Dry AMD review Detailed project description - updated 10th July 2017

This protocol was revised in February 2017, with three changes. Firstly, we included some additional outcome measures, so that we could include studies in early AMD before any changes were detectable by patients. Secondly, we took account of changes in the NICE clinical guideline development process and have included implantable telescopes. Thirdly, in liaison with one of the HTA Programme panels, we have included a review of statins, because the Cochrane review is now out of date and the HTA Programme is considering advertising for primary research.

It was amended again in July 2017, to cover the use of nutritional supplements, shown by the AREDS trial to reduce progression of dry AMD. It had originally been expected that the NICE guideline would cover the use of nutritional supplements.

Title: Systematic review of treatments for dry AMD and Stargardt's disease

Background and rationale

Age-related macular degeneration is the commonest cause of blindness in the UK. It affects mainly older people. The prevalence of AMD increases with age as shown in the table below (1). We have an ageing population with more people living longer due to reductions in (mainly) cardiovascular mortality. More people will live to develop AMD. They may otherwise be fit with good quality of life, so that visual loss may have a dramatic effect in their remaining years.

AMD is divided into early, intermediate and advanced stages. Most people with AMD are at the early stage. In this, there are whitish-yellow spots called drusen. These are found in the retinal pigment epithelium (RPE). The RPE and the choroid provide nourishment to the retinal photoreceptor cells. Drusen are associated with thinning of the overlying RPE.

	Drusen	Advanced dry AMD
Age		
65-69	Males 9.7% Females 9.8%	M 0.5% F 0.1%
70-74	M 12.5% F 17.3%	M 0.6% F 1.0
75-79	M 18.7 F18.1	M 1.9 F 1.2
80 and over	M 23.3 F 28.9	M 1.4 F 5.8
All ages over 65	15.4%	1.2%

Advanced AMD takes two forms. One is called neovascular, known as "wet" AMD. There have been advances in the treatment of wet AMD and it is not considered further in this proposal.

The other form of advanced AMD is "dry" AMD where the retina becomes atrophic ("geographic atrophy" – GA) leading to patches of sight loss. In the UK, there about 2.6 million people with early AMD, about 417,000 with wet AMD, and 203,000 with late dry atrophic AMD. The focus of this proposal is on

early and intermediate AMD, and whether progression to late forms (wet or dry) can be prevented or at least delayed, and on treatments for late dry AMD.

Retinal dystrophies such as Stargardts's often affect people in their 20s but can start at any age, and leads to loss of central vision. The loss of vision is usually slowly progressive but can be more rapid when the condition comes on in younger people. There is currently no treatment for Stargardt's that is proven to be effective.

Visual loss can have a devastating effect on quality of life. The Macular Society website (2) provides information on the effects of AMD, summarised here.

AMD causes central visual loss leading to gaps on items on which the eye naturally focuses such as words on pages, bus numbers, faces and television. Vision becomes distorted. Colours can fade, and adaptation to dark can be impaired. Driving may become impossible, which may lead to isolation. Visual impairment

increases the risk of falls and injuries, and leads to depression and social isolation. Getting out and about safely, for example to go shopping, may become difficult. Independent living may become impossible. Sight loss is a leading cause of suicide amongst older people (3).

Treatment of wet AMD with anti-VEGF drugs (ranibizumab, bevacizumab and aflibercept) has revolutionised the care of people with wet AMD, but puts great pressure on ophthalmology services because patients need injections every month, at least initially. The Macular Society is aware that the load on ophthalmology clinics has led in some areas to delays in patients being first seen. This is highly undesirable because wet AMD can rapidly lead to visual loss. Treatments that reduce progression from early AMD to wet AMD would reduce the need for anti-VEGF injections.

Unfortunately no treatment has yet been proven to be effective in dry AMD, and most patients diagnosed with dry AMD will leave the clinic with the message "monitor your vision and come back if you notice any change" – the aim being to detect the development of wet AMD in time for drug treatment. No treatments (other than visual rehabilitation services) are approved in the NHS for the treatment of early AMD (drusen and RPE changes) (to prevent or delay progression, or restore function) or atrophic dry AMD (to preserve or restore vision). There is good evidence from the Age-Related Eye Disease Study (AREDS 2) trial that nutritional supplementation can slow progression over 5 years from early to advanced AMD by about 25%. The supplements are not available through the NHS but can be purchased at around £60 for a month's supply.

There is currently no treatment for Stargardt's disease.

Many new treatments are being suggested. Our scoping searches have identified over 30 studies of treatment of dry AMD. About half were drug studies. The remainder include stem cells, genetic therapies, laser treatment, nutritional or herbal supplements, electrotherapy, ozone, light, retinal implants, rheohaemapheresis, and implantable telescopes. Some are used in only one or two countries. Few have been systematically reviewed. Most reviews in AMD have been of treatment of wet AMD.

Some treatments may be diffusing into private medicine. Others are appearing in "alternative medicine", such as "Airnergy" ("improvement in vision of up to 60%" by using "energised air") (4). Patients desperate for a treatment may seek help from non-evidence-based sources. A rigorous review would as a by-product, provide information on treatments which would be put on the Macular Society website in order to help people with AMD make more informed decisions.

We need clinical trials but we need to prepare for those by a rigorous review of the evidence to identify the treatments that should be prioritised for inclusion in trials.

Why is research needed now?

NICE has started the two-year process of developing a clinical guideline for AMD. A scoping meeting was held in April 2015, with August 2017 given as the provisional date for release of a guideline. The scope for the NICE guideline (5) notes that there are currently no proven treatments for dry AMD (Para3.1) and that;

"*Those with geographic atrophy will receive only limited treatment consisting of low vision aids, psychological support and advice*."

Geographic atrophy is advanced dry AMD.

NICE is correct in saying that there are no treatments for dry AMD that are currently proven to be effective. However, we think there are treatments emerging with efficacy as yet unproven but with sufficient evidence to justify trials. Our aim is identify the most promising ones. The NICE scope says that "*experimental treatments for dry AMD will be excluded from consideration in the guideline".*

The scope for the NICE guideline specifically excludes retinal dystrophies, of which Stargardts is the most common. The review we propose would complement the review that will underpin the NICE guideline, by examining experimental treatments with the intention of identifying those which look promising enough, with sufficient evidence, to justify primary research by the NIHR programmes.

Overlap will be minimised. Our review would not cover the following topics which NICE has indicated will be addressed in the guideline;

- Smoking cessation
- Diagnostic technologies including screening for AMD
- Monitoring and review
- Rehabilitation (called "reablement" in the final scope from NICE). This will include devices such as the Argus "bionic eye".

The Royal College of Ophthalmology guidelines (6) also cover some of these topics.

Aims and objectives

Aim: to carry out a systematic review of emerging treatments for dry AMD, covering all stages from early drusen to late geographic atrophy, and for Stargardt's disease. The review will identify the most promising treatments for HTA trials or EME research.

Research Plan

We expect to identify some trials, but will also include observational studies, since the natural history can be used as a comparator in some groups given long enough follow-up. For example, in patients with indistinct drusen at baseline, almost 20% had developed late AMD after 5 years (7) (Yang 2007, Blue Mountain study).

Search strategy: last 10 years only, no restriction by study design. MEDLINE, Embase, all sections of the Cochrane Library, Web of Science. Medline for studies published in full and Embase for conference abstracts, for emerging studies not yet published in full. Clinical trials databases for ongoing research.

We will use English language only but will search on all languages to assess the volume of non-English studies and origins. Some may have English abstracts. Even though we may not be able to translate, for example, studies in Chinese or Japanese, we should at least be aware of their existence. Scoping searches show that most studies in AMD come from (in order) USA, UK, China, Germany, with many of the Chinese and German papers published in English. Searches will be carried out of research database to identify trials in progress.

The search terms used in the scoping searches were as follows;

1. (dry adj3 age-related macular degeneration).tw.
2. (early adj3 age-related macular degeneration).tw.
3. (intermediate adj3 age-related macular degeneration).tw.
4. ((early or intermediate) adj3 (AMD or ARMD)).tw.
5. (nonexudative adj3 age-related macular degeneration).tw.
6. (non-exudative adj3 age-related macular degeneration).tw.
7. ((nonexudative or non-exudative) adj3 (AMD or ARMD)).tw.
8. geographic atrophy.tw.
9. (atrophic adj3 (age related macular degeneration or AMD or ARMD)).tw.
10. stargardt*.mp.
11. (therap* or treat* or intervention* or trial).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. 12 and 13

This will be refined in the light of experience. For example, some studies do not mention dry AMD anywhere in title or abstract, but use “geographic atrophy”.

Other terms will be added based on how retrieved studies were indexed, such as” non-neovascular” AMD. We will check references of retrieved studies. Some studies might be in people without AMD at baseline. We might re-run the search dropping the terms for treatment or therapy but would test

inclusion of the terms 'prevent or delay progression'. Some studies use the term 'various degrees of severity' which could also be added.

Searches will be run on named therapies.

The criteria for study inclusion in the systematic review are as follows:

Intervention	Any interventions which aim to preserve or restore vision in dry AMD. Our clinical experts and advisory group will be asked to identify treatments in development.
Participants	People with a confirmed diagnosis of dry AMD
Primary outcomes	Primary outcomes will include those that matter to patients: visual acuity, contrast sensitivity, macular sensitivity, adverse effects of treatment, adherence to treatment, reading speed, ability to drive, health-related quality of life, progression of disease.
Secondary outcomes We prefer visual outcomes but since progression progression of dry AMD is slow, it could be years before a trial could show that. Therefore, some intermediate outcomes can be accepted if there is good evidence that they are strong predictors of subsequent visual outcomes.	These will include changes detectable by investigation if they are reliably predictable of progression of disease, provisionally including; - Rod function may not correlate with visual acuity as central visual acuity, as measured using visual acuity charts, depends on foveal function, and the fovea is cone rich. Rod function though is one of the earliest abnormalities detected in people that will later develop geographic atrophy in AMD. - Macular pigment density, because it appears to be protective - Macular function as measured by micro-perimetry. - RPE thickness. - Autofluorescence - Drusen volume
Design	Ideally randomised controlled trials (RCTs) and controlled clinical trials (CCTs) with a concurrent control group. However observational studies will also be used when duration of follow-up is long enough to use natural history as a comparator.

Studies will be selected for inclusion through a two-stage process using predefined criteria. The full literature search results will be screened independently by two reviewers to identify all citations that may meet the inclusion criteria. Full manuscripts of all selected citations will be retrieved and assessed by two reviewers against the inclusion criteria. Studies published as abstracts or conference presentations will only be included if sufficient details are presented to allow an appraisal of the methodology and the assessment of results to be undertaken. The details may come from previously published protocols. An inclusion flow-chart will be developed and used for each paper assessed. Any

disagreements over study inclusion will be resolved by consensus or if necessary by arbitration by a third reviewer.

Exclusions: We will not review studies on interventions being reviewed in the NICE guideline process. These include smoking cessation, diagnostic technologies, monitoring and review, and rehabilitation support. We will not review lampalizumab since it is already being trialled.

Basic science studies will in effect be excluded by the focus on the outcomes listed above.

Trials should have a minimum of 10 patients per arm. Observational studies should have a minimum of 20 patients. One exception to these numbers will be stem cell and related interventions where smaller numbers will be accepted, especially in Stargardts, and particularly when the small studies report on the same treatment in different locations, so that results can be pooled.

Older reviews will be excluded if superseded by more recent ones.

When there is a recent good quality systematic review, we will not review the primary studies.*Data extraction and quality assessment.*

The extraction of studies' findings will use a pre-designed and piloted data extraction form to avoid any errors. Data will be extracted by one reviewer and checked by a second. The methodological quality of all included studies will be appraised using recognised quality assessment tools - Cochrane risk of bias tool for trials (8) and the Newcastle Ottawa checklist (9) for observational studies.

Any disagreements between reviewers will be resolved by consensus or if necessary by arbitration by a third reviewer.

Data synthesis

Studies will be synthesized through a narrative review with tabulation of results of included studies. If possible the results from individual studies will be synthesized through meta-analysis, with causes of heterogeneity of results examined, but our scoping searches suggest that there will be little if any opportunity for meta-analysis. The specific methods for meta-analysis and for the detection and investigation of heterogeneity would depend upon the summary measure selected.

Results

Interventions will be categorised as follows, with groups 4 and 3 being of most interest;

1. Research still at basic science stage, such as in vitro, including cell work, or methods of carriage of gene therapies into cells using viral carriers

2. Treatments with some evidence of efficacy in animal studies but not yet tested in humans. Such research would fall within the remit of the MRC Translational Research Programme.

3. Treatments where proof of concept in humans has already been achieved but where research is needed to evaluate clinical efficacy, and which might be suitable for the EME Programme.

4. Treatments where there is evidence that shows they can be effective, but where further research is needed to establish the clinical and cost-effectiveness for the NHS in comparison with the current best alternative. Such research falls within the remit of the HTA Programme.

5. Interventions where there is sufficient evidence that they are not effective, so that no further research is justified.

Scoping searches have found studies of many interventions. For many treatments, there are only single studies. We will develop a system to reflect the strength of evidence, based on factors such as;

- Number of studies
- Hierarchy of evidence – RCTs, non-randomised studies with control groups, case series
- Numbers of patients
- Quality assessment of studies

For identifying the interventions that seem most worthy of further research by the EME or HTA Programmes, we will also take into account;

- Effect size – how great an effect on preservation or restoration of vision
- Safety and tolerability issues
- Estimates of costs, if available
- Data on research currently underway.

Health technologies being assessed

Our scoping searches have identified over 30 studies of treatment of dry AMD. About half were drug studies.

Treatment of dry AMD

The drug treatments fall mostly into three groups;

- Treatment aimed at preserving the photoreceptor cells and the retinal pigment epithelium
- Prevention of oxidative damage
- Anti-inflammatory agents

The drugs that have or are being tried or suggested used include lampalizumab (being trialled), nucleoside reverse transcriptase inhibitors (NRTIs) (as used in HIV), glatiramer (Copaxone) (used in MS), statins, bevacizumab eye drops, cyclodextrin eye drops, inhibitors of lipofuscin and A2E

accumulation – fenretinide and ACU-4429, complement inhibitors (POT-4, eculizumab, ARC-1905, FCFD4514S, neutrazimab), doxycycline, hydroxychloroquine, fluocinolone, sildafenil, dobesilate, anecortave, trimetazidine, MC-1101, ciliary neurotrophic factor, tandospirone, brimonidine implant, RN6G(prevention of amyloid accumulation) and OT-551.

Cell technologies include transplantation of human embryonic derived stem cell retinal pigment epithelium, RPE cells from people with AMD, and induced pluripotent stem cells (iPSC) from skin cells.

Physical treatments include brachytherapy, other forms of radiotherapy, ozone, transpalpebral electrotherapy, implantable telescopes, rheohaemapheresis, Oraya (though it is mainly used in wet AMD), light (study underway in Bristol). Nutritional interventions include the AREDS2 supplement (of proven value so will not be included in this review), zinc alone, anti-oxidants alone (lutein and zeaxanthin), fortified hens eggs, enriched buttermilk drink (trial underway in Holland), omega 3 supplements and herbal supplements such as saffron.

Other interventions include retinal implants/transplants.

Treatment of Stargardt disease

The main interventions seem to be gene replacement and stem cells. Two trials are underway.

Dissemination

We will aim to present our results at an ophthalmology conference, partly to aid dissemination, but more to get feedback on what people think the research priorities are, and whether we have missed anything important.

Our results will be published in the HTA monograph series, but a shorter summary will be submitted for publication to an open access journal, either BioMed Central Ophthalmology or BMJ Open.

An important dissemination route will be via the website of the Macular Society, where we will create a version searchable by intervention in accessible language, checked via the Flesch Ease of reading tool available via http://www.readabilityformulas.com/free-readability-formula-tests.php . This will enable any patient or relative who has heard about a treatment (for example via the Internet) to check the evidence base for it.

The Macular Society has an annual meeting and we will present our results there. We will also include a summary in the MacSoc annual publication, Research Digest.

Cochrane reviews

Conversion of some sections of review into Cochrane reviews would further aid dissemination. We have had discussions with the Cochrane Eyes and Vision Group.

As stated earlier, our main aim is to identify the 4-6 interventions that appear ready for further primary research by the HTA Programme (or the EME one). We had considered producing Cochrane reviews for each of these, but the HTA Programme did not agree funding. The evidence might come from observational studies with natural history as the comparator, rather than RCTs. The Cochrane Eyes and Vision Group will consider reviews of observational studies where these provide sufficient evidence to support the development of a trial.

Timetable

The timelines below assume that the project would start in June 2016. The project will take 12 months, and will involve the following stages;

June and July 2016: literature searching and filtering.

August 2016 to November 2016: systematic reviewing

November 2016: workshop for patient representatives and MacSoc staff

January 2017 – progress report to NETSCC

January to April 2017: writing draft report

April 20th 2017. Second workshop. Presentation of draft report to patient representatives, the Macular Society Research Committee and MacSoc staff.

May to July 2017: writing of final report and submission to HTA programme by August 11th

September 2017 (estimate): receipt of HTA programme referees comments and revision of report.

Project management

Norman Waugh will be PI and would coordinate the project.

Emma Loveman will coordinate the work of the Effective Evidence team.

There will be three project meetings of the Warwick and Effective Evidence teams, and the MacSoc research manager, in Warwick Medical School. The first will be in October 2016 to review the volume and designs of retrieved studies, and to prepare for workshop 1. The second will be in January 2017 to review progress and resolve any problems. The third would be in March2017 to review draft report and prepare for workshop 2.

Patient involvement

Statement from the Macular Society

The Macular Society has been supporting people with macular conditions like age-related macular degeneration (AMD) for over 25 years. We offer information and support and we fund research to find a cure. However our funds are limited and are insufficient to fund large clinical trials. We would like to encourage major research funding organisations such as the HTA Programme to commission new research. We are very aware of emerging treatments and of the desperate need for effective treatments amongst our members. We are also aware of a good deal of “misinformation” about treatments of unproven value publicised on the Internet.

The Macular Society supports this bid, and if successful, our roles will include recruiting patients for an advisory panel, providing advice from ophthalmologists and others on our Research Committee, arranging a workshop to review the draft report and provide comments, helping write the final report (our research manager and one person with macular disease will be co-authors) and then publishing the evidence on our website as a service to members looking for reliable and unbiased information on treatments for dry AMD.

Our research manager will be actively involved in the project.

This bid is being led by Norman Waugh, who is a patient member of the Macular Society.

Justification of costs

The costs of the two researchers in Warwick Medical School (NW and PR) take into account the type of evidence expected, which means that a broad search with no filters will be required, followed by time-consuming checking by two people independently for inclusions. Norman Waugh will coordinate the project and write the draft and final reports. Pam Royle will do all the searches, obtain the studies and assist with reviewing.

The costs of the systematic reviewers in Effective Evidence are based on;

- the number of interventions that we expect to review

- an estimate of the total number of studies based on scoping searches

- a consideration of the types of study and the time cost of quality assessment. Many will be observational studies rather than randomised trials.

We have also included travel costs based on train fares in April 2015 upgraded by 5% for future price increases.

The costs for the Macular Society include time from the research manager, and support costs. The support costs comprise mainly travel costs for the patients and two ophthalmologist advisors (assuming one from London and one from Southampton). They also include catering costs for the two workshops, which will be held at the headquarters of the Macular Society in Andover.

Expertise in team. The Warwick and Effective Evidence teams have considerable academic expertise in systematic reviewing, including in eye problems, and members of the team have authored over 50 HTA monographs, often to support NICE appraisals. The Macular Disease Society input will include research awareness, patient perspectives and preferences.

Four members of the team have had past involvement in the HTA Prioritisation processes as panel researchers (writing vignettes), literature searching, panel senior lecturer, and chair of CETPG. Expert ophthalmological advice will be provided in the first instance by Professor Noemi Lois, who is a long-standing collaborator with Norman Waugh and Pamela Royle, going back to the days when all three worked in Aberdeen. Professor Lois has helped with six ERG reports for NICE appraisals, in four of which Norman Waugh led the ERGs. She has also been a collaborator with the Warwick team on a technology assessment report on laser photocoagulation for diabetic retinopathy, published as an HTA monograph. She has led the bid for the DIAMONDS project (HTA 13/142 Laser treatment for clinically significant diabetic macular oedema) in which Warwick Evidence is collaborating.
It is anticipated that further advice will be obtained from ophthalmologists on the Macular Society Research Committee.

Value for money

The total cost of the proposed review is considerably less than the cost of most systematic reviews commissioned by the HTA Programme. This is partly because much of the reviewing work would be done by members of Effective Evidence who are very experienced and efficient, and whose costs do not require the overheads imposed by universities. Similarly, the contribution by the research manager at the Macular Society would not incur significant overheads.

References

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http://www.macularsociety.org/

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4. Airnergy. http://airnergy-oxygen-therapy.co.uk/pages/Home.htm

5. NICE guideline development. http://www.nice.org.uk/guidance/indevelopment/gid-cgwave0658

(At the time of writing this bid, the final scope had not been put on to the NICE website and was not in the public domain. We used the draft version issued to the Macular Society as a consultee.)

6. The Royal College of Ophthalmologists Age-Related Macular Degeneration: Guidelines for Management September 2013.

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