Institution: The University of Oxford

Unit of Assessment: 1

Title of case study:

THE INTERNATIONAL SUBARACHNOID ANEURYSM TRIAL: CHANGING CLINICAL PRACTICE

Summary of the impact:

The University of Oxford's International Subarachnoid Aneurysm Trial (ISAT) changed clinical practice worldwide by showing that endovascular coiling is a more effective and safer treatment than neurosurgery following subarachnoid haemorrhage, with fewer complications and improved quality of life. Subarachnoid haemorrhages account for 1 in 14 strokes and are caused by bleeding in and around the brain; approximately 85% occur when cerebral aneurysms rupture. ISAT was the first trial to compare neurosurgery, or neuroradiological endovascular coiling in patients with ruptured cerebral aneurysms causing acute subarachnoid haemorrhage.

Underpinning research:

A subarachnoid haemorrhage occurs when a cerebral aneurysm (a bulge in a weakened wall of a brain blood vessel) ruptures. This predominately occurs in the subarachnoid space surrounding the brain and is responsible for up to 7% of all strokes[1], while 50% of haemorrhages are fatal[2]. For a long time the standard treatment for cerebral aneurysms was neurosurgical clipping, an invasive procedure requiring general anaesthetic and craniotomy, where the surgeon removes a small piece of bone from the skull and inserts a metal clip into the aneurysm to seal it.

In 1991, Dr Guido Guglielmi at the University of California Los Angeles[3,4] developed a less invasive technique called endovascular coiling. This technique uses detachable platinum coils, which are inserted into the aneurysm using a microcatheter via an artery in the leg or groin. The coils block blood flow to the aneurysm and stop the aneurysm from growing. Over time the coils seal the aneurysm off from the main artery to prevent rupture.
While this technique (which can be done under local anaesthetic) quickly became a popular alternative to neurosurgical clipping, the relative benefits of the two treatments remained uncertain.

In 1994 Professor Rury Holman of the University of Oxford's Diabetes Trials Unit collaborated with Mr Richard Kerr and Dr Andrew Molyneux from the University of Oxford's Neurovascular Research Unit, to design and manage a clinical trial on behalf of the International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. This compared the safety and efficacy of the new endovascular coiling treatment with neurosurgical clipping for subarachnoid aneurysms[5].

This five-year randomised controlled trial enrolled 2,143 patients with ruptured intracranial aneurysms from 42 neurosurgical centres in 12 countries throughout the UK and Europe, with 1,070 patients allocated to neurosurgical clipping and 1,073 to endovascular coiling. Clinical outcomes were assessed at two months and at one year after randomisation[5]. The trial was stopped early in May 2002 when data showed that patients receiving the neurosurgical clipping technique were at a significant disadvantage to those who were randomised to the endovascular coiling treatment[5]. The trial results, published in 2002, showed that patients allocated to endovascular treatment were 23% less likely to be dependent on carers, and 7% were less likely to have died than those allocated to neurosurgical clipping[5].

Results from this ISAT trial, which showed endovascular coiling to be the superior treatment for cerebral aneurysms, have led to the adoption of coiling as the preferred treatment worldwide for ruptured cerebral aneurysms.

References to the research:

1. Feigin, V. L. *et al.* Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. *Stroke* **36**, 2773–2780 (2005). ***Article providing an overview of the risk factors for subarachnoid haemorrhage.***

2. van Gijn, J., Kerr, R. S. & Rinkel, G. J. E. Subarachnoid haemorrhage. *Lancet* **369**, 306–318 (2007). ***Paper providing information about subarachnoid haemorrhage.***

3. Guglielmi, G., Viñuela, F., Sepetka, I. & Macellari, V. Electrothrombosis of saccular aneurysms via endovascular approach. Part 1: Electrochemical basis, technique, and experimental results. *J. Neurosurg.* **75**, 1–7 (1991). ***Part I: Primary paper from Doctor Guido Guglielmi, University of California Los Angeles, outlining the endovascular approach to treating aneurysms.***

4. Guglielmi, G., Viñuela, F., Dion, J. & Duckwiler, G. Electrothrombosis of saccular aneurysms via endovascular approach. Part 2: Preliminary clinical experience. *J. Neurosurg.* **75**, 8–14 (1991). ***Part II: Primary paper from Doctor Guido Guglielmi, University of California Los Angeles, presenting data from clinical trial for endovascular coiling.***

5. Molyneux, A. *et al.* International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* **360**, 1267–1274 (2002). ***Primary paper from ISAT clinical trial, which was managed by the University of Oxford's Diabetes Trials Unit and Neurovascular Research Unit.***

The pilot phase of this study was supported by a grant from Oxford Regional Health Authority Research and Development (1994–1997). The main trial was supported by grants from: the Medical Research Council, UK; and Programme Hospitalier de Recherche Clinique 1998 of the French Ministry of Health (AOM 98150). It was sponsored by Assistance Publique, Hôpitaux de Paris (AP-HP); the Canadian Institutes of Health Research; and the Stroke Association of the UK for the Neuropsychological assessments.

Details of the impact:

The International Subarachnoid Aneurysm Trial (ISAT) was the first of its kind to compare neurosurgical clipping and endovascular coiling for patients suffering from subarachnoid haemorrhage. It showed endovascular coiling to be the superior treatment for cerebral aneurysms, leading to significant changes in clinical guidelines for the management of aneurysmal subarachnoid haemorrhage, and major changes in practice around the world.

Clinical Guidelines:

In 2012 the American Heart Association and American Stroke Association issued guidelines for the management of aneurysmal subarachnoid haemorrhage, recommending endovascular coiling for patients with ruptured aneurysms[6]. The guidelines, which cite ISAT as their primary source of data, support the use of coiling as the preferred treatment for patients with aneurysmal subarachnoid haemorrhage, and also emphasise the importance of follow-up imaging for patients who have received both coiling and clipping treatments due to the small risk of re-bleeding, which was demonstrated in the trial[6]. Current National Institute for Health and Clinical Excellence (NICE) guidelines support the use of coil embolisation of ruptured intracranial aneurysms due to the safety and efficacy of the procedure in comparison to surgical clipping. They also stated that due to the small risk of re-bleeding, patients should receive long-term monitoring following both procedures[7]. In addition, the NICE Interventional Procedures Consultation Document for Embolisation of Intracranial Aneurysms states that the endovascular coiling procedure is superior to surgical clipping in the short term[8]. In 2009 the American Association of Neuroscience Nurses Clinical Practice Guidelines for the Care of Patients with Aneurysmal Subarachnoid Haemorrhage

recommended endovascular coiling as the preferred method of aneurysm treatment in cases where both surgical clipping and endovascular coiling are potential options[9].

Practice Patterns:
A 2003 Position Statement from the Executive Committee of the American Society of Interventional and Therapeutic Neuroradiology and the American Society of Neuroradiology concluded: *"the ISAT study was a well-designed and well-executed, randomized, controlled trial on a large number of patients. These data provide the highest level of evidence supporting the use of detachable coils for patients with ruptured cerebral aneurysms suitable for endovascular therapy"*[10]. The 2009 Stroke Association haemorrhagic stroke factsheet recommends coiling as the preferred treatment option for subarachnoid haemorrhage, because 77% of patients make a good or full recovery, in comparison to 70% following surgical clipping[11]. In the UK, endovascular coiling is increasingly the treatment of choice[12] and this is associated with a beneficial effect on survival. The NHS now claims that 65% of people survive aneurysms in comparison to the 50% mortality rate cited in Jan van Gijn's 2007 Lancet paper on subarachnoid haemorrhage[2]. Such an improved outlook is partly down to better treatment, and party due to more urgent admissions. Patients undergoing neurosurgery have to wait for up to a week to be stabilised for treatment, whereas coiling can be administered immediately.

In a 2011 review[13] analysing the impact of ISAT on clinical practice in the United States, it was concluded that as a result of the trial there were significant pattern changes in the treatment of ruptured aneurysms in the US, with far more patients undergoing the endovascular coiling treatment for ruptured aneurysms than clipping. Changes in clinical guidelines following the publication of ISAT also led to a 3% decrease in mortality for those suffering from ruptured aneurysms[13] in the period up to 2011. The report concluded: *"The results of the ISAT have been associated with a prominent change in practice patterns related to the treatment of ruptured aneurysms.* The review also claimed: *"The cost of hospitalization has increased and the mortality has decreased, presumably due to a larger proportion of patients receiving any treatment and endovascular (coil) treatment"*[13].

Sources to corroborate the impact:

6. Connolly, E. S. *et al.* Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* **43**, 1711-37 (2012).doi:10.1161/STR.0b013e3182587839. ***AHA and ASA guidelines supporting the use of coiling as the preferred treatment for subarachnoid hemorrhage, ISAT is cited as primary evidence.***

7. Coil embolisation of ruptured intracranial aneurysms. Interventional Procedure Guidance 106 (January 2005). *National Institute for Health and Care Excellence* at http://www.nice.org.uk/nicemedia/live/11036/30674/30674.pdf (Accessed 2013). ***Guidelines supporting the use of coil embolization of ruptured intracranial aneurysms in comparison to surgical clipping.***

8. Interventional procedures consultation document - embolisation of intracranial aneurysms. *National Institute for Health and Care Excellence* at http://www.nice.org.uk/guidance/index.jsp?action=article&o=30672 (Accessed 2013). ***NICE Interventional Procedures Consultation Document stating the short term superiority of endovascular coiling procedure in comparison to surgical clipping.***

9. Care of the Patient with Aneurysmal Subarachnoid Hemorrhage: AANN Clinical Practice Guideline Series. *American Association of Neuroscience Nurses* at http://www.aann.org/pdf/cpg/aannaneurysmalsah.pdf (Accessed 2013). ***AANN Clinical Practice Guidelines for the care of patients with aneurysmal subarachnoid hemorrhage, recommending coiling as the preferred method of***

aneurysm treatment in comparison to surgical clipping. ISAT cited as evidence.

10. Derdeyn, C.P. *et al*. The International Subarachnoid Aneurysm Trial (ISAT): a position statement from the Executive Committee of the American Society of Interventional and Therapeutic Neuroradiology and the American Society of Neuroradiology. *AJNR Am J Neuroradiol.* **24**,1404-8 (2003). ***Position statement on the ISAT study and the high level of evidence it presents to support the use of detachable coils.***

11. Haemorrhagic stroke - references used. *The Stroke Association* at http://www.stroke.org.uk/referenced/haemorrhagic-stroke (Accessed 2013). ***Stroke Association UK's haemorrhagic stroke factsheet, recommending coiling as the preferred treatment option for subarachnoid hemorrhage.***

12. Subarachnoid Haemorrhage. *NHS Choices* at http://www.nhs.uk/conditions/Subarachnoid-haemorrhage/Pages/Introduction.aspx (Accessed 2013). ***National Institute of Health UK, online fact sheet for subarachnoid haemorrhage.***

13. Qureshi, A. I. *et al.* Impact of International Subarachnoid Aneurysm Trial results on treatment of ruptured intracranial aneurysms in the United States. Clinical article. *J. Neurosurg.* **114**, 834–841 (2011). ***Paper analysing the impact of the ISAT on treatment patterns in the US.***