Institution: University of Glasgow (UofG)		
Unit of Assessment: UoA 1 (Clinical Medicine)		
Title of case study: Improving assessment of stroke outcomes for clinical trials and health services audit		
Period when the underpinning research was undertaken: 2000–2013		
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:**
(1) Dr Terry Quinn; **(2)** Prof Jesse Dawson; **(3)** Prof Matthew Walters; **(4)** Prof Peter Langhorne; **(5)** Prof Kennedy Lees.	**(1)** Clinical Research Fellow; Clinical Lecturer; Senior Clinical Lecturer; **(2)** Clinical Lecturer; Senior Clinical Lecturer; Professor of Stroke Medicine; **(3)** Professor of Clinical Pharmacology; **(4)** Senior Lecturer; Professor of Stroke Care; Senior Research Fellow; **(5)** Professor of Stroke Medicine; Fitness to Practise Officer.	**(1)** 2006–2008, 2010–2015; 2015–present; **(2)** 2008–2010; 2010–2015; 2015–present; **(3)** 2003–present; **(4)** 1994–2001; 2001–2020; 2020–present; **(5)** 1999–2018; 2018–present.
Period when the claimed impact occurred: August 2013–present		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

UofG researchers have improved assessment of post-stroke recovery in two settings. First, they developed online training and a video-based group adjudication platform for the modified Rankin Scale (mRS), the most frequently used endpoint in clinical stroke trials. Since August 2013, a total of 28,143 online mRS training certifications have been recorded (109 clinical trials, 69 countries), while mRS adjudication was used for 5,500 assessments (11 clinical trials, 23 countries). Second, they developed 'home-time' as a proxy measure of recovery for use in health services audit. Since 2018, the Scottish Stroke Care Audit has included home-time as a validated outcome measure for every person who experiences stroke in Scotland.

2. Underpinning research

The UofG Institute of Cardiovascular and Medical Sciences is a centre of excellence for stroke research. Work conducted since 2000 on tools to assess stroke recovery is internationally recognised, and has helped to raise standards for both clinical trials (mRS training and video adjudication) and health services audit (home-time).

Overcoming challenges for stroke outcome assessment in clinical trials

Recovery after stroke is typically assessed using the mRS, a short interview that generates a score for global disability ranging from 0 (no symptoms of disability) to 5 (severe disability requiring constant nursing care). The mRS is the most frequently used assessment tool in clinical stroke trials, yet the original version—developed by Dr John Rankin at UofG in 1957—was not designed for widespread use. Consequently, **Lees** explored ordinal approaches to improve statistical analysis of mRS assessment that are now recommended by regulatory bodies (e.g. European Medicines Agency; EMA) as the primary outcome measure for clinical trials (reviewed by the European Stroke Organisation Outcomes Working Group in 2012).

Training and raising standards for mRS assessment

As well as limitations in the analysis of mRS data, **Quinn**, **Dawson**, **Walters** and **Lees** have demonstrated inconsistency in how clinical researchers applied this tool, including substantial variability in the scores assigned (2009) [3.1]. Such disparity has negative consequences for clinical trials as misclassification of the mRS score can cause erroneous results (2008) [3.2]. To improve consistency and raise standards of mRS assessment, these UofG researchers developed and validated best-practice guidance for its use in clinical trials (2007) [3.3]. They produced a comprehensive mRS training programme comprising written content; exemplar video case studies (i.e. interviews of stroke survivors); and test materials for post-training certification. Utility and feasibility of the programme for mass training was demonstrated by

evaluating 1,800 end-of-training assessments collected from principal investigators, co-investigators, study nurses and research assistants from 25 countries who were involved in acute stroke trials. The rate of certification after training was 90% [3.3]. More than 3,000 certifications were submitted when the mRS training programme was directly delivered and managed by UofG (2004–2011).

Supporting mRS assessment
Even with training, assessors can find it difficult to accurately describe stroke recovery, especially in the setting of clinical studies that include large numbers of patients from multiple international sites [3.1]. To support outcome evaluation in clinical trials, **Quinn**, **Dawson**, **Walters**, **Langhorne** and **Lees** developed a novel video-based resource for remote adjudication of mRS (Central Adjudication of Rankin Scores; CARS), which enables real-time scoring of stroke assessments by experts (2013) [3.4]. The CARS approach improves quality of local assessments and reliability of scoring, thereby reducing both the number of participants and costs required for a successful clinical trial [3.4].

Overcoming challenges for stroke outcome assessment in health services audit
Indicators of stroke recovery used in health services audit should maintain the utility of mRS, while being collectable at scale without the need for direct interview. They should also be meaningful to survivors' experience of the recovery pathway, and reflect information routinely available in medical records or stroke registries. **Quinn**, **Dawson**, **Walters** and **Lees** derived 'home-time', a novel proxy measure for functional stroke recovery after hospital discharge, as an alternative to mRS for health services audit (2008) [3.5]. Home-time is calculated as the amount of time that a patient stays in their own home, from initial hospital admission up to 90 days post-stroke. Increasing duration of time spent at home demonstrated a statistically significant correlation with improvements in post-stroke disability; consequently, home-time offers health services a robust and valid approach to benchmarking stroke care.

3. References to the research

1. **Quinn TJ**, **Dawson J**, **Walters MR**, **Lees KR** (2009). Reliability of the modified Rankin scale: a systematic review. Stroke;40(10):3393–3395 (doi:10.1161/STROKEAHA.109.557256).
2. **Quinn TJ**, **Dawson J**, **Walters MR**, **Lees KR** (2008) Variability in modified Rankin scoring across a large cohort of international observers. Stroke;39(11):2975–2979 (doi:10.1161/STROKEAHA.108.515262).
3. **Quinn TJ**, **Lees KR**, Hardemark HG, **Dawson J**, **Walters MR** (2007) Initial experience of digital training for modified Rankin scale assessment in clinical trials. Stroke;38(8):2257–2261 (doi:10.1161/STROKEAHA.106.480723).
4. McArthur KS, Johnson PC, **Quinn TJ**, Higgins P, **Langhorne P**, **Walters MR**, Weir CJ, **Dawson J**, **Lees KR** (2013) Improving the efficiency of stroke trials: feasibility and efficacy of group adjudication of functional endpoints. Stroke;44(12):3422–3428 (doi:10.1161/STROKEAHA.113.002266).
5. **Quinn TJ**, **Dawson J**, Lees JS, Chang TP, **Walters MR**, **Lees KR** (2008) Time spent at home poststroke: "home-time" a meaningful and robust outcome measure for stroke trials. Stroke;39(1):231–233 (doi:10.1161/STROKEAHA.107.493320).

Grants

Dawson J, **Langhorne P**, **Lees K**, **Walters M**. *Central adjudication of modified Rankin scale disability assessments in acute stroke trials (CARS)*. Scottish Executive Health Department, GBP419,023 (2009–2011).
Quinn TJ. *Improving assessment in stroke*. Joint Chief Scientist Office and Stroke Association Senior Lecturer Fellowship, GBP196,546 (2015–2019).

4. Details of the impact

Stroke presents as an acute medical emergency; however, survivors can experience potentially lifelong consequences, including chronic disability. As stroke is estimated to affect one in six people worldwide, the health, societal and economic burdens are considerable.

UofG has a long-standing international reputation in stroke care. Key historical achievements include development of evidence-based treatments (e.g. acute thrombolysis, neuroprotectants)

and transformation of UK health service delivery (e.g. introduction of specialist stroke units). Valid and reliable measures for stroke recovery are essential to verify the success of such interventions. UofG research has improved post-stroke outcome assessment by **(1)** creating mRS training and adjudication platforms for use in clinical trials [3.3, 3.4], and **(2)** developing home-time as a patient-centred indicator for health services audit [3.5].

Overcoming challenges for stroke outcome assessment in clinical trials

Reliability of the mRS score as an endpoint for clinical trials is hampered by interobserver variability during assessment [3.1, 3.2]. UofG researchers therefore developed an mRS training and certification programme [3.3] and the CARS adjudication platform [3.4] to address this issue. These activities have raised clinical trials standards internationally, with UofG now considered the 'go to' institution for stroke trialists looking to improve outcome assessments.

Training and raising standards for mRS assessment

In 2011, the UofG team was approached by a US-based online provider of healthcare training (BlueCloud by HealthCarePoint) that proposed hosting the mRS training programme [3.3] for free on its interactive web-based platform. Other mRS training materials were available or being developed at the time; however, BlueCloud favoured the UofG training programme owing to its popularity and traction within the stroke research community. BlueCloud operates a membership model for training and has access to over 1.8 million healthcare professionals working within numerous participating organisations worldwide, including clinical trials sponsors, contract research organisations, hospitals, and other stakeholders in clinical research. By upscaling from in-house delivery of training to a global online presence, the partnership with BlueCloud has allowed UofG to increase visibility and uptake of the mRS training programme, while retaining ownership of the course materials.

Since moving to the BlueCloud platform, the mRS training programme has raised global standards for stroke assessment, as evidenced by the number of people who have successfully undergone training and certification [5.A]. During August 2013–December 2020, a total of 28,143 mRS certifications and/or recertifications were recorded via BlueCloud, with users representing 109 clinical trials in 69 countries [5.A]. BlueCloud also hosts UofG training materials for the Barthel Index, a measure of post-stroke performance in activities of daily living. During the same period, a total of 6,370 Barthel Index certifications and/or recertifications were recorded [5.A]. Users of these UofG training programmes include clinical research coordinators, clinical research nurses and study investigators [5.A]. The course materials have been delivered across 20 languages [5.A].

An additional benefit of the UofG mRS training programme is that it gives BlueCloud members a globally harmonised, standardised and certificated resource, which is accepted by clinical trial sponsors, contract research organisations and global regulatory agencies as the industry standard. Indeed, completion of mRS training with certification is mandatory for many commercially-funded clinical stroke studies. Certification for clinical trials is valid for 1 year, and users automatically receive reminders to undergo retraining and recertification to ensure they remain compliant. The BlueCloud platform also enables users to share their mRS certifications electronically across participating organisations (e.g. clinical trials sponsors), thereby minimising issues around regulatory compliance.

Clinical trials that have cited the mRS training programme as part of the study protocol include NEST-3 (transcranial laser therapy, 2014); SITS OPEN (thrombectomy, 2014); and PRECIOUS (prevention of complications among elderly stroke patients, 2018) [5.B]. SITS is endorsed by the EMA as its preferred stroke registry for follow-up of thrombolytic therapy. The Chair of SITS highlights the importance of mRS training for this initiative: "*To improve the assessment of mRS by SITS users, we worked with the team at UofG. To this end, as part of the training resources for use of mRS in clinical studies, we have included in the SITS Open a training manual and video-based training and certification program developed by UofG*" [5.C]. A lead investigator from Germany states: "*I have chosen to use the UofG materials as they are familiar to the stroke research community and come from a team with an international*

reputation in outcomes assessment. Through use of the structured training and certification, variability in assessment can be reduced. This improves the efficiency of trials and ultimately is time and cost saving" [5.C]. The British Association of Stroke Physicians (BASP) is creating an educational portal that will link to online mRS training via BlueCloud. According to the Chair of the BASP Scientific Committee: "*A priority for the portal is provision of training materials about the mRS. The UofG online training is validated, popular and has been used in many randomised controlled trials in stroke medicine. BASP will use these training materials for our training portal because of their successful track-record in training many researchers and clinicians around the world*" [5.C].

Supporting mRS assessment
UofG researchers developed the CARS platform for remote expert adjudication of mRS scoring to assist evaluation of stroke recovery in large clinical trials [3.4]. During August 2013–December 2020, CARS supported 5,500 assessments for 11 major clinical trials conducted across 23 countries worldwide. Industry supported clinical trials using CARS include CREGS-S (EVER Pharma, Austria), ACTIsSIMA (SanBio, Japan) and CBAF312X2207 (Novartis, Switzerland). Other clinical trials that incorporated CARS in the study protocol include EuroHYP-1 (therapeutic hypothermia plus best medical treatment, 2014); SITS OPEN; CLEAR III (thrombolysis, 2017); PRECIOUS; and MISTIE III (minimally invasive surgery with thrombolysis; 2019) [5.D].

Local investigators upload video recordings of mRS assessments via a dedicated CARS web portal curated by UofG. This fee-per-use system (GBP50–GBP75 per reviewer per assessment) allows for prompt, independent and blinded evaluation of the assessment by international experts, most of whom are part of the UofG research team. CARS offers same-day assessment and translation of non-English-language interviews. Protocols exist for cases where there is disagreement between local scoring and expert scoring, including the option of convening a multi-expert consensus review. CARS improves validity of the local assessments, as well as providing a mechanism for quality control and targeted training of clinical research centres. Where the local assessment is felt to be deficient or wrongly scored, this view is fed back to the clinical trial site with suggested remediation actions such as signposting to online mRS training [3.3] or recalling the patient for another interview. CARS also reduces mRS misclassification and 'noise', thereby allowing for efficiencies of time and resource as clinical trials can demonstrate effects with smaller sample sizes [3.4]. Reflecting these benefits, the Chair of SITS explains that the decision to use CARS for SITS OPEN was "*To ensure consistency and quality of the outcomes recorded in this important study*" [5.C].

Overcoming challenges for stroke outcome assessment in health services audit
UofG researchers developed home-time as a proxy measure of stroke recovery that uses information already available in medical records and stroke registries [3.5]. This metric is being used in Scotland and internationally as a patient-centred approach to help health services benchmark their post-stroke care.

Home-time as a patient-centred indicator for health services audit
In September 2013, the US-based Patient-Centered Outcomes Research Institute initiated PROSPER to help patients work with clinical staff to make informed decisions about their post-stroke care through comparative effectiveness research [5.E]. Survivors were involved in the design of PROSPER, and identified home-time [3.5] as the key meaningful outcome in their recovery pathway [5.E]. Using data from the American Heart Association Get With The Guidelines-Stroke registry, PROSPER demonstrated that new prescriptions of statins or warfarin at hospital discharge correlated with an increased number of days spent at home (2020) [5.E]. These findings are supporting US healthcare providers to maximise the time that survivors spend alive and out of hospital, without recurrent stroke.

The value of home-time [3.5] as a patient-centred metric for audit of stroke outcomes is increasingly recognised. For example, the US federal healthcare programme for adults older than 65 years (Medicare) records home-time to enable comparative effectiveness research for

projects such as PROSPER [5.E, 5.F]. In 2019, the American College of Cardiology highlighted the benefits of home-time for stroke services: "*Just as home time can reflect on patients' experiences, it can also shed light on health care utilization and cost by those who are generally older and frailer and by those who may experience the downward spiral of hospitalizations*" [5.F]. Analysis of a Canadian stroke registry (2019) found that home-time offered "*a quality indicator of stroke care and a pragmatic outcome in stroke health services research*" [5.F]. Likewise, an Australian analysis concluded "*home-time measured using administrative data is a robust, replicable and valid patient-centred outcome enabling inexpensive population-based surveillance and system-wide quality assessment*" (2020) [5.F]. Finally, home-time is transferable to other settings, including the postoperative period, community services for the elderly and end-of-life care (2020) [5.F].

Uptake of home-time as an audit outcome in NHS Scotland

Stroke is the most frequent cause of severe physical disability amongst Scottish adults. The Scottish Stroke Care Audit (SSCA) traditionally assessed data collected during acute hospital admissions, but lacked a system for reviewing long-term outcomes [5.G]. During 2017–2018, the SSCA Steering Group worked with **Quinn** to incorporate home-time as a validated audit measure for every person who experiences stroke in Scotland [5.G]. This collaborative project involved working with SSCA data analysts, operationalising home-time and providing advice on its interpretation. A 2019 analysis using an SSCA dataset confirmed the feasibility of calculating home-time from routinely recorded data stored in a national registry [5.G]. Home-time data are now being used to compare Scottish hospitals and address potential variations in outcomes as part of the Scottish Stroke Improvement Programme (SIP), which emphasises home-time as *"a very important quality and outcome measure from a patient perspective"* [5.G]. NHS Scotland stroke services are finding home-time a useful metric for improvement when they are identified as outliers for this outcome. For example, patients in NHS Grampian experienced fewer home days than did patients in the other 13 Scottish health boards during 2017; however, by 2018, its performance for home-time had markedly improved [5.G]. SIP noted that rising use of coordinated interventions for rehabilitation, such as early supported discharge services, would increase days spent at home for Scottish patients, whereas delays in accessing community care might reduce this measure. Home-time will help to capture the impact of such service changes in future SIP audits; however, the 2019 data have not yet been reported owing to Covid-related logistical issues for SIP audit activities during 2020.

5. Sources to corroborate the impact [PDFs of listed documents uploaded]

A. Online delivery of mRS training [3.3] by BlueCloud: (1) Course landing page, with UofG credited as the developer; (2) Summary of user data (August 2013–December 2020); (3) Training catalogue, listing translated versions of UofG course materials (see p.3, p.4).
B. Clinical trials using mRS training [3.3] in the study protocol, including NEST-3 (2014), SITS OPEN (2014), PRECIOUS (2018). Details/additional examples available as PDFs.
C. User testimony for mRS training [3.3] and CARS [3.4]: (1) Chair of SITS Coordinating Office; (2) Clinical trials lead investigator, Germany; (3) Chair of BASP Scientific Committee.
D. Clinical trials using CARS [3.4] in the study protocol, including EuroHYP-1 (2014); SITS OPEN (2014), PRECIOUS (2018), CLEAR III (2017), MISTIE III (2019). Details/additional examples available as PDFs.
E. Home-time [3.5] as a patient-centred outcome in PROSPER: (1) Project webpage; (2) Project design Am Heart J 2015;170:36–45.e11. See ref. 14; (3) Final report (2020).
F. Recognition of home-time [3.5]: (1) US Medicare: Stroke 2016;47:836–842. See ref. 5; (2) American College of Cardiology: editorial (2019). See ref. 1; (3) Canada: BMJ Open 2019;9:e031379. See ref. 4; (4) Australia: Int J Clin Pract 2020;74:e13484. See ref. 13; (5) Other settings: Healthcare 2020;8:100463. See ref. 2.
G. Uptake of home-time [3.5] in NHS Scotland: (1) Testimony from the Lead Clinician on Stroke/Clinical Lead, SSCA; (2) Stroke 2019;50:1282–1286; (3) SIP reports for the 2017 audit data (see p.10, p.46–p.47, Chart 8.3) and 2018 audit data (see p.36, p.38–39, p.40, Chart 9.3).