine, University of Southampton and Southampton University Hospitals NHS Foundation Trust
- Susan Downes, Consultant Ophthalmic Surgeon, Oxford Eye Hospital, John Radcliffe Hospital
- Steve Winyard, Royal National Institute for Blind People

5. Competing interests of authors

None

6. **Timetable/milestones**

If successfully commissioned we would anticipate the following milestones:

Months 1-2: finalise Advisory Group, undertake the literature searches, screen studies for inclusion, data extract and quality assess studies

Months 3-4: synthesise studies, draft the final report and submit to the Advisory Group for comments, finalise the report and submit to the HTA programme.

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Appendix 1. Draft search strategy for Ovid MEDLINE

Ovid Medline 1946-Current N=845 restricted to 1999-2014 & English Language 12/11/2014

1 (autofluorescen* and (fundus or fundi or fundal)).tw. (882)
2 FAF.tw. (564)
3 1 or 2 (1170)
4 topcon.tw. (406)
5 "confocal scanning laser ophthalmoscop*".tw. (568)
6 CSLO.tw. (160)
7 optos.tw. (52)
8 spectralis.tw. (333)
9 imagenet*.tw. (79)
10 bluepeak.tw. (2)
11 "heidelberg retina angiograph".tw. (91)
12 "heidelberg engineering".tw. (362)
13 "AO SLO".tw. (22)
14 "spectral domain OCT".tw. (442)
15 optovue.tw. (75)
16 "carl zeiss meditec".tw. (651)
17 or/4-16 (2535)
18 (fluorescen* or autofluorescen*).tw. (316302)
19 Fluorescence/ (32513)
20 or/18-19 (325237)
21 17 and 20 (282)
22 3 or 21 (1277)
23 (image* or imaging).tw. (667321)
24 (camera* or photograph* or laser* or infrared or ophthalmoscop* or instrument*).tw. (417588)
25 Tomography, Optical Coherence/ (15646)
26 Fluorescein Angiography/ (18748)
27 Optical Imaging/ (1600)
28 Electroretinography/ (14261)
29 Microscopy, Confocal/ (44420)
30 (diagnos* or electrodiagnos*).tw. (1619111)
31 Diagnosis, Computer-Assisted/ (20755)
32 Lasers/du, is [Diagnostic Use, Instrumentation] (4258)
33 Image Processing, Computer-Assisted/ (100013)
34 (automat* adj5 (detect* or captur* or quantif*)).tw. (10337)
35 or/23-34 (2556224)
36 22 and 35 (982)
37 exp Retinal Diseases/ (102500)
38 (retina* or retinitis or retinopath* or epiretina* or subretina* or preretina* or posterioretina* or intraretina* or chorioretinopath* or vitreoretinopath*).tw. (167310)
39 (macula* or maculopath* or "wet AMD" or "dry AMD" or "exud* AMD").tw. (38826)
40 ((fundus or fundi or fundal) adj5 (change* or impair* or disease* or disorder* or detect* or diagnos*)).tw. (2365)
41 (geographical adj atroph*).tw. (11)
42 hyperfluorescen*.tw. (821)
43 (RVO or CRVO or BRVO).tw. (1251)
44 (cone*1 adj2 dystroph*).tw. (846)
45 or/37-44 (212724)
46 36 and 45 (919)
47 (comment or editorial or letter).pt. (1325244)
48 46 not 47 (912)
49 limit 48 to english language (845)

Appendix 2. Draft data extraction form for primary studies

Reference and design	**Diagnostic tests**	**Participants**	**Outcome measures**
Author: Year: Country: Study design: Number of centres: Funding:	Index:[a] Reference standard:[b] Comparator:	Number of participants: Sample attrition/dropout: Inclusion criteria for study entry: Exclusion criteria for study entry: Participant characteristics:	Primary outcomes: Secondary outcomes: Methods of assessing outcomes: Recruitment dates:

	Population with disease on reference standard	**Population without disease on reference standard**	**Total**
Index test positive	a	b	a+b
Index test negative	c	d	c+d
Total	a+c	b+d	a+b+c+d

Calculate clinical sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) if possible and note whether these agree with any values that may be reported in the paper

		95% CI
Clinical sensitivity a / (a + c)		
Clinical specificity d / (b + d)		
PPV a / (a + b)		
NPV d / (c + d)		

Comments:

Repeat for other tests/thresholds as appropriate

[a] fundus autofluorescence imaging using cSLO
[b] fluorescein angiography

Appendix 3. Draft quality assessment form for primary studies

Quality assessment criteria (based on Reitsma et al.[66] adaptation of the QUADAS Tool[67])

1	Was the spectrum of patients representative of the patients who will receive the test in practice?	yes / no / unclear
2	Is the reference standard likely to classify the target condition correctly?	yes / no / unclear
3	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	yes / no / unclear
4	Did the whole sample or a random selection of the sample, receive verification using the intended reference standard?	yes / no / unclear
5	Did patients receive the same reference standard irrespective of the index test result?	yes / no / unclear
6	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	yes / no / unclear
7	Were the reference standard results interpreted without knowledge of the results of the index test?	yes / no / unclear
8	Were the index test results interpreted without knowledge of the results of the reference standard?	yes / no / unclear
9	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	yes / no / unclear
10	Were uninterpretable/ intermediate test results reported?	yes / no / unclear
11	Were withdrawals from the study explained?	yes / no / unclear