Research to Understand Stroke due to Haemorrhage

2024 Newsletter

A brief look back at 2024, as 2025 begins…

Welcome to the latest RUSH newsletter, which reflects on our activities and successes in 2024.

People keep RUSH going, and we've been lucky to be joined by new academic colleagues last year (e.g. Vega Pratiwi Putri and Alice Hosking), visited by others (e.g. Abel Sandmann), and joined by a new member of our Patient Reference Group (Dawn Smith). You can read more about some of these people in this newsletter.

Projects will keep us busy this year, including starting an international clinical trial (ASPIRING), continuing other studies (e.g. PLINTH), and seeking funding for another study (CARE MAP) that builds on the successful completion of the CARE pilot study in 2024.

Publications by us or with our collaborators numbered 21 last year; they're listed at the end for our most dedicated readers!

What's inside this newsletter:

ASPIRING beginnings

ASPIRING
Antiplatelet Secondary Prevention International Randomised study after INtracerebral haemorrhaGe

We've been eager to begin work on the Antiplatelet Secondary Prevention International Randomised study after INtracerebral haemorrhaGe (ASPIRING), since funding from the British Heart Foundation was confirmed in 2023, and other funding agencies in Australia, Canada, The Netherlands, and Belgium have since come on board to fund the recruitment and follow-up of 4,148 participants.

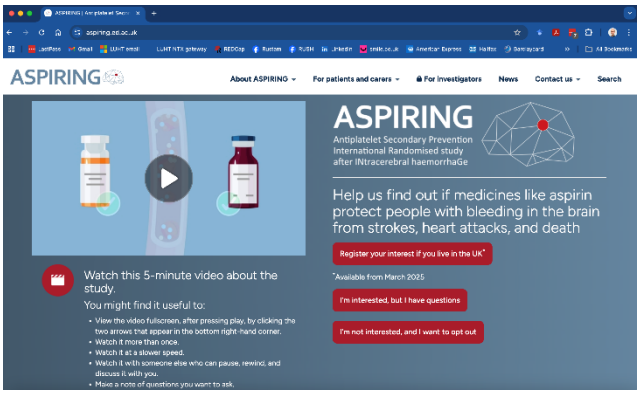
This international study aims to determine if antiplatelet therapy (with aspirin or clopidogrel) is of overall net benefit in reducing the incidence of major adverse cardiovascular and cerebrovascular events compared to avoiding antiplatelet therapy for adults with a history of stroke due to spontaneous intracerebral haemorrhage.

ASPIRING will be the largest and most reliable study to date to address this question.

An early release of funding in February enabled us to obtain regulatory approvals in the UK. We've begun work with our collaborators on regulatory approvals in the other countries.

The trial is registered here: www.isrctn.com/ISRCTN16705062.

Recruitment will begin in April/May 2025. You can watch a video about the study via our shiny new website at www.ASPIRING.ed.ac.uk...



CARE pilot study done

CareTrial
CAVERNOMAS: A RANDOMISED EFFECTIVENESS TRIAL

This project was the first step towards working out whether treatment of brain cavernoma with medical care and surgery (using either neurosurgery or stereotactic radiosurgery) reduces the risk of a stroke compared to medical care alone.

We showed that a randomised trial of surgery for brain cavernoma is possible.

We recruited more people than planned and found what helped or stopped recruitment.

A bigger randomised trial of surgery will require extensive international engagement from funders, doctors, and patients.

Alongside their publication in ***The Lancet Neurology***, Rustam presented the results at the Society of British Neurosurgeons meeting in April…

He was accompanied by representatives from Cavernoma Alliance UK: Ben Brady and Dawn Smith (who has joined our Patient Reference Group).

Find out more via the study's site www.ed.ac.uk/care-study and via https://cavernoma.org.uk/care-study/.

CARE MAP planning

In CARE, we found that many people with brain cavernoma would prefer to avoid surgery and would rather take a tablet to prevent brain haemorrhage.

Several oral medicines are promising candidates for this purpose. They include a beta-blocker (propranolol), blood thinners (e.g. aspirin), and cholesterol-lowering drugs (statins).

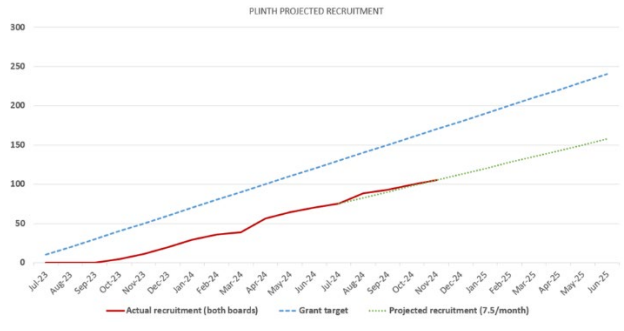
We have now applied three times to the UK National Institute of Health and Care Research for funding for a clinical trial involving some of these drugs, and – at the third attempt! – our CARE Multi-arm study of Aspirin and Propranolol (CARE MAP) has been invited to submit a full application in April/May 2025.

PLINTH progress

The PLatform study for INTracerebral Haemorrhage (PLINTH) feasibility study continues to recruit steadily in NHS Lothian and NHS Lanarkshire.

PLINTH

Our 18-month report has been submitted to our funder (Chief Scientist Office of the Scottish Government) and they approved it. As you can see from the graph below, our recruitment (in red) is the target we set ourselves. Nonetheless, we are gathering very useful information and finding that patients with brain haemorrhage and their relatives are finding our information video, streamlined design, and talks tailored to patients acceptable.



ENRICH-AF recruited

We have coordinated the UK's contribution to this international trial that is led by our collaborators at McMaster University in Canada. It's investigating the effects of the oral anticoagulant blood thinner Edoxaban for atrial fibrillation after brain haemorrhage. It follows our SoSTART pilot trial.

The UK is the country that has recruited the largest number of participants, so the Canadian team joined us for a meeting for UK investigators in Edinburgh to spur them on. The trial closed recruitment on 31 October with 948 participants. Results in 2026.

A few more trophies for the cabinet…

Congratulations to Sarah Risbridger, Senior Research Nurse in the EMERGE team supporting Edinburgh's Cerebrovascular Research Group. She completed her MSc in Advanced Nursing studies and graduated in the summer.

Congratulations to Tom Moullaali who led a successful £35,840 research project grant application to SHARP, to support Vega Pratiwi Putri's investigation of the risks and predictors of major

adverse cardiovascular and cerebrovascular events after stroke due to intracerebral haemorrhage in an international individual participant data meta-analysis.

Scottish Heart & Arterial disease Risk Prevention

Congratulations to Grant Mair (pictured below) for obtaining a £278,495 grant from the British Heart Foundation to collect brain scans of ASPIRING participants in the UK, so that we can investigate whether the response to antiplatelet drugs differs according to brain haemorrhage survivors' brain scan appearances.

Congratulations to Alice Hosking (pictured below with Rustam and others, in a cycling interlude at our academic retreat) for obtaining a prestigious Medical Research Council Clinical Research Training Fellowship so that she can study "multimorbidity in intracerebral haemorrhage: towards personalised risk, prognosis and treatment" for a PhD.

Rustam was privileged to lead the 'stroke and vascular dementia' theme of Edinburgh's bid for another 5-year Research Excellence Award from the British Heart Foundation. He attended an interview in London with cardiologists Dave Newby (centre, below) and Nick Mills (right, below) and three others from Edinburgh.

The BHF awarded The University of Edinburgh £5 million. Professor Bryan Williams, Chief Scientific and Medical Officer at the BHF, said, “We’re delighted to continue to support research at the University of Edinburgh addressing the biggest challenges in cardiovascular disease. This funding recognises the incredible research happening at Edinburgh and will help to further its reputation as a global leader in the field.” David McColgan, Head of BHF Scotland, said, “It is great news that the University of Edinburgh has once again been recognised as a centre of research excellence. Scotland has a strong tradition of leading the way in cardiovascular research and today's announcement will further reinforce this for years to come.”

In September Rustam was elected as a Fellow of the Academy of Medical Sciences. He gets an FMedSci post-nomial and another subscription to pay!

Stroke Association Trustee

Rustam served a full year as one of the 13 Trustees of The Stroke Association. They continue to

campaign for better availability of mechanical thrombectomy, support stroke survivors, and raise awareness, including a new moving TV campaign. Look out for a consultation about their new research strategy in 2025.

Rustam's profile: balancing depth and breadth?

In Context

Profile

Rustam Al-Shahi Salman: balancing depth and breadth with intracerebral haemorrhage

Rustam Al-Shahi Salman is head of the cerebrovascular group, honorary consultant neurologist, and clinical director of the clinical trials unit at the University of Edinburgh (Edinburgh, UK), where he also leads the Research to Understand Stroke due to Haemorrhage (RUSH) programme, aiming to improve outcomes for adults with diseases that can cause intracranial haemorrhage through rigorous randomised controlled trials. "My research, if nothing else, usually has a good acronym for it", he jokes. "It's deliberately called RUSH because we are literally in a rush to improve our understanding of the causes and mitigate the consequences of stroke due to brain haemorrhage." In line with Salman's appreciation of a good acronym, his future work is focused on ASPIRING (Antiplatelet Secondary Prevention International Randomised study after INtracerebral haemorrhaGe), which is a multicentre pragmatic trial looking at the effects of drugs such as aspirin in people who have had a brain haemorrhage and will be his main research focus for the next 6 years.

Although Salman describes himself as a clinician first and foremost, he became an academic because he saw too many unresolved questions in his day-to-day practice. As such, patients have always been at the heart of his research, and they now contribute to not only the identification of research questions but also their prioritisation, development of grant applications, project design, co-production of study materials, study oversight, and being advocates for participation in research. "For me, patient involvement with research is an end-to-end process", he explains. "It starts with the problems that are affecting people, all the way through to the dissemination of the results."

Salman's collaborative approach to research extends beyond patients to other researchers at every stage of their careers. "The thing I love about medical research is team science", he explains. "I'm naturally somebody who wants to collaborate rather than compete." For Salman, this inclination means that both mentorship and peer support have key roles. "I think [that] fostering a team science approach by encouraging researchers at all stages of their careers to set up systems for peer support is really important."

Salman was always interested in science at school, and being more interested in humans than machines made medicine the logical choice. He describes attending a residential congress at the age of 17, for students who were thinking about applying to medical school, as a formative experience. "I didn't have any doctors in my family", he says. "But suddenly I was thrown together with 250 other aspiring medical students and over a long weekend suddenly realised that this was my tribe." When it came to choosing a specialty, he was initially drawn to the diagnostic art of neurology. "That was the initial draw, but then actually the far bigger challenge for neurological disorders is understanding those diseases fully and improving their outcome, which for many people [can be] awful."

Salman adds that, although some progress has been made in the treatment of intracerebral haemorrhage, its severity means that prevention remains key. "By far the most effective approach, not only for stroke but for many other non-communicable diseases, is preventing [the need for] interventions in the first place", he believes. "So right now, if my only mission was to prevent stroke rather than also being lured by the interest of diagnosis, I would choose to go into a career that would allow me to influence political and public health decisions."

Salman believes that every clinical researcher faces the dilemma of depth versus breadth in their research. "With bright inquiring minds, people are always interested in a whole variety of things", he says. "That variety can also be perilous in academic medicine because you can wind up becoming involved in so much you just become overwhelmed." Although Salman's clinical practice is broader, he has made a conscious effort to maintain a research focus on intracerebral haemorrhage "because the disease really needs attention, and it's an interesting challenge", he explains. "It's also to stop my inquiring mind getting too distracted by other things." Nevertheless, where his work shows great breadth is in the types of research and methods involved, from brain banking, to imaging diagnostic tests, to genetics, epidemiological studies, prognostic studies, clinical trials, and meta-analyses—as long as intracerebral haemorrhage is the focus.

Outside of work, Salman's focus is not narrow. 15 years after being featured in a Lifeline in *The Lancet Neurology*, he remains a serial instrumentalist, and still tries to play the accordion. His son—now a teenager—has followed in his footsteps and is a keen drummer, and Salman is on the lookout for the perfect instrument to accompany him. He also practices yoga and is an enthusiastic cyclist, enjoying the remote routes in countryside surrounding Edinburgh. "Yoga, cycling, a quest for the right instrument—and, of course, a loving family. They're the things that keep me balanced", he beams.

Jennifer Thorley

For more on **Salman's research** see **Articles** *Lancet Neurol* 2024; **23**: 565–76

For **Salman's Lifeline** see **In Context** *Lancet Neurol* 2009; **8**: 787

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The Lancet Neurology wrote a Profile about Rustam, in which he said, "The thing I love about medical research is team science. I'm naturally somebody who wants to collaborate rather than compete." At the moment, Rustam is coaching six doctors leading clinical trials and mentoring one doctor from another institution, in addition to the PhD students, clinical fellows, and staff that he supervises. So sharing the load, succession planning, or cloning should be his priorities for 2025! You can read the profile online.

Neshika Samarasekera

Nesh Samarasekera has published a paper about the course of brain swelling after a brain haemorrhage, showing that

it increases in the first two weeks after a haemorrhage (details at the end of the newsletter). She is working on a larger analysis of whether brain swelling affects how well people recover. She has also had a paper accepted about what causes dementia in people before they have a brain haemorrhage; we looked at brain samples from people who died from brain haemorrhages and showed that people with dementia before their haemorrhage have more severe pathological changes in their brains of the type we find in Alzheimer's dementia. This helps us to understand what is contributing to dementia. The study used brain tissue from people who gave their consent as part of the Lothian INtraCerebral Haemorrhage Pathology, Imaging and Neurological outcome (LINCHPIN) study. We remain extremely grateful to the patients and their families for helping us to increase our understanding of the links between brain haemorrhage and dementia.

Vega Pratiwi Putri

Vega (pictured here with her husband, Dony Adhika, and their two children, Syafa and Khalid) joined the RUSH team in January 2024. She is from Indonesia, which is had one of the highest burdens due to brain haemorrhage worldwide. She has a scholarship from the Indonesian Endowment Fund for Education (LPDP). Her research focuses on developing a tool to predict the risk of major adverse vascular events after brain bleeding. She hopes this tool will help survivors of brain bleeds better understand their future health risks and guide improvements in their care. She will be working on this project for

the next 3 years, supervised by Rustam, Nesh and Tom.

Tom Moullaali

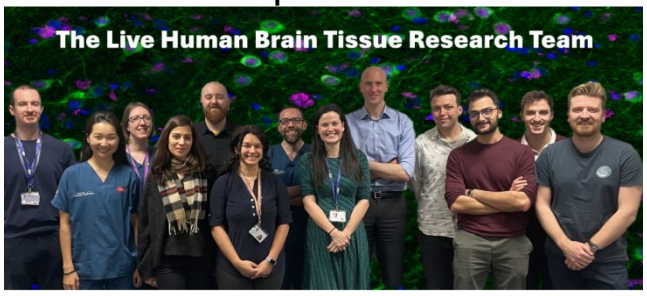
Tom continues his clinical training in neurology and is coming home to the stroke department in February 2025 to do his ‘subspecialty training in advanced stroke medicine’. Each Wednesday, he works with the RUSH team on several of our projects, such as PLINTH and supervising Vega. He is cultivating research ideas about using new technologies for very early diagnosis of stroke and other neurological disorders, by working with paramedics, emergency physicians and engineers from Edinburgh and beyond.

EMERGE nurse team

The team are kept on their toes with the Stroke and Neurosurgery research portfolio.

The research nurse team all took to the platform during the EMERGE 16th annual meeting in November with Sarah sharing her MSc experience and success, Anuka giving a preview of her Wilfred Card lecture “Career Progression Inequalities for Black and Minority Ethnic Nursing and Midwifery Staff at NHS Lothian" and Allan sharing personal impact of research from the participant perspective.

The team were delighted to receive a staff recognition award nomination from the University of Edinburgh for their work consenting patients with brain tumours for tissue donation and subsequent tissue collection. The whole team is pictured below.



Academic retreat

It's rare to have time to pause and reflect, but we were lucky to be able to do this by taking over Auchinleck House in Cumnock (below) for a few days thanks to the Landmark Trust Futures Scheme. The house is an 18th century mansion that was inhabited by James Boswell, the biographer of Samuel Johnson.

The Futures scheme provides free Landmark stays aimed at groups of four or more people for academic purposes: study, discussion, teaching, field study or writing.

The retreat was focussed on early- to mid-career researchers, to reflect on their research plans in a series of 'fireside chats' (above) to explore potential research projects, personal career progression (and hone our culinary skills!).

Alice Hosking

In July, Alice started work on her PhD (funder by a Medical Research Council fellowship), looking at risk factors for brain bleeding. If we can work out who is at highest risk of stroke due to bleeding, we can target preventative measures. She is using data from millions of people, collected routinely when people are admitted to hospital or visit their GP. She is enjoying

working with people across the University, including the computer science department.

She joined some of the other RUSH team at the European Stroke Organisation Conference in Switzerland this year, to present a poster on a way to use data to make clinical trials more efficient. She also sampled the local chocolate.

Arthur Fonville Award for Stroke Research

This year was the 10th anniversary of Arthur Fonville's passing. To mark this milestone, the RUSH team travelled to Amsterdam to join the Fonville family and Jonathan Coutinho of Amsterdam University Medical Centre for an in-person celebration of the life of Arthur and the successes of the part winners of this award.

There was a large in-person presence of both family members and researchers at the meeting in-person and online. Rustam told the story of Arthur's journey to join the RUSH team, his work with us, his promising future, and the influence that his award has had on so many students since. We remembered the immense talent and the loss of such a talented young man. We also celebrated the achievements and impacts of previous award were celebrated.

Chris Lerpiniere (below) gave an emotional and personal tribute to Arthur on behalf of herself and Rosemary, his two "Edinburgh Mums".

Arthur's father Joost replied with his own touching tribute to his

son, before thanking the RUSH team with a framed collage of all the previous award winners over the last 10 years.

The winners of the 2024 award were:

James Aspden (below) and **Saumya Maheshwari** (below) from The University of Edinburgh for their dissertation, “Exploring the mechanisms of action of a novel immunomodulatory cell therapy for the treatment of intracerebral haemorrhage”.

Abris Mumcuoglu (pictured left with Joost Fonville and Rustam) from Amsterdam University for his dissertation, “Admission blood pressure and clinical outcomes after endovascular thrombectomy in patients with an acute ischemic stroke: an international multicenter cohort study from the EVA-TRISP collaboration.”

Visitors

We hosted **Dr Raffaele Ornello** from Italy (pictured at the back, second from right, with the RUSH team). He was a European Stroke Organisation (ESO) Department-to-department scheme visitor. You can read Raffaele’s full report on his visit on the ESO website.

We were visited for 3 months by Abel Sandmann (seated, above, with the RUSH team) from the University of Amsterdam. He won the Arthur Fonville award in 2023. He used this achievement to secure funding for a 3-month study period with the RUSH team in Edinburgh. His main goal was to study the long-term prognosis of people with a cerebral cavernous malformation (CCM), analysing data from the Scottish Audit of Intracranial Vascular Malformations (SAIVMs).

Abel writes that he found Edinburgh to be a vibrant city with a rich history and beautiful architecture. After a cultural orientation with a campervan trip along the North Coast 500 and attending several shows at the Edinburgh Fringe, he began work! Abel also attended the European Stroke Organisation (ESO) 3-day Edinburgh Stroke Research Workshop in September, which he found to be an inspiring and insightful experience. Abel completed data collection for the 10-year cohort of people with CCM in Scotland, and finishing off analyses for publication. Before leaving, Abel managed to climb 5 Munros, he visited Dundee, St Andrews, the Isle of Skye and the Cairngorms, and he even saw the Northern Lights in Edinburgh. He'll need a rest after all of that!

Patient reference group: new members welcome!

We welcomed Dawn Smith as the ninth member of the RUSH Patient Reference Group. She joined the group having been a participant in the CARE pilot trial.

We are fortunate that Dawn works in public engagement with research and is passionate about involving people in research, ensuring it's accessible and making sure their voices are heard.

If you are a brain haemorrhage survivor or carer interested in joining our Patient Reference Group, please get in touch. In particular, we seek women and people with disability.

BHF Heart Matters

We contributed to an article about mini stroke in the 'Ask the Expert' section of the BHF Heart Matters magazine. You can read it on the BHF website.

Raising money for RUSH

We are extraordinarily grateful to our donors. Brain haemorrhage survivors have donated money to our projects to understand and treat swelling of the brain after brain haemorrhage. Friends and relatives of the Fonville family continue to donate to the Arthur Fonville Award fund. If you want to make a donation, you can find out how at www.RUSH.ed.ac.uk

Contact us

Feel free to contact us using any of the methods described below:

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2024 RUSH publications (highlights in red):

1. Jørgensen CM, Boe NJ, Hald SM, Meyer-Kristensen F, Norlén MM, Ovesen C, Möller S, Høyer BB, Bojsen JA, Elhakim MT, Harbo FSG, Al-Shahi Salman R, Goldstein LB, Hallas J, García Rodríguez LA, Selim M, Gaist D. Association of Prior Antithrombotic Drug Use with 90-Day Mortality After Intracerebral Hemorrhage. Clin Epidemiol 2024;16:837-848
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3. Guo J … 39 authors … Al-Shahi Salman R, Anderson CS, Song L for CHAIN investigators. The traditional Chinese medicine FYTF-919 (Zhongfeng Xingnao oral prescription) for the treatment of acute intracerebral haemorrhage: a multicentre, randomised, placebo-controlled, double-blind, clinical trial. *The Lancet* 2024;404:2187-96
4. Griffiths J, Adshead F, Al-Shahi Salman R, Anderson C, Bedson E, Bliss J, Boshoff A, Chen X, Cranley D, Doran P, Dunne F, Gamble C, Gillies K, Hood K, Kavanagh C, Malone J, McGregor N, McNamara C, Midha E, Moore K, Murphy L, Newman C, O'Reilly S, Perkins AM, Pett S, Sydes MR, Whitty L, You F, Fox L, Williamson P. What is the carbon footprint of academic clinical trials? A study of hotspots in 10 trials. *BMJ Open* 2024;14:e088800
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7. Samarasekera N, Ferguson K, Parry-Jones AR, Rodrigues M, Loan J, Moullaali TJ, Hughes J, Shoveller L, Wardlaw J, McColl B, Allan SM, Selim M, Norrie J, Smith C, Al-Shahi Salman R. Perihaematomal Oedema Evolution over 2 Weeks after Spontaneous Intracerebral Haemorrhage and Association with Outcome: A Prospective Cohort Study. *Cerebrovascular Diseases* 2024 (in press)

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9. Beck J … 15 authors … Al-Shahi Salman R … 34 authors … on behalf of the SWITCH study investigators. Decompressive craniectomy plus best medical treatment versus best medical treatment alone for spontaneous severe deep supratentorial intracerebral haemorrhage: a randomised controlled clinical trial. *Lancet* 2024;403:2395-404

10. Al-Shahi Salman R, Forsyth L, Lewis SC, Loan JJM, Neilson AR, Stephen J, Kitchen N, Harkness KA, Hutchinson PJA, Mallucci C, Wade J, White PM, on behalf of the CARE pilot trial collaboration. Medical management and surgery versus medical management alone for symptomatic cerebral cavernous malformation (CARE): a feasibility study and randomised, open, pragmatic, pilot phase trial. *The Lancet Neurology* 2024;23:565-76

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19. Vacek A, Mair G, White P, Bath PM, Muir KW, Al-Shahi Salman R, Martin C, Dye D, Chappell FM, von Kummer R, Macleod M, Sprigg N, Wardlaw JM. Evaluating artificial intelligence software for delineating hemorrhage extent on CT brain imaging in stroke. *J Stroke Cerebrovasc Dis* 2024;33:107512
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