Professional organisation statement template

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: [redacted]

Name of your organisation: The Royal College of Ophthalmologists

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ✓
- 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.)?

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.

Retinal Vein Occlusion (RVO) is presently managed differently dependent on whether the vascular occlusion involves the central retinal vein (CRVO), or a branch of the retinal venous system (BRVO). In addition, there are differences in management strategies dependent on whether the goal is to control neovascularisation and prevent vitreous haemorrhage and/ or rubeotic glaucoma, or in preventing / reversing visual loss due to macular oedema. For the purposes of this appraisal I will restrict my comments to the management of macular oedema due to RVO.

Macular oedema due to BRVO has traditionally been managed with a period of observation. This provided time for blood to clear from the macular region allowing correct interpretation of fundus fluorescein angiography (FFA) necessary to plan and deliver laser photocoagulation treatment effectively. The period of observation also allowed the clinician to identify any cases that spontaneously improve. If at 3 months macular oedema was still reducing acuity to a level between 6/12 and 6/60, in the absence of significant foveal ischaemia, then macular grid laser photocoagulation has been proven in a large randomised controlled trial (RCT) to be an effective treatment in up to 30% of cases and is widely practiced. In contrast, macular oedema due to CRVO irrespective of the VA, fails to respond to grid laser (although there is a trend to treatment benefit in younger patients) and is therefore rarely used. Intravitreal steroid injections have been used widely over the past decade in an attempt to treat macular oedema due to both BRVO and CRVO in the absence of any other useful treatment. The most commonly used formulation is intravitreal triamcinolone acetonide (IVTA) (preserved triamcinolone) in the form of off label use of Kenalog (Squibb) which is unlicensed for this indication. Although 4mg IVTA has been commonly used there is much variation in practice in terms of dosage (1mg – 20mg), timing (early versus delayed use in laser resistant cases) and frequency (3 monthly/ 6monthly etc). The short-lived benefit of this form of IVTA along with the significant risk of raised intraocular pressure requiring treatment, cataract formation

and sterile inflammatory endophthalmitis has led to a fall in its use of the past 2-3 years. However, there is some renewed interest in its potential use in CRVO following publication of the SCORE–CRVO trial (SCORE study report 5. Arch Ophthalmol 2009; 127:1101-14). In this RCT a specially prepared preservative-free formulation of IVTA was used (TRIVARIS, Allergan) and did show some sustained benefit with an acceptable safety profile for the 1mg dose. Unfortunately, this preparation is commercially unavailable and differences between it and Kenalog in terms of preservatives, particle size and pH limit any direct comparison between Kenalog and the SCORE data.

Over the past few years anti-vascular endothelial growth factor (anti-VEGF) intravitreal injections have been used increasingly to treat macular oedema due to both BRVO and CRVO. Most commonly, this has been with the use of off-label use of intravitreal bevacizumab (Avastin). This practice varies from unit to unit dependent on local pharmacy approvals, and there is significant variation in dosing schedules and no universally agreed treatment protocols. Although some case series have shown benefit in treatment of macula oedema in RVO there is a lack of RCT evidence of efficacy, or safety, and long-term data.

Ranibizumab 0.5mg (LUCENTIS, Novartis) is another anti-VEGF agent which has recently reported significant benefits in RCTs for BRVO and CRVO macular oedema (Ophthalmology 2010; 117:1102-1112 and Ophthalmology 2010; 117:1124-1133). The reported significant visual gains in 50-60% of cases are the most impressive results to date for management of macular oedema in RVO. Ranibizumab 0.5mg has recently received regulatory approval for use in RVO in the US but EU approval is not expected until 2011. There is minimal use of ranibizumab for RVO in NHS units in the UK at present but a growing use in the independent sector.

Alternative therapies such as radial optic neurotomy, arteriovenous sheathotomy and laser induced chorio-retinal anastomosis have all been tried with varying reports of success but are infrequently used in the UK. These are only experimental at the present.

The technology under appraisal, dexamethasone biodegradable implant (Ozurdex, Allergan) has only very recently received EU approval for use in RVO and at present is rarely used in the NHS. However, there is a growing interest for its use in both BRVO and CRVO macular oedema. The technology is unsuitable for use in primary care settings and should be delivered by an ophthalmologist experienced in medical retinal disorders.

Patients with significant retinal ischaemia (as evidenced by relative afferent pupil defect, significant non-perfusion on FFA or other ancillary tests) were specifically excluded from the GENEVA trials of Ozurdex and are unlikely to benefit from the technology. Patients with significant macular ischaemia are likewise unlikely to benefit and should be excluded from treatment.

The latest guidelines on management of RVO from the Royal College of Ophthalmologists (unpublished guidelines, in confidence attached) specifically recommend Ozurdex as first line treatment for CRVO macular oedema for patients with vision of 6/9 or worse and to be considered as first line management in patients with BRVO macular oedema of 6/9 or worse as an alternative to macular grid laser.

As can be seen from the guidelines, ranibizumab is foreseen as a potential first line alternative to Ozurdex but as yet is unlicensed.

The attached guidelines include a description of the methodology used in development and specifically reference evidence underpinning the recommendations.

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?

The introduction of Ozurdex will be a significant step forward in the management of patients with RVO in the NHS. Previously, care was centred around identifying modifiable risk factors, dealing with and preventing ischaemic complications and, only had limited treatment options with varying outcomes and limited evidence base for managing macular oedema (except for the use of grid laser in BRVO). With the new technology there will be a significant shift in emphasis on treating macular oedema with proven efficacy. This will require improvements in referral pathways and treatment algorithms (see RCOphth guidelines) and extra provision for increased frequency of intravitreal injections.

Although these patients are already attending ophthalmic units for monitoring of their condition there will be an increase in frequency of visits up to 4x and increased diagnostic input with up to 2x increase in FFA and 4x Optical Coherence Tomography (OCT) assessment in the first 12 months . Many of the early cases are anticipated to be given in theatre conditions but it is highly likely that there will be a shift to dedicated injection rooms as utilized in the management of AMD intravitreal injections. The technique for intravitreal injection is more complex than with other commonly performed intravitreal injections due to the larger gauge delivery system but only limited training and a short learning curve is required for the trained ophthalmologist. Many of the ancillary tests such as OCT assessment of retinal thickness and FFA are routinely used in the care of RVO patients already.

Certain subgroups of patients with significant retinal and / or macular ischaemia are unlikely to improve acuity and are not recommended for treatment with Ozurdex. Although not specifically contraindicated, the use of the Ozurdex implant should be with caution in those patients who have persisting uncontrolled high intraocular pressure. Patients with macular oedema of greater duration than 12 months were excluded from the GENEVA study and thus it is debatable whether they will benefit from the Ozurdex technology. Subgroup analysis from the study showed an improved benefit from earlier treatment.

Recommended treatment algorithms are available in the RCOphth latest guidelines (unpublished guidelines, in confidence attached) and are summarised here for the use of Ozurdex.

In the case of BRVO macular oedema, Ozurdex should be considered as first line treatment for patients with visual acuity of 6/9 or worse with central retinal thickness >250 microns as an alternative to grid laser. The follow up scheduling has not been precisely determined and will vary from patient to patient not only with regard to monitoring of macular oedema but also with regard to risk of developing ischaemic complications such as retinal new vessel formation or rubeosis, and/or detection of adverse events. It is anticipated that there may be up to monthly assessments for the first 6 months, followed by 3 monthly, looking for signs of benefit from Ozurdex and known risks such as raised intraocular pressure. Retreatment will be considered if macular oedema (> 250 microns) persists and vision is 6/7.5 or below. The exact timing of retreatment is uncertain and will vary from patient to patient. It is likely to be used somewhere between 4 and 6 monthly. It must be remembered that we only have an evidence base presently for 6 monthly dosing but that the peak benefit of the treatment is between 3 and 4 months and thus it is likely that ophthalmologists will use the treatment at these shorter intervals to maintain an improvement in visual acuity. Discontinuation of the Ozurdex treatment should be considered if there has been no therapeutic benefit in terms of visual acuity or if uncontrolled raised intraocular pressure (or other complications) ensues.

In the case of CRVO macular oedema, Ozurdex should be considered as first line treatment for patients with visual acuity of 6/9 or worse with central retinal thickness >250 microns**.** The follow up schedule and discontinuation rules will be similar as for BRVO outlined above although the risk of conversion to ischaemic complications is greater and thus more frequent follow up is necessary in certain patients.

The trial design very well reflects the typical patient presenting with RVO in the UK. It is likely that in the case of BRVO given the efficacy of the Ozurdex and proposed guidelines that patients will be treated earlier than the 3 month initial duration period used in the studies. The primary outcome used in the GENEVA trial was time to reach 15 letter gain but this is not as useful as mean gain in visual acuity and percentage of patients reaching 15 letters or more improvement in LogMAR visual acuity which were secondary outcomes presented in the data.

It would be useful to know the percentage of patients improving to commonly predefined thresholds such as 6/12 (driving equivalence) or 6/60 (partial sight registration). The long term outcomes for vision and complications are unknown. The available data gives us information for 12 months at 6 monthly dosing but it is highly likely that dosing will be more frequent (eg 4 monthly) and longer (eg 24 months). The most concerning side effect is the risk of raised intraocular pressure (IOP). This is presented in a multitude of different ways within the data but I find the most useful is the number of patients requiring at least 1 medication to lower the IOP after the

Ozurdex injection. This is approximately 20% after one injection and rising to 25% after a second 6 monthly injection. As this raised IOP is manageable with topical medication and reversible in the majority of cases then this appears an acceptable safety profile. However, there is a >1% risk of developing IOP to a level where intervention with glaucoma surgery is required after 2 injections. Once again this is an acceptable safety profile given the efficacy of the treatment and the lack of proven alternatives. Reassuringly, the data indicates that the percentage of patients, and the course of raised intraocular pressure remains similar after repeated injections.
The anticipated increased frequency of dosing will need to monitor for a potential increase in IOP cases.

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.

The latest unpublished guidelines on management of RVO from the Royal College of Ophthalmologists (attached, in confidence) are a significant change from previously published UK guidelines. It is expected that the final version of RCOphth Guidelines on the management of RVO will be published by the 18th November 2010.

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)?

The patient group that may benefit from the Ozurdex technology are already attending ophthalmic units for monitoring. However, there will be an increase in frequency of visits up to 4x and increased diagnostic input with up to 2x increase in

FFA and 4x Optical Coherence Tomography (OCT) assessment in the first 12 months .With appropriate funding then this should be achievable.
The technique for intravitreal injection is more complex than with other commonly performed intravitreal injections due to the larger gauge delivery system but only limited training and a short learning curve is required. Many of the ancillary tests such as OCT assessment of retinal thickness and FFA are routinely used in the care of RVO patients already.

There will be an immediate impact on service provision and in many cases initially may be dovetailed in to already an already overstretched AMD service provision.
The expertise among ophthalmologists with interest in treating RVOs exists already.
However, staff and facilities to fulfil the general nature of the guidance may require some expansion, which should be available within the proposed 3 months.
A variation to the 3 month mandatory implementation of guidance on this technology will be unwelcome.

It is imperative that the provision and funding of service reflects the standard outlined in the RCOphth guidelines (in confidence attached).