Institution: The University of Edinburgh

Unit of Assessment: 4

Title of case study: J: Thrombolysis for acute ischaemic stroke is effective for a wide range of patients, including those over 80 years, and improves long-term function and quality of life

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

Impact: Health and welfare; a large randomised controlled trial (third International Stroke Trial (IST)-3) and meta-analysis determined that the thrombolytic agent recombinant tissue plasminogen activator alteplase is a long-term effective treatment for acute ischaemic stroke in a wide range of patients.

Significance: Thrombolysis would result in 1488 more stroke patients being alive and independent per year in the UK.

Beneficiaries: Stroke patients, the NHS and healthcare delivery organisations, the UK economy.

Attribution: The IST-3 trial was led from UoE (Sandercock), with UoE (Wardlaw, Dennis) and University of Sydney (Lindley) colleagues.

Reach: Worldwide. Applicable to 4 million stroke patients per year; guidelines changed in Europe, N America, Asia, Australia.

2. Underpinning research (indicative maximum 500 words)

Professor Peter Sandercock (Professor of Medical Neurology, UoE, 1987–present) led the third International Stroke Trial (IST-3) (with Professor Joanna Wardlaw (Professor of Applied Neuroimaging, UoE, 1994–present), Professor Martin Dennis (Professor of Stroke Medicine, UoE, 1990–present) and Dr Richard Lindley (Honorary Senior Lecturer, UoE until 2004; then University of Sydney)), which demonstrated that recombinant tissue plasminogen activator (rt-PA; alteplase) is a long-term effective treatment for acute ischaemic stroke in a wide range of patients.

IST-3 was a randomised controlled trial in patients with acute ischaemic stroke of intravenous thrombolysis with rt-PA within 6 hours of stroke onset, evaluating the safety and efficacy of intravenous rt-PA. rt-PA is a serine protease that catalyses the activation of plasminogen to plasmin, the primary thrombolytic enzyme. The study—funded by grants of £5.3M from the UK Medial Research Council, UK Stroke Association, UK Health Foundation, Australian National Health and Medical Research Council and other international agencies—recruited 3035 patients from 2000–2011, the largest-ever randomised trial of this treatment. IST-3 showed that, for a wide range of patients including those with perceived stroke-related contraindications such as ischaemic change on imaging or prior stroke, the odds of surviving to six months with an improved level of disability after rt-PA treatment were 27% greater than in those who did not receive rt-PA [3.1]. The benefits were greatest for those treated early: for every 1000 patients treated within 3 hours of onset, 79 more were alive and independent.

IST-3 provided the first reliable evidence of benefit in people aged over 80. rt-PA is not approved for use in patients over 80 in the European Union, because, prior to IST3, fewer than 100 patients had been included in randomised trials of the treatment. Since about one third of all strokes occur in patients aged over 80, IST-3 sought to evaluate rt-PA in this neglected patient group. IST-3 included 1617 patients aged over 80 and showed that the benefits were no less in this age group than in younger patients [3.1].

IST-3 also demonstrated a long-term improvement in functional ability and quality of life after stroke. Of the 11 previous randomised controlled trials, ten reported outcomes only up to 90 days,

only one small trial reported outcomes at 12 months and none reported effects on health-related quality of life. IST-3 showed that, at 18 months, for patients treated with rt-PA, the odds of surviving with less disability were 30% greater than in those not receiving rt-PA (p = 0.002), overall health-related quality of life was better, and patients reported fewer problems in daily life and less need of help with daily activities after stroke. IST-3 is the first thrombolysis trial to show sustained benefit to 18 months from thrombolysis, and also that it improves health-related quality of life [3.2].

Cumulative systematic reviews led by Wardlaw established benefit in selected patients [3.3, 3.4], and confirmed that the effects in the wider IST-3 population were entirely consistent with previous trials. Moreover, the reviews strengthened the evidence confirming the greatest benefit was obtained when the treatment was given within 3 hours and that older patients benefit as much as younger patients [3.5].

3. References to the research (indicative maximum of six references)

3.1 Sandercock P, Wardlaw J, Lindley R, Dennis M, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. Lancet. 2012;379:2352–63. DOI: 10.1016/S0140-6736(12)60768-5.

3.2 Sandercock P, Wardlaw J, Lindley R, Dennis M, et al Effect of thrombolysis with alteplase within 6 h of acute ischaemic stroke on long-term outcomes (the third International Stroke Trial [IST-3]): 18-month follow-up of a randomised controlled trial. Lancet Neurol. 2013 12:768–76. DOI: 10.1016/S1474-4422(13)70130-3.

3.3 Wardlaw J, Murray V, Berge E, del Zoppo G. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2009;4:CD000213. DOI: 10.1002/14651858.CD000213.pub2.

3.4 Wardlaw J, Koumellis P, Liu M. Thrombolysis (different doses, routes of administration and agents) for acute ischaemic stroke. Cochrane Database Syst Rev. 2013;5:CD000514. DOI: 10.1002/14651858.CD000514.pub3.

3.5 Wardlaw JM, Murray V, Berge E,…Sandercock P, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet. 2012;379:2364–72. DOI: 10.1016/S0140-6736(12)60738-7.

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

Pathways to impact

The UoE stroke group (Wardlaw) contributed to the conditional European licensing of rt-PA by presenting data to meetings of the European Medicines Evaluation Agency in Berlin and London. Subsequent to this licensing, they have designed, provided expertise to, or led, three trials that preceded IST-3 (including Multicentre Acute Stroke Trial (MAST)-I in 1995, European Cooperative Acute Stroke Study (ECASS)-3 in 2008) and contributed to the design and image interpretation of a registry of patients treated within the conditional licence (Safe Implementation of Thrombolysis in Stroke: A Multicentre Multinational Monitoring Study of Safety and Efficacy in Stroke (SITS-MOST)).

Sandercock, Wardlaw and members of the IST-3 group have presented the findings at conferences on every continent during 2012–2013, and there has been substantial coverage in the print and broadcast media and on the internet (www.ist3.com). In addition, the 2012 Lancet articles by Sandercock and Wardlaw [3.1, 3.5] have already been cited 153 times (Web of Science, last accessed 7th October 2013); the Lancet 2012 paper [3.1] was the most highly cited article published in the journal that year on a neurological topic.

Impact on public policy

This research has led to the revision of stroke guidelines internationally, with one or more of the references in section [3] cited in UK, USA, Japanese, Korean and Polish national guidelines [5.1–5.5, respectively].

Impact on clinical practice

Participation in the trial has had a direct impact on the development of stroke thrombolysis services in the UK. Seventy-five UK hospitals took part in IST-3, and the majority had limited or no prior experience of thrombolysis. The trial provided training and support for these centres to enable them to establish thrombolysis for stroke.

In the UK, the administration of thrombolysis within 3 hours is a quality standard against which services are judged nationwide. The National Stroke Strategies in England and Scotland state that thrombolysis should be administered as soon as possible after onset of stroke [5.6]. In 2012, in England 90%, and in Wales and Northern Ireland 100% of hospitals admitting patients with acute stroke provided a 24/7 thrombolysis service, on-site or in collaboration with neighbouring hospitals [5.6]. This meant that that in the first quarter of 2013, 12% of patients were thrombolysed in the UK; in the London area, where major service re-design has occurred, 18% were thrombolysed [5.7]. In Scotland, a 2012 audit revealed that the 2009 target of at least 3% of all new patients to be treated with thrombolysis had been exceeded; in fact approximately 8% had been treated [5.8].

Impact on health and welfare

Professor Charles Warlow (Professor of Neurology, now Emeritus, UoE, 1987–1998) estimated that in a typical European population of 1 million people, in 1 year, 2260 people would have a stroke and, without treatment, by one year, 700 would have died and 1240 would be dead or dependent [5.9]. The effect of giving alteplase to the 226 (10%) of the patients whose stroke is ischaemic and could be treated within 3 hours with alteplase, would be to reduce the number of patients who are either dead or dependent by 24 [5.9]. Applied to the UK population of 62 million, assuming that 10% of ischaemic strokes received rt-PA, 1488 (24 × 62) more people would be alive and independent. Applying the same estimates (106 per 1000 treated avoid death or dependency) to the 4 million strokes per year occurring in the developed world, where health services have the resources to deliver thrombolysis [3.1], about 100,000 more people would be alive and independent after their stroke as a result of the treatment.

Impact on the economy and commercialisation

The UoE group contributed to the successful market authorisation by the European Medicines Authority of alteplase for acute ischaemic stroke. In 2002, Sandercock estimated the UK annual cost to health and social services of a dependent stroke survivor to be £11,292, and that of an independent survivor to be £876. Thus, the avoidance of post-stroke dependency is an important contributor to reducing the burden of care on the NHS and social services. The National Institute for Health and Care Excellence, using Wardlaw's 2009 Cochrane systematic review [3.3] and updating Sandercock's previous analysis, estimated that rt-PA is cost-effective over a 12-month period, with an incremental cost-effectiveness ratio of £14,026 per quality-adjusted life-year gained, well below its threshold value of £30,000 per quality-adjusted life-year [5.10].

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

5.1 Intercollegiate Stroke Working Party. National clinical guideline for stroke. 4th ed. Royal College of Physicians, London; 2012. http://www.rcplondon.ac.uk/sites/default/files/national-clinical-guidelines-for-stroke-fourth-edition.pdf. *[UK guidelines.]*

5.2 Jauch E, Saver J, Adams H, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44:870–947. DOI: 10.1161/STR.0b013e318284056a. *[USA guidelines.]*

5.3 Minematsu K, Toyoda K, Hirano T, et al. Guidelines for the intravenous application of recombinant tissue-type plasminogen activator (alteplase), the second edition, October 2012: a guideline from the Japan Stroke Society. J Stroke Cerebrovasc Dis. 2013;22:571–600. DOI: 10.1016/j.jstrokecerebrovasdis.2013.04.001. *[Japanese guidelines.]*

5.4 Cho K, Ko S, Kim D, et al. Focused update of Korean clinical practice guidelines for the thrombolysis in acute stroke management. Korean J Stroke. 2012;14:95–105. *[Korean guidelines. Available on request]*

5.5 Expert Group of the Section of Cerebrovascular Diseases of the Polish Neurological Society. Management of Acute Stroke – guideline update 2013: thrombolysis. Neurol Neurochir Pol. 2013;47:303–9. DOI: 10.5114/ninp.2013.36754. *[Polish guidelines.]*

5.6 Sentinel Stroke National Audit Programme (SSNAP) (2012). Acute organisational audit report. http://www.rcplondon.ac.uk/sites/default/files/ssnap_acute_organisational_audit_-_public_report_2012_0.pdf *[Corroborates change to clinical guidelines in UK.]*

5.7 Unpublished audit data. SINAP Audit 2013 (personal communication from the London Stroke Clinical Director). *[Corroborates change in clinical practice in London. Available on request.]*

5.8 Scottish Stroke Care Audit. 2013 National Report. http://www.strokeaudit.scot.nhs.uk/Downloads/2013_report/SSCA-report-2013-web.pdf *[Audit demonstrating change in clinical practice in Scotland.]*

5.9 Warlow C, Van Gijn J, Dennis M, Wardlaw J, et al. Stroke: Practical Management. 3rd edition. Oxford: Blackwell Publishing, 2008, sections 18.3.1–2. *[Available on request. Corroborates calculations for improved health and welfare.]*

5.10 Jones ML, Holmes M. Alteplase for the treatment of acute ischaemic stroke: a single technology appraisal. Health Technol Assess. 2009;13 Suppl 2:15–21. DOI: 10.3310/hta13suppl2/03. *[Corroborates calculations for economic benefit.]*