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Research for Patient Benefit
Final Report Form

Project Title	Desmopressin for treatment of patients taking Antiplatelet agents with Stroke due to Haemorrhage
Reference Number	PB-PG-0816-20011
Contracting Organisation	Nottingham University Hospitals NHS Trust
Approved Duration	22
Current Duration	49
Contracted Start Date	01/06/2018
Contracted End Date	30/06/2022
Original Award	248,547.00
Current Award	330,991.00

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Full Name	Professor Nikola Sprigg
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Research Team

Chief Investigator	Professor Nikola Sprigg (University of Nottingham)

Joint Lead Applicant:	

Co-Investigators:	Professor Timothy Coats (University of Leicester) Professor Philip Bath (University of Nottingham) Professor Robert Dineen (University of Nottingham) Dr Michael Desborough (Oxford University Hospitals NHS Foundation Trust) Mrs Trish Hepburn (University of Nottingham) Professor Rustam Al-Shahi Salman (University of Edinburgh) Dr Paul Brennan (University of Edinburgh) Mr Philip Johnson (University of Nottingham) Professor Simon J Stanworth (NHS Blood and Transplant)

Selection List	Professor Nikola Sprigg
Role in research	Chief Investigator

Selection List	Dr Michael Desborough
Role in research	Deputy CI and expert haematologist

Selection List	Professor Philip Bath
Role in research	Expert in clinical trials, Nottingham Stroke Trials Unit Head

Selection List	Mrs Trish Hepburn
Role in research	Trial Statistician

Selection List	Professor Robert Dineen
Role in research	Neuroradiology expert

Selection List	Professor Rustam Al-Shahi Salman
Role in research	Expert in ICH and clinical trials

Selection List	Professor Simon J Stanworth
Role in research	Expert in haematology and clinical trials

Selection List	Professor Timothy Coats
Role in research	Expert in emergency medicine and clinical trials
Selection List	Dr Paul Brennan
Role in research	Expert in neurosurgery
Selection List	Mrs Diane Havard
Role in research	Senior Clinical Trial Manager
Selection List	Mr Philip Johnson
Role in research	Stroke survivor and PPI representative

Involvement of NIHR Infrastructure

Please indicate which NIHR Infrastructure organisations were involved in your research.
CTUs, CRN

Please describe the role of each organisation in your research
The study was adopted to the NIHR portfolio and delivered in stroke units supported by CRN research staff who screened identified and enrolled participants and then collated and entered data on to the online electronic case report forms. Three members of the Nottingham CTU were involved in the DASH trial. Trish Hepburn (Senior Medical Statistician) provided crucial input to the development of the proposal, the design, statistical analyses and implementation of the trial. Trish Hepburn remained blinded throughout the trial. Wei Tan and subsequently, Cydney Bruce, were unblinded statisticians from Nottingham CTU that ran reports for Data Monitoring Committee meetings.

Changes to Research Team

Please outline any changes that have been made to the research team over the course of the research, including an explanation of why they were required.
The deputy CI Dr Mike Desborough took over the role of CI from May 2021 as Prof Nikola Sprigg was on long term sick leave. Dr Desborough acted as CI whilst Prof Sprigg was on a phased return to work. Prof Sprigg resumed her role as CI in Oct 2022. The following staff employed by the Stroke Trials Unit, Nottingham continue to work on the DASH trial: Diane Havard - Senior Trial Manager (Dec 2018 - present) Lee Haywood - Web Application/Database Programmer (Oct 2018 – present) Lisa Woodhouse - Medical Statistician (Jan 2019 – present) Iris Mhlanga – Statistician (Aug 2022 – present) Jennifer Craig - Follow Up Coordinator (Aug 2021 – present) Kailash Krishnan – Scan Adjudication (Mar 2021 – present) Robert Dineen – Neuroimaging Lead (Mar 2021 – present) The following members of the research team changed roles or left the Stroke Trials Unit during the course of the trial: Patricia Robinson - Trial Administrator (Oct 2018 – Nov 2021) Cameron Skinner - Follow Up Coordinator (Feb 2021 – Aug 2021) Sharon Ellender – Coordinator & Follow Up Coordinator (Jul 2019 – Dec 2020) Robert Gray – Trial Coordinator (Oct 2018 – June 2019)

Scientific Summary

Please provide a structured summary of your work.

Background
The risk of death and disability from spontaneous intracerebral haemorrhage is elevated for people taking antiplatelet drugs.
Original objective
We assessed the feasibility of randomising patients with spontaneous intracerebral haemorrhage to desmopressin or placebo to reverse or reduce the antiplatelet drug effect.
Methods
This was a phase II blinded randomised controlled feasibility trial. Patients were recruited from ten stroke centres in the United Kingdom. Participants were eligible if they had a spontaneous intracerebral haemorrhage, were aged 18 years or above, had stroke symptom onset within 24 hours of randomisation, and were taking an antiplatelet drug.
Participants were randomly allotted 1:1 to a single dose of intravenous desmopressin 20 µg or matching placebo. The primary outcome was feasibility assessed as number of eligible patients randomised and proportion of eligible patients approached. The trial was prospectively registered (ISRCTN67038373) and is closed to recruitment. The study was paused due to the pandemic from 26 March 2020 to 29 June 2020, after which centres re-opened according to capacity at sites.
Key Findings
54 participants were recruited between 01 April 2019 and 12 Mar 2022. 1380 potential participants were screened for eligibility. 1204 were considered ineligible. 176/1380 (12.8%) participants were potentially eligible, with 54/176 (30.7%) recruited. The main reasons for eligible patients not being recruited were the patient arriving out of hours (74/122 (61%)) and doctors being unavailable (17/122 (14%)). 27 participants were allocated to desmopressin and 27 to placebo. All participants remained in their allocated group for the duration of the trial with no participants lost to follow-up or withdrawing from the trial. All 54 participants had day 90 outcome data (the anticipated primary outcome in a definitive trial).
26 participants in the desmopressin arm received all the trial treatment and one received part of the trial treatment because of a fault with a leaking bag of sodium chloride.
100/140 (71.4%) treatment packs of desmopressin or placebo were exposed to at least one temperature excursion.
Death or dependency at day 90 was 6/27 (22.2%) in the desmopressin arm and 10/27 (37%) in the placebo arm. Change in intracerebral haematoma volume at 24 hours was 0ml (IQR -1.4 to 2.0) in the desmopressin arm and 0.5ml (IQR -0.7 to 2.1) in the placebo arm. Haematoma expansion occurred in 5/24 (20.8%) in the desmopressin arm and 5/22 (22.7%) in the placebo arm.
Serious adverse events occurred in 12/27 (44.4%) participants in the desmopressin arm and 13/27 (48.2%) in the placebo arm.
Outputs, impact and dissemination
The results were presented at UK Stroke Forum on 1st December and are being submitted to peer review journal.
Conclusion
These results demonstrate that it should be feasible to conduct a definitive trial to determine if desmopressin improves outcome in patients with antiplatelet drug associated spontaneous intracerebral haemorrhage.
Future plans
A future clinical trial to assess efficacy would be more likely to be successful if it were embedded into clinical practice to allow clinical teams to randomise patients out of hours; and if a pragmatic approach to temperature monitoring utilised.

Keyword 1:	Desmopressin

Keyword 2:	intracerebral haemorrhage

Keyword 3:	Anti-platelet

Keyword 4:	feasibility
Keyword 5:	randomised trial
Keyword 6:	hyperacute
Keyword 7:	stroke
Keyword 8:	

Plain English Summary

Please provide a plain English summary of your research.

Aims and objectives
To assess whether it is feasible to run a large trial to see if desmopressin can reduce the number of people who die or are disabled after intracerebral haemorrhage.
Background
Intracerebral haemorrhage is caused by bleeding in the brain. Patients who are taking blood-thinning drugs (antiplatelet drugs, such as aspirin) are more likely to die or be disabled if they have intracerebral haemorrhage. Desmopressin is a drug which may reverse the effects of antiplatelet drugs and stop bleeding in the brain.
Methods
Participants with intracerebral haemorrhage while taking antiplatelet drugs (or their relatives if patients were too unwell) were asked if they wished to take part in the trial. Treatment with either desmopressin or a dummy drug was given as a drip. Researchers contacted participants 3-months after stroke to follow-up their condition.
Key findings
54 participants were recruited across 10 UK hospitals between October 2018 and June 2022 demonstrating that it is possible to recruit patients despite the pandemic. All participants received the trial treatment, there were no concerns regarding the safety of desmopressin. The commonest reason eligible patients were not enrolled was if they came to hospital overnight or when a research doctor was unavailable.
Most eligible patients (or relatives) approached agreed to take part and follow-up was completed in everyone at 3 months, suggesting the consent and follow-up methods worked well.
Patient and public involvement
PPI representatives attended Trial Committee meetings; informing decisions made regarding the consent process, recruitment period, trial extensions, and an animated results video.
Conclusions and future plans
Whether desmopressin reduces the number of people who die or are disabled after intracerebral haemorrhage is an important question to answer in a larger trial. The DASH trial highlighted what worked well and what could be improved in a larger trial.

Please tick the box if this section of the report has been written with members of the public who have been involved in the research.

☒ Confirmed

Aims and Objectives

Please describe the original aims and objectives of the research.

Primary objective:
To assess the feasibility of randomising, administering the intervention, and completing follow-up for patients treated with desmopressin or placebo to inform a definitive trial.

Feasibility outcomes:

- Proportion of eligible patients who are enrolled and receive randomised treatment
- Proportion of patients who were screened who were eligible
- Proportion of eligible patients approached who were randomised
- Rate of participant recruitment per month per site
- Time to randomisation following hospital admission
- Adherence to allocated treatment
- Proportion of participants followed up to 90 days and reasons for loss to follow up
- Proportion of randomised participants with the proposed primary and secondary outcome data available

Secondary outcomes:
The following variables are expected to be outcomes in a subsequent definitive trial and are being collected in this trial:

- Death or dependency at day 90 (modified Rankin scale)
- Early mortality <28 days
- Mortality up to day 90
- Serious adverse events (including thromboembolic events) up to day 90
- Change in intracerebral haemorrhage volume at 24 hours
- Discharge destination
- Disability (Barthel index, day 90)
- Quality of life (EuroQol, day 90)
- Cognition (telephone MMSE day 90)
- Length of hospital stay
- Health economic assessment (EQ-5D)
- Hyponatraemia at 24 hours

Centralised laboratory analysis to answer two key questions:
1.Is it feasible to measure plasma von Willebrand factor (VWF) and factor VIII (a proposed secondary outcome for the definitive study) across multiple sites?
2. Is it feasible to identify patients with impaired platelet function due to anti-platelet agents on the basis of clinical history alone?

Changes to Aims and Objectives

If the aims and objectives changed, please explain in what way and why.
No changes were made to the aims and objectives. **Changes to the research plan:** - A 9-month costed extension granted to extend initial end date to 31/12/20 due to contracting/pharmacy issues delaying start of recruitment. CI and research team worked with R&D teams and pharmacy team to resolve issues. - A no-cost extension was granted to extend the trial end date to 14/01/22 - A further no-cost extension was granted to extend the end date to 30/06/22 - Extension of final report deadline and end of grant to 31/12/22 was granted by the Programme Manager. - COVID caused significant delays to recruitment due to research site temporarily halts to recruitment throughout 2020 and 2021. The research team worked with site research teams to support the re-opening of sites. - Inclusion criteria caused a significant number of patients to be excluded. Inclusion criteria amended to allow longer time from stroke, which increased recruitment. - IMP excursions caused IMP to be quarantined regularly. The trial team worked with pharmacy and the manufacturer to clarify temperature guidelines and reduce the number of excursions. - Due to the extension of the trial, IMP packs expired. IMP at the host pharmacy had to be split to send to recruiting sites which caused substantial delays. **Final timeline:** Trial Start date – 01/06/2018 Recruitment start date – 15/02/2019 End of recruitment - 31/03/2022 Final date for follow ups - 30/06/2022 Data cleaning and analysis - June – September 2022 Final report/end date of the grant - 31/12/2022

Description of Research

Please provide a structured summary of your work.

Background

Approximately 3 million deaths were due to spontaneous intracerebral haemorrhage (SICH) worldwide in 2015[NS2] . Two-thirds of survivors are left dependent on others. One third of patients are taking antiplatelet drugs at the time of SICH in high-income countries, and this proportion is increasing. Pre-stroke antiplatelet drug use is associated with a 27% relative increase in one-month case fatality compared to patients not using antithrombotic drugs. There is no proven effective drug treatment for SICH, although blood pressure lowering might improve outcome.

Outcome after SICH is closely related to haematoma expansion which is associated with worse outcome (death and disability). Use of antiplatelet drugs or anticoagulants, time from onset of symptoms to baseline imaging, and intracerebral haematoma volume on baseline imaging are independent predictors of haematoma expansion. Desmopressin (1-deamino-8-D-arginine vasopressin; DDAVP) is a licensed pro-haemostatic drug that is commonly used in the treatment of inherited bleeding disorders and may reduce the risk of bleeding for patients taking antiplatelet drugs. Prior to the DASH trial, there were no randomised trials of desmopressin compared to placebo for SICH. There are conflicting recommendations internationally on whether desmopressin should be considered for patients with antiplatelet-drug associated SICH.

A definitive randomised controlled trial is required to determine the effectiveness of desmopressin. However, at this point there is insufficient evidence about whether participants can be recruited to such a trial, and if so, the rate of such recruitment. It was therefore decided that a feasibility trial should be conducted.

Methods

DASH was a multicentre blinded randomised placebo-controlled, parallel-group phase II feasibility trial. Ethical approval was obtained (18/EM/0184). Inclusion criteria: adults (≥18 years); taking a daily oral antiplatelet drug in the preceding seven days. Initially, participants were eligible if randomised within 12 hours of symptom onset. Following a substantial amendment (SA/03/19, 22/11/2019), participants could be recruited if randomised within 24 hours from onset.

Exclusion criteria: known secondary causes of SICH; patients at risk of fluid retention; systolic blood pressure less than 90mmHg; drug eluting stent previous 3 months; allergy to desmopressin; pregnant or breast-feeding; life-expectancy < 4 hours or planned for palliative care only; Glasgow Coma Scale < 5; modified Rankin Scale (mRS) > 4.

Patients with capacity to give informed written consent were approached directly. If this was not possible, a relative or close friend was approached for consent. Otherwise, a professional not associated with the trial could then be approached for proxy consent.

Participants were randomised centrally using a computer-generated randomisation sequence in real-time. Treatment allocation was concealed from all staff and patients. Randomisation involved minimisation on key prognostic risk factors.

Patients were randomised to either 20µg intravenous desmopressin (DDAVP, 4µg/ml 1ml glass ampoules, Ferring Pharmaceuticals) or placebo of intravenous Sodium Chloride 0.9%. Either desmopressin 20µg (5x 4µg/ml) was added to 50ml Sodium Chloride 0.9% and infused over 20 minutes, or three 2ml Sodium Chloride 0.9% were added to 50ml Sodium Chloride 0.9% and infused over 20 minutes.

We developed a pharmacy manual such that IMP was quarantined in the event of temperature excursions (as per stability data).

Sites were required to complete screening logs on consecutive patients with intracerebral haemorrhage.

Haematoma volume was measured centrally, masked to treatment allocation using semi-automated segmentation.

Baseline platelet dysfunction was measured (P-selectin) and change in factor VIII, VWF antigen and VWF activity one hour after administration of desmopressin.

At day 90, central assessors masked to treatment allocation followed up each participant by telephone.

This was a feasibility trial and the **primary outcomes** were: number of eligible patients who receive allocated treatment; rate of eligible patients randomised; proportion of eligible patients approached; proportion of eligible patients randomised and reasons for non-randomisation; adherence to intervention; proportion of participants followed up to 90 days, reasons for loss to follow up; proportion of randomised participants with full outcome data

available, and reasons for non-availability.
Secondary outcomes included haematoma expansion, change in haematoma volume and hyponatraemia at 24 hours, length of hospital stay, discharge destination and mortality within 28 days. At day 90, outcomes included death or dependency (mRS>4), mortality, serious adverse events.
Centralised laboratory analysis to answer two key questions:
1.Is it feasible to measure plasma von Willebrand factor (VWF) and factor VIII (a proposed secondary outcome for the definitive study) across multiple sites?
2. Is it feasible to identify patients with impaired platelet function due to antiplatelet agents on the basis of clinical history alone?
A statistical analysis plan (SAP) was agreed prior to database lock and release of randomisation codes.

Findings 54 patients were recruited from ten UK stroke centres between 01 April 2019 and 12 March 2022. The study was paused due to the pandemic from 26 March 2020 to 29 June 2020, after which centres re-opened according to capacity at sites. One site did not reopen.

Feasibility outcomes:
Recruitment:
The overall primary outcome was the feasibility of recruitment. We initially hypothesised that feasibility will be confirmed if 50 participants were randomised in a 12 month period. However, we encountered a number of barriers to this objective.
1380 potential participants were screened for eligibility. 1204/1380; 87% were considered ineligible. The most common reasons for ineligibility were no history of antiplatelet use (843/1204; 70.0%) or presentation to hospital more than 24 hours after symptom onset (152/1204; 12.6%) 176/1380 (12.8%) participants were potentially eligible with 54/176 (30.7%) randomised. The most common reasons for eligible patients not being randomised were the patients arriving out of hours (60.7%), no doctor being available (13.9%) and recruitment being on hold (8.2%). 27 were allocated to desmopressin and 27 to placebo.
Retention: All participants remained in their allocated group for the duration of the trial with no participants lost to follow-up or withdrawing from the trial. All 54 participants had day 90 outcome data (the anticipated primary outcome in a definitive trial).
Compliance: 26 participants in the desmopressin arm received all the trial treatment and one received part of the trial treatment because of a fault with a leaking bag of sodium chloride. All participants in the placebo arm received the allocated treatment in full.
Storage of IMP: 100/140 (71.4%) treatment packs of desmopressin or placebo were exposed to at least one temperature excursion. 69/140 (49.3%) were quarantined at least once and 59/140 (42.1%) treatment packs were destroyed. 25/54 (46%) participants received treatment from a pack which had been exposed to a temperature of less than 2°C and/or more than 8°C at some point during its storage.

Radiological outcomes: The feasibility of measuring change in intracerebral haemorrhage volume at 24 hours, a proposed outcome for the definitive study, was assessed. 46/54 (85%) patients had follow up imaging enabling assessment of haematoma expansion and change in haematoma volume[NS7] .
Change in intracerebral haematoma volume at 24 hours was 0ml (IQR -1.4 to 2.0) in the desmopressin arm and 0.5ml (IQR -0.7 to 2.1) in the placebo arm. Haematoma expansion occurred in 5/24 (20.8%) in the desmopressin arm and 5/22 (22.7%) in the placebo arm. The incidence of hyponatraemia was 3/27 (37.5%) in the desmopressin arm and 2/27 (20%) in the placebo arm. Hospital length of stay was 9 (IQR 3 to 15) days in the desmopressin arm and 6 (2 to 22) days in the placebo arm. Early mortality at less than 28 days was 5/27 (18.5%) in both the desmopressin and placebo arms. At day 90, in the desmopressin arm 18/27 (66.7%) were at home, 4/27 (14.8%) were in hospital or in residential care, and 5/27 (18.5%) died. In the placebo arm 16/27 (59.3%) were at home, 4/27 (14.8%) were in hospital or residential care, and 7/27 (25.9%) died. Death or dependency at day 90 was 6/27 (22.2%) in the desmopressin arm and 10/27 (37%) in the placebo arm.

Safety:
Serious adverse events occurred in 12/27 (44.4%) participants in the desmopressin arm and 13/27 (48.2%) in the placebo arm. After 24 hours, mild hyponatraemia (sodium 125 to 134mmol/L) was present in 8/23 (34.8%) patients in the desmopressin arm and 3/24 (12.5%) in the placebo arm. No patient in either arm had a sodium less than 125mmol/L. Thrombotic events were reported for 1/27 (3.7%) in the desmopressin arm (non-ST-elevation myocardial infarction) and 1/27 (3.7%) in the placebo arm (ischaemic stroke).

Secondary functional outcomes: Follow up via telephone at day 90 was feasible with good data completion. At day 90, Barthel index was mean 71.6 ± 33.1 in the desmopressin arm and 67.4 ± 33.6 in the placebo arm (n=41). EuroQol-5D was 0.37 ± 0.40 in the desmopressin arm and 0.34 ± 0.35 (n=53). TICS-m score was 22.3 ± 6.4 in the desmopressin arm and 22.9 ± 4.0 in the placebo arm.

Haematological analysis:
In answer to our two key questions:
1. Is it feasible to measure plasma von Willebrand factor (VWF) and factor VIII (a proposed secondary outcome for the definitive study) across multiple sites?
Measurement of plasma von Willebrand factor (VWF) and factor VIII was only possible in 24/54 (44%) of participants.
In the desmopressin arm the change in blood tests before and one hour after treatment was: VWF antigen 0.11 ± 0.66 iu/mL, VWF activity 0.20 ± 1.11 iu/mL and factor VIII 0.26 ± 1.35 iu/mL. In the placebo arm the change in blood tests before and one hour after treatment was: VWF antigen 0.05 ± 0.20 iu/mL, VWF activity 0.09 ± 0.26 iu/mL and factor VIII 0.15 ± 0.27 iu/mL.

2. Is it feasible to identify patients with impaired platelet function due to antiplatelet agents on the basis of clinical history alone?
The first 28 patients recruited into the DASH trial would have been eligible for P-Selectin testing and 14 (50%) had the tests done.[J(8] The manufacturers of the P-Selectin tests went out of business before the end of the trial, so these tests were not available for the last 26 patients recruited to DASH.
Baseline, pre-treatment samples were available for 14 patients: nine taking aspirin and six taking clopidogrel (one patient was on both drugs)
Negative controls (no agonist) and positive controls (thrombin as agonist) all worked appropriately.
Of those participants reported to be taking aspirin, 3 (33%) demonstrated platelet inhibition and 6 (67%) were not inhibited.
Of those participants reported to be taking clopidogrel 4 (67%) demonstrated platelet inhibition and 2 (33%) were not inhibited.
There is no validated cut-off for the P-Selectin test for determining resistance to antiplatelet drugs. It is possible that these results may show high rates of either antiplatelet drug resistance or non-compliance. However the small numbers of patients who had these tests run and limitations of the sensitivity and specificity of these tests also must be taken into account.

Therefore It does not appear to be feasible to run platelet function tests for patients in a larger trial to determine whether they are taking antiplatelet drugs.

Conclusions
This is the first randomised trial comparing desmopressin to placebo. It demonstrates the feasibility of performing a large randomised trial to assess efficacy and has shown no safety signals. Death or disability was lower for those treated with desmopressin rather than placebo although the sample size was too small to assess efficacy.
The DASH trial was conducted during a global pandemic where staff were redeployed to work in other areas. In addition there were significant capacity issues at sites (both clinicaly and with research and innovation departments) which meant that a number of sites were not able to re-open after COVID. Hence it is possible that participant recruitment could also be increased from that observed in this trial.
Recruitment rate increased after the enrolment time window was increased to 24 hours post stroke onset. The rationale for this increased time window was that the antiplatelet drug effect persists for 5 to 7 days after cessation of the drug and optimal timing of administration of prohaemostatic therapy is unknown. However this long time window is in contrast to ongoing trials of other prohaemostatic drugs such as recombinant factor VIIa and tranexamic acid, which have opted for much tighter time windows as haematoma expansion occurs early after ICH.
We had pre-specified number of participants who had desmopressin administered within three hours of symptoms onset versus administered later for subgroup analysis in the definitive study. However there were only 10 [NS10] enrolled < 3 hours of symptom onset.The commonest modifiable reason for non-enrolment of eligible patients related to lack of ability to recruit patients who present out of hours, often when an enrolling doctor was not available. This highlights the need for simplified trials embedded into clinical practice.

The desmopressin and placebo were administered in full in all but one case. Temperature monitoring of the IMP added significant burden to sites; given that desmopressin is used routinely in clinical practice future studies should attempt to reduce this burden. A more pragmatic approach to temperature monitoring should be

considered, for instance requiring that desmopressin should be stored in a fridge in line with current clinical practice.
The measures in place to follow up participants were very successful and would be repeated for a definitive trial. We estimate that 176/1380 (12.8%) patients with SICH would potentially be eligible for a definitive trial. Of these 54/176 (30.7%) were recruited in the DASH trial.
This trial demonstrates the need for a large simple randomised trial to assess the efficacy of desmopressin compared to placebo for patients with antiplatelet drug-associated spontaneous intracerebral haemorrhage.

A future clinical trial would be most likely to be successful if it were embedded into clinical practice so that it is possible for clinical teams to randomise patients out of hours.

Intellectual Property, Commercialisation and Clinical Adoption

Please provide brief details of IP outputs arising from this research.
Nothing applicable to list here as this was a feasibility trial. Below is the information we provided on the original submission and nothing has since changed. There will be know-how and IP in the form of copyright. We will build on knowledge by assessing the feasibility of randomising, administering the intervention and completing the follow up. This data will be used to inform the protocol for the definitive trial for a future funding application (NIHR HTA). Any arising IP such as know-how and copyright, will be initially recognised through project management and will be discussed with and managed by Nottingham University Hospitals (NUH)'s Head of Project Development / IP. NUH NHS Trust will lead on the management of the IP in consultation with the University of Nottingham (UoN). As part of our strategy any IP generated will be monitored and protected appropriately via collaboration agreements to relevant parties. If this study confirms feasibility to test desmopressin in a randomised controlled trial in acute intracerebral haemorrhage, we will be able to rapidly proceed to a definitive phase III trial with potential for substantial impact. NUH and The UoN will work together, and with local networks, to ensure the most appropriate method of adoption and dissemination. Despite advances in treatment of ischaemic stroke, there is no effective drug treatment for intracerebral haemorrhage. Treatment for intracerebral haemorrhage has been identified as a priority area by Stroke Association and stroke survivors. It is affordable, available and could be implemented clinically with immediate benefit for stroke patients, their families and society. We don't anticipate any potential regulatory hurdles and should the intervention be effective we would perform a health economic analysis to demonstrate cost effectiveness.

Actual and Anticipated Impact

Please provide a brief impact statement.
Our evidence demonstrates the need for a large simple randomised trial to assess the efficacy of desmopressin compared to placebo for patients with antiplatelet drug-associated spontaneous intracerebral haemorrhage.

Describe the impact the research has already achieved or might achieve in the short, medium and long term.
Despite advances in treatment of ischaemic stroke, there is no effective drug treatment for intracerebral haemorrhage. In the England, Wales and NI just under 3000 patients had ICH last year – approximately a quarter of these will be taking anti-platelet therapy and this number is likely to increase due to the ageing population. Treatment for intracerebral haemorrhage has been identified as a priority area by the Stroke Association and identified in top 3 priorities in recent priority setting James Lind Alliance for acute stroke. Desmopressin is affordable, available and could be implemented clinically with immediate benefit for stroke patients, their families and society.

Dissemination

Please describe how you have disseminated your research findings and what your plans for further dissemination are.
Findings from the trial were presented at the UK Stroke Forum in Liverpool on 1st December 2022. An abstract focusing on temperature monitoring of IMP during the DASH trial was presented at the International Clinical Trials Methodology Conference in Harrogate in October 2022. Findings may be presented at other conferences in 2023, such as European Stroke Conference, World Stroke Congress, International Society on Haemostasis and Thrombosis, British Society for Haematology annual meeting, and American Society for Haematology annual meeting. We plan to post a lay summary of the findings on the Nottingham Research support group (PPCIE) website and DASH trial website. We are also working in collaboration with a NIHR communications specialist to develop a results video aimed at communicating the research findings to the general public. PPI representatives have been providing guidance on this and we hope to have the video ready to share on the DASH website and via social media by spring 2023. For research participants who have requested feedback about the trial, we will provide them with a lay summary of the findings, and details about accessing the results video.

Publications

Number published	4
Number in press	0
Number submitted	0
Number in preparation	1

Publications and Other Outputs

Grant holders are required to ensure that NIHR is named and acknowledged appropriately when submitting a paper or report for publication. Please ensure that the following statement is included in any presentations, posters or papers.
STARTS
This project is funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number NIHRXXXXXX/PG-PB-XXXX-XXXXX). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.
ENDS
Use of the correct project reference greatly aids the automated identification of publications and contributes to NIHR's ability to report accurately on the outputs, outcomes and impact of the work we fund.
It is no longer a requirement to notify us of your dissemination outputs, however you are still required to send details of all media activity (e.g. press releases, media exclusive journalist briefings etc) to RfPB@nihr.ac.uk.
ENDS

Please add any research outputs that incorporate findings from the research and have been published since the last progress report.
Where outputs have not been published online (or the full text is not available through Europe PubMed Central (Europe PMC) or open access from the publisher) please append a copy of the final version as an annex to this report in the **'supporting documentation'** section.

Output Title	Desmopressin for reversal of Antiplatelet drugs in Stroke due to Haemorrhage (DASH): protocol for a phase II double-blind randomised controlled feasibility trial.
Was this output submitted to CCF?	No
Type of Output	Academic manuscript
Is the output available in PubMed?	Yes
PubMed ID (PMID) for output	PMID: 33172941
Is the full text of this output available on Europe PubMed Central?	Yes
If the output makes any recommendations for policy and/or clinical practice, please provide details	

Is this output published open access?	Yes

How could this output be utilised? (Please tick the one option that is most applicable):	Informing further research

Date output appeared/published:	10/11/2020

Output Title	Desmopressin for Reversal of Antiplatelet Drugs in Stroke due to Haemorrhage (DASH): Interim Report on Recruitment from a Phase II Double Blind Randomised Controlled Trial. Research and Practice in Thrombosis and Haemostasis

Was this output submitted to CCF?	No

Type of Output	Conference Poster

Is the output available in PubMed?	No

Place where the output appeared e.g. journal or conference
Journal

If the output makes any recommendations for policy and/or clinical practice, please provide details

Please provide a reference, if available:	2020;4(S1):PB1390

If this was previously submitted to a different journal, what journal was it?

Name of journal, output submitted to:	Research and Practice in Thrombosis and Haemostasis

If available online please provide a hyperlink:	

How could this output be utilised? (Please tick the one option that is most applicable):	Informing further research

Date output appeared/published:	01/04/2020

Output Title	DASH Statistical Analysis Plan

Was this output submitted to CCF?	No

Type of Output	Academic manuscript

Is the output available in PubMed?	No

Place where the output appeared e.g. journal or conference
Other

If the output makes any recommendations for policy and/or clinical practice, please provide details

Please provide a reference, if available:	SAP version 1.0 26July2022 SAP dummy tables 1.0 26July2022

For 'other', please specify where the output appeared:
http://dash-1.ac.uk/docs/

If available online please provide a hyperlink:	http://dash-1.ac.uk/docs/

How could this output be utilised? (Please tick the one option that is most applicable):	Informing further research

Date output appeared/published:	26/07/2022

Output Title	Experience from the Desmopressin for reversal of Antiplatelet drugs in Stroke due to Haemorrhage (DASH) trial.

Was this output submitted to CCF?	No

Type of Output	Conference Poster

Is the output available in PubMed?	No

Place where the output appeared e.g. journal or conference
Conference

If the output makes any recommendations for policy and/or clinical practice, please provide details

If available online please provide a hyperlink:	

Please give the venue:	Harrogate

How could this output be utilised? (Please tick the one option that is most applicable):	Informing further research

Date output appeared/published:	04/10/2022

Output Title	Results of DASH feasibility trial

Was this output submitted to CCF?	No

Type of Output	Presentation

Is the output available in PubMed?	No

Place where the output appeared e.g. journal or conference
Conference

If the output makes any recommendations for policy and/or clinical practice, please provide details

If available online please provide a hyperlink:	

Please give the venue:	Liverpool UK Stroke Forum

How could this output be utilised? (Please tick the one option that is most applicable):	Informing further research

Date output appeared/published:	01/12/2022

Please detail any awards and/or prizes received by the team as a result of undertaking the research.
No specific awards or prizes

Identifying newsworthy, impactful or sensitive research

Is the research likely to generate newsworthy and/or potentially impactful outputs?	Yes

Is the research likely to generate politically sensitive outputs?Is the research likely to generate politically sensitive outputs?
No

If you answered yes to either of these questions, please provide brief details as to why.
Stroke is medical emergency - and intracerebral haemorrhage in particular needs treatments. This is the first ever trial of a drug that could potentially improve outcome after ICH. Public are increasingly aware of the need for clinical trials to test new treatments.

Patient and Public Involvement

Please provide a summary of the patient and public involvement in this research.

Aim:
We aimed to involve and engage PPI representatives throughout the research process to ensure that the DASH trial was designed, conducted and disseminated in a manner that was appropriate to the needs of stroke patients.
Methods:
A two-tiered approach to PPI was adopted. Involvement from PPI representatives on the Trial Steering Committee, and the wider group of PPI members in the Nottingham Stroke Research Partnership Group (NSRPG), all of whom are stroke survivors, carers or members of the public, facilitated PPI involvement throughout the trial.
Study results:
PPI representatives were involved in all stages of the trial from design through to dissemination. The project and protocol was discussed with the NSRPG who reviewed the trial design and were highly supportive of the project. The consent procedure was reviewed and discussed with the group, and they felt strongly that potential participants should not be denied access to the study because they lacked capacity, had no relative present. Two members of the NSRPG were lay members of the Trial Steering Committee which met during the trial. The NSRPG group provided valuable input on dissemination plans, in particular by providing feedback on the DASH results video aimed at communicating the results of the trial to the public.
Discussion and conclusions:
PPI representatives involved with the DASH trial were a valuable part of the team, using their lived experiences to ensure the trial was designed, conducted and disseminated in a manner that was appropriate to the needs of stroke patients
Reflective/critical perspective:
We acknowledge that all PPI representatives in the DASH trial were white. For future trials, it would be preferable to also involve PPI representatives from minority ethnic groups to ensure that the wider population is considered during the research process. It wasn't always possible for PPI representatives to attend TSC meetings and although meetings were intended to be lay-friendly. PPI representatives sometimes focused their attention on areas we were not expecting. For example, when discussing the DASH results video with the NSRPG, they suggested solutions to address IMP temperature monitoring when we had expected the meeting to focus on finding out how they would like the trial results to be presented. Overall, PPI involvement helped to improve the quality and relevance of the DASH trial.

When asked to reflect on their involvement in the DASH trial, one of our PPI representatives confirmed that 'My involvement as a lay member and
Stroke Survivor has been a good experience to be involved and participate within the Project Team from its inception to conclusion and outcomes, gaining knowledge from the process and the benefits of this very important aspect of Stroke Research and Treatment and I look forward to participating in future Projects'.

Please tick the box if this section of the report has been written with members of the public who have been involved in the research.

☐ Not Confirmed

Future Research Plans

Please outline your next steps to maximise patient benefit or to further inform policy development/evaluation.

The DASH trial has demonstrated that it would be feasible to conduct a definitive trial to determine if desmopressin improves outcome in patients with antiplatelet drug associated spontaneous intracerebral haemorrhage. Three different approaches to undertaking 'DASH-2' have been discussed with the Trial Steering Committee, as detailed below:

1. DASH-2 as a stand-alone definitive phase 3 RCT

Suggested funding sources:
NIHR: Efficacy and Mechanism Evaluation (EME) Programme. Stage 1 applications now open, closing date 25 April 2023.
Medical Research Council: Developmental Pathway Funding Scheme. Applications open 06 February 2023, closing date 22 March 2023.

2. DASH-2 added into the ongoing large RCT TICH-3 Funded by: NIHR HTA- NIHR129917 as a substantial protocol amendment

Prof Nikola Sprigg, is CI of TICH-3 and the trial is coordinated by the Stroke Trials Unit, Nottingham. TICH-3 Aims to assess the clinical effectiveness of tranexamic acid after intracerebral haemorrhage and determine whether tranexamic acid should be used in clinical practice. This is a multi-national pragmatic phase III prospective blinded randomised placebo-controlled trial.
Considerations:
It may be feasible to amend the current TICH-3 protocol such that TICH-3 participants taking an antiplatelet medication could also be randomised to either desmopressin or placebo.
Adding DASH-2 into TICH-3 would help to save on infrastructure.
A large number of UK sites are already taking part/due to take part in TICH-3 and may not have the capacity to set up another separate ICH trial.
The TICH-3 funder, TSC, DMC would need to be approached to discuss the feasibility of making such an amendment and additional funding would be required.

3. DASH-2 as part of a stroke/haemorrhage platform trial

Following the success of the COVID-19 platforms such as RECOVERY, NIHR are now seeking platforms in other disease areas based on collaborative groups across the UK. Prof Philip Bath (Stroke Trials Unit, Nottingham) and colleagues including Prof Nikola Sprigg are applying for a one year Accelerator Grant to help prepare for the main grant submission to run one or more platform trials in stroke.
If the platform trial grant application is successful, it is possible that desmopressin could be one of the interventions.

Publication of Research Findings

Please indicate if there is any information that you do not wish us to place in the public domain and explain why.
We have no objection to information about the DASH trial being placed in the public domain.

Data Sharing

Where applicable, please provide a statement about your data sharing and accessibility. It should provide a clear and positive indication: • Where and when the data will be shared • Who can access the data • How the data can be obtained
The trial chief investigators (Prof Nikola Sprigg and Dr Michael Desborough) will consider requests to share anonymised individual participant data via email at: dash@nottingham.ac.uk. Submitted requests will require a protocol detailing hypothesis, aims, analyses, and intended tables and figures. Where possible, we will perform the analyses; alternatively, de-identified data and a data dictionary will be supplied for the necessary variables for remote analysis. Any sharing will be subject to a signed data access agreement. Individual participant data will eventually be shared with the Virtual International Stroke Trials Archive (VISTA) collaboration.

Post-Award Monitoring

Please provide the details of the individual whom we can contact for post-award monitoring of this project. Usually this will be the Chief Investigator, however, another individual, for example a project manager, may be named instead.

Contact name	Professor Nikola Sprigg (Chief Investigator) Professor of Stroke Medicine Stroke Trials Unit
Contact address	D floor South Block Room 2106 QMC Campus University of Nottingham NG7 2UH
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Supporting Documentation