Institution: University of Southampton		
Unit of Assessment: 01 Clinical Medicine		
Title of case study: 01-09 Use of bevacizumab in common and rare eye diseases		
Period when the underpinning research was undertaken: July 2007 – March 2017		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Andrew Lotery	Professor of Ophthalmology	September 2002 – present
James Raftery	Professor of Health Technology Assessment	February 1996 – present
Angela Cree	Senior Research Manager in Vision Sciences	March 2005 – present
J. Arjuna Ratnayaka	Lecturer in Vision Sciences	April 2013 – present
Period when the claimed impact occurred: October 2013 – July 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

University of Southampton research has led to the use of the cancer drug bevacizumab as an alternative cost-effective treatment for Age-related Macular Degeneration (AMD). Led by Professor Andrew Lotery, the research and subsequent engagement with health commissioners, regulators and professional bodies has informed significant policy and clinical guideline changes by the General Medical Council, NICE and WHO. Lotery's research and evidence was pivotal in the successful outcome of a judicial review of a legal challenge from two major pharmaceutical companies against the NHS's use of the less expensive drug. The work paved the way for the routine use of bevacizumab, with a cost saving to the NHS estimated at GBP500m per year. Further research led by Lotery identified bevacizumab as the first ever treatment for Sorsby Fundus Dystrophy, a rare juvenile form of macular degeneration. The treatment is subsequently being used in the NHS for the first time.

2. Underpinning research

Age-related Macular Degeneration (AMD) is a common condition of the eye that affects central vision. It usually first affects people in their 50s and 60s and can happen gradually over several years (known as 'dry' AMD) or quickly over a few weeks or months (known as 'wet' AMD). AMD is the commonest cause of blindness in the elderly in the developed world and is thought to affect half of the 370,000 people registered as blind or partially sighted in the UK. The current UK prevalence of late stage AMD is 2.4% of the adult population, totalling nearly 700,000 cases in 2020. In those aged 65 or over, prevalence of late stage AMD is 4.8% and in those aged 80 or over, 12.2%.

The licensed treatments in the UK and EU for wet AMD are ocular injections of either aflibercept or ranibizumab, drugs that block growth of the fragile blood vessels. However, they are expensive, costing around GBP700 per patient per injection, in comparison with bevacizumab, which has the same mechanism of action yet costs GBP50 per patient per injection.

After reporting effective use of the cheaper alternative, bevacizumab, in a retrospective study of 118 Southampton AMD patients in 2007 [**3.1**], Professor Andrew Lotery was invited to be a co-investigator and member of the executive committee for the NIHR Health Technology Assessment-funded IVAN trial (2007-2013). IVAN was the first randomised, controlled trial to compare ranibizumab and bevazicumab for treating wet AMD. Lotery contributed to the design of the study, was on the trial's executive group and was PI on the IVAN genetics sub-study, with all study DNA samples analysed at Southampton [**3.2**]. IVAN involved 610 patients over the age of 50 with untreated wet AMD from eye clinics across the UK, with a significant number of patients recruited from Lotery's clinic. Patients were randomly assigned to be treated with ranibizumab or bevacizumab for two years and their progress was tracked. The IVAN trial

demonstrated that bevacizumab was equally as effective as ranibizumab in targeting retinal blood vessels and managing wet AMD. This provided robust clinical evidence that bevacizumab should be used as a treatment for this disease on the NHS [**3.3, 3.4**].

Sorsby Fundus Dystrophy is an autosomal dominant macular dystrophy with an estimated prevalence of 1 in 220,000. As of 1 October 2020 Southampton Eye Unit had eight patients with Sorsby Fundus Dystrophy, from a population of 1.76 million people in Hampshire. Onset of the disease is around the 3rd to 6th decade of life [**3.5**]. An early symptom is night blindness, with retina cells later starting to die off and new blood vessels potentially growing into the retina, causing loss of central vision similar to symptoms of AMD. In 2011, a team led by Lotery were the first to demonstrate that bevacizumab is a viable treatment for this rare inherited eye disease. The effective treatment pathway allowed patients to maintain vision in what was previously an untreatable disease [**3.6**].

3. References to the research

3.1 Madhusudhana KC, Hannan SR, Williams CPR, Goverdhan SV, Rennie C, **Lotery AJ**, Luff AJ, Newsom RSB. Intravitreal bevacizumab (Avastin) for the treatment of choroidal neovascularization in age-related macular degeneration: results from 118 cases. British Journal of Ophthalmology 2007; 91(12): 1716-7. https://doi.org/10.1136%2Fbjo.2006.108639

3.2 Lotery AJ, Gibson J, **Cree AJ**, Downes SM, Harding SP, Rogers CA, Reeves BC, Ennis S, Chakravarthy U; Alternative Treatments to Inhibit VEGF in Patients with Age-Related Choroidal Neovascularisation (IVAN) Study Group. Ophthalmology. 2013;120(12):2637-2643. https://doi.org/10.1016/S0140-6736(13)61501-9

3.3 Dakin HA, Wordsworth S, Rogers CA, Abangma G, **Raftery J**, Harding SP, **Lotery AJ**, Downes SM, Chakravarthy U, Reeves BC, Investigators IS. Cost-effectiveness of ranibizumab and bevacizumab for age-related macular degeneration: 2-year findings from the IVAN randomised trial. Bmj Open 2014; 4(7). https://doi.org/10.1136/bmjopen-2014-005094

3.4 Chakravarthy U, Harding SP, Rogers CA, Downes SM, **Lotery AJ**, Culliford LA, Reeves BC, Investigators IS. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet 2013; 382(9900): 1258-67. https://doi.org/10.1016/s0140-6736(13)61501-9

Grants supporting 3.1 – 3.4:

A PI Professor Usha Chakravarthy, Co-I Lotery, Raftery et al.

Title: A randomised controlled trial (RCT) of alternative treatments to Inhibit VEGF in patients with Age-related choroidal Neovascularisation (IVAN). GBP3.34m. Grant Ref 07/36/01, 01/07/2007 to 31/12/2013

B Five year observational follow-up of the IVAN trial cohort: a study of function and morphology Grant Ref 07/36/501 from 01/10/2015 to 31/03/2017

3.5 Christensen DRG, Brown FE, **Cree AJ**, **Ratnayaka JA**, **Lotery AJ**. Sorsby fundus dystrophy - A review of pathology and disease mechanisms. Exp Eye Res. 2017 Dec; 165:35-46. https://doi.org/10.1016/j.exer.2017.08.014

3.6 Gemenetzi MK, Luff AJ, **Lotery AJ**. Successful treatment of choroidal neovascularization secondary to sorsby fundus dystrophy with intravitreal bevacizumab. Retin Cases Brief Rep 2011; 5(2): 132-5. https://doi.org/10.1097/icb.0b013e3181cc216b

4. Details of the impact

Southampton's distinguished research in Age-related Macular Degeneration (AMD), led by Lotery, has supported the use of a more cost-effective treatment, bevacizumab, which has changed clinical practice in the UK and abroad, helping thousands of patients. It also led to the discovery that the same drug could be used to treat a previously untreatable disease, Sorsby Fundus Dystrophy.

4.1 Bevacizumab for the treatment of AMD

4.1.1 Influence on WHO guidelines

Based on major clinical trials including the IVAN study, in October 2013 the World Health Organisation included bevacizumab in its essential medicine list for the treatment of AMD and continued to include it in its revised lists in 2015, 2017 and 2019 [**5.1**].

4.1.2 Influence on policy and guidelines of the General Medical Council (GMC) and NICE

The regulatory hurdles to adopting bevacizumab for treatment of AMD in the NHS were discussed in a 2014 British Medical Journal editorial written by Lotery and the President of the Royal College of Ophthalmologists Professor Carrie MacEwen [**5.2**]. Drawing on the IVAN study, they argued that ranibizumab and bevacizumab have the same efficacy in the treatment of AMD, but since they were both manufactured by Roche, then the company had little incentive to request NICE appraisal for the cheaper, unlicensed drug. They noted that ranibizumab was marketed by Novartis in the UK.

Further, given bevacizumab wasn't licensed by the MHRA for treatment of AMD, its use would go against guidance from the General Medical Council (GMC) that doctors should prescribe unlicensed drugs only if "there is no suitably licensed medicine that will meet the patient's need", with no consideration of cost effectiveness. Without unequivocal GMC and NICE support, Lotery and MacEwen argued that ophthalmologists were "understandably concerned that they may be assuming unacceptable personal liability by using an unlicensed drug when a licensed alternative exists."

This editorial and the IVAN study were prominently cited by a group of 120 NHS Clinical Commissioning Groups (CCGs representing almost 60% of the UK) in February 2015 when they wrote to the Secretary of State for Health, the Chair of NICE, the GMC and the chief of NHS England [**5.3**] in order to:

- Ask the GMC to provide a specific exception to their standard guidance to support practitioners who wish to prescribe bevacizumab 'off-licence' for use in the eye on the basis of clinical and cost effectiveness;
- Ask the Secretary of State for Health to ask NICE to consider the status of the current Technology Appraisal guidance and authorise NICE to undertake an multiple treatment appraisal looking the comparative cost effectiveness of bevacizumab with ranibizumab and aflibercept;
- Ask the chief of NHS England to support the case for change and to support clinical commissioners who wish to make local commissioning decisions to prescribe bevacizumab 'off-licence' on the grounds that it is safe and a cost effective treatment.

The response from the Department of Health was that "it would not only be unlawful but against the wider public interest if ministers were to attempt to set aside [the EU medicines licensing legislation] in order purely to cut costs." [**5.4**].

The increasing challenge of delivering healthcare equitably continued to concern health commissioners. To estimate the potential savings, a group of ophthalmologists from University Hospital Southampton used freedom of information requests to identify how much bevacizumab, ranibizumab and aflibercept were prescribed in the NHS during January 2015. Their calculations, published in *Eye* in August 2016, showed a potential saving to the NHS of GBP449m (GBP539m with VAT) per year if all injections used bevacizumab [**5.5**].

In his role as Chair of the Scientific Committee of the Royal College of Ophthalmologists, Lotery participated in meetings held at the College with CCGs and the General Medical Council (GMC) to determine if the GMC could permit ophthalmologists to use bevacizumab outside its licensed indication and not risk disciplinary procedures by the GMC. Following these discussions, in which the impact of the GMC advice on ophthalmologists was conveyed to the GMC, on 23 January 2018 the GMC changed their position on the use of bevacizumab in the treatment of AMD, ostensibly in response to NICE guideline NG82 that was published the same day.

The GMC Chief Executive stated: “We expect doctors to make good use of the resources available to them and sympathise with the concerns of ophthalmologists making decisions between using a cheaper product outside the terms of its license or a more expensive licensed alternative. We cannot of course give specific clinical or legal advice. But we can say that where doctors are working in partnership with patients, following clinical guidance and making prescribing decisions in good faith on the basis of evidence and experience, the use of Avastin [bevacizumab] would not cause us any concerns.” [**5.6**]

In NICE guideline *NG82 Age-related macular degeneration* published the same day, the committee for the guideline recognised the results of the IVAN trial, stating that “no clinically significant differences in effectiveness and safety between the different anti-VEGF treatments have been seen in the trials.” In a footnote they cautioned that bevacizumab didn’t have UK marketing authorisation for AMD, but added: “Given the guideline committee's view that there is equivalent clinical effectiveness and safety of different anti-VEGF agents (aflibercept, bevacizumab and ranibizumab), comparable regimens will be more cost effective if the agent has lower net acquisition, administration and monitoring costs.” [**5.7**]

4.1.3 Influence on NHS policy and defence of subsequent legal challenge

In late 2017 the North East and North Cumbria CCG Forum, made up of 12 NHS CCGs in the region, agreed on a policy to offer patients diagnosed with wet age-related macular degeneration the choice of bevacizumab as preferred treatment. Citing a BMJ article in which the IVAN trial and Lotery featured prominently [**5.8**], the Chair of the Forum stated: “We intend to share information with patients through accessible media (including leaflets and audiovisual material) about the treatment options available, the evidence base, and the comparative costs—and allow them to make their own choice. The policy could save the region’s NHS up to GBP13.5m a year over the next five years. That could pay for an extra 270 nurses or 266 heart transplants every year. In a financially stretched NHS, the alternative for CCGs is that we may have to make less evidence based savings, including rationing other treatments such as in vitro fertilisation.” [**5.9**]

The policy was immediately met with a threat of legal action from Bayer PLC and Novartis Pharmaceuticals UK Ltd, who held UK marketing authorisations for ophthalmic use of aflibercept and ranibizumab respectively. In 2018 they applied for a judicial review, arguing that the CCGs’ use of bevacizumab, manufactured by Roche, to treat wet AMD was unlawful under EU law because Roche holds no marketing authorisation for ophthalmic use [**5.10**].

The review was dismissed, with Mrs Justice Whipple, who heard the case, calling the argument an “absurd proposition.” She said: “It would give unbounded power to the pharmaceutical companies to decide which medicines to make available for which purposes.” She added: “That would be seriously detrimental to the wider public interest in maintaining a cost effective public health system.” [**5.11**].

Lotery was the single expert witness for the CCGs and his evidence is listed in the judgement. As well as evidence to demonstrate its cost effectiveness, Lotery described the extensive peer reviewed clinical trial data that bevacizumab was a clinically efficacious treatment for macular degeneration and summarised the bevacizumab safety data from multiple clinical trials.

The judgement on the initial judicial review was upheld in March 2020 after Bayer PLC and Novartis Pharmaceuticals UK Limited appealed it [**5.12**], paving the way for the use of bevacizumab in treating AMD in the NHS.

In 2019 Southampton clinicians administered 540 bevacizumab doses instead of ranibizumab. Based on current costs of bevacizumab at GBP50 per dose, the Southampton team saved approximately GBP243,000.

4.1.4 Influence on MHRA policy

In September 2019 the MHRA changed its position on bevacizumab following a request from Mrs Justice Whipple. They stated: “The Agency accepts that when prescribed and/or used by a healthcare professional, this does not create an unlicensed medicine and falls under the scope of ‘off-label’ use.” They also state: “Professional governance bodies have published advice to prescribers that should be taken into account.” This is a significant change in their position following the initial Judicial Review and guidance from the Royal College of Ophthalmologists

and allows clinicians the freedom to choose to use bevacizumab without any legal complications. Lotery was heavily involved in both of these processes [**5.13**].

4.2 Bevacizumab for the treatment of Sorsby Fundus Dystrophy

Research by Lotery's team [**3.6**] has led to new treatments for Sorsby Fundus Dystrophy (SFD). In previous studies, treatment with bevacizumab allowed stabilisation or improvement in SFD patients. The Southampton research showed that intravitreal bevacizumab should be considered as a safe and effective treatment for choroidal neovascularization secondary to SFD, with 5 patients reported so far. It prevented blindness in these rare disease patients, so the impact on their quality of life was significant [**5.14**]. One patient said: "If it wasn't for [bevacizumab] I would have lost my eyesight over 10 years ago. I have been having this treatment for over 13 years and it has reduced the deterioration of my vision by 90%. I can still read large print and do what I need to. I consider this treatment miraculous and am so thankful for its availability." [**5.15**] It is now an accepted treatment in University Hospital Southampton NHS Foundation Trust, and Southampton have provided the evidence base for this treatment to be used elsewhere in the NHS for this small but deeply affected patient group.

5. Sources to corroborate the impact

5.1 WHO Technical Report Series 985 approved October 2013. IVAN study cited on p71 https://www.who.int/publications/i/item/9789241209854 Bevacizumab listed on p141 and still listed in 2019, p46: https://www.who.int/publications/i/item/WHOMVPEMPIAU2019.06

5.2 What is stopping the NHS from using bevacizumab for macular degeneration and other retinal disorders? BMJ 2014; 349: g6887. https://doi.org/10.1136/bmj.g6887

5.3 Coverage of CCGs' letter, February 2015 http://www.pmlive.com/pharma_news/uk_doctors_call_on_nhs_to_use_avastin_for_wet_amd_661157

5.4 Letter from George Freeman MP to CCGs http://qna.files.parliament.uk/qna-attachments/227552/original/NHS%20Commissioner%20Letter.pdf

5.5 Shalaby AK, Lewis K, Bush K, Meredith PR, Di Simplicio S, Lockwood AJ. Licence to save: a UK survey of anti-VEGF use for the eye in 2015. Eye (Lond) 2016; 30(11): 1404-6. https://doi.org/10.1038/eye.2016.154

5.6 GMC press release stating their change of position https://www.gmc-uk.org/news/media-centre/media-centre-archive/gmc-responds-to-new-nice-guidance

5.7 NICE Guideline NG82 https://www.nice.org.uk/guidance/NG82 (quoted passages p11 & p17)

5.8 Cohen D. Are the odds shifting against pharma in the fight for cheaper treatment for macular degeneration? BMJ 2017;359:j5016 https://doi.org/10.1136/bmj.j5016

5.9 Hambleton D. Commentary: NHS patients should have a choice of drug for wet [AMD], despite pressure from pharma BMJ 2017;359:j5013 https://doi.org/10.1136/bmj.j5013

5.10 Judicial review summary. https://www.judiciary.uk/wp-content/uploads/2018/09/bayer-and-novartis-v-nhs-darlington-ccg-summary.pdf. This review details the ruling on bevacizumab use for AMD.

5.11 BMJ report of judicial review https://doi.org/10.1136/bmj.k4035

5.12 The High Court of Justice appeal decision http://www.landmarkchambers.co.uk/wp-content/uploads/2020/03/Bayer-for-hand-down-24.3.2020.pdf

5.13 Update on the licensing status of Avastin when intended for intravitreal administration https://www.gov.uk/government/news/update-on-the-licensing-status-of-avastin-when-intended-for-intravitreal-administration – this document refers to the judicial review.

5.14 Tsokolas G, Almuhtaseb H, Lotery A. Evaluation of Pro-re-Nata (PRN) and Treat and Extend Bevacizumab treatment protocols in Sorsby Fundus Dystrophy. Eur J Ophthalmol 2018: 1120672118811568. https://doi.org/10.1177%2F1120672118811568

5.15 Patient letter (contact details redacted).