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PRevention Of Hypertensive Injury to the Brain by Intensive Treatment after IntraCerebral Haemorrhage (PROHIBIT-ICH)

Submission date 13/03/2019	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 18/03/2019	**Overall study status** Completed	
Last Edited 06/06/2023	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims

About 1 in 10 strokes are due to a bleed into the brain from a ruptured (burst) artery, called intracerebral haemorrhage (ICH). The symptoms of ICH are due to nerve cell damage or swelling, and depend on where in the brain the bleeding has occurred; they can include drowsiness, nausea and vomiting, headaches, weakness of one or more limbs, loss of vision or speech, or seizures. In some cases, ICH is caused by injury or surgery, in others it happens suddenly without warning ("spontaneous"). Spontaneous ICH is sometimes the result of high blood pressure (BP) which, over time, causes damage to the small blood vessels supplying the brain, making them more likely to rupture. The main cause of spontaneous ICH is called "small vessel disease" (SVD), this may be because of poor BP control. Magnetic Resonance Imaging (MRI) has improved our ability to see the effects of SVD on scans of the brain after ICH. The aim of this study is to determine whether frequent measurements of BP using a monitor that securely sends readings automatically to our research team by Bluetooth technology (called "telemetric" monitoring) can be used to safely guide medication changes to "intensively" lower BP (to a target of 120/80 mmHg) to reduce damage to the small blood vessels in the brain after spontaneous ICH.

Who can participate?

Patients over the age of 30 who have had a spontaneous ICH, most likely due to small vessel disease, confirmed on a brain scan

What does the study involve?

Participants meet a member of the research team at the hospital, who answers any questions they may have. If they are eligible and willing to participate in the study, they are given a unique study number; information is collected regarding their health status, memory and thinking (cognition), and quality of life. A small blood sample (equivalent to one teaspoonful or 5-10 millilitres of blood) is taken, and the participant has an MRI scan of the brain. The participants are invited back for follow-up after 3 months and 1 year, where they are asked about any medical problems or admissions to hospital since they joined the study and how they are recovering. The participant is also asked to do some memory tests and is fitted for 24 hours with a BP monitor that records BP every 30 minutes during the day and hourly at night. They have

another MRI of the brain at the 1 year follow-up. Half of the participants are randomly (by chance) allocated to monitor their BP at home using a telemetric monitor. BP data is automatically sent to monitor and change the medicine dose to reach a BP target of 120/80 mmHg. The other half of the participants receive usual clinical care including BP control monitored by their hospital stroke team and their General Practitioner. If the participant is selected to monitor their blood pressure at home, they are shown how to use the monitor and are asked to measure their blood pressure in a seated position three times over 10 minutes (in their non-dominant arm [the one that they don't usually use for things like writing] unless they have been told otherwise), when waking in the morning, in the early afternoon, and before going to bed. This needs to be done for at least one month, and possibly up to three months, depending on how quickly their blood pressure reaches the intensive target. These BP measurements are transmitted to a coordinating centre in Oxford via Bluetooth technology and assessed daily by a dedicated research team of nurses and doctors who contact the participant by phone if a change in medication is indicated. The GP is also notified by the coordinating centre. After three months, they are asked to take readings three times over 10 minutes, once a week until the participant is seen again at one year.

What are the possible benefits and risks of participating?
Telemetric home monitoring is a promising strategy to facilitate home BP monitoring after stroke, which should improve adherence and optimize medication to better control BP. Telemetry allows patients with hypertension to monitor their own BP and automatically send the information to a secure website, available to their clinicians to monitor and adjust their treatment. All participants will benefit from access to an expert research team. This study does not pose major risks or ethical issues. The procedures that will be carried out will be a blood test and MRI scan that will be carried out by an experienced professional to minimise any discomfort.

Where is the study run from?
1. UCL Stroke Research Centre (UK)
2. University of Oxford (UK)

When is the study starting and how long is it expected to run for?
March 2019 to January 2023

Who is funding the study?
Stroke Association (UK)

Who is the main contact?
Prof. David Werring, d.werring@ucl.ac.uk

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

ClinicalTrials.gov (NCT)
NCT03863665

Protocol serial number
PROHIBIT01; 38628

Study information

Scientific Title
Prevention Of Hypertensive Injury to the Brain by Intensive Treatment after IntraCerebral Haemorrhage: a pilot randomised trial of home telemetry-guided treatment

Acronym
PROHIBIT-ICH

Study objectives
The trial will investigate whether intensive lowering of blood pressure (BP) using telemetric home monitoring in survivors of intracerebral haemorrhage (ICH) is feasible, safe and effective in reducing brain injury. If successful this study will be a precursor for a larger definitive trial. Our intervention should allow survivors of ICH to know, understand, and manage their own BP to prevent strokes and cognitive impairment, and improve outcomes.

Primary Objective:
1. BP study:
Does the use of centralised telemetric home BP monitoring to guide intensive BP treatment in patients with spontaneous (non-traumatic) ICH achieve a reduction in 3-month BP compared with standard primary care?
2. Imaging study:
Does intensive BP treatment using centralised telemetric home monitoring result in a reduction in progression of small vessel disease (SVD)-related brain injury assessed on MRI (including, but not limited to, white matter hyperintensities (WMH), white matter structural integrity, incident cerebral microbleeds (CMBs), and brain atrophy) compared with standard care?

Secondary Objective(s):
1. BP study:
1. Is it feasible in a multi-site setting to intensively lower BP using telemetric home BP monitoring for an extended period of time following spontaneous ICH?
2. Is it safe to intensively lower BP for an extended period of time following a spontaneous ICH, or are there adverse responses (including increased progression of cognitive decline)?
3. Is the intervention acceptable to participants, including measures of quality of life?

2. Imaging study:
1. Does any reduction in recurrent vascular events (including ICH) or progression of cognitive decline on intensive BP treatment correlate with baseline measures of changes in quantitative and structural brain scan markers of small blood vessel health?
2. Are there any adverse effects on neuroimaging measures (e.g. increased white matter ischaemic injury) associated with intensive BP treatment?

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 11/06/2018 by London - Camden & Kings Cross Research Ethics Committee, NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, Tel: +44 (0)207 104 8086, Email: nrescommittee.london-camdenandkingscross@nhs.net, REC ref: 18/LO/0866
2. Approved 17/08/2018 by Scotland A Research Ethics Committee, Research Ethics Service, 2nd Floor, Waverley Gate, 2-4 Waterloo Place, Edinburgh, EH1 3EG, Tel: +44 (0)131 465 5680, Email: manx.neill@nhslothian.scot.nhs.uk, REC ref: 18/SS/0059

Study design
Randomized controlled trial

Primary study design
Interventional

Study type(s)
Quality of life

Health condition(s) or problem(s) studied
Spontaneous intracerebral haemorrhage (ICH)

Interventions
PROHIBIT-ICH will randomise participants to compare a strategy of intensive BP treatment (target <120/80 mm Hg) guided by telemetric home monitoring, versus standard primary care (current RCP guideline is 130/80 mm Hg), in 112 adult survivors of hypertension-related ICH. The study will establish the feasibility and safety of the intervention, the efficacy of BP reduction, and explore whether it reduces the progression of SVD-related injury on brain MRI.

Randomisation:
Patients will be randomized in a 1:1 group assignment ratio to intensive BP lowering (intervention group) or standard care (control group) using an online randomization service (Sealed Envelope), available 24 hours a day.

When a person agrees to participate demographic, contact and medical history information necessary to conduct the study will be recorded. Each participant will be allocated a unique trial number. Relevant sections of medical notes and data collected during the study may be looked at by the researchers from regulatory authorities or from the NHS Trust, where it is relevant to the subject's participation in the trial.

The participants randomised to the intervention group will receive a telemetric Bluetooth home BP-monitoring device. It will facilitate the Oxford BP-monitoring team to closely monitor the participant's BP to keep to the target of <120/80 mmHg. If this is not achieved then BP

medication will be adjusted accordingly in order to achieve the target by the 3-month follow-up visit. BP readings (3 readings over 10 minutes in the seated position in the non-dominant arm, unless there is severe hemiparesis) will be taken 3 times daily (early morning, early afternoon and evening). All BP data will be automatically transmitted centrally in real-time to the device coordination site in Oxford. A dedicated research member will be responsible for checking all BP data daily on patients in the study and will advise on adjusting medication according to the latest BHS guideline, to ensure BP is lowered to the intervention arm target. The local study centre will send new prescriptions directly to patients (with communication simultaneously with the GP). For dose changes, advice will be given to participants by phone by the central study team. All medication changes will be notified to the local research team and GP; responsibility for BP treatment will be by the local PI.

The data will be compared the control who will not receive the device and will be under the standard primary care.

Follow up:
3-month follow-up (visit two): Completion of 3-month CRF, blood pressure recorded and completion of Cognitive assessment, EQ-5D questionnaire and home blood pressure acceptability questionnaire. 24-hour ABPM to be performed at the time of the 3-month follow-up visit.

12-month follow-up (final visit): Completion of 12-month CRF, blood pressure recorded, and completion of Cognitive assessment and EQ-5D questionnaire. 24-hour ABPM to be performed at the time of the 12-month follow-up visit.

An MRI scan will be performed at baseline and the 12-month follow-up visit on all participants to identify markers of cerebral small vessel disease including:
1. Change in white matter hyperintensity volume
2. Change in white matter microstructure (DTI)
3. Change in the number of CMBs
4. Change in cerebral atrophy

Intervention Type
Device

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Device name: A&D BP Digital Blood Pressure Monitor (UA-767PBT-Ci), CE Declaration UA-767PBT-Ci

Primary outcome(s)
1. The efficacy of telemetric BP monitoring to guide intensive BP treatment in ICH survivors by detecting a statistically significant reduction in BP in the intervention compared to the control arm at 3 months
2. The feasibility of telemetric BP lowering in ICH survivors by detection of how many eligible participants agree. Feasibility criteria are at least ≥50% of eligible participants agrees to participate. This will be measured at 3 months from randomisation
3. The feasibility of telemetric BP lowering in ICH survivors by detection of how many drop outs there are in the intervention arm detected 3 months from randomisation

4. The feasibility of telemetric BP lowering in ICH survivors by detecting patient approval of the device by acceptability questionnaire at 3 months
5. Efficacy of brain imaging by detecting the progression in MRI white matter hyperintensity (WMH) volume over 1 year at 12 months from randomisation
6. The safety of telemetric BP lowering in ICH survivors measured by serious adverse events related to reducing BP in the intervention arm at 12 months from randomisation

Key secondary outcome(s))
1. Any incidence of vascular events reported in both arms at 12 months from randomisation
2. Cognitive ability assessed by the Cognitive Assessment (MoCA) questionnaire in both arms at 12 months from randomisation
3. The number of BP lowering drugs at 3 months and at 12 month follow-up visits. This will detected in both arms and compared
4. Mean daytime BP on 24-hour ABPM in both groups at 12 months from randomisation
5. Neuroimaging outcomes: the proportion of patients who develop new cerebral microbleeds (CMBs) over 12 months
6. Neuroimaging outcomes: the proportion of patients who develop new infarcts or intracerebral haemorrhages at 12 months
7. Neuroimaging outcomes: mean diffusivity (MD) at 12 months
8. Neuroimaging outcomes: fractional anisotropy (FA) at 12 months
9. Neuroimaging outcomes: cerebral blood flow (CBF) on 3T PCASL at 12 months
10. Neuroimaging outcomes: total brain volume, white matter volume and grey matter volume on 3T T1 volumetric images at 12 months
11. Neuroimaging outcomes: composite neuroimaging measures (e.g summary SVD scores) at 12 months

Completion date
31/01/2023

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 18/04/2020:
1. Adults (aged ≥30 years) with spontaneous primary ICH (i.e. without known underlying structural, macrovascular or other cause (e.g. arteriovenous malformation, tumour) after adequate investigation at the discretion of the local investigator). This will include participants presumed to have cerebral SVD (both hypertensive arteriopathy and cerebral amyloid angiopathy)
2. Clinical team opinion that BP control since the ICH is not adequate AND the measured SBP prior to randomisation is ≥130 mm Hg
3. Recruitment soon after ICH, ideally at hospital discharge or within weeks, is encouraged; recruitment at a later stage after ICH is also exceptionally allowed if there is evidence of inadequate BP control AND SBP at randomisation is ≥130 mm Hg
4. Willingness and demonstration of ability to undertake home BP measurements, either unassisted or with the help of a relative, friend or carer
5. Ability and willingness to complete an MRI scan
6. Ability and willingness to attend and complete the study assessments including cognitive screen
7. Ability and willingness to provide informed consent, or with a suitable consultee available and able to participate in the intervention (e.g. with a motivated carer)

Previous participant inclusion criteria:
1. Adults (aged ≥40 years) with spontaneous primary ICH (i.e. without known underlying structural, macrovascular or other cause (e.g. arteriovenous malformation, tumour) after adequate investigation at the discretion of the local investigator). This will include participants presumed to have cerebral SVD (both hypertensive arteriopathy and cerebral amyloid angiopathy)
2. Clinical team opinion that BP control since the ICH is not adequate AND the measured SBP prior to randomisation is ≥130 mm Hg
3. Recruitment soon after ICH, ideally at hospital discharge or within weeks, is encouraged; recruitment at a later stage after ICH is also exceptionally allowed if there is evidence of inadequate BP control AND SBP at randomisation is ≥130 mm Hg
4. For patients recruited in hospital there should be a plan for home discharge (not to a nursing or care home) after their inpatient stay, or living at home at the time of recruitment
5. Willingness and demonstration of ability to undertake home BP measurements, either unassisted or with the help of a relative, friend or carer
6. Ability and willingness to complete an MRI scan
7. Ability and willingness to attend and complete the study assessments including cognitive screen
8. Ability and willingness to provide informed consent, or with a suitable consultee available and able to participate in the intervention (e.g. with a motivated carer)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
30 years

Sex
All

Total final enrolment
86

Key exclusion criteria
1. Inability to provide informed consent or lack of suitable consultee (if unable to provide personal consent, lack of suitable consultee)
2. Evidence of a macrovascular or structural cause for ICH (e.g. AVM or tumour)
3. Diagnosis of dementia (DSM IV criteria, or self-reported or documented in medical records)
4. Low Functional status (MRS ≥4) before or after ICH or frailty likely to make participation in 1-year follow-up difficult for the participant
5. Life expectancy <2 years
6. Taking more than 2 BP-lowering medications (i.e. 3 or more) at the time of consent
7. Consistently good BP control (below 130/80 mm Hg on measures taken as part of routine clinical care) prior to planned recruitment, judged not to require more intensive treatment
8. Known flow-restricting intracranial/extracranial large arterial stenosis

9. Known contraindication to MRI
10. Known absence of mobile phone coverage from all network operators and home internet at the participant's home
11. Known sensitivity or contra-indication to BP treatments (e.g. symptomatic postural hypotension) is not an absolute exclusion criterion, but more information must be provided
12. Note that participation in other CTIMP or device trial is NOT an automatic exclusion criterion

Date of first enrolment
22/03/2019

Date of final enrolment
31/01/2022

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
University College London Hospital
Russell Square House
10-12 Russell Square
London
United Kingdom
WC1B 5EH

Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name
Stroke Association

Alternative Name(s)
TheStrokeAssociation, TheStrokeAssoc

Funding Body Type
Private sector organisation

Funding Body Subtype
Associations and societies (private and public)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
HRA research summary			28/06/2023	No	No
Protocol file	version v5	13/06/2018	02/04/2019	No	No
Protocol file	version v7.0	04/11/2019	24/04/2020	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes