Institution: University of Edinburgh		
Unit of Assessment: 4		
Title of case study: H: Identifying cost-effective imaging strategies to diagnose acute stroke and to prevent secondary disabling stroke		
Period when the underpinning research was undertaken: 2000 – 2020		
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:**
Joanna Wardlaw	Chair of Applied Neuroimaging	1994 – present
Francesca Chappell	Senior Statistician	2005 – present
Period when the claimed impact occurred: 2014 – 2020		
Is this case study continued from a case study submitted in 2014? This case study reports both continued impact from REF2014/4/C and new impact from research conducted since REF2014.		

1. Summary of the impact

Underpinning Research: As reported in REF2014, Edinburgh Neuroscience researchers showed that immediate computerised tomography (CT) is the most cost-effective way to use brain imaging to diagnose acute stroke. Since then, work addressing the secondary prevention of stroke following transient ischaemic attack (TIA) or minor stroke has shown that diagnostic risk stratification scores are not cost-effective. Rapid assessment by a stroke specialist is needed, and, where magnetic resonance diffusion-weighted brain imaging is used, a blood sensitive sequence must be included.

Significance and Reach of Impact: Since REF2014, key clinical stroke guidelines recommending immediate CT scanning after acute stroke based on Edinburgh Neuroscience research, have been published by the UK Royal College of Physicians (RCP; 2016) and American Heart Association (AHA; 2019). These recommendations have resulted in marked reductions in the time between hospital admission and CT scanning: in the UK in 2020, 55% of patients with suspected stroke had a CT scan within 1 hour, compared with 42% in 2013. A global stroke registry (n=244,907) showed that median door-to-CT time fell by 12% from 25 to 22 minutes between 2013 and 2019.

The continued impact of immediate CT scanning in the UK has been 42,000 more quality-adjusted life-years and a reduction in the cost of stroke for the NHS by between GBP1,100,000,000 and GBP2,200,000,000 over the REF2021 census period.

As a result of the new work on secondary stroke prevention, the UK National Institute for Health and Care Excellence (2019), RCP (2016) and AHA (2019) all now recommend that suspected TIA should lead to rapid full diagnostic assessment without score-based risk stratification, citing Edinburgh Neuroscience papers.

2. Underpinning research

The Challenge: The need for accurate diagnosis of the cause of acute stroke, and the prevention of secondary stroke in at-risk individuals

The clinical management of stroke presents two major challenges. The first is the differentiation between ischaemic stroke, haemorrhagic stroke and stroke mimics; this is paramount to guide treatment, because treatment of acute *ischaemic* stroke (thrombolysis or thrombectomy, i.e. clot-busting drugs or clot-removal, respectively) could be highly damaging in cases of *haemorrhagic* stroke.

The second challenge is the identification of those at increased risk of secondary, disabling stroke soon after an apparent TIA or minor stroke. If TIA is diagnosed in a timely and accurate manner, the risk of secondary stroke can be mitigated with appropriate preventative treatment. For this reason, and because TIA and minor stroke are very common, it is vital that stroke prevention

services can triage each patient swiftly and correctly towards appropriate treatment. Prior to Edinburgh Neuroscience research, the most accurate and cost-effective approach to triaging patients with suspected TIA or minor stroke had not been systematically investigated.

Reported in REF2014: CT is the most cost-effective strategy for acute stroke diagnosis
Edinburgh Neuroscience researchers have, since 2002, led ground-breaking primary and meta-analysis studies, which demonstrated that immediate CT scanning in acute stroke was both the most practical and most cost-effective method to diagnose acute stroke [3.1].

NEW since REF 2014: Routine use of magnetic resonance imaging is not cost-effective in secondary stroke prevention
Having established the optimal method for diagnosing acute stroke, the researchers next turned their attention to the second challenge of preventing secondary stroke. The prevailing view at the time was that routine scanning of all patients with suspected TIA or minor stroke using magnetic resonance (MR) diffusion-weighted imaging was preferable to CT brain imaging to confirm the presence of ischaemia, and thus the group of patients at highest risk of secondary stroke. However, MR imaging is costly, time-consuming, of limited availability and its role in cost-effective secondary stroke prevention had not been formally evaluated.

To address this gap, Edinburgh Neuroscience researchers conducted a literature review and deterministic and probabilistic modelling to evaluate the accuracy and cost-effectiveness of MR imaging in assessing patients with suspected TIA or minor stroke. This revealed that MR imaging, though able to detect small ischaemic lesions, revealed no changes in approximately 70% of specialist-confirmed TIAs, and was therefore unhelpful in diagnosis. Thus, relying solely on MR imaging would fail to identify many patients at risk of secondary stroke, who require preventative treatments [3.2; 3.3].

The Edinburgh Neuroscience research therefore concluded that routine use of MR imaging was highly unlikely to be cost-effective in secondary stroke prevention [3.2; 3.3]. The analysis did, however, identify circumstances where MR imaging was beneficial: notably to diagnose haemorrhage in patients presenting more than a week after symptoms. Importantly, the analysis highlighted that wherever MR imaging is used in suspected TIA or stroke, it was essential to use blood-sensitive sequences [3.2].

NEW since REF2014: Diagnostic scores such as ABCD2 are not effective at preventing stroke and rapid specialist assessment is the best approach
As part of their evaluation of approaches to prevent stroke after TIA, Edinburgh Neuroscience researchers also assessed the use of risk prediction scores, chiefly the ABCD2 score, which had been recommended by several leading clinical guidelines, including the National Institute for Health and Care Excellence (NICE; 2008) and AHA (2009).

Using a systematic review and meta-analysis, Edinburgh Neuroscience researchers demonstrated that the ABCD2 score does not reliably discriminate between patients at low versus high risk of secondary stroke. It also cannot identify patients with carotid stenosis needing urgent intervention, or streamline clinic workload [3.4]. Instead, the analyses found that rapid assessment by a stroke specialist, selective use of MR imaging and identification of serious underlying stroke risk factors, such as carotid stenosis, using non-invasive vascular imaging such as ultrasound, are the most cost-effective approaches to preventing secondary stroke following TIA or minor stroke [3.2]. The research therefore concluded that stroke prevention services need adequate capacity for prompt specialist clinical assessment of all suspected TIA patients to enable preventative treatments to be initiated as early as possible when required [3.4].

3. References to the research

[3.1] Wardlaw J, Seymour J, Cairns J, Keir S, Lewis S, Sandercock P. Immediate computed tomography scanning of acute stroke is cost effective and improves quality of life. Stroke. 2004;35:2477-83. doi: 10.1161/01.STR.0000143453.78005.44. [**submitted to REF2014**]

[3.2] Wardlaw J, Brazzelli M, Miranda H, Chappell F, McNamee P, Scotland G, Quayyum Z, Martin D, Shuler K, Sandercock P, Dennis M. An assessment of the cost-effectiveness of magnetic resonance, including diffusion-weighted imaging, in patients with transient ischaemic attack and minor stroke: a systematic review, meta-analysis and economic evaluation. Health Technol Assess 2014;18(27) doi: 10.3310/hta18270. [**new research**]
[3.3] Brazzelli M, Chappell F, Miranda H, Shuler K, Dennis M, Sandercock PAG, Muir K, Wardlaw JM. Diffusion-Weighted Imaging and Diagnosis of Transient Ischemic Attack. Ann Neurol 2014;75:67–76 doi: 10.1002/ana.24026 [**new research**]
[3.4] Wardlaw JM, Brazzelli M, Chappell FM, Miranda H, Shuler K, Sandercock PAG, Dennis M ABCD2 score and secondary stroke prevention: Meta-analysis and effect per 1,000 patients triaged. Neurology 2015;85:373-380 doi: 10.1212/WNL.0000000000001780 [**new research**]

Selected grants:

[3.5] NHS R&D Health Technology Assessment. "Accurate, practical and cost-effective assessment of carotid stenosis in the UK", GBP110,572.00, 1st Mar 2003 – 30th Sep 2004. Principal Investigator: Professor J Wardlaw Ref No: 01/37/03.

[3.6] National Institute for Health Research Health Technology Assessment Programme. "An assessment of the cost-effectiveness of magnetic resonance including diffusion-weighted brain imaging in patients with transient ischaemic attack and minor stroke", GBP264,260 1st Sep 2010 to 31 Jul 2012. Principal Investigator: Professor J Wardlaw. Ref No: 09/22/169.

4. Details of the impact

Continued impact from REF2014: Further guidelines recommend immediate CT scanning to diagnose acute stroke

Further to the impact documented in REF2014, in 2016 the UK Royal College of Physicians (RCP) updated their guidelines to recommend a CT scan within 1 hour, citing Edinburgh Neuroscience research [5.1]. AHA also further updated their recommendations on brain imaging in 2019 based on Edinburgh Neuroscience cost-effectiveness work [5.2]. These updates followed previous influential guideline changes to recommend immediate CT scanning, e.g. NICE (2008), European Stroke Organization (2008) and Australia (2010), which were reported in REF2014/4/C.

Continued impact from REF2014: Impact on practice

The inclusion of immediate CT scanning after acute stroke in many international clinical stroke guidelines based on Edinburgh Neuroscience research (both before and after REF2014) has been translated into practice nationally and internationally, resulting in marked reductions in the time between hospital admission and CT scanning.

In England, Wales and Northern Ireland, the median time before a CT scan decreased by 43% from 88 minutes in 2013/14 to 50 minutes in 2019/20 (**Table 1**) [5.3]. CT scans within 1 hour after acute stroke increased from 41.9% in March 2013 to 55.3% in March 2020 [5.3]. Over 9.5 in every 10 stroke patients in the UK are now scanned within 12 hours (**Table 1**). For example, in Plymouth Hospital NHS Trust, time to brain imaging was reduced from a median time of 1 hour 43 minutes in 2013 to 35 minutes in the first quarter of 2017 [5.4a]. NICE uses this Trust as a shared learning example [5.4b].

Internationally, the Safe Implementation of Thrombolysis in Stroke (SITS) registry of 244,907 patients monitored globally, showed a reduction in median door-to-CT time of 12% from 25 minutes in 2013 to 22 minutes in 2019 [5.5].

Table 1: Data on the % of patients scanned within 1 and 12 hours and median time between clock start and scan, collected by the Sentinel Stroke National Audit Programme (SSNAP) for England, Wales and Northern Ireland, covering all admissions and discharges between April 2013 and March 2020 [5.3].

	Apr 13-Mar 14	*Apr 14-Mar 15*	*Apr 15-Mar 16*	*Apr 16-Mar 17*	*Apr 17-Mar 18*	*Apr 18-Mar 19*	*Apr 19-Mar 20*
% patients scanned within 1 hour of clock start	41.9	44.1	47.4	51.3	52.5	54.5	55.3
% patients scanned within 12 hours of clock start	84.5	88.2	91.2	93.5	94.3	95.2	95.6
Median time between clock start and scan (hours:mins)	1:22	1:15	1:06	0:58	0:55	0:52	0:50

Continued impact from REF2014: Impact on economy, health and welfare
In 2014, published Edinburgh Neuroscience research estimated that immediate vs. delayed brain imaging in suspected stroke would result in a total of 6,000 more quality-adjusted life-years (QALYs) for the 135,000 people who experience a stroke per year in the UK, i.e. 6,000 more years of better quality life for patients who have a stroke each year in the UK through faster imaging, diagnosis and subsequent treatment.

This has led to NHS savings between GBP156,000,000 and GBP312,000,000 per year [3.1]. Thus, for the REF impact period 2013–2020, total estimated QALY gains and cost-savings due to practice changes based on Edinburgh Neuroscience work were 42,000 QALYs and between GBP1,100,000,000 and GBP2,200,000,000, respectively.

NEW impact since REF2014: Impact on guidelines
The Edinburgh Neuroscience research on the value of diagnostic scores and MR imaging since REF2014 has directly led to changes in key national and international stroke guidelines, which now recommend the following best clinical practices in stroke prevention and treatment:

1) Suspected TIA should lead to immediate and full specialist assessment without score-based risk stratification: RCP (2016) and AHA (2019) now recommend that suspected TIA should lead to urgent full diagnostic assessment without score-based risk stratification, citing Edinburgh Neuroscience research [3.2-3.4] [p. 36; 39 in 5.1; 5.2]. NICE updated their guidelines on TIA in 2019 [NG128; 5.6], reversing their previous recommendation and stating now that risk prediction scores such as ABCD2 are not diagnostic tests for TIA. They also stated that there is no reliable diagnostic test for TIA and every TIA should be regarded as a high risk for stroke; closely reflecting the conclusions of paper [3.2] [5.7].

2) If using MR imaging after suspected TIA, perform blood-sensitive sequences: AHA and NICE (2019) guidelines have changed their recommendations to the use of blood-sensitive sequences when MRI is considered [5.2; 5.6]. For example, NICE states: *"1.2.2: After specialist assessment in the TIA clinic, consider MRI (including diffusion-weighted and blood-sensitive sequences) to determine the territory of ischaemia, or to detect haemorrhage or alternative pathologies. If MRI is done, perform it on the same day as the assessment. [2019]"* [5.6]. Paper [3.2] was used in the NICE surveillance report and by the panel as a 'key paper' when discussing the review question "After TIA, what is the optimal brain imaging strategy?" [p.6; 5.8].

NEW impact since REF2014: Impact on economy, health and welfare
Edinburgh Neuroscience work further suggests that excessive use of MRI in TIA clinics inflates NHS costs by between GBP7,000,000 and GBP37,000,000 per year, while reducing QALYs by

450–12,960 per year [5.9]. Uptake of the NICE guidelines, updated in 2019 to reflect Edinburgh Neuroscience research findings [5.6], will lead to a reduction in these excess costs.

People who have had a stroke have double the risk of dementia of the general population. Thus, while the impact on health and welfare is currently difficult to quantify, effective stroke prevention and treatment is expected to also reduce the likelihood of the risk of cognitive impairment and dementia, helping maintain patient independence and reducing the burden on health and social care services.

5. Sources to corroborate the impact

[5.1] Royal College of Physicians 2016 National clinical guideline for stroke
Immediate CT scanning: Recommendation 2.3.1 E; citing [3.2] and [3.3]
Full diagnostic assessment after TIA: Recommendation 3.2.1 D,E; citing [3.3]

[5.2] American Heart Association 2019 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Powers *et al* Stroke 2019; doi: 10.1161/STR.0000000000000211. [e13, Section 2.2; e46, Section 6.1]

[5.3] Table 1 was compiled using data extracted from the SSNAP clinical audits, specifically:
a. National clinical audit results 2013–2020
b. SSNAP Annual Results 2018/19
c. SSNAP Annual Results Portfolio 2019/2020

[5.4] NICE Examples to evidence decreased time until imaging
a. NICE Impact Report (May 2019), p. 8
b. NICE Shared Learning Example Plymouth Hospitals NHS Trust (Jan 2018)

[5.5] SITS Data, provided by Chairman of SITS International and Associate Professor of Neurology at Karolinska Institute

[5.6] NICE Guideline 2019 [NG128]: Stroke and transient ischaemic attack in over 16s: diagnosis and initial management [Recommendations 1.1.5; 1.1.6; 1.2.2]

[5.7] NICE Guideline NG128 Evidence review B Evidence review for transient ischaemic attack (TIA) prediction rules (Review question "How accurately do scoring systems predict the risks of future ischaemic stroke or TIA within the first 7 days in people with suspected TIA or minor stroke?")

- Publication [3.2] is included as an information source as 1 of 2 key papers; p.29/30; Table 11.
- The health economic evidence (p.59-61; Appendix F) refers to NICE guideline CG68 (2008), which solely relied on data from Wardlaw et al 2006 (doi: 10.3310/hta10300).

[5.8] NICE Guideline NG128 Evidence review C Evidence review for TIA imaging

[5.9] Calculation based on [3.2]: Using immediate MR vs. immediate CT costs GBP77 more and creates 0.0005 less QALYs, and only treating TIA patients who show positive MR diffusion weighted imaging, rather than all specialist-confirmed TIAs, costs GBP407 more and creates 0.144 less QALYs [3.2]. Thus, the net effect on the 90,000 patients per year in UK with suspected TIA (including mimics) of using MR in most patients is to inflate cost by GBP6,900,000–GBP36,600,000 while losing 450–12,960 QALYs each year.
(NB. These amounts are estimates since no good data are available on the effect of using more MR imaging on outcomes after TIA. Also note that MR only starts to increase QALYs when used more than 7 days after stroke, assuming blood-sensitive sequence used, but still costs more since it is inherently more expensive than CT.)