

## **Spreading our wings...**

We put the pandemic behind us this year. Medical research was central to the UK's recovery from the COVID-19 pandemic. So we have been pleased to see research into non-communicable disease (like brain haemorrhage) regain momentum. In this newsletter, you will find updates about these activities in 2022:

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## **ASPIRING starts**

The Antiplatelet Secondary Prevention International Randomised trial after Interacerebral haemorrhage (ASPIRING) is for any survivor of brain haemorrhage. We will need more than 4,000 people to take part. Building on the results of our RESTART trial, we aim to produce reliable information about whether antiplatelet drugs like aspirin, which thin the blood, benefit any brain haemorrhage survivor. The results will affect how brain haemorrhage survivors are treated worldwide.



We're running a 'pilot phase' of ASPIRING in 20 hospitals in China and Australia to try out the trial with 120 participants. We're up to 71 already (see <https://aspiringtrial.org/>).



**R**esearch to  
**U**nderstand  
**S**troke due to  
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This year, we've been working hard to find funding to run ASPIRING worldwide. The trial has been endorsed by the Global Cardiovascular Research Funders Forum (GCRFF) Multinational Clinical Trials Initiative. This is a coalition of major international funders of cardiovascular clinical research. Its aim is to help researchers in different countries collaborate on multinational clinical trials that might not be feasible in a single country or with support from only one funder.

The **good news** is that the Canadian Institutes of Health Research has funded recruitment to ASPIRING in Canada!



**CIHR IRSC**

 Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

There are promising signs that the Dutch Heart Foundation and

the British Heart Foundation will also fund the trial. For more updates, keep in touch or look out for our 2023 newsletter...

### **CARE continues**



We are running the CARE pilot study in partnership with Cavernoma Alliance UK (CAUK), to address the top uncertainty for people with cavernoma, “Does treatment with neurosurgery or stereotactic radiosurgery improve outcome for people diagnosed with brain cavernoma in comparison to treatment without surgery?”

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With funding from NIHR in the UK, we started a pilot phase study in 2021 to see if this uncertainty could be resolved.

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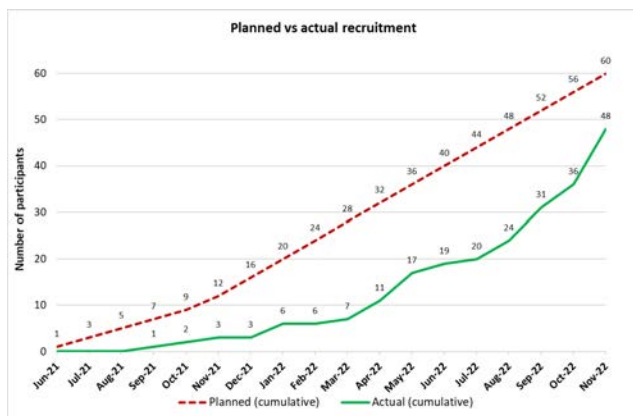
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Currently, 24 neurosurgical centres are active in the trial, and 48 people have taken part. We are 80% of the way to our target of 60 participants and have until the end of February to do so!

the Treat\_CCM trial. We were involved in running this trial, which was published in *The Lancet Neurology* in 2022 (reference 4 in the publications section of this newsletter).



What's needed now is a large, international platform trial of all of the drugs that are promising for cavernoma. So we applied for an NIHR 'Acceleration Award' to design the first international platform trial of targeted drug treatment for cavernoma and submit a funding application in May 2023. We were successful!

You can follow progress via: [www.ed.ac.uk/care-study](http://www.ed.ac.uk/care-study).

## CARE PREP starts

Many people with cavernoma who have been invited to take part in the CARE pilot study would rather not have surgery. They would prefer to try a drug to prevent their cavernoma from bleeding. There are several promising drugs for cavernoma, including the beta-blocker Propranolol, which was tested in



We were pleased to attend the 18<sup>th</sup> Alliance to Cure Cavernous Malformation International Scientific Meeting in Durham, North Carolina, USA in November 2022, to present CARE and CARE PREP

alongside the presentation of the Treat\_CCM trial results. Here you see members of the CARE PREP steering committee at the meeting in Durham (Rustam managed an 80km bike ride and a college basketball match at Duke on either side!).



## **Staff updates**

### **Research nurses**

There are now four research nurses in the Edinburgh Cerebrovascular Research Group (CVRG) EMERGE team.

The nurses support studies run by researchers in the RUSH team and other researchers in the Edinburgh CVRG. They also approach people in Edinburgh

who are seen in hospital after a stroke to offer them the opportunity to take part in research studies run from elsewhere in the UK. These include studies like ENRICH-AF, TRIDENT, and TICH-3 to which they have recruited 16, 11, and 3 participants respectively.

The research nurses (Allan Macraill, pictured below) were out in force to support World Stroke Day 2022, by providing education, information and blood pressure assessments.



## Dr Tom Moullaali

Dr Tom Moullaali is in higher specialist training to be a neurologist after completing a PhD. This year, he was awarded a Scottish Clinical Research Excellence Development Scheme (SCREDS) lectureship, giving him one day each week to support RUSH research and develop his own plans for his own research in the future.



Tom's family is growing: Chelsea and Tom welcomed Theodore

('Teddy') in December 2021, and Rory turned three in October.

Tom just heard that he has been awarded the John Chalmers Doctoral Award for the work he did for his PhD with The George Institute for Global Health in Australia. Well done, Tom!



## Dr Jamie Loan

Jamie Loan has now returned to clinical neurosurgical training, after completing a PhD. Jamie holds a clinical lectureship that allows him to dedicate a portion of his time towards conducting research into brain haemorrhage. Using this time, his immediate goal is to finish off some studies of whether inflammation after

brain haemorrhage in mice can be modified by a drug and then to write this up as a paper for publication.

Jamie was awarded the Chiene Medal in 2022 by Prof Stephen Wigmore at the Royal College of Surgeons of Edinburgh for his research studying the influence of inflammation on outcome after brain haemorrhage. Well done, Jamie! Here he is:



### **Arthur Fonville Award for Stroke Research**

This year there were 7 applicants for the award, which is an annual award for a stroke research dissertation by a medical student in Edinburgh or Amsterdam.

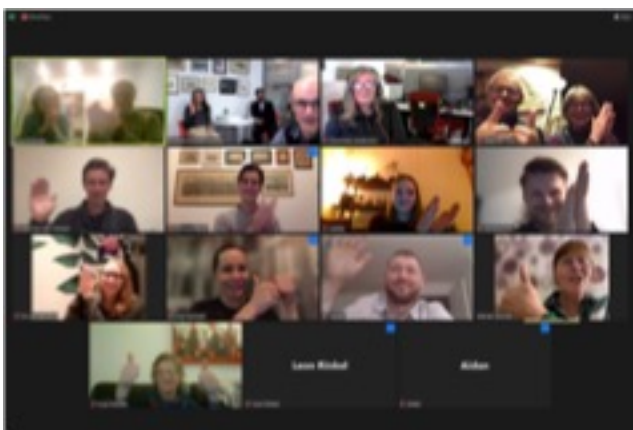
After independent adjudication the two winners were:



**Mohshin Syed** for his project “Selective outcome reporting in randomised controlled trials including participants with stroke or transient ischaemic attack: a systematic review” and **Serena Baker** for her project “Are There Sex Differences in Thrombectomy Utilisation in Treatment of Acute Ischaemic Stroke? A Systematic Review.”

Congratulations to both of them! They each received the Arthur Stone, a £100 cash prize, and the opportunity to receive a bursary of up to £750 towards presenting their research at a stroke conference.

We held the award ceremony with the Fonville family and friends via Zoom on 25th November 2022. 30 attendees from The Netherlands, France, Belgium and the UK attended to hear the two prize-winning questions and the customary inquisition from Joost Fonville and Rustam Al-Shahi Salman!

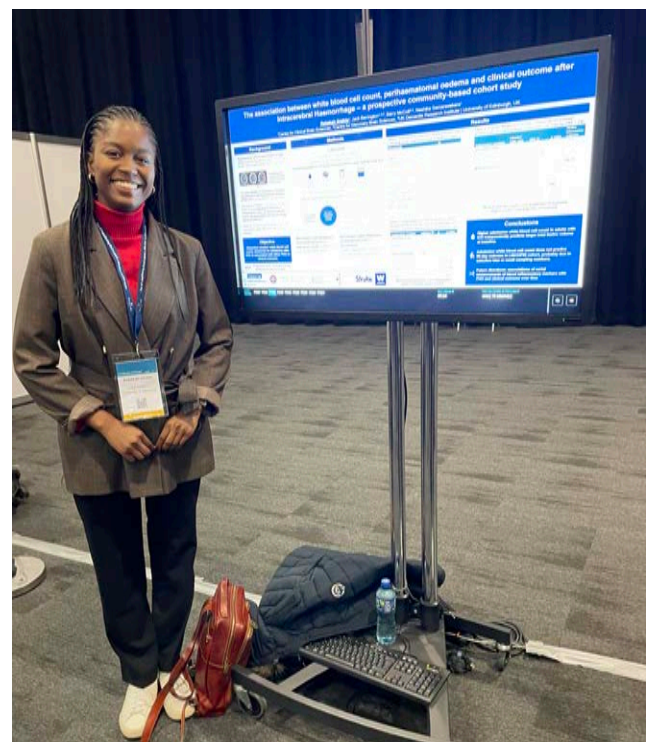


### ***Supporting students***

We were very pleased with the successes of some of the other

students who have joined RUSH research projects over the last year. We take pleasure in helping to advance their careers by conducting, presenting, and publishing research projects.

**Rebekah Smikle** is a PhD student in Translational Neuroscience at the University of Edinburgh. She conducted a project with Nesh Samarasekera about swelling after brain haemorrhage. Here she is presenting it as an e-poster at the 2022 UK Stroke Forum...



**Alexia Cochrane** is an undergraduate medical student at the University of Edinburgh. She updated a Cochrane systematic review about the effects of blood-thinning drugs after brain haemorrhage. Here she is with Rustam at the UK Stroke Forum, where she won the best e-poster prize. Bravo!



## ***Patient Reference Group***

The RUSH [Patient Reference Group](#) (PRG) is integral to our research. There are 6 members, but we're looking for more...

**Contact us if you are a brain haemorrhage survivor or carer interested in joining our PRG. We seek women and people with disability in particular**

**Gwynneth Clay** (pictured below, taking big strides forward after her brain haemorrhage) is a member of the PRG. She helped us to develop two research proposals this year.



One of the grant proposals was to the Chief Scientist Office of the Scottish Government, for a study of the feasibility of performing a Platform study for INTracerebral Haemorrhage (PLINTH). Can you spot another one of Rustam's acronyms?! Platform studies are efficient



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ways of studying several treatments at the same time. The RECOVERY trial of treatments for COVID is a recent example of a successful platform trial.

Gwynneth helped to confirm that the study design would be acceptable for patients and carers and that the plain English summary made sense.

The Chief Scientist Office has just confirmed that they would like to fund our PLINTH feasibility study, so you'll be hearing more about this next year...

## European Stroke Organisation (ESO)



Members of our group are active contributors to the ESO, whose mission is to reduce the burden of stroke and improve stroke care by providing medical education to healthcare professionals and the public.

For example, **Tom Moullaali** is an active member of the ESO Young Stroke Physician and Researcher (YSPR) committee, and wrote about it in [this blog](#). Tom is also a member of the faculty of the [ESO Stroke Research Workshop](#), which is an annual 3-day course in Edinburgh, to help clinical academics develop a research question for a stroke-related PhD or MD project.

We present our research at the [ESO conference](#), like Rustam did this year in Lille (below).



Rustam also spoke at the [ESO Summer School](#) in Birmingham, which is a prestigious educational meeting for stroke trainees throughout Europe. He's also the Vice Chair of the group developing ESO Guidelines for

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Intracerebral Haemorrhage in 2023. Rustam has also just been appointed the Chair of ESO's [Garmisch Stroke Science Workshop](#), at which stroke specialists and mid-career colleagues meet in Garmisch to explore cutting edge clinical and research aspects of stroke.

### **Engagement**

Engagement with the public, patients and stroke communities is a high priority for RUSH. We do this in various ways.

We set up a stand to inform people about stroke clinical care and research at the Edinburgh Royal Infirmary on World Stroke Day in October 2022:



**WORLD  
STROKE  
DAY** 29TH  
OCT

Now that many of the restrictions of the COVID-19 pandemic have

been lifted, we have been able to welcome overseas visitors back to our group.

### **Dr Helle**

**Eilertsen** (pictured) joined us for two months this year to learn about how to perform a Cochrane systematic review. She successfully updated an important review about [drugs to stop bleeding for people with brain haemorrhage](#), in collaboration with colleagues from Nottingham University. We expect it to be published in 2023.

The COVID-19 recovery has allowed face-to-face meetings to resume, so Rustam has had to travel, although he regrets that not all of these trips have been by bicycle. Rustam spoke about reducing risk alongside author and neurosurgeon Mr Henry Marsh in Bergen, Norway.



Closer to home, a group of medical students from Nijmegen in The Netherlands came to visit us in Edinburgh for inspiration...



...and Rustam gave talks to staff at the Chief Scientist Office of the Scottish Government in Edinburgh about, “A day in the life of a clinical academic” and another about “Environmentally sustainable clinical trials” at the International Clinical Trials

Methodology Conference in Harrogate, Yorkshire.

### ***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. And we received a generous legacy donation from someone whose family was affected by brain haemorrhage. If you want to make a donation, you can find out how at [www.RUSH.ed.ac.uk](http://www.RUSH.ed.ac.uk)

### ***Contact us***

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

#### **RUSH**

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Web [www.RUSH.ed.ac.uk](http://www.RUSH.ed.ac.uk)

Twitter [@BleedingStroke](https://twitter.com/BleedingStroke)

Facebook [www.facebook.com/bleedingstroke](https://www.facebook.com/bleedingstroke)

***Publications in 2022 that involved the RUSH team:***

1. Martí-Fàbregas J ... 44 authors ... Al-Shahi Salman R ... 25 authors ... Prats-Sanchez L. Stroke risk and antithrombotic treatment during follow-up of patients with ischemic stroke and cortical superficial siderosis. *Neurology* 2022 (in press)
2. Boe NJ, Hald S, Jensen MM, Bojsen JA, Elhakim MT, Florisson S, Saleh A, Clausen A, Möller S, Harbo FSG, Graumann O, Hallas J, Rodríguez LAG, Al-Shahi Salman R, Goldstein LB, Gaist D. Association between statin use and intracerebral hemorrhage location. A nested case-control registry study. *Neurology* 2022 (in press)
3. Cochrane A, Chen C, Stephen J, Rønning OM, Anderson CS, Hankey GJ, Al-Shahi Salman R. Antithrombotic treatment after stroke due to intracerebral haemorrhage. *Cochrane Database of Systematic Reviews* 2022 Art. No.: CD012144 (in press)
4. Lanfranconi S, Scola E, Meessen JMTA, Pallini R, Bertani GA, Al-Shahi Salman R, Dejana E, Latini R on behalf of the Treat\_CCM Investigators. Propranolol for treatment of familial cerebral cavernous malformations (Treat\_CCM): a phase 2, randomised, open-label, blinded endpoint pilot trial. *Lancet Neurol* 2022;22:35-44
5. Hostettler IC, Seiffge DJ, Wong A, Ambler G, Wilson D, Shakeshaft C, Banerjee G, Sharma N, Jäger HR, Cohen H, Yousry T, Al-Shahi Salman R, Lip GYH, Brown MM, Muir KW, Houlden H, Werring DJ. Apolipoprotein E and cerebral small vessel disease markers in patients with intracerebral haemorrhage. *Neurology* 2022 (in press)
6. Mair G, White P, Bath PM, Muir KW, Al-Shahi Salman R, Martin C, Dye D, Chappell FM, Vacek A, von Kummer R, Macleod M, Sprigg N, Wardlaw JM. Artificial Intelligence software to interpret brain computed tomography in patients with stroke: external validation of e-ASPECTS software. *Ann Neurol* 2022;92:943-57

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9. Gaist D, Hald SM, García Rodríguez LA, Clausen A, Möller S, Hallas J, Al-Shahi Salman R. Association of Prior Intracerebral Hemorrhage With Major Adverse Cardiovascular Events. *JAMA Netw Open* 2022;5(10):e2234215
10. Charidimou A ... 50 authors ... Al-Shahi Salman R, Smith EE, Werring DJ, Greenberg SM. The Boston Criteria version 2.0 for cerebral amyloid angiopathy: a multicenter, retrospective, MRI-neuropathology diagnostic accuracy study. *Lancet Neurology* 2022;21:714-25
11. Zuurbier SM, Hickman CR, Rinkel LA, Berg R, Sure U, Al-Shahi Salman R, for the Scottish Audit of Intracranial Vascular Malformations Steering Committee and Collaborators. Association between beta-blocker or statin drug use and the risk of hemorrhage from cavernous malformations. *Stroke* 2022;53:2521-7
12. Schwarz G, Banerjee G, Hostettler IC, Ambler G, Seiffge DJ, Brookes TS, Wilson D, Cohen H, Yousry T, Al-Shahi Salman R, Lip GYH, Brown MM, Muir KW, Houlden H, Jäger R, Werring DJ, Staals J on behalf of the CROMIS-2 investigators. Magnetic resonance imaging-based scores of small vessel diseases: associations with intracerebral haemorrhage location. *J Neurol Sci* 2022;434:120165

13. Christopher E, Loan JJM, Samarasekera N, McDade K, Rose J, Barrington J, Hughes J, Smith C, Al-Shahi Salman R. Nrf2 activation in the human brain after stroke due to supratentorial intracerebral haemorrhage: a case-control study. *BMJ Neurology Open* 2022;4(1):e000238
14. Law ZK, Appleton JP, Scutt P, Roberts I, Al-Shahi Salman R, England TJ, Werring DJ, Robinson T, Krishnan K, Dineen RA, Laska AC, Peters N, Egea-Guerrero JJ, Karlinski M, Christensen H, Roffe C, Bereczki D, Ozturk S, Thanabalan J, Collins R, Beridze M, Ciccone A, Duley L, Bath PM, Sprigg N, for the TICH-2 Investigators. Brief consent methods enable rapid enrolment in acute stroke trial: results from TICH-2 randomised controlled trial. *Stroke* 2022;53:1141–8.
15. Loan JJM, Gane AB, Middleton L, Sargent B, Moullaali TJ, Rodrigues MA, Cunningham L, Wardlaw JM, Al-Shahi Salman R, Samarasekera N on behalf of the Lothian Audit of the Treatment of Cerebral Haemorrhage Collaborators. Association of baseline haematoma and oedema volumes with one-year outcome and long-term survival after spontaneous intracerebral haemorrhage: a community-based inception cohort study. *Int J Stroke* 2020;16:1747493020974282
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20. Loan JJM, Kirby C, Emelianova K, Dando OR, Poon MTC, Pimenova L, Hardingham GE, McColl BW, Klijn CJM, Al-Shahi Salman R, Schreuder FHBM, Samarasekera N. Secondary injury and inflammation after intracerebral haemorrhage: a systematic review and meta-analysis of molecular markers in patient brain tissue. *JNNP* 2022;93:126-32
21. Loan JJM, Al-Shahi Salman R, McColl BW, Hardingham GE. Activation of Nrf2 to Optimise Immune Responses to Intracerebral Haemorrhage. *Biomolecules* 2022;12(10):1438
22. Morotti A, Boulouis G, Dowlathshahi D, Li Q, Shamy M, Al-Shahi Salman R, Rosand J, Cordonnier C, Goldstein JN, Charidimou A. Intracerebral haemorrhage expansion. *Lancet Neurol* 2022 (in press)