Institution: University of Leicester

Unit of Assessment: 1 Clinical Medicine

Title of case study: Improving patient outcome after ischaemic and haemorrhagic stroke

Period when the underpinning research was undertaken: 01 January 2003 to 30 April 2018

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Professor Thompson G Robinson	Professor of Stroke Medicine	1993-present

Period when the claimed impact occurred: 1 August 2013 to 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

University of Leicester research led by Professor Robinson since 2003 has improved stroke patient outcomes, including survival, neurological and functional recovery, and the safety of thrombolytic therapy. This research has influenced national and international medical guidelines, and informed the treatment of >100,000 acute stroke patients per annum in the UK alone since 2013. Survivor independence from haemorrhagic stroke improved by 13 percent. Changing treatment to low-dose thrombolysis could prevent approximately 20,000 stroke-related deaths worldwide. These findings have informed UK and US guidance for individualised treatment, which improves long-term functional outcomes after stroke.

2. Underpinning research

Stroke is the fourth leading cause of death and the leading cause of adult disability in the UK. In the UK, there are over 1.2 million stroke survivors and two thirds live with stroke-related disability. This reduces quality-of-life for patients and family carers, and costs the UK economy £26 billion annually. Hypertension in acute stroke is common but globally under-researched, requiring new stroke treatment protocols to reduce death and prevent neurological deterioration and disability.

Professor Robinson's stroke research **[R1 – R6]** since 2000 has informed stroke management guidelines in the UK, Europe, and the USA, and treatment for >100,000 acute stroke patients per annum in the UK alone. Based within the University of Leicester's Cerebral Haemodynamics in Ageing and Stroke Medicine Research Group since 1993, Robinson has acted as Chief Investigator or National Co-ordinating Investigator of large, international randomised clinical trials since 2003 **[G1–G6]**.

Robinson's research on cerebral autoregulation and potential dangers to neurological health from sudden reductions in blood pressure informed the COSSACS trial and subsequent individual patient data meta-analysis that proved that pre-existing antihypertensive therapy following acute ischaemic and haemorrhagic stroke should be discontinued until patients are stable and able to swallow safely **[R1-R2, G1]**. This contributed to fewer deaths and savings for the NHS by removing costs for unnecessary medication.

Intracerebral haemorrhage—bleeding within the brain tissue—is the most devastating form of stroke, with significant mortality and long-term neurological disability and dependency. As Co-I of the Intensive blood pressure reduction in acute intracerebral haemorrhage (2008-2013) study **[G2]**, Robinson compared guideline-versus-intensive blood pressure lowering within six hours of onset in spontaneous intracerebral haemorrhage (ICH). Intensive blood pressure lowering was found to be safe, and can be effective for improving functional outcome **[R3]**.

Intravenous thrombolysis is the only licensed therapy for acute ischaemic stroke, but increases the risk of symptomatic ICH (sICH) by two to eight per cent; approximately half are fatal. As CI (UK) **[G4-G5]** and Co-I (International) **[G3, G6]** of the ENCHANTED trials (2012-2019), Robinson compared guideline-versus-intensive blood pressure lowering in alteplase-treated acute ischaemic stroke with respect to superiority for efficacy (modified Rankin scale (mRS) score shift) and safety (sICH). Intensive blood pressure lowering was safe and associated with a significant reduction in intracranial bleeding and serious clinician-reported bleeding but did not affect functional outcome at 90 days **[R4]**. Robinson also compared standard- versus low-dose alteplase for non-inferiority with respect to efficacy (dichotmised mRS: independent 0 to 1 vs. death/ dependency 2 to 6) and superiority with respect to sICH (2012 – 2016) **[G3-G6]**. The trial reported a lower risk of ICH and early mortality with the lower dose, without conclusively demonstrating that the doses were of equivalent efficacy. However, UK guideline interpretations indicate that the patient or physician may wish to forgo potential disability benefit from standard dose in order to reduce the early risk of ICH through use of the lower dose **[R5]**.

As Co-I of HeadPoST (2015-2017) **[G7]** (>11,000 patients in nine countries), Robinson compared the efficacy of head positions on stroke outcome in the first 24 hours following acute ischaemic and haemorrhagic stroke. Lying flat improves cerebral blood flow, but potentially increases intracranial pressure and pneumonia rates. Sitting up increases blood return to the heart but reduces cerebral blood flow. The findings of the HeadPoST trial demonstrated no significant recovery benefit from head positioning, eliminating the need for expensive specialist beds for acute stroke management, with worldwide healthcare implications **[R6].**

3. References to the research

R1. Robinson TG, Potter JF, Ford GA, Bulpitt CJ, Chernova J, Jagger C, James MA, Knight J, Markus HS, Mistri AK, Poulter NR. “Effects of antihypertensive treatment after stroke in the Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial”. *Lancet Neurology*, 9, (2010), pp 767-775.

R2. Woodhouse LJ, Manning L, Potter JF, Berge E, Sprigg N, Wardlaw J, Lees KR, Bath PM, **Robinson TG**. “Continuing or temporarily stopping prestroke antihypertensive medication in acute stroke. An individual patient data meta-analysis”, *Hypertension*, 69, (2017), pp 933-941.

R3. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, Lindley R, **Robinson T**, Lavados P, Neal B, Hata J, Arima H, Parsons M, Li Y, Wang J, Heritier S, Li Q, Woodward M, Simes RJ, Davis SM, Chalmers J (the INTERACT2 Investigators). “Rapid Blood-Pressure Lowering in Patients with Acute Intracerebral Hemorrhage”. *New England Journal of Medicine*, 368, (2013), pp 2355-2365.

R4. Anderson CS, Huang Y, Lindley RI, Chen X, Arima H, Chen G, Li Q, Billot L, Delcourt C, Bath PM, Broderick JP, Demchuk AM, Donnan GA, Durham AC, Lavados PM, Lee TH, Levi C, Martins SO, Olavarria VV, Pandian JD, Parsons MW, Pontes-Neto OM, Ricci S, Sato S, Sharma VK, Silva F, Song L, Thang NH, Wardlaw JM, Wang JG, Wang X, Woodward M, Chalmers J, **Robinson TG**. “Intensive blood pressure reduction with intravenous thrombolysis therapy for acute ischaemic stroke (ENCHANTED): an international randomised, open-label, blinded-endpoint phase 3 trial”. *Lancet*, 393, (2019), pp 877-888.

R5. Anderson CS, **Robinson T**, Lindley RI, Arima H, Lavados P, Lee T-H, Broderick JP, Chen X, Chen G, Sharma VK, Kim JS, Thang NH, Cao Y, Parsons MW, Levi C, Huang Y, Olavarria V,

Demchuck A, Bath PMW, Donnan GA, Martins S, Pontes-Neto OM, Silva F, Ricci S, Billot L, Woodward M, Li Q, Wang JG, Chalmers J. "Trial of low-dose versus standard-dose intravenous alteplase in patients with acute ischemic stroke". *New England Journal of Medicine*, 374, (2016), pp 2313-2323.

R6. Anderson CS, Arima H, Lavados P, Billot L, Hackett ML, Olavarria VV, Venturelli PM, Brunser A, Peng B, Cui L, Song L, Rogers K, Middleton S, Lim JY, Forshaw D, Lightbody CE, Woodward M, Pontes-Neto O, De Silva HA, Lin R-T, Lee T-H, Pandian JD, Mead GE, **Robinson T**, Watkins C. "Cluster-randomized, crossover trial of head positioning in acute stroke", *New England Journal of Medicine*, 376, (2017), pp 2437-2447.

Grants

G1. Robinson, Thompson G, PI: Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS). Health Foundation Project Grant, 2003-2006, GBP307,592.

G2. Robinson, Thompson G, Co-I: Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT2). Australian National Health and Medical Research Council, via The George Institute for Global Health 2011-2012. GBP10,580.

G3. Robinson, Thompson G, Co-I: Enhanced Control of Hypertension and Thrombolysis in Stroke Study (STAY ENCHANTED). Australian National Health and Medical Research Council 2015-2018, AUD3,422,286.

G4. Robinson, Thompson G, PI: Enhanced Control of Hypertension and Thrombolysis Stroke Study (STAY ENCHANTED). Stroke Association, 2015-2017, GBP209,999.

G5. Robinson, Thompson G, PI: Enhanced Control of Hypertension and Thrombolysis Stroke Trial, (ENCHANTED). 2013-2016. Stroke Association. GBP 202,055.

G6. Robinson, Thompson G, Co-I: Enhanced Control of Hypertension and Thrombolysis Stroke Trial, (ENCHANTED). Australian National Health and Medical Research Council, via The George Institute for Global Health 2012-2014. GBP75,947.

4. Details of the impact

Someone has a new or recurrent stroke every five minutes in the UK; >100,000 strokes per annum. Since 2016, outputs from Robinson's research with the completed COSSACS, ENCHANTED, HeadPoST and INTERACT2 trials **[R1, R3-R6]** informed stroke patient management worldwide following citations in UK, European and United States clinical guidelines **[E1–E6]**. Overall, these results improve outcome and survival for approximately 50,000 stroke patients per annum in the UK on pre-existing antihypertensive therapy, 15,000 acute haemorrhagic stroke patients, and 20,000 patients treated with intravenous thrombolysis.

New acute stroke blood pressure guidelines improve stroke patient management worldwide

Fifty percent of acute stroke patients are on pre-existing blood pressure lowering therapy. The primary trial results of COSSACS (2010) **[G1, R1]** informed the *National Clinical Guideline for Stroke 2016* for treating approximately 50,000 UK patients annually **[E4]**. The individual patient data meta-analysis of all trials addressing the continuation or stopping in the immediate post-stroke period (2017) **[R2]** mean that pre-existing blood pressure treatment should be stopped until the patient is medically stable and able to swallow safely **[E4, E6]**. This guidance reduces cerebral hypoperfusion-related brain damage from unnecessary antihypertensive-therapy-induced blood pressure reduction for 50,000 patients, and reduces pneumonia for 2,000 patients annually **[E4, E6]**.

Intravenous thrombolysis (clot-busting therapy), the only licensed therapy for acute ischaemic stroke, is associated with an increased risk of potentially disabling or fatal bleeding (symptomatic

intracerebral haemorrhage rate of two to eight percent). The ENCHANTED trial **[G3-G6]** showed that intensive blood pressure lowering was safe, and associated with a significant reduction in any intracranial bleeding and serious clinician-reported bleeding but did not affect functional outcome at 90 days **[R4]**. This led to new *Stroke* (USA, 2019) **[E6]** guideline revisions for post-thrombolysis blood pressure management—particularly in emergencies. **[E6]**.

Intracerebral haemorrhage (bleeding in the brain)—the most devastating form of stroke—accounts for 15 percent of strokes worldwide. The INTERACT2 **[G2]** findings changed four international guidelines. *Stroke* (USA, 2015) **[E1]**; *International Journal of Stroke* (Europe, 2014) **[E2]**; *Royal College of Physicians National Clinical Guideline for Stroke* (UK 2016) [**E4]**; and *NICE* (UK, 2019) **[E5]** recommend intensive blood pressure reduction within six hours of onset, and to achieve target blood pressure within one hour of treatment. This new guidance is associated with a 13 percent shift towards better stroke patient independence, compared to previous guideline blood pressure lowering **[R3]**.

Personalising intravenous thrombolysis treatment for acute ischaemic stroke
The ENCHANTED trial findings **[G3-G6]** are cited in both the UK **[E4]** and the US **[E6]** for thrombolysis (clot-busting therapy) - the only licensed medical treatment for acute ischaemic stroke. Thrombolysis is used in approximately 15 percent of these patients, totalling more than 12,000 patients per annum in the UK. The ENCHANTED outcomes **[R5]** showed that for every 1,000 patients treated with low- compared to standard-dose clot-busting therapy, 19 more patients would survive at three months. Although 40 per 1,000 more would be disabled, only eight of these would require daily care. The UK Royal College of Physicians National Stroke Guidelines newly concluded that ". . . there may be circumstances in which the treating physician and/ or patient wish to forgo some of the potential disability benefit from standard dose in order to reduce the early risk of symptomatic intracerebral haemorrhage through use of the lower dose" **[E4]**.

Head positioning trial supports patient preference in positioning during rehabilitation
The HeadPoST trial of over 11,000 patients **[G7]** assessed the effect of two recovery positions—upright versus lying flat—within the first 24 hours of hospital admission following acute ischaemic and haemorrhagic stroke on outcome at 90 days. HeadPoST identified that there was no significant difference in outcomes with either head position. NICE guidelines recognised that "optimal positioning is an important part of early acute stroke management and rehabilitation". On the basis of the HeadPoST trial, NICE recommended "positioning people according to their preferences and individual requirements . . . to establish their optimum position, which should be individually suited to each patient" **[E5]**. Whilst reinforcing current UK practice, Robinson's findings remove the need for specialist, adjustable head positioning beds for the management of acute stroke patients, instead focussing on patient comfort and wellbeing. "[When] positioning patients with acute stroke . . . lying flat is often difficult and uncomfortable for patients . . . adding to a sense of disorientation after stroke, but may be of benefit for some. Sitting up . . . enables patients to interact with their surroundings and is a more natural posture for eating and drinking [and] often the precursor for more challenging functional activity such as mobilisation" **[E5]**.

5. Sources to corroborate the impact

E1. US Guidelines: INTERACT2: Hemphill JC, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. "Guidelines for the Management of Spontaneous Intracerebral Hemorrhage". *Stroke*. 2015; DOI: 10.1161/STR.0000000000000069. https://www.ahajournals.org/doi/pdf/10.1161/STR.0000000000000069

E2. European Guidelines: INTERACT2: Steiner T, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, et al. "European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage". *International Journal of Stroke*. 2014; 9: 840-855. https://journals.sagepub.com/doi/pdf/10.1111/ijs.12309

E3. European Guidelines: ENCHANTED: Ahmed N, Steiner T, Caso V, Wahlgren N; for the ESO-KSU session participants. Recommendations from the ESO-Karolinska Stroke Update Conference, Stockholm, 13–15 November 2016. European Stroke Journal 2017; DOI:

10.1177/2396987317699144. https://pubmed.ncbi.nlm.nih.gov/29900406/

E4. UK Guidelines: COSSACS, INTERACT2, ENCHANTED: Intercollegiate Stroke Working Party. "National Clinical Guideline for Stroke 2016". Royal College of Physicians. Fifth Edition, 2016. https://www.rcplondon.ac.uk/guidelines-policy/stroke-guidelines

E5. UK Guidelines: INTERACT2, HeadPoST: National Institute for Health and Care Excellence. Stroke and transient ischaemic attack in over 16s: diagnosis and initial management (NG128). NICE 2019. www.nice.org.uk/guidance/ng128

E6. US Guidelines: COSSACS, ENCHANTED, HeadPoST: Powers W, Rabinstein A, Ackerson T, Adeoye O, Bambakidis N, Becker K, et al. "Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke. A Guideline for Healthcare Professionals From the American Heart Association/ American Stroke Association". *Stroke.* 2019; e344-e418. https://www.ahajournals.org/doi/10.1161/STR.0000000000000211