Institution: Queen's University Belfast		
Unit of Assessment: UoA 2		
Title of case study: IVAN proves that a cheaper drug (bevacizumab/Avastin) is as good as much more expensive ranibizumab (Lucentis) for neovascular age-related macular degeneration		
Period when the underpinning research was undertaken: 2008 to 2012		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Usha Chakravarthy	**Role(s) (e.g. job title):** Professor of Ophthalmology and Vision Sciences; Centre for Public Health; School of Medicine, Dentistry and Biomedical Sciences	**Period(s) employed by submitting HEI:** 1989 onwardsI am
Period when the claimed impact occurred: 1 August 2013 onwards		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

The IVAN trial, led by Professor Chakravarthy, is regarded by the National Institute of Health Research as one of the most important trials of the last decade. It proved that bevacizumab (Avastin) is a much cheaper, effective alternative to ranibizumab (Lucentis) for neovascular age-related macular degeneration. This led to widespread demand by healthcare providers in the UK and internationally to be able to use the cheaper drug, a 2018 judicial decision in England and Wales (upheld by the Court of Appeal in 2020) to approve this switching, favourable comments about bevacizumab in the NICE guidelines (2018), use of bevacizumab instead of ranibizumab in NHS Scotland (2019) and a decision to no longer update the relevant Cochrane Review because the evidence to which IVAN makes such an important contribution was so robust (2019).

2. Underpinning research

The ophthalmology group at Queen's University Belfast was established more than 30 years ago and has developed internationally-recognised expertise in the genetics and treatment of age-related macular degeneration (AMD). It was ranked among the top 20 institutions in the world for research into macular degeneration in 2020, with Professor Chakravarthy in the top dozen global experts (http://expertscape.com/ex/macular+degeneration). In 2007, under her leadership, the group was funded by the NIHR Health Technology Assessment (HTA) programme to work with colleagues in the universities of Bristol, Liverpool, Oxford and Southampton, and with the NIHR Biomedical Research Centre at Moorfields Hospital in London and Oxford University Hospitals NHS Trust to conduct a randomised trial of the clinical and cost-effectiveness of alternative treatments to inhibit vascular endothelial growth factor (VEGF) in age-related choroidal neovascularisation, called IVAN for short (ISRCTN92166560). IVAN recruited, randomised and treated 610 participants across 23 ophthalmic units in the NHS from March 2008 to October 2010, with the final primary outcome (best corrected distance visual acuity at two years follow-up) being collected in November 2012. The trial sought to answer two main treatment questions through a head-to-head comparison of bevacizumab versus the more expensive ranibizumab, and a second randomisation of patients to continuous or discontinuous treatment.

The clinical results were published in a landmark paper in the Lancet in July 2013 (less than nine months after the last patient had their 2-year check-up) **[R1],** following the publication of the 1-year findings the year before **[R2].** These papers were followed by the health economic findings in 2014 **[R3]** and the full NIHR HTA monograph in 2015 **[R4].** The results showed that the two drugs improve eyesight by a similar amount and that monthly treatment improves eyesight slightly more than intermittent treatment and appeared to be safer.

The results, coupled with the within-trial economic evaluation of the incremental cost and cost-effectiveness of discontinuous and continuous treatment from the cost perspective of the NHS and the health perspective of participants clearly showed that ranibizumab was not cost-effective compared with bevacizumab. Two years of treatment with ranibizumab cost more than GBP18,500 compared with GBP3000 for bevacizumab. The health economic analysis showed that continuous ranibizumab would only be cost effective compared with continuous bevacizumab if the NHS were willing to pay GBP3,500,000 million per quality-adjusted life year (QALY) **[R3].**

The cohort of patients in IVAN have also continued to be followed up producing important findings on the relationship between fluctuations in retinal thickness and prognosis for patients with neovascular age-related macular degeneration **[R5]** and the trajectory of functional decline in their study eye **[R6].**

IVAN's findings have also had an important influence on the results and conclusions for Cochrane Reviews of the safety and effectiveness of anti-VEGF treatments for AMD (Moja 2014; Solomon 2019):

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, Virgili G. Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration. Cochrane Database of Systematic Reviews 2014;(9):CD011230 doi: 10.1002/14651858.CD011230.pub2

Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. Cochrane Database of Systematic Reviews 2019;(3):CD005139 doi: 10.1002/14651858.CD005139.pub4

3. References to the research

R1. **Chakravarthy U**, Harding SP, Rogers CA, Downes SM, Lotery AJ, Culliford LA, Reeves BC; IVAN study investigators.. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet 2013;382:1258-67 doi: 10.1016/s0140-6736(13)61501-9

R2. IVAN Study Investigators, **Chakravarthy U**, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S, Reeves BC. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology 2012;119(7):1399-411 doi: 10.1016/j.ophtha.2012.04.015

R3. Dakin HA, Wordsworth S, Rogers CA, Abangma G, Raftery J, Harding SP, Lotery AJ, Downes SM, **Chakravarthy U**, Reeves BC, IVAN Study Investigators. Cost-effectiveness of ranibizumab and bevacizumab for age-related macular degeneration: 2-year findings from the IVAN randomised trial. BMJ Open 2014;4:e005094 doi: 10.1136/bmjopen-2014-005094

R4. **Chakravarthy U**, Harding SP, Rogers CA, Downes S, Lotery AJ, Dakin HA, Culliford L, Scott LJ, Nash RL, Taylor J, Muldrew A, Sahni J, Wordsworth S, Raftery J, Peto T, Reeves BC.. A randomised controlled trial to assess the clinical effectiveness and cost-effectiveness of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN). Health Technology Assessment 2015;19(78):1-298 doi: 10.3310/hta19780

R5. Evans RN, Reeves BC, Maguire MG, Martin DF, Muldrew A, Peto T, Rogers C, **Chakravarthy U**. Associations of variation in retinal thickness with visual acuity and anatomic outcomes in eyes with neovascular age-related macular degeneration lesions treated with

anti-vascular endothelial growth factor agents. JAMA Ophthalmology 2020;138(10):1043-51 doi: 10.1001/jamaophthalmol.2020.3001

R6. Evans RN, Reeves BC, Phillips D, Muldrew KA, Rogers C, Harding SP, **Chakravarthy U**, IVAN Study Group. 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 2020;127:1191-200 doi: 10.1016/j.ophtha.2020.03.020

4. Details of the impact

AMD affects more than 600,000 people in the UK and tens of millions globally and, without treatment, it quickly leads to blindness. Modern treatments, such as anti-VEGF drugs injected directly into the eye (e.g. ranibizumab and bevacizumab) typically limit the loss of vision over 5 years to 1 to 2 lines of the eye test letter chart, with many patients maintaining vision sufficient to hold a driving licence. However, the very high cost of ranibizumab imposes a huge burden on healthcare services around the world. For instance, in their longitudinal study of the use of anti-VEGF therapy for a variety of eye conditions (including AMD) in England between 2005 and 2015, Hollingworth *et al* concluded in 2017 that 'The high and rising cost of anti-VEGF therapy affects the ability of the NHS to provide care for other patients'. They noted how 'current regulations encourage the increasing use of ranibizumab and aflibercept rather than bevacizumab, which evidence suggests is more cost-effective' and concluded that 'NHS patients in England do not have equal access to the most cost-effective care'.**[S1]**

It is against this backdrop that IVAN has had such an impact. The trial is regarded by the NIHR as one the most important trials of the last decade, and it featured as a NIHR Impact Case Study in August 2019, highlighting that 'The IVAN trial led to significant cost savings for the NHS as well as leading to new clinical guidelines from the National Institute for Health and Care Excellence. It also had international repercussions: the trial's finding were [sic] the basis for new recommendations in a World Health Organisation report'.**[S2]**

IVAN had a rapid impact on policy, practice, and debate. As arguments in favour of using bevacizumab are won, the impact on policy and practice is growing, with policy makers and clinicians switching from ranibizumab to bevacizumab.

WHO Essential Medicines

In 2013, the World Health Organisation (WHO) added bevacizumab to its list of essential medicines (EML) for macular degeneration, citing the IVAN findings on safety and efficacy.**[S3]** When the list was revised 2 years later, Novartis (the pharmaceutical company that made both drugs) applied to have ranibizumab added but this was rejected by the WHO Expert Committee, who referred again to the IVAN findings and kept bevacizumab on the list, rejecting the option of showing ranibizumab as an alternative to bevacizumab, noting 'given the difference in current prices of the 2 products and the legislation relating to "off-label" use of medicines in many countries, the Committee decided that indicating interchangeability could well result in considerable additional expenditure at country level, without additional clinical benefit' and 'The Committee considered that inclusion only of the less expensive bevacizumab on the EML might serve to facilitate its use (albeit off-label) for this indication'.**[S4]**

Impact on policy in the UK

In the UK, IVAN catalysed the debate about the cost of medicines and led to a campaign for approval for use of bevacizumab. NHS Commissioners joined with doctors in calling for the right to use the drug, lobbying the National Institute for Health and Care Excellence (NICE), the Department of Health, the Secretary of State and the General Medical Council. It was reported in February 2015 that 'clinical leaders from 120 Clinical Commissioning Groups, representing almost 60% of all CCGs, have come together to call on the doctors' regulator the General Medical Council, the Department of Health and NHS England to remove the current barriers preventing CCGs from commissioning safe and effective eye care services using the drug Avastin 'off- licence' to treat the debilitating condition of Wet Age related Macular

Degeneration (AMD)'.**[S5]** In September 2018, in a ruling welcomed by the Royal College of Ophthalmologists,**[S6]** the High Court of England and Wales supported the request from 12 NHS clinical commissioning groups (CCG) in the north of England to give bevacizumab to people with worsening sight loss, upholding the principle that commissioners of health care and doctors may offer patients this drug instead of ranibizumab or other more recently licensed treatments,**[S6]** and the ruling was upheld by the Court of Appeal in March 2020.**[S6]** In 2019, practitioners in NHS Scotland began to use bevacizumab in preference to ranibizumab.

Impact on policy elsewhere in Europe
In November 2017, the European Union Court of Justice supported the use of bevacizumab for AMD by agreeing that it is not contrary to EU law for a national healthcare insurance system to reimburse the costs of a medicinal product for a use not covered by its marketing authorisation (off-label use).**[S7]** In September 2020, France fined Novartis and Roche EUR444,000,000 after its competition authority ruled that the drug companies used abusive practices to promote the use of one of their drugs Lucentis (ranibizumab) over Avantis (bevacizumab).**[S8]**

Impact on guidance in the UK
Current NICE guidance on AMD (published in January 2018) makes wide use of IVAN. The Guideline Committee took the view 'that there is equivalent clinical effectiveness and safety of different anti-VEGF agents (aflibercept, bevacizumab and ranibizumab)', but that 'At the time of publication (January 2018), bevacizumab did not have a UK marketing authorisation for, and is considered by the Medicines and Healthcare products Regulatory Agency (MHRA) to be an unlicensed medication in, this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the prescribing decision. Informed consent would need to be obtained and documented'.**[S9]** The Royal College of Ophthalmologists noted 'There is now the potential to make considerable cost savings whilst empowering ophthalmologists to make clinical judgements with individual patients on the most appropriate choice of treatment'.**[S10]**

Impact on health expenditure in the USA
In financial terms, in 2014, Hutton et al estimated that switching to bevacizumab from other anti-VEGF agents could lead to total health savings of up to USD29,000,000,000 over 10 years in the USA.**[S11]** A later study, published in 2018, estimated that Medicare in the USA had saved USD17,300,000,000 billion between 2008 and 2015 from the use of bevacizumab for AMD.**[S11]**

Impact on the evidence base
In March 2019, the most recent update of the Cochrane Review of anti-VEGF treatments of AMD concluded that 'ranibizumab and bevacizumab have equivalent safety and effectiveness in such eyes' and that the stability of this evidence meant that the authors 'do not anticipate a need for future updates to this systematic review'.**[S12]**

Finally, IVAN's importance was also a key factor in awards received by Professor Chakravarthy. These include her CBE (2016), the Bowman award from the Royal College of Ophthalmologists (2018), the Gass Medal from the international Macula Society (2019) and a lifetime honorary Fellowship at the Royal College of Ophthalmologists (2019).

5. Sources to corroborate the impact

S1. Hollingworth W, Jones T, Reeves BC, Peto T. A longitudinal study to assess the frequency and cost of antivascular endothelial therapy, and inequalities in access, in England between 2005 and 2015. BMJ Open 2017;7(10):e018289 doi: 10.1136/bmjopen-2017-018289.

S2. NIHR case study for IVAN. www.nihr.ac.uk/documents/case-studies/ivan-impact-case-study/21912 (accessed 1 February 2021).

S3. WHO Expert Committee. The Selection and Use of Essential Medicines. World Health Organisation, 2013 (especially page 70). Available at apps.who.int/iris/bitstream/handle/10665/112729/WHO_TRS_985_eng.pdf (accessed 1 February 2021).
S4. WHO Expert Committee. The Selection and Use of Essential Medicines. World Health Organisation, 2015. Available at apps.who.int/iris/bitstream/handle/10665/189763/9789241209946_eng.pdf (accessed 1 February 2021).
S5. News release from NHS Clinical Commissioners. Available at www.nhscc.org/latest-news/doctors-unite-seeking-support-commissioning-safe-effective-eye-care-services-will-save-nhs-millions/ (accessed 1 February 2021).

S6. News articles on High Court Decision. Multiple sources combined as one pdf:

- News release from Royal College of Ophthalmologists. Available at www.rcophth.ac.uk/2018/09/the-royal-college-of-ophthalmologists-is-delighted-that-the-high-court-has-found-in-favour-of-the-use-of-avastin-for-wet-amd/ (accessed 1 February 2021).

- Cohen D. CCGs win right to offer patients Avastin for wet AMD. BMJ 2018;362:k4035 doi: 10.1136/bmj.k4035.

- Court of Appeal judgement. Available at www.landmarkchambers.co.uk/wp-content/uploads/2020/03/Bayer-for-hand-down-24.3.2020.pdf (accessed 1 February 2021).

S7. Press release from Court of Justice of the European Union. Available at curia.europa.eu/jcms/upload/docs/application/pdf/2018-11/cp180181en.pdf (accessed 1 February 2021).

S8. Reuters news release. Available at www.reuters.com/article/us-novartis-roche-lucentis-idUSKBN2601SD (accessed 1 February 2021).

S9. National Institute for Health and Care Excellence. Age-related macular degeneration: NICE Guideline NG82. NICE, 2018 (page 172). Available at www.nice.org.uk/guidance/ng82/evidence/full-guideline-pdf-170036251098 (accessed 1 February 2021).

S10. News release from Royal College of Ophthalmologists. Available at www.rcophth.ac.uk/2018/01/new-nice-age-related-macular-degeneration-guidance-supports-potential-cost-savings-for-the-nhs/ (accessed 1 February 2021).

S11. Articles on cost savings. Multiple sources combined as one pdf:

- Hutton D, Newman-Casey PA, Tavag M, Zacks D, Stein J. Switching to less expensive blindness drug could save Medicare Part B $18 billion over a ten-year period. Health Affairs 2014;33(6):931-9 doi: 10.1377/hlthaff.2013.0832.

- Rosenfeld PJ, Windsor MA, Feuer WJ, Sun SJJ, Frick KD, Swanson EA, Huang D. Estimating Medicare and patient savings from the use of bevacizumab for the treatment of exudative age-related macular degeneration. American Journal of Ophthalmology 2018;191:135-9 doi: 10.1016/j.ajo.2018.04.008.

S12. Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. Cochrane Database of Systematic Reviews 2019;(3):CD005139 doi: 10.1002/14651858.CD005139.pub4.