Institution: University of Strathclyde

Unit of Assessment: 10

Title of case study: Changes to European Society of Cataract and Refractive Surgery guidelines reduces loss of sight for patients undergoing cataract surgery

1. Summary of the impact (indicative maximum 100 words)

Research at Strathclyde has brought about a change in eye surgery practice throughout Europe and worldwide. A four-year cross-Europe study in collaboration with the European Society of Cataract and Refractive Surgery (ESCRS) investigated antibiotic treatment to prevent endophthalmitis, a complication arising during cataract operations which typically results in loss of sight. The findings showed that when the treatment is given at the start of surgery it leads to a 5-fold reduction in the risk of endophthalmitis. The European Society of Cataract and Refractive Surgery has endorsed the discovery and widely promoted the uptake of the treatment through publications and guidelines, which over the last 6 years has led to the prevention of loss of sight in thousands of patients. In Europe alone it is estimated that each year there have been 7500 fewer cases of blindness following cataract surgery as a result of the ESCRS guidelines.

2. Underpinning research (indicative maximum 500 words)

Context: Cataract surgery with intra-ocular lens implantation is the most commonly performed surgical procedure in the aging European population. In 2003, almost 2.5 million operations were performed in France, Germany, Italy, Spain and the United Kingdom [1]. With an increasing elderly population, the number of people worldwide requiring such surgery will rise in the decades to come. Although cataract surgery procedures are usually successful in restoring failing eyesight, they were responsible for permanent and significant loss of vision resulting from severe postoperative infective endophthalmitis, acute inflammation of the eye arising from bacterial infection, in up to 0.1% of patients. This unacceptably high risk of post-operative infection with loss of vision was an important unsolved problem of the procedure. In 2003, the only prophylactic procedure against infection regarded as proven was the use of povidone iodine (5%) in the conjunctival sac just before surgery. Numerous retrospective, comparative or single-use studies had been published in support of various proposed regimes of antibiotic use as prophylaxis. All, however, could be suspected of bias, or were of insufficient power to provide convincing evidence of benefit.

Key findings: Because of the rarity of the complication, the size of study needed to establish the benefit of any proposed regime was beyond the reach of any single ophthalmic unit. In recognition of this the European Society of Cataract and Refractive Surgery approached the Informatics and Epidemiology modelling group at the University of Strathclyde to design and execute a large scale clinical European study, together with state-of-the-art statistical analysis. This group was internationally recognised for their work on integrating mathematical and information modelling approaches in areas such as differential diagnosis of disease using a Bayesian belief network [5] and a decision support system on drug use for control of trypanosomiasis in Africa [6], and this previous research led directly to the invitation from ESCRS.

The statistical design identified was a prospective randomised study based on Fisher's classical 2x2 factorial design principle. Such a design was novel for a cataract study and rarely possible in such large scale multinational studies for ethical and logistical reasons, but optimum for estimating treatment effects and their interaction. The study involved twenty-four hospitals and ophthalmic clinics in Austria, Belgium, Germany, Italy, Poland, Portugal, Spain, Turkey, and the United Kingdom. It tested the use of the cefuroxime antibiotic and one other treatment, the perioperative use of drops of the antibiotic levofloxacin. The study was led by the statistical and data management unit at the University of Strathclyde involving staff in the Department of Mathematics and Statistics and the Department of Computer Science, and supported by an administrative office in Ireland and a co-ordinating centre in England.

By December 2005 the study had recruited almost 14000 patients and it was becoming clear that the study was almost certainly demonstrating that at least one of the methods of prophylaxis under test was proving to be effective. As a result, recruitment of patients into the study was brought to an end in January 2006, by which date over 16000 patients had been recruited. The principal result was that levofloxacin administered topically was ineffective, whereas those patients receiving intracameral cefuroxime injection had a large reduction in the incidence of endophthalmitis. This led to publication of the preliminary results [2] in the Journal of Cataract and Refractive Surgery in March 2006. This journal was chosen by the European Society of Cataract and Refractive Surgeons so that the results could be directly disseminated to a large proportion of the community of European ophthalmic surgeons as quickly as possible. Full publication of the definitive results took place in 2007 so that the follow-up of late recruits to the Study could be completed [3]. This showed to the community of ophthalmic surgeons that this use of cefuroxime as a prophylactic results in an approximate 5-fold reduction in the risk of post-operative endophthalmitis.

The use of intracameral cefuroxime led to a reduced endophthalmitis incidence rate of 5 per 10000 patients compared to 35 per 10000 patients in the control group. A further publication [4] investigated more fully those cases of endophthalmitis which had occurred during the study and in particular all clinical outcomes associated with the endophthalmitis cases.

Key researchers: The key researchers were Professor George Gettinby and Mr Magnus Peterson of the Department of Mathematics & Statistics who designed the study, undertook the analyses and prepared the papers for publication, and Professor Crawford Revie and Ms Fiona Lees of the Department of Computer and Information Sciences who developed the multi-site database and undertook data acquisition and management operations over the 5 year period of the study. Medical contributions were provided by the Study Director, Dr Peter Barry, a consultant ophthalmic surgeon based in Dublin and the Clinical Trial Coordinator, Dr David Seal, a consultant ophthalmologist based at the University of London.

3. References to the research (indicative maximum of six references)
References 2, 3 and 4 best indicate the quality of the underpinning research

1. Seal, D.V., Barry, P., Gettinby, G., Lees, F., Peterson, M., Revie, C. & Wilhelmus, K.R. (2006) ESCRS study of prophylaxis of postoperative endophthalmitis after cataract surgery: Case for a European multicentre study. Journal of Cataract and Refractive Surgery, 32(3), 396- 406

2. Barry, P., Seal, D.V., Gettinby, G., Lees, F., Peterson, M. & Revie, C. (2006) ESCRS study of prophylaxis of postoperative endophthalmitis after cataract surgery: Preliminary report of principal results from a European multicentre study. Journal of Cataract and Refractive Surgery, 32(3), 407-410

3. Barry, P., Seal, D.V., Gettinby, G., Lees, F., Peterson, M. & Revie, C. (2007) ESCRS Endophthalmitis Study Group. Prophylaxis of postoperative endophthalmitis following cataract surgery: results of the ESCRS multicentre study and identification of risk factors. Journal of Cataract Refractive Surgery, 33(6), 978-988

4. Barry, P., Gardner, S., Seal, D., Gettinby, G., Lees, F., Peterson, M. & Revie, C. (2009) Clinical observations associated with proven and unproven cases in the ESCRS study of prophylaxis of postoperative endophthalmitis after cataract surgery. Journal of Cataract & Refractive Surgery, 35, 1523-1531.

5. McKendrick. I.J., Gettinby, G., Gu, Y., Reid, S.W.J. and Revie, C. (1999) Using a Bayesian belief network to aid differential diagnosis of tropical bovine diseases. Preventive Veterinary Medicine , 47: 141-156

6. Gu, Y., Gettinby, G., McKendrick. I.J., Murray, M., Peregrine, A. and Revie, C. (1999) Development of a Decision Support System for Trypanocidal Drug Control of Bovine Trypanosomosis in Africa. Veterinary Parasitology, 87: 9-23

Other evidence for quality of research:
References 2, 3 and 4 were the journal's most cited papers in their respective year of publication. Since publication, references 2 and 3 have been cited 223 and 157 times respectively. Reference 3 provided further in-depth findings following the completion of the study. All papers were published in the same journal at the request of the funding body in order to ensure the most rapid and effective dissemination of results to the European community of cataract surgeons.
A series of grants valued at €314,000 were made to the University of Strathclyde between March 2002 and Feb 2007 for the study of Antibiotic Prophylaxis in Cataract Surgery by the European Society of Cataract and Refractive Surgery.

4. Details of the impact (indicative maximum 750 words)

Process from research to impact:
In 2002, a leading Swedish cataract surgeon reported low rates of endophthalmitis following the use of an injection of the antibiotic cefuroxime into the anterior chamber of the eye at the time of cataract surgery. The European Society of Cataract and Refractive Surgeons (ESCRS) required further evidence, and the President of ESCRS confirms that "in 2002, Profs Gettinby and Revie were approached by a consultant ophthalmologist acting on behalf of the European Society of Cataract and Refractive Surgeons with a view to designing and implementing a large scale randomised endophthalmitis study, and they were approached on the basis of this work in this field and their expertise in the analysis of large datasets" [Source 1]. Gettinby and Revie recommended a controlled clinical trial and were subsequently commissioned to implement what would be referred to by leading European surgeons as "one of the largest prospective European clinical studies of antibiotic prophylaxis and the largest in ophthalmology" [Source 2].

The publication of results in 2006 and 2007 showed to the community of ophthalmic surgeons that this use of cefuroxime as a prophylactic results in an approximate 5-fold reduction in the risk of post-operative endophthalmitis. At this point use of the published findings was having a greater impact and many surgeons were adopting the use of cefuroxime injection.

The President of ESCRS confirms that "the results of the study had direct influence on the ESCRS guidelines on 'Prevention, Investigation and Management of Post-Operative Endophthalmitis', which were revised in 2007 on the basis of Gettinby and Revie's published research" [Source 1]. Central to these new guidelines [Source 3] was the recommendation that surgeons consider the use of cefuroxime intracameral injection. Although cefuroxime was unlicensed and the decision to use it was at the discretion of the surgeon, this was the beginning of changing practices by cataract surgeons in Europe.

Types of Impact: the publication of Gettinby and Revie's study has led directly to impact on professional practice, patient welfare, and wider benefits:

Changes to professional practice: The publication of the results and changes to ESCRS guidelines has led to a change in the way that cataract surgery is supported by antibiotic treatment since 2008 onwards. The reach in Europe has been extensive. The European Society of Cataract and Refractive Surgery [Source 4] has been successfully promoting the findings, with uptake of their guidelines first reaching significant levels from 2008 to 2010, [Source 5]. For example, the Austrian Society of Ophthalmology recommended adoption of the ESCRS guidelines with its focus on the use of the study findings concerning cefuroxime, and there was evidence (Ocular Surgery News Europe/ Asia – Pacific Edition December 1 2008) of cefuroxime being used in hospitals in Italy, Spain and Ireland.

The following are quotations which appeared in the ESCRS Eurotimes vol. 18, Issue 3, March 2013, pages 4-6 [Source 6]:

"The survey has not been repeated, but since that time I think that more American surgeons are using intracameral antibiotics following publication of the study, compared to before." (Clinical Professor of Ophthalmology, University of California & Chinese University, Hong Kong)

"In my country almost nobody has any doubts with regard to the cefuroxime efficiency in endophthalmitis prophylaxis." (Citation from Boris Malyugin MD, International Ophthalmologists Academy, Russia)

"The ESCRS Endophthalmitis Study has made a revolutionary change not only in my practice, but also many practices in India. The use of intracameral moxifloxacin has become routine." (Keiki Mehta MD Medical Director and Chief of the Mehta Charity Eye Hospital, Karja, India).

The president of ESCRS [Source 1] has stated that "From 2008 the guidelines significantly increased the use of antibiotic intracameral injections following cataract surgery on an international scale. This change in clinical practice has undoubtedly reduced the incidence of blindness resulting from post-operative infections of the eye."

Benefits to patients: A cefuroxime injection to the eye at time of surgery will prevent endophthalmitis occurring post operatively; and this procedure has now been widely adopted by eye surgeons internationally. The adoption of this simple process has saved the sight of thousands of patients annually who may otherwise have developed infection of the eye. Based on data from the Organisation of Economic Cooperation and Development it is estimated that ophthalmologists undertake more than three million cataract operations in Europe each year. It is estimated that there are now 2500 fewer cases of loss of sight per 1,000,000 cataract patients, leading to 7500 fewer cases of blindness per year in Europe alone. This estimate is conservative as uptake of the study findings worldwide is expected to lead to thousands more patients avoiding loss of sight.

Wider impact: The influence of the original research is still gaining momentum. In 2013 one commercial company was granted a marketing authorisation for an injectable cefuroxime product for the prevention of endophthalmitis. The president of ECSRS has also confirmed that "the guidelines have been re-written by me and others and submitted to the publishers for re-launching at our annual congress in Amsterdam in October 2013. They contain a further wealth of published evidence of the world-wide benefits accruing from the original study" [Source 1].

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Statement from President of the European Society of Cataract and Refractive Surgery and Consultant Ophthalmic Surgeon Royal Victoria Eye and Ear and St Vincent's University Hospitals Dublin Ireland, supports the claim(s) that Gettinby and Revie were approached on the basis of their prior research, that their research influenced ESCRS guidelines and there has been an international impact in reducing blindness in cataract patients.
2. Izdebska J and Szaflik JP (2005) Levofloxacin (oftaquix) a fluoroquinolone of a new generation in prevention of the postoperative endophthalmitis following uncomplicated cataract surgery - the study of the European Society of Cataract and Refractive Surgeons (ESCRS). Klinika Oczna. 107: 344-347.
3. Document - ESCRS Guidelines on prevention, investigation and management of post-operative endophthalmitis (August 2007)
4. European Society of Cataract and Refractive Surgery website http://www.escrs.org/
5. Ocular Surgery News – shows increased used of antibiotic injections across Europe http://www.healio.com/ophthalmology/cataract-surgery/news/online/%7B7f141eb8-dfd9-4f2f-b341-18cb41bbdf7f%7D/increasing-number-of-european-ophthalmologists-rely-on-intracameral-cefuroxime-for-endophthalmitis-prevention
6. ESCRS EUROTIMES vol 18, Issue 3, March 2013 pages 4-6: http://issuu.com/eurotimes/docs/et18-3 with testimonials from surgeons