Institution: University of Bristol		
Unit of Assessment: 1) Clinical Medicine		
Title of case study: Radical advance in treating age-related macular degeneration leading to global impact in prevention of blindness		
Period when the underpinning research was undertaken: 2007 - 2020		
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:**
Barnaby C Reeves	Professor of Health Services Research	05/2005 – present
Chris A Rogers	Professor of Medical Statistics and Clinical Trials	10/2002 – present
Period when the claimed impact occurred: 2012 - 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

University of Bristol research has increased availability of treatment at reduced cost for a major worldwide cause of blindness, namely wet age-related macular degeneration (AMD). Clinical trial data confirmed that an inexpensive drug (Avastin®/bevacizumab) is as successful in treating wet AMD as the licensed one (Lucentis®/ranibizumab) and equally effective and safe given only when the disease is active. This evidence has informed UK, European and wider international clinical guidelines, including India and Brazil, and enabled cost-effective 'off-label' treatment without reduction in quality of care. Cost-effectiveness has increased availability of treatment for disadvantaged patients, particularly in low and middle-income countries. Brazilian health policy highlights the ability to treat five additional patients with bevacizumab for every one with the costly alternative. Treating only active disease is more convenient and less stressful, benefitting patient well-being without detriment to eye health.

2. Underpinning research

The cause of wet AMD is an altered production of vascular endothelial growth factor (VEGF) which stimulates aberrant blood vessel formation. The first biological anti-VEGF, ranibizumab, entered clinical practice in 2007 and hugely improved prognosis. However, the high cost of the drug, and the requirement for repeated injections into the vitreous of the eye, imposed a huge burden on patients and health care services. Consequently, an alternative biological anti-VEGF drug was used "off-label" by ophthalmologists, bevacizumab, (Avastin®) the parent molecule of ranibizumab (Lucentis®); reports suggested that this drug offered equivalent visual benefits at a more affordable cost. In 2007 the IVAN (Alternative Treatments to Inhibit VEGF in Patients with Age-Related Choroidal Neovascularisation) study was developed to robustly assess the efficacy and safety of ranibizumab and bevacizumab to treat wet AMD.

The trial was designed, conducted and analysed by Prof Reeves and Prof Rogers at the Bristol Clinical Trials and Evaluation Unit and in collaboration with Prof Chakravarthy (Queen's University Belfast), and funded by the National Institute of Health Research (NIHR) [i, ii].

The IVAN trial aimed to compare the effectiveness of bevacizumab and ranibizumab in usual care settings, as well as to compare regular monthly treatment (continuous) with treatment-as-needed (discontinuous). The multicentre, factorial randomised controlled trial recruited 610

patients from 23 NHS hospitals. The key research findings were that, in the setting of the UK NHS and with respect to visual acuity, bevacizumab was non-inferior to ranibizumab, and only treating active disease (discontinuous treatment) was non-inferior to monthly (continuous) treatment [1, 2, 5].

Analysis of cost-effectiveness revealed that total costs ranged from GBP3,002 per patient for discontinuous treatment with bevacizumab, to GBP18,590 per patient for continuous treatment with ranibizumab [3]. The analysis demonstrated that bevacizumab would achieve substantial cost-savings over ranibizumab with negligible differences in quality of life. In England, switching patients to bevacizumab could save at least GBP102 (USD160) million per year [3].

The safety of bevacizumab is paramount given that its use is classified as unlicensed when used to treat neovascular AMD. Reeves and Rogers were co-authors of a 2014 Cochrane review [4], of nine non-industry sponsored RCTs, including IVAN [3] trial safety data. The study concluded that bevacizumab was as safe as ranibizumab, and that health polices recommending ranibizumab on the grounds of safety were not sustained by evidence [4]. Most recently an international collaboration, investigated safety in more detail by considering individual patient data from six clinical trials, providing information on 3,052 patients with the same finding [6].

3. References to the research

[1] Chakravarthy U, Harding SP, **Rogers CA**, Downes SM, Lotery AJ, Wordsworth S, **Reeves BC**. (2012). Ranibizumab versus bevacizumab to treat vascular endothelial growth factor in age-related choroidal neovascularization. One year findings from the IVAN randomized trial. *Ophthalmology,* 119 (7): 1399-1411. DOI:10.1016/j.ophtha.2012.04.015

[2] Chakravarthy U, Harding SP, **Rogers CA,** Downes SM, Lotery AJ, **Culliford LA, Reeves BC**, IVAN Study Investigators. (2013). Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: two-year findings of the IVAN randomised controlled trial. *Lancet,* 382 (9900): 1258-67. DOI:10.1016/S0140-6736(13)61501-9

[3] Dakin HA, Wordsworth S, **Rogers CA,** Abangma G, Raftery J, Harding SP, Lotery AJ, Downes SM, Chakravarthy U, **Reeves BC**, on behalf of the IVAN Study Investigators. (2014). Cost-effectiveness of ranibizumab and bevacizumab for age-related macular degeneration: 2-year findings from the IVAN randomized trial. *BMJ Open,* 4: e005094. DOI:10.1136/bmjopen-2014-005094

[4] Moja L, Lucenteforte E, Kwag KH, Bertele V, Campomori A, Chakravarthy U, D'Amico R, Dickersin K, Kodjikian L, Lindsley K, Loke Y, Maguire M, Martin DF, Mugelli A, Mühlbauer B, Püntmann I, **Reeves B**, **Rogers C,** Schmucker C, Subramanian ML, VirgiliG. (2014). Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration. *Cochrane Database of Systematic Reviews,* 7: CD011230. DOI:10.1002/14651858.CD011230.pub2

[5] Chakravarthy U, Harding SP, **Rogers CA**, Downes S, Lotery AJ, Wordsworth S, **Culliford L, Scott L,** Nash RL, Taylor J, Muldrew A, Sahni J, Dakin H, Raftery J, Peto T, Mitchell J, Bradley C, **Reeves BC**, for the IVAN Investigators. (2015). A randomised controlled trial of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN). *Health Technology Assessment,* 19 (78): 1-298. DOI:10.3310/hta19780

[6] Maguire MG, Shaffer J, Ying G-S, Chakravarthy U, Berg K, Bragadóttir R, Decullier E, Huot L, Kodjikian L, Martin DF, **Reeves BC, Rogers CA,** Schauwvlieghe A-SME, Schlingemann RO. (2017). Serious adverse events with bevacizumab or ranibizumab for age-related macular degeneration: meta-analysis of individual patient data. *Ophthalmology Retina,* 124 (10): 1432-1436. DOI:10.1016/j.oret.2016.12.015

Key grants:

[i] Chakravarthy U, **Reeves BC,** Harding SP, **Rogers CA,** Wordsworth S, Lotery AJ, Talks J, Downes S, Raftery JP. A randomised controlled trial of alternative treatments to inhibit VEGF in age-related choroidal neovascularisation (IVAN). NIHR Health Technology Assessment, 2007-2010, GBP2,800,119

[ii] Chakravarthy U, **Reeves BC**, Harding SP, **Rogers CA**, Wordsworth S, Lotery AJ, Downes S, Raftery JP. Alternative treatments to inhibit VEGF in age-related choroidal neovascularion (IVAN). NIHR HTA, 2010-2012, GBP546,251

[iii] Chakravarthy U, **Reeves BC**, Harding SP, **Rogers CA,** Wordsworth S, Lotery AJ, Downes S. Five-year observational follow-up of the IVAN trial cohort: a study of function and morphology. NIHR HTA, 2015 – 2018, GBP331,810

4. Details of the impact

In the absence of treatment, wet AMD rapidly leads to severe visual disability – around 38% of affected eyes reading three or more lines fewer on the letter (Snellen) chart by 12 months after diagnosis. As a result of an ageing population, the number of people with AMD globally is estimated to reach 243 million by 2030. Wet AMD accounts for 10% of those cases but 90% of AMD central vision loss.

Informing UK clinical guidance and practice

In 2014, The Royal College of Ophthalmologists cited the initial findings from the IVAN trial [1] in calls for an urgent review of the licensing and use of bevacizumab in AMD. New National Institute for Health and Care Excellence (NICE) clinical guidelines on the treatment of AMD, published in 2018, referenced both 1-year [1] and 2-year [2] findings from the IVAN trial concluding with the view that there are *'no clinically significant differences in effectiveness and safety between the different anti-VEGF treatments'* [A].

Cost-effectiveness data from the IVAN trial [3] were also included in the NICE health economic analysis [Aiii]. The guideline committee concluded that '*treatment with bevacizumab would be unequivocally cost effective'* while noting the drug did not currently have UK marketing authorisation. Based on this guidance, 12 NHS Clinical Commissioning Groups (CCGs) in the North of England adopted a policy offering patients an informed choice between the two drugs, which could enable cost savings without a reduction in quality of care [B].

In March 2020, the UK Court of Appeal dismissed a legal challenge against the group of CCGs, by the pharmaceutical industry, and referred heavily to evidence of safety, efficacy, and cost-effectiveness in the NICE guideline (underpinned by the IVAN trial [3]), in support of the decision [B].

International changes in clinical guidance and treatment practice

The IVAN trial was one of only two clinical trials which directly informed the European Society of Retina Specialists (EURETINA) guidance 2014 for the management of wet AMD [C]. The guidance recommendations stated that *'The CATT and IVAN results indicate that ranibizumab and bevacizumab both confer solid visual function benefits'* [C]. 2019 survey data show bevacizumab is used across the 22 most populous countries in the EU, with 5 countries reporting >70% use of bevacizumab [D]. Specific national guidance documents also cite the

IVAN trial [1, 2, 3] and Cochrane review [4], including the Netherlands [Ei] and Finland [Eii], where bevacizumab accounts for ≥75% of intravitreal injections [D].

As a direct result of the one-year findings of the IVAN trial [1] and US CATT trial, bevacizumab was added to the World Health Organisation (WHO) Model List of Essential Medicines in 2013 [Fi], which is a key tool for achieving universal health coverage. Subsequent updates in 2015 [Fii], and 2017 [Fiii], continued to cite the IVAN trial [1, 3], and Cochrane review [4], as evidence for the efficacy, safety and cost-effectiveness of bevacizumab, including reviews that considered requests to add ranibizumab (2015) and delete bevacizumab (2017). The Expert Committee concluded that bevacizumab is the preferred option and inclusion of ranibizumab might *'divert relevant resources from other interventions'* [Fi].

The WHO recommendation is used by countries as evidence supporting use of bevacizumab. Following a temporary ban, in 2016, bevacizumab was re-authorised for use by the Drug Controller of India [G]. Underpinning the decision to re-authorise the drug the Indian Ministry of Health and Welfare cited the WHO Essential Medicines List (2015) [G]. The formal notice noted that *"the bevacizumab injection is 40 times cheaper than other available drug"* so use would *"put less financial burden on patients and prevent blindness of many"* [G]. The treatment cost for wet AMD using licensed medication is unmanageable in real-life practice in most Asia-Pacific countries [H].

In 2015, the Brazilian Ministry of Health rejected an application for the use of ranibizumab in their publicly funded health system [Ii], following an in-depth review of the evidence including the IVAN trial [1, 2]. They concluded that it *'equates in efficacy and safety to bevacizumab'* and pointed to the *'unfavourable cost-effectiveness ratio'.* The report noted that the cost per dose of ranibizumab (BRL126.88) could reach six times that of bevacizumab (BRL21.18) and that, if ranibizumab were incorporated and used, *'the Ministry of Health would be failing to treat 5 patients [with bevacizumab] for every 1 treated [with ranibizumab]'* [I]. In 2018, a new Clinical Protocol and Therapeutic Guideline for AMD cited the IVAN study [1, 2, 3] in its review of the evidence and recommend bevacizumab as the drug of choice due to its cost-effectiveness [Iii].

A 2018 study estimated that the United States citizens and healthcare system saved USD17.3 billion over a seven-year period by using bevacizumab to replace ranibizumab and aflibercept. Across Europe, a study published in 2018 found that *"Bevacizumab treatment costs EUR27,087 per year, about EUR4,000 less than aflibercept and EUR6,000 less than ranibizumab"*

Healthcare systems relying on the licensed medication have gained a better cost price. Many patients previously could not afford the expensive licensed preparation, and so risked blindness as a result of not getting treatment. This was true even in insurance schemes if co-payments were required. The IVAN and CATT studies widened access for these patients by identifying affordable treatment. In the US, injections of bevacizumab for wet AMD have reached usage levels equivalent to the licensed medication and have increased under Obamacare.

Patient benefit

Patients having intravitreal injections of an anti-VEGF drug have benefitted since a regimen only treating active disease is less stressful and more comfortable. The recently completed follow-up of the IVAN trial, describing outcomes over 5-7 years of anti-VEGF treatment showed 60% of surviving patients were still requiring anti-VEGF treatment up to 7 years after starting anti-VEGF

treatment in the IVAN trial, and had substantially better vision than would be expected without treatment [J].

The follow-up study of the IVAN trial [J], successfully obtained information for 98% of participants who completed the study, including those who had since died. The unprecedented completeness of information about participants allowed us to estimate ongoing decline in vision more accurately than had previously been done. This information has enduring important value for future economic assessments by NICE of the likely cost-effectiveness of new treatments over a long-time horizon.

5. Sources to corroborate the impact

[A] i) NICE (2018). NICE guideline NG82 Age-related macular degeneration
ii) Appendix E: Evidence Tables - *Underpinning research 1, 3, 4, 5 cited*
iii) Appendix J: Health Economics – *Underpinning research 1, 3, 5 cited*

[B] Bayer plc & Or *v* NHS Darlington CCG & Ors (2020). EWCA Civ 449

[C] Schmidt-Erfurth *et al.* (2014). Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). *The British Journal of Ophthalmology,* 98, 1144–1167. DOI:10.1136/bjophthalmol-2014-305702

[D] Bro *et al.* (2020). Off-label use of bevacizumab for wet age-related macular degeneration in Europe, *Graefe's Archive for Clinical and Experimental Opthalmology,* 258, 503-511. DOI:10.1007/s00417-019-04569-8

[E] i) Dutch Ophthalmic Society (2014). Directive: Age related Macular Degeneration
ii) Tuuminen *et al.* (2017). The Finnish national guideline for diagnosis, treatment and follow-up of patients with wet age-related macular degeneration. *Acta Ophthalmologica*, 95, 1–9. DOI:10.1111/aos.13501

[F] WHO Technical Report Series:
i) 2015 The Selection and Use of Essential Medicines (including the 19th Model List)
ii) 2017 The Selection and Use of Essential Medicines (including the 20th Model List)

[G] i) Directorate General of Health Services, Office of Drugs Controller India. (2016). Notice F. No. 12-52/2004-DC (Part 1), (11.03.16)
ii) Fierce Pharma (2016). Regulatory: India lifts alert on Roche's Avastin use for eye injection

[H] Healio (2014). *Ocular Surgery News:* AMD treatment too high a burden in real-life practice in most Asia-Pacific countries

[I] i) Ministry of Health (Brazil) (2016). Ranibizumab for Age-Related Macular Degeneration
ii) Ministry of Health (Brazil) (2018). Clinical Protocol and Therapeutic Guidelines of Age-Related Macular Degeneration

[J] Evans RN, **Reeves BC**, Phillips D, Muldrew A, **Rogers CA,** Harding SP, Chakravarthy U, IVAN study Group. (2020). Long-term Visual Outcomes after Release from Protocol in Patients who Participated in the Inhibition of VEGF in Age-related choroidal Neovascularisation (IVAN) Trial. *Ophthalmology,* Article in press. DOI:10.1016/j.ophtha.2020.03.020