Title/Topic: Oraya Therapy (IRay®) for Wet Age related Macular Degeneration

Date: December 2015
Oraya Therapy (‘IRay®) for Wet Age Related Macular Degeneration

1 Recommendations

Oraya Therapy (IRay®) in conjunction with anti-VEGF treatment is not recommended in Greater Manchester as part a commissioned pathway in the treatment of wet Age Related Macular Degeneration.

Oraya Therapy (IRay®) offers a means of delivering Stereotactic Radiotherapy (SRT) for patients with chronic neovascular (or wet) age-related macular degeneration (wAMD) in conjunction with anti-vascular endothelial growth factor (Anti-VEGF) treatments in an outpatient setting.

A Phase 2 clinical study has identified a reduction in the number of Anti-VEGF treatments required over 1 year with a slightly greater reduction over 2 years in a selected subgroup of patients. It does not however improve patient's visual acuity.

Although there are safety concerns regarding radiation induced changes, there does appear to be reassurance that microvascular abnormalities (MVAs) are not a concern, although longer experience is required as abnormalities can occur up to 3 years post exposure. Therefore, on the basis of currently available data, actual patient risk is unquantified.

The quantity of clinical evidence on its use is limited and the cost consequences of adoption, when compared with conventional anti-VEGF, will depend on patient selection and the cost of a commissioned service. Commissioners are strongly advised to await the outcome of a Phase 3 study, currently underway within the NHS, before deciding on commissioning this intervention.

Greater financial savings and increased capacity would be more likely to accrue from reviewing and redesigning current pathways.
2 The condition

2.1 Current management

Age-related macular degeneration (AMD) is the term applied to changes, that occur with ageing and without any other obvious cause, in the central area of the retina (macula) in people 50 years of age or older. AMD is the most common cause of blindness in the UK.

A number of treatments are approved by NICE for the management of wet AMD. These include photodynamic therapy, ranibizumab and aflibercept\textsuperscript{1,2,3,4} all of which are funded by the NHS in accordance with NICE guidance; from NHS and independent providers across GM. A NICE clinical guideline for AMD will publish in mid 2017\textsubscript{5} which may consider radiotherapy as a treatment option.

The current treatment regimens require, often quite frail elderly, patients to attend a distant hospital outpatient department for an ocular coherence tomography (OCT) scan, then be assessed monthly or bimonthly by an ophthalmologist, with an anti-VEGF being injected into the eye to arrest disease progression. Treatment is withdrawn if a person's vision gets worse and there are changes inside the eye which show that treatment isn't working. The common protocol is to review monthly and inject when required (PRN) to manage disease progression. Many sites are unable to consistently offer monthly appointments, thus patients may suffer poorer outcomes due to this of capacity. Therefore treatments which would allow extension of time between clinics and/or fewer injections would have patient, capacity and economic benefits to the system.

2.2 Demographic pressures

People who are blind or with significant sight loss (73,513 in 2011), are often unable to live an independent life, thus requiring significant care and support from health, social and voluntary care services. As the name suggests wAMD prevalence increases with years, with an ageing population this patient group will increase significantly.

The RNIB has a predictive tool\textsuperscript{6}, which estimates current and future prevalence (identified and treated disease will be lower). It is expected that GM currently has approximately 20,000 patients with AMD, of which 13,000 are over 80 years of age; with 14,000 late stage wAMD patients (potentially suitable for anti-VEGF treatment).

The RNIB data suggests that GM expected prevalence of AMD is lower than the national average, driven principally by the young Manchester population. All areas have lower than NW and England levels except Stockport and Trafford, driven by their older population.

Projections on the population impact by 2020 and 2030 vary with an average increase of 0.8% of the total population with sight loss (95,000), with many areas ‘catching up’ quicker than the average, due to demographic profiles.

2.3 Current treatment patterns

Usage and cost of anti-VEGF treatment is increasing at around 38% and 20% per annum respectively across GM. The overall treatment cost is in excess of £20m for GM – see appendix.

This indicates that 23,144 treatments were given, but only 5186 spells were recorded, due to ‘package’ pricing at the main provider (CMFT). This equates to around 3900 patients being treated (assuming ave 6 injections annually), some way short of the 13,000 the RNIB tool predicts may be suitable.

This difference could be due to access or consent for those newly diagnosed, and/or due to patients whose disease state is beyond the stage treatments can be effective.
3 The technology

3.1 Description of the technology
Radiotherapy is commonly used in oncology and its use is increasing in the treatment of non-neoplastic diseases. It is believed that it can preferentially damage dividing and fast growing cells more than normal supporting cells. There is also evidence to suggest that fractionation of irradiation greatly reduces the toxicity but preserves the DNA-damaging effects in rapidly dividing cells.

The IRay System (Oraya Therapy) is a non-invasive treatment for patients with wet AMD delivering stereotactic radiotherapy to the retina. It delivers highly targeted (4mm diameter), low dose (16, 24 Gy) x-rays to the diseased area of the eye and is intended to be a one-off outpatient procedure. It is usually delivered early within an anti-VEGF regime for treating wet AMD, it claims to reduce the need for anti-VEGF treatments, having been tested with when required (PRN) ranibizumab (Lucentis) in clinical trials.

The IRay Radiotherapy system is a CE marked medical device, approved for use in the EU. In the U.S., the IRay system is an investigational device and is not available for sale.

3.2 How the intervention might work
Clinical experience suggests that cumulative doses of up to 25 Gy cause no damage to the retina or optic nerve. As the endothelial cells in wet AMD are dividing it is possible that radiotherapy can stop the growth, inhibit inflammation and fibrosis and induce regression of new blood vessels without significant damage to the retina.

This is theoretically not dissimilar to the adjuvant treatment of cancer with chemotherapy and radiotherapy to enhance effect, reduce side effects or both. The INTREPID series of trials were designed to add this intervention to existing usual care of anti-VEGF treatment, to test this hypothesis.

3.3 Existing guidance on radiotherapy for AMD
Most professional body guidance has been recently updated, but even those published after the INTREPID trial reported in 2013 do not support Oraya Therapy (radiotherapy) as a mainstream treatment.

Cochrane review of radiotherapy in AMD from 2010, prior to INTREPID trial publication found that:

‘This review currently does not provide convincing evidence that radiotherapy is an effective treatment for neovascular AMD. If further trials are to be considered to evaluate radiotherapy in AMD then adequate masking of the control group must be considered.’

The Royal College of Ophthalmologists guidelines (Sept 2013) for managing AMD stated:

‘Thus the use of radiotherapy as an adjunctive treatment remains a viable tool as it has the potential to reduce the need for high frequency treatment rates with anti-VEGF agents in the medium to longer term.’ ‘Concluding: The role of ...... radiotherapy continue to be investigated.’

clarifying later the role of radiation monotherapy:

‘Submacular surgery, macular translocation or radiation monotherapy are not recommended for the management of nvAMD.’

European guidelines for the management wAMD from June 2014 recommend when considering for radiation therapy in wAMD:

‘At present, the only scientific argument to support the use of irradiation for the treating of neovascular AMD is the reduction in the number of retreatments necessary, but its delivery methods, efficacy and safety results are still controversial and need further investigations.’

American AMD standards from October 2014 discussed best practice treatment for wAMD. This includes all anti VEGF treatments and photodynamic therapies, but stereotactic radiotherapy as not a treatment option discussed, thus not recommended.
The most recent publication is a joint German professional societies’ opinion document from June 2015, reviewing the evidence of all radiotherapy in wAMD, including previous unsuccessful radiotherapy options.

It reviews previous radiotherapy treatments that were not effective, with some harmful. It suggests that while ‘promising’, Oraya therapy should only be offered with full written patient consent, with all patients entered into a central register and monitored for three years. They will then review their opinion in three years, after reviewing register data. (N.B. German language document translated using web based translator)

3.4 Drug licensing issues
There are two licensed anti-VEGF treatments in the UK – ranibizumab (Lucentis) and aflibercept (Eylea) and an unlicensed preparation bevacizumab (Avastin), which have comparable effectiveness and safety data, bevacizumab is substantially less expensive and requires to be manipulated to intravitreal injections.

The INTREPID trial was conducted with ranibizumab. We have contacted both manufacturers of the licensed preparations for their opinion on the licensed status of the concomitant use of their drugs with Oraya Therapy.

Novartis, have replied with details of the clinical trials and said that:

*Please be advised that the combined use of Lucentis and radiotherapy is not currently a licensed treatment regimen and, as such, is not something that Novartis can recommend.*

Bayer, have responded as follows:

*The concomitant use of Eylea with any other treatment has not been studied. Therefore any use of Eylea in this way would be considered off license and at the discretion and responsibility of the prescriber. You may wish to contact the manufacturers of Oraya and Iray Therapies, who may be able to help further.*

4 Clinical evidence
4.1 Summary of primary clinical evidence for Oraya Therapy
The Oraya Therapy device has been assessed in a series of trials called ‘IRay in Conjunction with Anti-VEGF Treatment for Patients with Wet AMD’ (INTREPID).

4.1.1 The INTREPID trial
The trial recruited 230 patients with chronic neovascular (CNV), active wet-AMD already receiving at least 3 Anti-VEGF treatments, with a lesion ≤6mm in size, with the primary efficacy outcome of assessing mean number of ranibizumab (Lucentis) injections in the first 52 weeks. Manchester Royal Eye Hospital was one of the 21 study sites.

Interventions:
All participants received a 0.5mg intravitreal ranibizumab injection at baseline. Thereafter, ranibizumab was administered on a monthly ‘when required’ basis, using defined retreatment criteria. Participants were randomised to 4 groups - 16-Gray, 24-Gray or 2 groups of sham radiotherapy; all plus ‘when required’ ranibizumab.

Results
At 12 months both the 16-Gray and 24-Gray stereotactic radiotherapy arms received significantly fewer ranibizumab injections (primary outcome measure) compared with the sham arms: mean numbers of treatments, 2.64, 2.43 and 3.74 respectively (P= 0.013 and P= 0.004 respectively vs sham).

The secondary outcome measures - mean change in visual acuity was not statistically significant, with the mean change in subfield thickness was -85.12 (p=0.0054), -68.56 (p=0.0186), and -33.46, respectively showing improvement. However the INTREPID trial
was not designed to show superiority or non-inferiority of visual acuity, and a larger phase 3 trial would be needed to draw conclusions on safety and visual efficacy, so this should be seen as indicative only.

The authors concluded that in patients with previously treated chronic, active CNV resulting from wAMD, the addition of a single dose of 16 Gy or 24 Gy SRT resulted in a reduced frequency of anti-VEGF retreatment over a 12-month period compared with anti-VEGF monotherapy, and with encouraging structural and functional outcomes. Future studies could consider a more stringent retreatment regimen, and be powered to detect a difference in visual acuity and infrequent adverse events.

4.1.2 Subgroup analysis of INTREPID

An ‘exploratory’ post hoc subgroup analysis was made which included participants with lesions ≤ 4 mm in greatest linear dimension and active leakage (macular volume > 7.4mm). The researchers hypothesised that this group of participants may respond better to stereotactic radiotherapy – radiation is known to preferentially damage proliferating cells, and it is possible that actively proliferating endothelial cells are more likely to leak fluid. 26.1% of the trial population met both of these criteria (i.e. 60 participants – 40 of whom had received active treatment).

The rationale for this analysis was ‘Appropriate case selection is important now that the device is being used commercially in Europe’, thus the influence of the manufacturer needs to be considered and thus potentially treated with caution.

Results:
At one year, patients in the subgroup had a mean reduction in ranibizumab injections over 12 weeks = 2.52 injections (2.08 vs 4.6 = 55% relative reduction). This is highly statistically significant (p=0.0002). However the results need to be seen as indicative as the trial was not powered to provide a reliable result from this data.

There was also statistically significant improvements in both visual acuity (p=0.0284) and central subfield thickness (p=0.0270).

Patients with lesions > 4mm in greatest linear dimension and macular volume ≤ 7.4mm appeared to have worse outcomes. Eyes in this subgroup had a mean number of ranibizumab retreatments that was very similar to the sham arm (3.50 vs 3.65 injections, p=not significant).

The authors concluded that the INTREPID study ‘may potentially refine our knowledge of whom best to treat with stereotactic radiotherapy, suggesting that lesions smaller than the 4mm treatment zone do better. It also suggests patients are more likely to respond to SRT when they have significant fluid accumulation. These hypotheses, generated from sub-group analysis, need to be tested in a prospective trial’.

4.1.3 Intrepid 2 year trial results

The INTREPID study participants were reassessed at 2 years, as an ‘exploratory’ analysis as safety consequences (microvascular abnormalities - MVAs) of radiotherapy and the durability of the effect cannot be established until this time has elapsed. They reverted to ‘usual care’ which was less intensive than contemporary ‘treat until dry’ regimens advocated in the CATT study.

The safety outcomes were blindly independently assessed to see if MVAs were likely to be radiotherapy related. The ‘exploratory’ subgroup identified earlier was also assessed at 2 years.

Results:
At year 2, the primary outcome measure, 16 and 24 Gray arms received fewer PRN ranibizumab treatments compared with sham (mean 4.5, P = 0.008; mean 5.4, P = 0.09; and mean 6.6, respectively). Only the 16Gy group had a significant reduction.
Over the full 104 weeks, the patients given 16 and 24Gray SRT had 3 fewer injections vs sham (7.4 vs 10.3 p=0.009).

The secondary outcomes - Change in mean BCVA, mean central subfield thickness, mean total active lesion area and mean CNV area were all not significant changes or not statistically reported, so no conclusions should be drawn from the reported figures.

The exploratory subgroup analysis (26% of the trial participants) found that lesions with a greatest linear dimension ≤4 mm (the size of the treatment zone) and a macular volume greater than the median (7.4 mm³) were more responsive to SRT, with 3.9 PRN injections versus 7.1 in comparable sham-treated participants (P = 0.001) – 45% fewer injections, but no change in best corrected visual acuity vs sham.

A small cohort (15%) of SRT recipients required no anti-VEGF injections and 45% had fewer than 3 injection in the 2 years they were monitored.

**Safety:**
An independent reading centre detected microvascular abnormalities in 6 control eyes and 29 SRT eyes, of which 18 were attributed to radiation; however, only 2 (1%) of these possibly affected vision.

The authors concluded, ‘this study found that SRT was associated with significantly reduced anti-VEGF retreatment over 2 years. Microvascular changes may have occurred in response to radiation, but they seldom affected vision’.

**4.1.4 Future evidence:**
A 3 year safety analysis will be conducted on the INTREPID study

A UK based trial, Stereotactic Radiotherapy for Wet AMD (STAR), recently started recruiting in 10 centres, to establish the impact of treating just the patients in the INTREPID subgroup with lesions ≤4mm linear diameter and a macular volume ≥ 7.4mm³ using the 16GY beam only. STAR has a similar protocol to the INTREPID series, more reflective of current practice with a 2 year duration, likely to report in 2022. **Assuming the results are replicated, this should provide sufficient clarity to allow the NHS to commission a service with confidence.**

**4.1.5 Caution with Research findings**
There are a number of assumptions made in the papers that patients should be selected from the subgroup analysis, as they are ‘super responders’, but caution should be exercised, as these results may or may not be borne out in longer term trials, powered to show this difference conclusively. Indeed this may have be a chance finding, given that this was not a pre-specified subgroup to be analysed at the outset of the trial, so may not be reliable. However the magnitude of the effect claimed is substantial and could, if borne out in the real world significantly change the pathway by which wet AMD is managed in the NHS.

At the time of the design of INTREPID, the monthly PRN protocol was contemporary with clinical practice. In the meantime a more aggressive protocol is used, akin to that in the CATT study, so the number of injections in 2 years in more likely to be 12 rather than 10, with the reduction from the influence of Oraya Therapy less clear.

**4.1.6 Real world data**
The NHS is already commissioning this service in a limited number of locations - most extensively in Sheffield by 37/39 Yorkshire and Humber CCGs. There is also private availability in Greater Manchester through the Optegra clinic in South Manchester, charging £4,995 per treatment.
The Sheffield cohort\(^{22}\) was presented at a sponsored session at the Euretina conference in September 2015. Of 193 patients treated with SRT and injected with Anti-VEGF, 25 have reached 12 months with 58 having received 6 month treatment. The site selected the sub-group of patients with ≤4mm diameter and ≥7.4mm volume for Oraya Therapy, akin to the INTREPID subgroup\(^{10}\).

Of those reaching 12 months, the SRT group received an average of 4.6 injections vs 5.6 receiving usual care (all patients receiving 3 loading doses). This audit data shows a significantly lower difference between comparators vs. the trial findings in a real world environment; similar to GM. Benefits in visual acuity are claimed, but as this is an observational audit with unmatched controls, the unintentional influence of bias cannot be excluded.

### 4.1.7 Non-radiotherapy alternatives to monthly PRN regimens

The outcomes of alternatives to the fixed monthly/bi-monthly and monthly when required (PRN) regimes used widely with anti-VEGF treatment alone should also be considered. Newer ‘treat and extend’ and ‘monitor & extend’ protocols achieve improved or sustained visual acuity and reduced (mostly second year) injection numbers.

An Australian study\(^{20}\) looked at the effect of using a treat and extend protocol, based on intensive treatment to achieve dry eyes, then extending the time to next injection, removing monitoring visits, based on response. 1198 eyes from 1011 patients were assessed across 2 years.

This large retrospective database observational trial found that:
- Mean Visual Acuity (VA) increased from 56.5 letters at initial visit to 61.8 letters at 2 years.
- These VA gains were related to the number of injections received over 2 years:
  - 2.7 letters for eyes commencing in 2007 after a mean of 9.7 injections,
  - 7.8 letters for eyes commencing in 2012 after a mean of 14.2 injections
- 90.5% of eyes avoided a vision loss of 15 letters.
- There was an overall mean of 13.0 injections over the 24 months, 7.5 injections in the first year and 5.5 in the second year.
- Mean of 14.8 clinic visits.

The authors conclude that: These data indicate that eyes managed in routine clinical practice with a treat and extend regimen can achieve good visual outcomes while decreasing the burden of treatments and clinic visits.

The clinical review by Freund et al\(^{21}\) summarised the benefits of treat and extend below and seems to be the preferred approach to treatments by many ophthalmologists, but is limited by capacity constraints.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>- Fewer recurrences</td>
<td>- Over-treatment/may inject eye with a dry retina and achieve no VA change</td>
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<tr>
<td>- Better long-term vision outcomes</td>
<td>- Does not identify the patient who may remain stable without treatment</td>
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<tr>
<td>- More likely to keep retina dry</td>
<td>- (particularly for DME and RVO)</td>
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<td>- Less patient visits</td>
<td>- Potentially greater risk of geographical atrophy</td>
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<tr>
<td>- More proactive Limited evidence</td>
<td>- Increased chance of getting an adverse event</td>
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<tr>
<td>- Guarantee of some injections</td>
<td>- No stop criteria in DME and RVO</td>
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<tr>
<td>- Reduced risk of haemorrhage</td>
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<tr>
<td>- Adherence, logistics, costs</td>
<td></td>
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<tr>
<td>- Better disease control/stability</td>
<td></td>
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<tr>
<td>- Individualized to patient</td>
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<td>- More predictable injection workload</td>
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DME, diabetic macular edema; PRN, pro re nata; RVO, retinal vein occlusion; TER, treat-and-extend; VA, visual acuity.
5 NHS considerations

5.1 System impact considerations

As discussed above there are issues with access and capacity with all sites unable to see all current patients at required review periods for a monthly when required protocol. With the addition of rising population demand, the current pathway is not sustainable.

In addition GM providers have high costs for the service when benchmarked with other areas, with costs also opaque, due to ‘bundling’ of prices by some providers and inconsistent coding used by all.

A different pathway24 – potentially involving local ocular coherence tomography scans with rapid access to more locally based treatment centres would be more patient focused, given the significant reliance of patients on carers and/or ambulances to take them to central hubs.

Procurement would be required to make such changes, but would save significant money on pathway costs, be more patient focussed and likely achieve the required review times; thus creating the ability to invest in best care standards for the increasing population.

Oraya Therapy has been commissioned in Yorkshire, but fewer than half of the expected patient numbers have been identified. So the selected trial population may not be reflective of the Sheffield or Greater Manchester population23,24, thus a smaller effect size could be seen in real world practice.

While many CCGs in South Yorkshire commission this service, NHS Telford and Wrekin CCG25 considered the use of Oraya therapy and concluded:

_Until more robust evidence for clinical, safety and cost-effectiveness is available, Telford and Wrekin CCG considers the use of stereotactic radiotherapy in wet age-related macular degeneration to be a LOW PRIORITY intervention that is not routinely commissioned._

6 Cost considerations

6.1 Cost impact evidence

The benefit of using Oraya therapy is predicated only on the ability to reduce the number of ranubizumab injections from an average of 10 in 2 years to 7 thus saving 2 to 3 injections, plus the associated clinic tariff costs and associated injection risks. Patients are still required to attend clinics on the monthly PRN regime, so may not significantly affect capacity constraints. _It has not been shown to improve visual acuity._

The cost effectiveness of the introduction of Oraya Therapy depends on the cost of a treatment (£1250 plus NHS tariff – range £167-£400) being less than the ‘usual care’ over the treatment cycle of a patient; but importantly also having safety, quality and patient experience benefits.

Factors to consider are:

- Cost of Oraya – NHS tariff fees significant differences e.g. Sheffield vs Manchester
- Access improved? – not if present fixed monthly PRN/ Bi monthly maintained?
- Reduction is cost of injections PLUS tariff. Bigger savings could be made by moving to best practice tariff and reducing number of injections.
- Could a cost/ patient per year – outcomes based approach be adopted?
- real world experience in Sheffield has not yielded the same results as expected from trials, and has identified around half the expected number of eligible patients22.

_NB please note that all costs have been removed from this document, for NHS users please contact the GM shared service._
7 Conclusions
The clinical evidence for Oraya Therapy involves one trial, with extensions and an exploratory subgroup.

Whilst a trial of 230 patients on a device is unusual and to be commended that it was run to standards expected in drug trials, it does not provide conclusive proof to change the GM system wholesale, given that one CCG refers more patients per year for wAMD than the entire cohort within the INTREPID trial.

The decision to commission Oraya Therapy is one of economic gain rather than clinical benefit as it will likely reduce the number of anti-VEGF treatments required, but not improve visual acuity.

It is possible that savings (per patient) of £4317 could be generated, based mostly on reduction in activity, but could be enhanced further by beneficial tariff changes. There is also the risk of a cost increase of £1650 if the treatment does not reduce injection rates.

GM NHS organisations should take this into account, alongside other pathways, such as ‘treat and extend’, which may have higher year one costs, but may sustain visual acuity improvements, which were not observed with Oraya Therapy.

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Greater Manchester Shared Services
December 2015
## 8 References: Sources of evidence considered

<table>
<thead>
<tr>
<th>Database</th>
<th>Result</th>
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<tbody>
<tr>
<td>NICE</td>
<td><a href="www.nice.org.uk">AMD guidance</a></td>
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<td>6. <a href="www.rnib.org.uk">Sight Loss Data Tool Version 2.2. Royal National Institute of Blind People</a></td>
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<td>12. Age-Related Macular Degeneration: Guidelines for Management. The Royal College of Ophthalmologists. September 2013 <a href="www.rcophth.ac.uk">www.rcophth.ac.uk</a></td>
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<td>17. Bayer – Afiblercept (Eylea) Personal communication – 23/10/15 – ‘Unlicensed’</td>
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<td>18. Stereotactic Radiotherapy for Wet AMD (STAR) ClinicalTrials.gov Identifier:NCT02243878 <a href="clinicaltrials.gov">clinicaltrials.gov</a></td>
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<td>NHS organisations</td>
<td>22. Sheffield Teaching Hospital FT, Sheffield CCGs – Personal communication Business case and evidence review, conference presentations of recent evidence</td>
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<td>23. Optegra treatment price list <a href="www.optegra.com">www.optegra.com</a></td>
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<td></td>
<td>24. Manchester and Trafford CCG eyecare business cases – Personal communication</td>
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