Appendix D – Clinical specialist statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Aflibercept solution for injection for the first line treatment of wet age-related macular degeneration (AMD)

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: **Robert Johnston**

Name of your organisation **Gloucestershire Hospitals NHS Foundation Trust**

Are you (tick all that apply):

YES a specialist in the treatment of people with the condition for which NICE is considering this technology?

YES a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

NO an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?

I am one of the Revalidation Leads for The Royal College of Ophthalmologists but not specifically in relation to age-related macular degeneration

- other? (please specify)
- I am the Medical Director of Medisoft Limited that is the provider of the most widely used ophthalmology electronic medical record system in the UK and provides detailed audits of anti-VEGF clinical outcomes

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Current NHS practice for wet age-related macular degeneration
Wet age-related macular degeneration has been almost universally treated in the NHS with intravitreal injections of ranibizumab since implementation of NICE TA155. The vast majority of UK centres use a PRN treatment regime after an initial loading phase of 3 monthly injections, despite the landmark trials for this drug using monthly injections for 2 years. The intended follow up frequency is monthly until the disease is judged to be stable. At each follow up assessment intravitreal injections may or may not be given guided by clinical examination and optical coherence tomography (OCT) scanning of the retina. On average real world clinical outcomes suggest patients in the UK can achieve good clinical outcomes when receiving 5-6 injections in year 1 and 3.5-4 injections in years 2 and 3 but many centres have struggled to create sufficient capacity to follow up patients with the required frequency.

There is also considerable geographical variation in patients considered eligible for ranibizumab treatment, with many centres rigidly imposing the NICE TA155 visual acuity criteria of 6/12 to 6/96 and other centres following The Royal College of Ophthalmologists guidance to offer treatment to all eyes with vision better than 6/96 if clinically indicated. In my own centre (Gloucestershire) the below graph stratifies patients by baseline visual acuity.
Please note that 16.5% of eyes treated in Gloucestershire could be considered outside NICE TA155 guidance at baseline. When judging the success of treatment the landmark clinical trials focus on mean improvement in vision, which is important to prove the efficacy of a drug but as the below graph illustrates mean improvement in vision in age-related macular degeneration is mostly a function of how poor the

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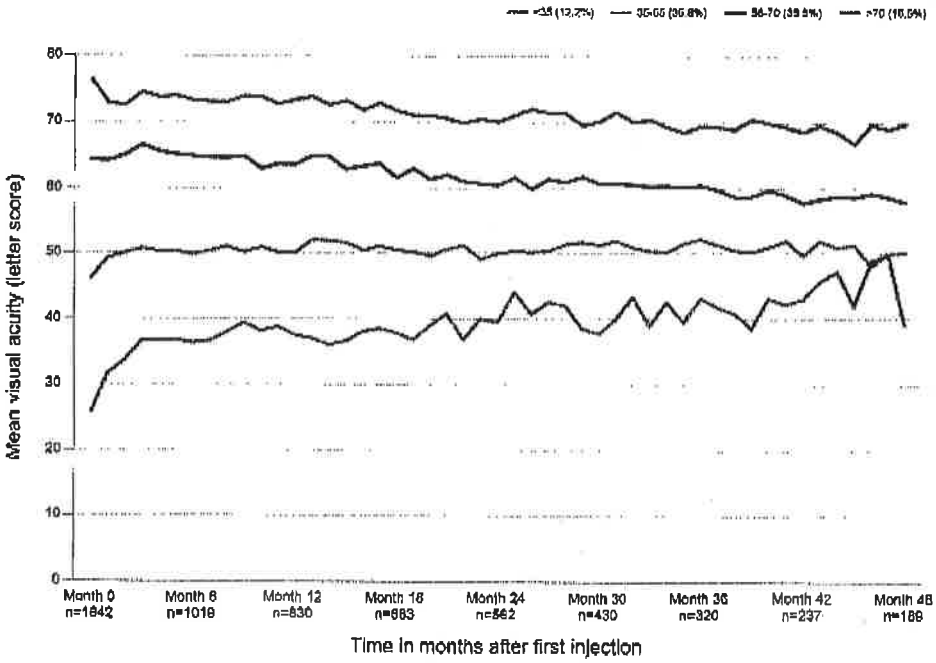
visual acuity is at baseline. The eyes with fewer than 35 letters at baseline gained the most vision but the vision was, on average, still poor at 1 year and beyond. It is, however, the patients in the 70 letters or more group who can still read and drive with the affected eye, even though such eyes may on average lose a few letters over time. In my opinion these patients are a subgroup who have perhaps the greatest benefit from anti-VEGF drugs but are not recognised within current NICE criteria as they were excluded from the early landmark trials. Eyes with good vision at baseline are often "second-treated eyes" detected during follow up of first eyes and such eyes are always excluded from clinical trials. The natural history of 'wet' age-related macular degeneration is very poor with the vast majority of eyes losing 20-30 letters over 2 years compared to 5 letter loss in our treated cohort at 4 years.

Mean visual acuity over time according to baseline visual acuity category (Gloucestershire runs an entirely electronic service and the below graph represents all our patients/eyes treated since 2008). The below graph is not yet published but 2 year results are published and other centres have published similar findings.



The intravitreal injections are universally administered in secondary care, traditionally by doctors but there are increasing numbers of nurses trained to perform intravitreal injections. Many centres utilise non-medical staff (nurses and optometrists) for assessing patients and making treatment decisions and many use virtual review of data captured by technicians. Pilot schemes are being established where community optometrists can capture the OCT images and visual acuity data and electronically send this to the hospital for a follow up treatment decision.

The Royal College of Ophthalmologists Guidelines for the management of Age-Related Macular Degeneration from 2009 are in the process of being updated. They

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were developed based on a thorough literature review using Pubmed, Cochrane Library and personal collections as the source. The main point on which they differed from NICE TA155 guidance was in supporting treatment of all eyes with active disease if the visual acuity is better than 6/96, regardless of whether it was better than 6/12 vision..This view is supported by more recent RCT data (the CATT trial had a better vision cut off of 20/25 (6/7.5) and the IVAN trial did not have a better visual acuity cut off) and several real-world case series, including the data from Gloucestershire shown in the graph above.

No UK guidelines currently exist for aflibercept but these are likely to be included in The Royal College of Ophthalmologists' updated guideline later this year.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Advantages and disadvantages of aflibercept for age-related macular degeneration

Aflibercept given in a loading phase of 3 injections following by fixed injections every 2 months in year 1 and a 'capped' PRN regimen in year 2 has shown comparable visual acuity results to ranibizumab in the VIEW 1 and VIEW 2 trials.

This potentially has the advantage of reducing the burden on patients, carers and healthcare providers by reducing the numbers of visits to hospital during each year of follow up, whilst achieving similar visual acuity outcomes. If the drug is given at fixed intervals, particularly in the first year, then a simplified care pathway is possible as patients would not require OCT scans at every follow up visit after the loading phase.

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There is no clinical consensus yet about how aflibercept will be used in the 'real-world'. Although departments may choose fixed dosing in the first year to allow predictable service delivery in second and successive years it is likely (I think certain) that clinicians will adopt a PRN approach to assessment and treatment.

In the VIEW studies patients were in fact followed monthly and in the second year of follow up a significant number of patients received aflibercept more often than every 8 weeks. The logical conclusion of this is that if a decision is made not to inject a patient at any visit then they would require their next follow up visit in 4 weeks but that if an injection was administered it may be possible to extend the follow up to 8 weeks.

Wet AMD services have in fact also turned into screening services for high-risk fellow eyes as almost all centres will routinely perform an OCT scan of both eyes at each visit. Second treated eyes are therefore often detected earlier with on average 10 letter better vision than first treated eyes and this benefit is maintained in the long-term (unpublished data) after treatment is initiated. This benefit could potentially be lost if the care pathways for aflibercept are 'injection only' and do not include regular OCT scanning.

The comparison of the advantages of aflibercept verses ranibizumab is therefore complex and will depend on a balance of comparing the costs of the whole care pathway, the impact on patients and carers and the drug cost. In the first year a fixed regimen of 7-8 injections with aflibercept will require 5 fewer hospital attendances but will result in 2-3 more injections than are given in UK clinical practice at present with ranibizumab.

The VIEW trial with aflibercept, in common with the ANCHOR and MARINA trials with ranibizumab did not address the benefits of the substantial cohort of patients with vision better than 73 letters (6/12 at baseline), although the CATT and IVAN trials and case series suggest that anti-VEGF in these subgroups is particularly beneficial.

There is much debate about the systemic adverse event rates with the different anti-VEGF drugs but aflibercept and ranibizumab appear comparable in this regard.

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Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Equality and diversity
I am not aware of any specific problems in this area.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Additional sources of data
My own service in Gloucestershire probably has the most complete data on all patients treated with anti-VEGF drugs as the service has been entirely electronic using an Electronic Medical Record (EMR) since inception.
Mr Adnan Tufail from Moorfields Eye Hospital is the principal investigator for a study collating anonymised clinical outcomes data on a very large patient cohort having anti-VEGF therapies (>12,000 patients and 100,000 anti-VEGF injections) in the UK from centres using the same EMR. This provides the best 'real-world' data on clinical outcomes in the UK, or internationally, for patients with age-related macular degeneration. The data have been presented at scientific meetings and are in preparation for peer reviewed publications.

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All data were extracted from a single electronic medical record system that is widely used in NHS eye departments. I am the Medical Director of the company providing the EMR.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Implementation

Over the last 4 years since NICE TA155 all NHS eye departments have expanded dramatically to cope with providing anti-VEGF services for patients with age-related macular degeneration. They should already have a trained workforce appropriate equipment and staff, although many sites still do not have sufficient capacity to meet current and future demand. Switching some or all of their patients to aflibercept is likely to reduce the burden on patients, their carers and healthcare providers compared with current therapies as fewer visits are required, particularly in the first year of treatment.

It is clear that the advent of anti-VEGF therapies for age-related macular degeneration have turned a once rapidly visual disastrous disease into a chronic disease and the cohort of patients requiring ongoing monitoring is growing every year. This will continue regardless of whether ranibizumab or aflibercept is used and therefore plans for continued expansion of AMD services urgently need to be made.

In my view innovative ways need to be found to manage lower risk, more stable patients who have not required injections for several months outside the hospital environment. The graph from my hospital information department below shows the scale of the problem facing all eye services for AMD.

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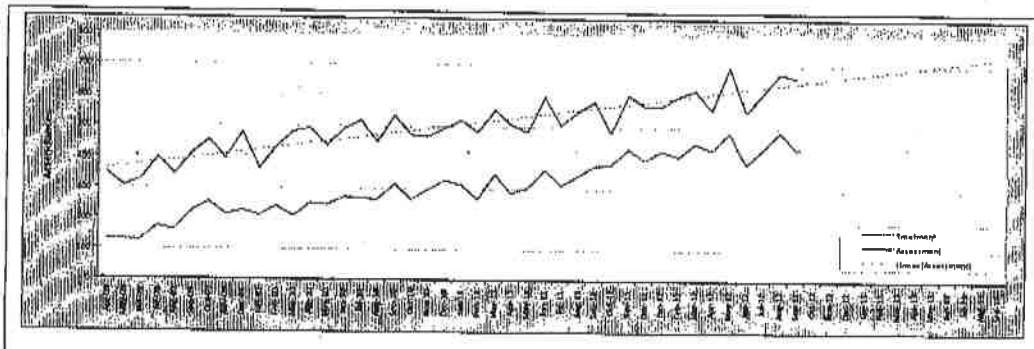

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