

Institution: Queen's University Belfast		
Unit of Assessment: UoA 2		
Title of case study: EAGLE transforms the evidence base for primary angle-closure glaucoma, changing guidance and practice		
Period when the underpinning research was undertaken: 2009 to 2016		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Augusto Azuara-Blanco	Role(s) (e.g. job title): Clinical Professor; Centre for Public Health; School of Medicine, Dentistry and Biomedical Sciences	Period(s) employed by submitting HEI: 2013 onwards
Period when the claimed impact occurred: 2016 onwards		
Is this case study continued from a case study submitted in 2014? No		
1. Summary of the impact <p>Glaucoma is the leading cause of irreversible blindness in the world but this global burden is being reduced because EAGLE showed the benefits of clear lens extraction (CLE) surgery for angle-closure glaucoma. Globally, 20 million people have primary angle closure glaucoma and 4 million have been blinded by it, mostly in low- and middle-income countries. EAGLE, described as a landmark glaucoma trial by the European Glaucoma Society provided robust evidence, supporting a change in practice. It showed that initial CLE is associated with better clinical and patient-reported outcomes and is likely to be cost-effective in publicly funded health systems. It has led to changes in practice and national and international guidelines, with important impacts in East Asia in particular, where this condition is most prevalent.</p>		
2. Underpinning research <p>The Effectiveness, in Angle-closure Glaucoma, of Lens Extraction (EAGLE) randomised trial (ISRCTN44464607) provides robust, up-to-date evidence about the treatment of primary angle closure glaucoma (PACG), which is a severe condition that can lead to irreversible blindness. The trial was led by Professor Azuara-Blanco, whose research at QUB is focused on improving eye care and investigating the efficacy, efficiency and safety of new technologies for diagnosing and treating eye diseases through large publicly-funded multicentre trials. (https://pure.qub.ac.uk/en/persons/augusto-azuara-blanco)</p> <p>EAGLE was funded by the Medical Research Council and managed by the National Institute for Health Research. The design of the trial included several innovative methodological aspects and novel features, in particular the use of a patient-reported, general health utility measure (EQ-5D) as primary outcome, which is well accepted as a particularly useful measure to directly inform health policy. Furthermore, alongside randomisation to form the two treatment groups, EAGLE's strengths include its prospective data collection, pragmatic design, large sample size, involvement of multiple centres in the UK, Asia (China (including Hong-Kong), Singapore and Malaysia), and Australia, and the masking of the clinical assessments in particular for intraocular pressure (IOP), visual acuity and refraction, which minimised the potential risk of bias. Patients and a glaucoma patient organisation (the International Glaucoma Association, IGA) had active input to the trial's design, conduct and dissemination. EAGLE also had robust safety monitoring by an independent committee and, with strong support from patients and the IGA, used a patient-reported outcome (PRO) in its primary analysis.</p> <p>EAGLE recruited 419 participants from 30 hospital eye services in 5 countries, from January 2009 to December 2011 and randomised them to clear lens extraction (CLE) surgery or laser peripheral iridotomy (PI), which has been the standard of care for several years and often requires the patient to use eye drops for some time after the procedure. EAGLE patients had either PAC with</p>		

intraocular pressure (IOP) of 30 mmHg or higher or non-severe PACG. The trial showed that patients who were treated with CLE surgery had better quality of life based on the EQ-5D measurements, better IOP control, and required fewer medications and surgeries to control their glaucoma, than those undergoing laser PI. Visual acuity outcomes were similar between the two treatments and there were low rates of surgical complications and irreversible vision loss in both groups. Of note, 126 (60.6%) patients in the CLE surgery group did not require any medication to control their condition at 3 years, and only 1 participant (0.5%) required glaucoma surgery. In contrast, in the standard care group (laser PI), only 45 (21.3%) participants did not require medications and 24 (11.3%) participants required further glaucoma surgery by 3 years [R1, R2]. Given these positive findings, EAGLE provides practitioners and patients with robust evidence that the decision on whether or not to perform CLE surgery as primary therapy for PACG patients should depend largely on an individualised approach to the potential harms and benefits.

Furthermore, the EAGLE economic evaluation shows that CLE surgery offers a cost-effective approach to treatment in patients with newly diagnosed PAC or PACG. The incremental cost-effectiveness ratio versus standard care was £14,284 per quality adjusted life year (QALY) gained at three years, giving CLE a 67-89% chance of being cost-effective at that time point (assuming a willingness to pay value of £20,000 per QALY gained), and extrapolation suggests that it may be cost saving by ten years [R3].

3. References to the research

1. **Azuara-Blanco A**, Burr J, Ramsay C, Cooper D, Foster PJ, Friedman DS, Scotland G, Javanbakht M, Cochrane C, Norrie J, EAGLE study group. Effectiveness of early lens extraction for the treatment of primary angle-closure glaucoma (EAGLE): a randomised controlled trial. *Lancet* 2016;388:1389-97 doi: 10.1016/S0140-6736(16)30956-4
2. Day AC, Cooper D, Burr J, Foster PJ, Friedman DS, Gazzard G, Che-Hamzah J, Aung T, Ramsay SR, **Azuara-Blanco A**. Clear lens extraction for the management of primary angle closure glaucoma: surgical technique and refractive outcomes in the EAGLE cohort. *British Journal of Ophthalmology* 2018;102:1658-62 doi: 10.1136/bjophthalmol-2017-311447
3. Javanbakht M, **Azuara-Blanco A**, Burr JM, Ramsay C, Cooper D, Cochran C, Norrie J, Scotland G. Early lens extraction with intraocular lens implantation for the treatment of primary angle closure glaucoma: an economic evaluation based on data from the EAGLE trial. *BMJ Open* 2017;7:e013254 doi: 10.1136/bmjopen-2016-013254

4. Details of the impact

Although the effects of the COVID-19 pandemic and its associated measures on eye surgery have had a detrimental effect on the speed of EAGLE's impact, much has already been achieved. This is important given that 76 million individuals are living with glaucoma and it has a global prevalence of 3.54% in people aged 40-80 years. Although primary open angle glaucoma (POAG) is the more prevalent type, primary angle closure glaucoma (PACG) - the condition studied in EAGLE - is more severe and more likely to cause irreversible blindness, has a profound impact on quality of life and places a high economic burden on individuals, health systems and society [S1]. PACG is most prevalent in East Asia but approximately 130,000 people are living with PACG in the UK, and it is more common in women with prevalence increasing with age. Implementation of EAGLE's findings is made easier because the lens extraction procedure is already widely used for cataract surgery. It is the commonest surgical procedure performed in the western world, and one of the commonest operations in low- and middle-income countries (LMICs). As such, the necessary equipment and skills are available to allow the swift and straightforward change in management policy without additional training or capital expenditure.

The pragmatic nature of EAGLE and its inclusion of 30 sites in 5 countries with very different healthcare models and average income have been recognised as important features by commentators [S2], and helped demonstrate the generalisability of its findings and are facilitating

their uptake. There has been substantial international interest in EAGLE with Professor Azuara-Blanco invited to present the findings at the World Glaucoma Congress and meetings of the European Glaucoma Society, UK and Ireland Glaucoma Society, Canadian Ophthalmological Society and German Ophthalmological Society. He was awarded the **King James IV Professorship by the Royal College of Surgeons of Edinburgh** in 2020 for his work on the EAGLE trial. The EAGLE findings were also welcomed by organisations such as the Glaucoma Research Foundation [S3] and, as noted in the President of the European Glaucoma Society's *Lancet* commentary [S4] which accompanied the 2016 paper: 'This is also the first prospective randomised therapeutic trial in ophthalmology in which one of the primary outcome measures is patient reported, through quality-of-life questionnaires. ... **This pragmatic trial is clinically relevant because it addresses a topic with widespread practical implications**'. In 2019, a review article in *Eye*, the journal of the Royal College of Ophthalmologists concluded that the evidence from EAGLE that CLE was the superior treatment for both patient reported quality of life and IOP control indicates that CLE should be considered for first-line treatment of more advanced angle-closure disease, and that '[t]he **EAGLE study has laid the foundations for CLE to be implemented into the UK**' [S5].

Impact on practice in East Asia

The evidence from EAGLE that CLE is superior for patient, clinical and economic outcomes, along with the absence of any serious safety issues with the procedure, provided compelling evidence to support a change in practice towards improved health outcomes for people with primary angle-closure glaucoma and has particular relevance to LMICs where access to chronic medical therapy for the management of glaucoma is often not possible, but the skill and facilities to undertake lens extraction is well developed. As a consequence, EAGLE's findings have led to changes in national and international guidelines (see below) and had important impacts on practice in East Asia, where this condition is particularly prevalent. For example, following EAGLE, Professor Jelinar Mohamed Noor from the Ministry of Health in Malaysia said '**early lens removal is the current practice amongst us all who are with the Ministry of Health Malaysia**' and his colleague, Professor Jemaima Che hamzah, Head and Consultant Ophthalmologist at the Hospital Universiti Kebangsaan Malaysia noted 'this practice is being used by most of my colleagues across Malaysia and Singapore'. Furthermore, in China, Professor Yuanbo Liang, professor and director of the Clinical and Epidemiological Eye Research Center, in Wenzhou Medical University said: 'In our hospital, 60% of glaucoma patients had been treated with phaco, and Asia pacific cataract guideline has recommended phaco as a treatment method for PACG. Which means clear lens extract is an option for any PACG' and ophthalmologists in Korea [S6] used the EAGLE results to note 'these approaches [CLE] are likely to be effective for a public support health care system'.

Impact on practice in the UK

The importance of EAGLE to practitioners in the UK is emphasised by the fact it was **one of only two trials** that were specifically asked about in a survey of glaucoma specialists to inform the Royal College of Ophthalmologists' latest guidelines. Among the 28 glaucoma experts who responded to this survey, 10 (36%) replied that the EAGLE results mean that they now routinely offer CLE to all patients with PACG and PAC with high IOP and a further 11 (39%) now consider CLE in some of these patients.

Impact on guidelines

EAGLE has influenced guidelines about the management of angle-closure glaucoma from the American Academy of Ophthalmology, the Royal College of Ophthalmologists and the European Glaucoma Society. All these guidelines, which were due to be published in 2020, were delayed by COVID-19 but their recommendations reflect the conclusions of EAGLE about CLE surgery being an important and acceptable alternative to laser PI. For example, a key feature of the new European Glaucoma Society guidelines is the change from the 4th edition in 2014 [S7], which stated that the use of laser iridotomy as the initial procedure for patients with PACG 'is justified in practically every case' (page 112) to a new strong recommendation in the 5th edition giving equal status to that technique and CLE based on the findings of EAGLE which is listed as one of **landmark glaucoma trials** (pages 26, 36 and 47) [S8]. These guidelines will be promoted across the European Glaucoma Society's platforms, and their widespread dissemination is likely to

exceed the 200,000 printed copies, over 100,000 downloads and translations into 12 languages of the 4th edition. Furthermore, in keeping with the impact on practice in East Asia, local guidelines there now reflect the findings of EAGLE. For example, the glaucoma guidelines for Malaysia recommend that 'early lens extraction may be considered as first-line treatment in primary angle closure and primary angle closure glaucoma' (page 24) [S9].

5. Sources to corroborate the impact

S1. WHO website on blindness and vision impairment. Available at www.who.int/health-topics/blindness-and-vision-loss (accessed on 27 January 2021).

S2. Chan PP, Tham CC. Commentary on effectiveness of early lens extraction for the treatment of primary angle-closure glaucoma (EAGLE). *Annals of Eye Science* 2017;2:4 doi: 10.21037/aes.2017.03.01.

S3. News release from the Glaucoma Research Foundation. Available at www.glaucoma.org/news/blog/could-cataract-surgery-be-a-new-treatment-option-for-primary-closed-angle-glaucoma.php (accessed on 27 January 2021).

S4. Traverso CE. Clear-lens extraction as a treatment for primary angle closure. *Lancet* 2016;388:1352-4 doi: 10.1016/S0140-6736(16)31746-9.

S5. Tanner L, Gazzard G, Nolan WP, Foster PJ. Has the EAGLE landed for the use of clear lens extraction in angle-closure glaucoma? And how should primary angle-closure suspects be treated? *Eye* 2020;34(1):40-50 doi: 10.1038/s41433-019-0634-5.

S6. Sung KR, Lee JY, Kim JM. Clear lens extraction as the first line treatment of primary angle closure/primary angle closure glaucoma. *Annals of Eye Science* 2017;2:6 doi: 10.21037/aes.2017.01.06.

S7. European Glaucoma Society. Terminology and Guidelines for Glaucoma, 4th edition. 2014. Available at bj.o.bmj.com/content/101/5/73 (accessed on 11 March 2021).

S8. European Glaucoma Society. Terminology and Guidelines for Glaucoma, 5th edition. 2020. Available at www.eugs.org/eng/guidelines.asp (accessed on 11 March 2021).

S9. Malaysian Health Technology Assessment Section. Management of Glaucoma, 2nd edition. Malaysian Health Technology Assessment Section: Putrajaya, Malaysia 2017. Available at [www2.moh.gov.my/moh/resources/Penerbitan/CPG/Eye%20Condition/CPG%20Management%20of%20Glaucoma%20\(Second%20Edition\).pdf](http://www2.moh.gov.my/moh/resources/Penerbitan/CPG/Eye%20Condition/CPG%20Management%20of%20Glaucoma%20(Second%20Edition).pdf) (accessed on 11 March 2021).