Clinical Investigational Plan (CIP) for Medical Device Studies

Full title of Investigation:	**PRevention Of Hypertensive Injury to the Brain by Intensive Treatment after IntraCerebral Haemorrhage: a pilot randomised trial of home telemetry-guided treatment**
Short title:	**PROHIBIT-ICH**
Version and date of Clinical Investigation Plan (CIP):	Version 7.0, 4th November 2019
Sponsor:	University College London
Sponsor CIP number:	PROHIBIT-ICH01
Funder (s):	Stroke Association Priority Programme Grant

Revision History:

Version numbers	Date	Summary of revisions in the case of amendments	Protocol Updated by [insert name & Signature]
1.0	**12/12/2017**	Template and list of amendments requested by Sponsor	Professor David Werring Professor Peter Rothwell Shahena Butt Ian McGurgan Louise Silver
2.0	**21/02/2018**	Section: a.7.4 who will hand the information sheets out, who will go through this with the patients. when does the research team get involved, do they do the second approach Section: A8 when will consent be taken, how long between receiving the PIS will the patients be expected to consent	Shahena Butt
3.0	**15/03/2018**	This needs to state how capacity will be assessed by who and how	Shahena Butt
4.0	**18/04/2018**	Section 13.5 of the protocol states that only initials and unique trial number will be stored on the CRF. Please consider updating this section so it is consistent with the information in section A11 of the Protocol	Shahena Butt
5.0	**13/06/2019**	Amendments 1. Removing inclusion criteria 4 (no need for a plan for home discharge) 2. Reducing the age limit to 30 and above 3. Displaying posters for patients and doctors in clinics and wards	Shahena Butt

		4. Patients can be identified from site databases (clinical and research) and then invited to consider participation in the study 5. NHS Patient Identification Centre (PIC) sites will be identified for the study. 6. 3 month and 12 month GP letters	
6.0	**25/09/2019**	1. potential participants will be contacted by email and post 2. participants are sent the invitation letter/PIS by post	Shahena Butt

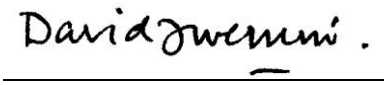
Signatures

The Chief Investigator (CI) and the JRO have discussed this Clinical Investigation Plan (CIP). The investigator agrees to perform the investigations and to abide by this CIP.

The investigator agrees to conduct the Investigation in compliance with the approved CIP, EU Good Clinical Practice (GCP) and UK Regulations for Devices (SI 2002/618; as amended) for regulated studies, the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator

Professor David Werring



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Signature | **04/11/2019** Date

Contents

LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
ABPM	Ambulatory Blood Pressure Monitoring
BP	Blood Pressure
CMB	Cerebral microbleed
CA	Competent Authority
CI	Chief Investigator
CIA	Clinical Investigation Agreement
CIP	Clinical Investigation Plan
eCRF	electronic Case Report Form
CRO	Contract Research Organisation
DCF	Data Clarification Form
DD	Device Deficiency
EC	European Commission
EU	European Union
EUDAMED	European Medical Devices Regulatory Database
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HRA	Health Research Authority
IB	Investigator Brochure
ICF	Informed Consent Form
IMD	Investigational Medical Device
ISF	Investigator Site File
JRO	Joint Research Office
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
NCA	National Competent Authority
NHS	National Health Service
NHS R&D	National Health Service Research & Development
NICE	National Institute of Clinical Excellence

NIST	National Institute of Standards and Technology
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SVD	Small Vessel Disease
TMG	Trial Management Group
TSC	Trial Steering Committee
UADE	Unanticipated Adverse Device Effect
UK	United Kingdom
USADE	Unanticipated Serious Adverse Device Effect
WMH	White Matter Hyperintensities

Sponsor

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A.1 Overall Synopsis of Clinical Investigation

Title:	**PRevention Of Hypertensive Injury to the Brain by Intensive Treatment after IntraCerebral Haemorrhage: a pilot randomised trial of home telemetry-guided treatment**
Short title:	**PROHIBIT-ICH**
Device:	A&D BP Digital Blood Pressure Monitor (UA-767PBT-Ci) CE Declaration UA-767PBT-Ci
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. Our **primary objectives** are: (i) BP study. Does the use of centralised telemetric home BP monitoring in patients with spontaneous (non-traumatic) ICH achieve a reduction in 3-month BP compared with standard care? (ii) 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? Our **secondary objectives** are: (i) BP study 1. Is it feasible in a multi-site setting to intensively lower BP using centralised 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 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? (ii) 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?
Type of Investigation:	A pilot multi-site randomised controlled trial in approximately 112 adult survivors of spontaneous (SVD-related) ICH.
Investigation design and methods:	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. We 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.
Investigation duration per participant:	12 Months
Estimated total Investigation duration:	36 Months
Planned Investigation sites:	Multi-Site
Total number of participants planned:	112
Main inclusion/exclusion criteria:	**Inclusion criteria:** 1. Adults (≥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 allowed if there is evidence of inadequate BP control AND SBP at randomisation is ≥130 mm Hg 4. Ability and willingness to undertake BP measurements, either unassisted or with the help of a relative, friend or

carer; this can be undertaken in any destination after hospital discharge (e.g. home, rehabilitation unit, nursing or care home)
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)

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

Statistical methodology and analysis:

Primary outcomes:
(a) BP study
(i) Efficacy: the magnitude of difference in BP at 3 months in the intervention arm versus control arm compared with baseline measures
(ii) Feasibility: consent rate; dropout rate from the intervention prior to 1 month; patient approval of the monitoring process
(iii) Safety: serious adverse event related to reducing BP in

intervention arm
(b) Imaging study
(i) Efficacy: the progression in MRI white matter hyperintensity (WMH) volume over 1 year

Secondary outcomes:
(a) BP study: clinical outcomes including recurrent vascular events and cognition; number of BP lowering drugs at 3 months and at 1 year follow-up visits; mean daytime BP at 1 year on 24-hour ABPM
(b) Imaging study: neuroimaging outcomes including (but not limited to) the proportion of patients who develop new cerebral microbleeds (CMBs) over 1 year; number of new CMBs at 1 year; new infarcts or intracerebral haemorrhages at 1 year; change in mean diffusivity (MD), fractional anisotropy (FA) and other 3T DTI metrics; change in cerebral blood flow (CBF) on 3T PCASL; change in total brain volume, white matter volume and grey matter volume on 3T T1 volumetric images; composite neuroimaging measures (e.g summary SVD scores)

A.2 Background and Rationale

Intracerebral haemorrhage (ICH)

Spontaneous intracerebral haemorrhage (ICH) is a type of stroke due to bleeding within the brain parenchyma (which may also extend to ventricular and subarachnoid space) that is not caused by trauma.(1) ICH accounts for 10-15% of all strokes in Western populations, while in Asia it accounts for 15-30%.(1, 2) In the UK, out of the total 150,000 strokes per year, about 15,000 to 23,000 are due to ICH. The 30-day case-fatality for ICH is about 40%(2) (higher than the other stroke types, ischaemic stroke (IS) or subarachnoid haemorrhage (SAH)). Less than a half of patients with ICH survive 1 year and less than a third survive 5 years, while survivors have substantial cognitive and physical impairments.(3) ICH additionally places a substantial economic burden on society, a challenge which will increase with our ageing population;(4) a meta-analysis demonstrated that ICH incidence remained constant between 1980 and 2008,(2) making ICH a persistent challenge for stroke research.

The challenge of secondary prevention after ICH

About 40% of ICH strokes are recurrent, resulting in higher mortality and disability than the first occurrence.(5) A recent systematic review of mainly hospital-based ICH cohorts found that the rate of recurrent ICH is between about 1.4% and 7.4% per year.(3) There is also a high risk of dementia after ICH (incidence 14.1% at one year in a recent prospective observational cohort study),(6) making reduction of cognitive and physical disability a key research challenge. Recurrent ICH risk seems to reduce over time: one study found that in the first year, the rate of recurrence was 2.1 out of 100 patients per year, which decreased to 1.2 out of 100 patients per year, but remained comparable with ischaemic stroke recurrence rates (1.3 out of 100 patients per year)).(7) 'Lobar-lobar'(8) is reported to be the most common pattern of ICH recurrence, likely due to cerebral amyloid angiopathy (CAA); moreover, CAA-related ICH has been reported to have a much higher recurrence risk than other types.(9) With the high incidence, prevalence, mortality, disability, socioeconomic impact and recurrence rates of ICH, the benefits of high-quality research to improve outcome are likely to be significant. However, there remains a lack of randomised controlled trials of interventions in ICH survivors to reduce recurrence, brain injury, and cognitive impairment. Well-established risk factors for ICH recurrence include increasing age,(10) hypertension,(11) smoking,(12) excessive alcohol use,(13) and the presence of cerebral microbleeds on magnetic resonance imaging (MRI).(8) The most important and prevalent risk factor for recurrent stroke, including ICH, is hypertension, making this an obvious therapeutic target. Recent observational research suggests that improving long-term lowering of BP after stroke due to ICH might reduce recurrence.(11)

Hypertension and ICH

Long-term hypertension is the most significant risk factor for stroke in general, but particularly for ICH. People with hypertension have five times the risk of ICH compared to those without.(14) This association might be explained by the effect of poorly controlled hypertension on small blood vessel walls, leading to hypertensive arteriopathy, a form of cerebral small vessel disease (SVD) which causes

them to weaken and rupture. Small vessel disease (including hypertensive arteriopathy and CAA) is the major cause of spontaneous (non-traumatic) ICH.

Research on lowering blood pressure after ICH

Following ICH, patients often have early hematoma expansion, a marker of poor prognosis.(15) Admission systolic BP (SBP) of ≥200 mm Hg is associated with haematoma expansion and higher mortality.(16) A recent trial showed that acute lowering of BP (within the first 6 hours) improves outcomes after ICH (INTERACT-2).(17) Recent observational data suggests that even short-term increases in BP might trigger ICH(18) and emphasises the important role of BP management as means of secondary prevention for ICH. BP variability (e.g. day-to-day or between hospital visits) has also recently been shown to be an independent risk factor for stroke, and to influence outcome after ICH.(19)

Less research has focused on sustained post-acute BP management, which holds the most potential to improve long-term prognosis and recurrence following an ICH. There have been no dedicated trials targeting long term BP reduction after ICH. The main prospective randomised data on the effects of long term BP lowering after ICH come from the PROGRESS trial, in which treatment of patients with ICH with the BP lowering agents perindopril (an angiotensin-converting enzyme inhibitor) and indapamide (a thiazide-like diuretic) led to a mean difference of 11 mm Hg systolic and 4 mm Hg diastolic BP between treated and placebo arm participants, with a reduction in the absolute rate of ICH from 2% to 1% over 3.9 years of follow-up. This 50% relative risk reduction for ICH was higher than the 24% reduction in ischaemic stroke.(20, 21) Consistent with this substantial risk reduction in ICH, a recent trial in 3020 patients with recent subcortical infarction (presumed due to SVD, the main cause of ICH) showed that the risk of future ICH was significantly reduced (by 60%) by intensive BP lowering (target systolic BP <130 mm Hg compared with 130-139 mm Hg).(22) There are, nevertheless, also concerns that intensive BP lowering may have an adverse impact in older populations by reducing cerebral perfusion, causing cerebral ischaemia, progression of cognitive impairment and falls.(23) Thus, although intensive BP lowering is a very promising secondary prevention intervention in ICH, the optimum long term target BP remains uncertain.

The challenge of long-term sustained blood pressure control after stroke

Current UK guidelines suggest a systolic BP target after stroke of 130 mm Hg (Royal College of Physicians National Guideline for Stroke, 2016). Nevertheless, in practice control of BP remains poor. In the UK, only 35% of stroke patients achieved the guideline standard,(24) while 41% of stroke patients in the PROFESS study had systolic BP >140 mm Hg at follow-up, with an increased risk of recurrent stroke.(25) The proportion of stroke patients taking antihypertensive drugs declines rapidly (by about 25%) in the first 2 years after stroke,(26) suggesting that patient adherence is an important barrier to effective BP treatment. Poor adherence to BP medications is also clearly associated with an increased risk of stroke.(27) Adherence for secondary prevention after stroke is challenging because: (1) many new medications (e.g. antithrombotic drugs, statins, antihypertensives) are all started at once; (2) there are often physical or cognitive impairments; (3) there is no immediate relief of symptoms; and

(4) reductions in future vascular events may take months or years to accrue. A systematic review of interventions to improve adherence found few high-quality studies, with a need to improve objective monitoring of adherence and BP.(28) A recent comprehensive review of research gaps in BP treatment after stroke concluded that clinical trials evaluating implementation of evidence-based strategies for BP control to prevent recurrent stroke are needed.(29)

A.3 Identification and description of the investigational device

Home telemetric home monitoring device for PROHIBIT-ICH

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. Home telemetric Bluetooth BP monitoring has been evaluated in patients with TIA and predominantly non-disabling stroke in the setting of the Oxford Vascular (OXVASC) Study by the Centrally Observed home telemetric Monitoring of BP to Manage Intensive Treatment (COMMIT) Study. In this population, the intervention was safe and effective, with few adverse events and high patient satisfaction. However, more research is required on the feasibility of use of this strategy in more disabling stroke and in patients with ICH, as well as on transferability to multiple centres beyond the previous research setting in Oxfordshire. A key aim of the present application is to obtain essential feasibility data in a pilot randomised controlled trial in a cohort of ICH survivors (in whom the expected benefit of the intervention is the largest of all stroke types) in a multi-site setting. In the COMMIT Study, we studied consecutive eligible consenting patients in the Oxford Vascular Study. After prescription of initial BP-lowering therapy, if required, patients measured their BP 3 times over 10 minutes on 3 occasions per day at home with a Bluetooth-equipped monitor for 1-3 months, depending on control. Measurements transmitted automatically in real time were checked daily on a secure web page. If BP was consistently above 130/80 mm Hg or below 100/60 mm Hg antihypertensive therapy was adjusted. The results outlined below are from the first 1000 recruits (mean/SD age=69/13; range=21-98yr; 23% ≥ 80 years): (1) Rates and risk factors for masked hypertension. The prevalence of hypertension after TIA and stroke is often underestimated, with rates of “masked” hypertension (normal clinic BP but elevated home readings) ranging from 10-30%. In COMMIT, masked hypertension (BP ≤ 140/90 mm Hg at initial assessment and mean BP > 135/85 mm Hg across the first 3 days of monitoring; AHA definition) was found in 344 (34.4%). The much more detailed record of BP obtained on home telemetric BP-monitoring thus provided clinically important data that were not available from occasional clinic measurements. Masked hypertension has not been investigated in ICH; (2) Feasibility, medication changes and control of BP. BP-lowering medication was initiated or increased at the pre-monitoring baseline visit in 555 (55.5%) patients. Medication was further initiated or adjusted at least once within the first month of home-monitoring in 558 (55.8%) patients and from 1-3 months in 393 (39%) patients. Mean BP measured on clinic follow-up fell from 141/83 mm Hg at entry to 130/74 mm Hg at 1-month ($p<0.001$) and to 127/72 mm Hg at 3-months ($p<0.001$) (see Figure 1 for an example BP trace). Telemetric home BP monitoring was feasible irrespective of age, and informed titration of medication in the majority of patients and was associated

with good BP control; (3) Acceptability of telemetric home-monitoring to patients. Of 1000 patients recruited, 576 (57.6%) returned an anonymised questionnaire after 1 month of monitoring. 533 (90.8%) approved of the intensive monitoring, 522 (89%) felt reassured by the central surveillance and 500 (85.2%) thought it helpful to be able to discuss their BP readings over the phone. However, 72 (12.3%) patients reported that monitoring their BP made them anxious and 83 (14.1%) felt it was time consuming. Mean (SD) overall satisfaction (0%-extremely dissatisfied to 100%–extremely satisfied) was 89 (14) %; (4) Comparison with 24-hour ambulatory monitoring (ABPM). We validated telemetric HBPM and ABPM by association with hypertensive arteriopathy and risk of recurrent vascular events. Mean SBP at 1-month on nocturnal ABPM, awake ABPM and HBPM (3 measurements, 3 times daily for 7 days) was related to five markers of hypertensive arteriopathy (creatinine > 120 mmol/L; aortic pulse wave velocity > 12m/s; advanced leukoaraiosis on brain imaging; Montreal Cognitive Assessment < 25; stroke vs. TIA) and to risk of recurrent stroke, coronary events and death. Among 1000 patients, hypertensive arteriopathy was more strongly associated (p-diff=0.007) with HBPM-SBP (odds ratio per 10 mm Hg: 1.42, 1.28-1.56, p<0.0001) than with awake or nocturnal ABPM (awake 1.11, 1.00-1.24; nocturnal 1.28, 1.17-1.40). During 2775 patient-years of follow-up, residual hypertension at 1-month on HBPM (n=218/23%) predicted the risk of recurrent events (HR=2.00, 1.28-3.12, p=0.002) better than on awake ABPM (n=207/20%, HR=1.24, 0.78-1.98, p=0.37) or nocturnal ABPM (n=307/39%, HR=1.47, 0.95-2.26, p=0.08). In models combining all 3 measures, only HBPM independently predicted recurrent events (HR=1.34, 1.11–1.63, p=0.003). Thus, residual hypertension is more strongly associated with hypertensive arteriopathy and risk of recurrent vascular events on HBPM than on ABPM. HBPM is therefore likely to be the better measure of BP-control after TIA/stroke, but has not yet been tested in major stroke or ICH.

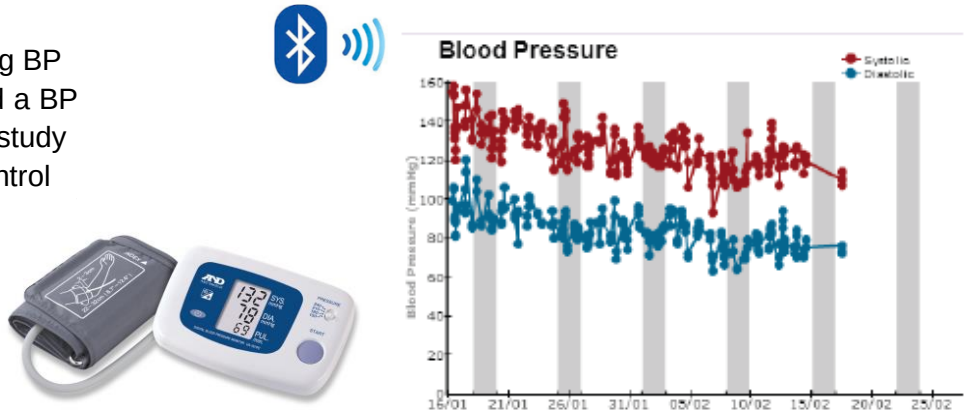


Figure 1: Home monitoring BP cuff and monitor (left), and a BP trace from the COMMIT study showing improved BP control over time (right)

Potential role of MRI in understanding the effects of BP treatment after ICH

MRI has rapidly improved our ability to see SVD disease processes related to ICH in vivo. Markers of small vessel disease on standard MRI include white matter hyperintensities (WMH), dilated perivascular spaces, lacunes and cerebral microbleeds (CMBs) whereas quantitative measures (e.g. diffusion tensor imaging (DTI)) provides information on microscopic tissue changes. White matter hyperintensities are the commonest marker of SVD, and can assessed semi-quantitatively using rating scales or quantitatively. The inter-rater and intra-rater reliability for both qualitative and quantitative

analysis of white matter hyperintensity is high if done by trained raters, with intraclass correlation coefficients generally above 0.90.(30) CMBs are small areas of bleeding detected on blood-sensitive MRI sequences (including T2*-weighted gradient-echo and susceptibility–weighted imaging), found in about 50-80% of patients with ICH, with value in diagnosing the type of SVD.(31) CMBs are also related to the risk of future ICH.(8) We showed that in patients with ischaemic stroke and TIA that the development of new CMBs was strongly related to baseline BP (Figure 2).(32) CMB accumulation might thus be plausibly reduced by intensive BP lowering

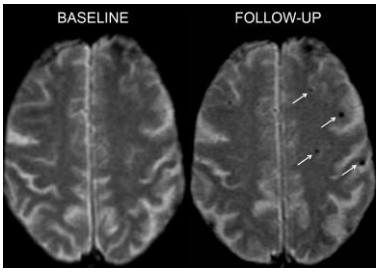


Figure 2. *Axial GRE T2* MRI scans at baseline and follow-up (after 5 years) showing the development of new CMBs (small black dots; white arrows). The development of new CMBs was strongly related to baseline systolic BP (OR 1.28 per unit increase, 95%CI 1.23-1.33, p<0.001). (from ref 32)*

In spontaneous ICH there is also a high prevalence of clinically "silent" acute ischaemic lesions (about 20% of patients),(33, 34) which has been associated with rapid acute BP lowering.(35) Longer term BP lowering in SVD has been hypothesised to cause white matter ischaemia or infarction, potentially worsening cognitive outcomes.(23) Thus, any treatment aiming to reduce recurrent ICH must also consider the risk of ischaemic brain injury. The key MRI manifestations of SVD have recently been reviewed (including WMH, lacunes, and CMBs).(30) These abnormalities evolve over time, and reflect brain injury relevant to the adverse consequences of SVD, including cognitive impairment. Measuring these as a surrogate outcome marker is attractive for a clinical trial, because it may be possible to assess beneficial or hazardous effects of an intervention in a much small number of participants in comparison to clinical event outcomes (e.g. recurrent stroke). Observational longitudinal studies in SVD indicate that WMH volume and diffusion tensor imaging (DTI) parameters are most sensitive to change and therefore have the smallest sample size estimates for trials of interventions, and progress over shorter time periods than cognition.(36) A recent review of imaging outcome markers for clinical trials in CAA suggested that CMBs and WMH were promising surrogate measures of SVD-injury, but further prospective data are needed to validate them.(37) In the PROHIBIT-ICH trial, we will test the hypothesis that intensive and sustained long-term BP control after ICH might reduce the progression of MRI markers of SVD, the underlying process that is likely to cause the long term adverse outcomes following ICH.

A.4 Justification for the design of the clinical investigation

Summary of rationale for the trial

ICH remains a devastating disease for which prevention of recurrent stroke is a research priority. BP lowering is the most promising preventive strategy, but adherence and BP control in clinical practice remain poor. There is thus an urgent need to improve ICH secondary prevention through improved long term BP control, including outcomes related to cognition and progression of the underlying SVD process. The concerns and views of stroke survivors, the recent development of home telemetric monitoring technology and improved understanding of MRI markers of SVD make this a unique and timely opportunity to commence a pilot a trial addressing these important research questions.

A.5 Risks and benefits of the investigational device and clinical investigation

The table below summaries the risks and mitigations of **the investigational procedures** that are being performed:

Table 1

Name of IMD	**Potential risk**	**Risk Frequency**	**Risk Management**
To be invited in the study by giving them an invitation letter and patient information sheet (PIS)	No potential Risk	0	Research practitioner or member of research/ clinical teams, in hospital ward or clinic.
Baseline consent	No potential Risk	0	Research practitioner or member of research/ clinical teams, in hospital ward or clinic.
Completion of eCRFs (baseline (visit one), 3 month follow up (visit two) and 12 month follow up (last visit)).	No potential Risk	0	Research practitioner or member of research/ clinical teams, in hospital ward or clinic.
Cognitive functional assessment (Montreal Cognitive Assessment)	No potential Risk	0	Research practitioner or member of research/ clinical teams, in hospital ward or clinic.
EQ-5D questionnaire	No potential Risk	0	Research practitioner or member of research/ clinical teams, in hospital ward or clinic.

The table below summaries the risks and mitigations of all tests above standard care that are being performed:

Table 2

Intervention	Potential risk	Risk Management
Blood Test	May cause discomfort or result in brusing	Performed by trained phlebotomist. Follow trust standard operational procedures.
MRI Scan	Patients may experience claustrophobia	Performed by a competent professional. Follow trust standard operational procedures.
Blood Pressure	The squeezing sensation may be uncomfortable but only lasts a few seconds.	Performed by the informed participant (if at home) and a competent professional.

The classification of medical devices in the European Union is outlined in Annex IX of the Council Directive 93/42/EEC (as amended). There are four classes, ranging from low risk to high risk.

Class I
Class IIa
Class IIb
Class III

The Medical Device used in this investigation is classified as **Class I**

A.6 Objectives and hypotheses of the clinical investigation

A.6.1 Hypotheses

Primary and secondary, to be accepted or rejected by statistical data from the clinical investigation.

A.6.2 Primary Objective

(i) 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?

(ii) 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?

A.6.3 Secondary Objective(s)

(i) BP study

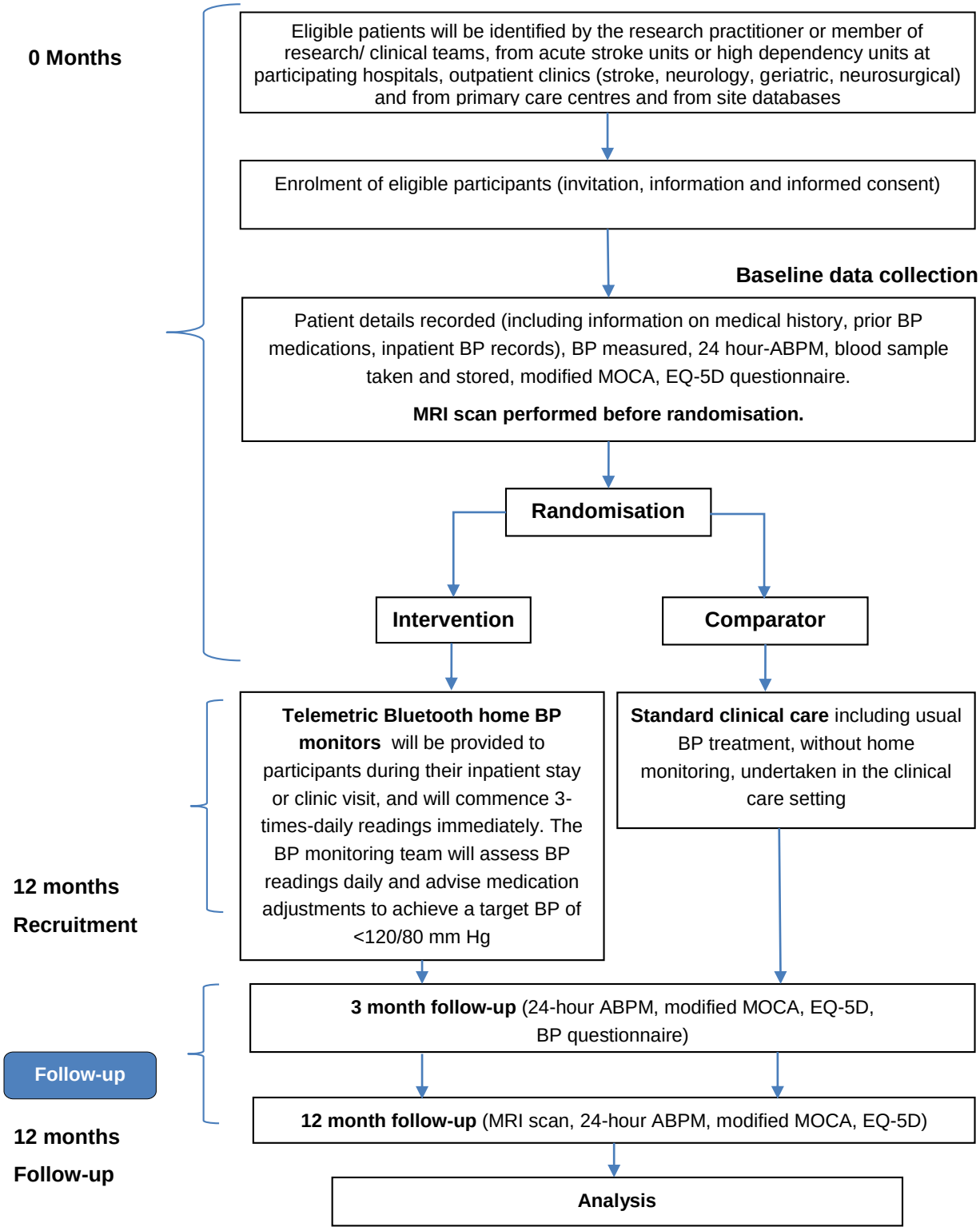
1. Is it feasible in a multi-site setting to intensively lower BP using telemetric home BP monitoring for an extended period of time following spontaneous ICH?
2. Is it safe to intensively lower BP for an extended period of time following a spontaneous ICH, or are there adverse responses (including increased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

(ii) 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?

A.7 Design of the clinical investigation

A.7.1 General



A.7.2 Investigational device and comparators

Patients will be assessed for their eligibility during hospital inpatient stays, in outpatient clinics or primary care centres. Patients will also be identified from site records/databases and will be sent via post a patient invitation letter and patient information sheet (PIS). At the time of hospital discharge or at a dedicated clinic session with a research practitioner, eligible patients will be randomised in a 1:1 group assignment ratio to either telemetric home BP monitor-guided intensive BP lowering (intervention group) or standard care (control group) constituting usual primary-care led BP treatment, without home telemetric monitoring. For inpatients, the randomisation process will be undertaken as close as possible to discharge. All participants will be fitted with a 24-hour ABPM on the day of discharge (or in a dedicated clinic session for outpatients) by the research practitioner. The intervention group will also receive a telemetric Bluetooth home BP-monitoring device in addition to the ABPM and will be trained how to set this up in their home and use it. For the control group, the results of the baseline 24-hour ABPM (as for subsequent follow-up 24-hour ABPM) will not be communicated to the patient or GP unless mean daytime BP is sufficiently different to the patient's known recent daytime BP (based on recorded inpatient and baseline BP measurements) to justify informing on the basis of clinical need.

Intervention:

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 mm Hg. 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 BP-monitoring research team will be responsible for checking all BP data daily, and will directly advise patients by telephone on starting or adjusting BP medication according to a standard protocol based on the latest British Hypertension Society guideline, to ensure that BP is lowered to the intervention arm target. For the treatment-naïve participant, first line treatment (in the absence of contraindications) will usually be either combination therapy with perindopril arginine 5mg and indapamide MR 1.5mg per day, or amlodipine 5mg, increased to 10mg if needed. Subsequent treatment will be decided on a patient-specific basis, taking into account previous treatment trials and treatment responses, but will be likely to include the addition of spironolactone 25mg per day, doxasozin 4mg per day and nebivolol 2.5-5mg per day, alone or in combination. All such medication changes will be notified to the local research team and GP, with the GP providing prescriptions to participants based on correspondence from the central BP-monitoring team. If the target BP is consistently achieved after a minimum of one month of monitoring, Bluetooth monitors will be collected and conventional monitors issued to the intervention group only. At the 3 month follow-up visit, it is expected that the majority of patients will be able to replace their Bluetooth monitor for a conventional monitor, unless extenuating circumstances result in a need for prolonged monitoring and further treatment to achieve the BP target. The conventional monitors will be used at the patient's discretion to allow them to assess their own BP and contact their GP with any concerns about high/low readings. The responsibility for BP treatment will return to the GP

after 3 months of follow-up. Participants will also be asked to record a weekly BP reading on a sheet which will be returned with the monitor at the end of the 12 month follow-up period. GP letters will be sent at 3 month and 12 month follow up to provide the GPs with the patient's blood pressure readings.

A.7.3 Subjects

Inclusion criteria

1. Adults (≥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 allowed if there is evidence of inadequate BP control AND SBP at randomisation is ≥130 mm Hg
4. Ability and willingness to home BP measurements, either unassisted or with the help of a relative, friend or carer; this can be undertaken in any destination after hospital discharge (e.g. home, rehabilitation unit, nursing or care home).
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)

Exclusion criteria:

8. Inability to provide informed consent or lack of suitable consultee (if unable to provide personal consent, lack of suitable consultee)
9. Evidence of a macrovascular or structural cause for ICH (e.g. AVM or tumour)
10. Diagnosis of dementia (DSM IV criteria, or self-reported or documented in medical records)
11. Low Functional status (MRS ≥4) before or after ICH or frailty likely to make participation in 1-year follow-up difficult for the participant
12. Life expectancy <2 years
13. Taking more than 2 BP-lowering medications (i.e. 3 or more) at the time of consent
14. 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
15. Known flow-restricting intracranial/extracranial large arterial stenosis
16. Known contraindication to MRI
17. Known absence of mobile phone coverage from all network operators and home internet at the participant's home

18. 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
19. Note that participation in other CTIMP or device trial is NOT an automatic exclusion criterion

Subject Eligibility

Once written informed consent has been obtained, the electronic case report form (eCRF) will be completed to document adherence to the inclusion and exclusion criteria.

Where a subject fails to fulfil any element of the inclusion and exclusion criteria, this will be documented and the signed consent form and completed inclusion/exclusion criteria retained by the principal investigator. The subject will not be advanced any further into this clinical investigation.

Subject Identification

Patients will be identified by members of the care team from the expected NHS hospital sites (acute stroke units or high dependency units), from outpatient clinics (stroke clinics, neurology clinics, geriatric clinics, neurosurgical clinics) and at primary care sites.

Patients can also be identified from site clinical and research databases of patients who have had a previous ICH at any time, including databases of participants included in previous clinical trials (subject to agreement with the Chief Investigator of the other trial). Potential eligible patients will be contacted email or post, for screening and informed consent. Patient Invitation letter and patient information sheet (PIS) will be sent to patients via post.

We will also provide posters which give information on the study, to be displayed at participating sites (including NHS PIC sites, see below); suitable locations include doctors or nurses offices, noticeboards, or in outpatient clinics.

NHS Patient Identification Centre (PIC) sites will be included in the study. These sites can will be NHS sites; the staff at these sites will identify potential patients and inform the study team at local PROHIBIT-ICH recruiting sites.

When a subject is identified and considered eligible for entry into this clinical investigation, the subject will be allocated the next available investigation number (subject ID number).

For subjects enrolled, this number will consist of 01 for the first subject, 02 for the second subject and so on. This number will be the unique identifier of the subject and noted on the electronic CRF and all other documentation relating to that subject.

Each subject that is enrolled into the study will have their study participation recorded and details of the device recorded in their hospital notes, a copy of their signed consent form and patient information

sheet should also be placed on his/her hospitals notes to identify the subject as participating in a clinical investigation.

A.7.4 Recruitment

Participant recruitment at a site will only commence when the trial has been initiated by the Sponsor (or it's delegated representative), and issued with the 'open to recruitment' letter.

Potentially eligible participants will be identified in person by the clinical staff at site during their inpatient stay or when they attend a clinic or primary care appointment or by site databases. The participants will be handed an information leaflet and a letter of invitation by the clinical staff at the site. Patients will have at least 24 hours to consider the information before being telephoned or approached by a member of the research practitioner or member of research/clinical teams at the NHS site to see if they are interested in taking part in the trial. If they are, a convenient time will be arranged for them to meet a research staff member delegated by the CI to discuss the study, go through the information sheet, assess eligibility and answer any questions they may have. Patients who are eligible and give consent will be enrolled and randomised to an intervention group or control group.
Patients will be provided with a participant information leaflet. An opportunity to meet a member of the research team will be arranged in person by a member of the clinical care team or subsequently by phone by a member of the research team. All interested participants will have an opportunity to ask questions about the study and these will be answered by a member of the research team prior to enrolment.

A.7.5 Randomisation Procedures

Following participant consent and confirmation of eligibility, the registration/randomisation procedure described below will be carried out.
Participants will be considered to be enrolled into the trial following: consent, pre-treatment assessments (see section A.7.6), confirmation of eligibility, completion of the registration/randomisation process, allocation of the participant trial number and treatment by the central coordinating team.
When a person agrees to participate, demographic, contact and medical history information necessary to conduct the study, including a record/chart of their inpatient BP measurements, 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.
Patients will be randomised in a 1:1 group assignment ratio to intensive BP lowering (intervention group) or standard care (control group) using an online randomisation service (Sealed Envelope), available 24 hours a day.
Clinical data will be collected by an established electronic randomisation and eCRF system with a database managed from UCL by the study coordinator.

A.7.6 Procedures

The following examinations and investigations (if not already performed as part of routine standard of care) shall be performed for determining eligibility for enrolment into this investigation:

Pre-intervention assessments

Baseline

We will request that recruiting sites collect data on the number of patients who are potentially eligible for the study. At baseline, the following trial-specific procedures will be carried out after consent as a requirement for the study to commence:

- Medical history recorded, including details of the ICH, previous medical history, and inpatient BP records for every participant. The most recent three consecutive inpatient/outpatient BP readings, not including any taken specifically to assess for entry eligibility, will be used to assess for the BP inclusion and exclusion criteria
- Blood pressure medication and dose recorded, including reactions to prior poorly-tolerated BP medications, if applicable
- 3 BP measurements (2 seated and one standing after a minimum of 3 minutes). The initial measurement should be taken in both arms; if there is a significant difference (>20 mm Hg systolic) between them then the arm with the higher value should be used for subsequent monitoring
- Baseline 24-hour ABPM will be fitted and recorded in all participants
- Blood test (venepuncture)
- MRI brain scan (performed prior to randomisation).
- Cognitive functional assessment (modified Montreal Cognitive Assessment; see appendix 2)
- Completion of the EQ-5D questionnaire (appendix 3)

All pre-treatment procedures will be carried out as specified in the schedule of assessments (appendix 1).

The MRI protocol will be harmonised at all study sites based on EPAD (European Prevention of Alzheimer's Dementia) protocols for each major MRI scanner manufacturer (Siemens, GE, Philips), and will include the following sequences (with approximate timings):

1. 3D T1 (5min)
2. 3D FLAIR (5min)
3. DTI (simplified) (5min)
4. 3D SWI (5min)
5. Axial T2 (2min)

Other advanced MRI sequences (including, but not limited to, Arterial Spin Labelling (PCASL)) will be acquired as optional extra sequences at sites with capacity to undertake them. We aim to keep the total MRI scan time below 1 hour.

A.8 Informed Consent Process

It is the responsibility of the investigator, or a person delegated by the investigator to obtain written informed consent from each subject prior to participation in the Investigation, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study.
The capacity of the patient will be assessed by a trained clinician on site that will be managing their clinical care.

The person taking consent must be GCP trained, suitably qualified and experienced, and have been delegated this duty by the CI/PI on the delegation log.

“Adequate time” will be given given for consideration by the patient before taking part. The PI must record when the patient information leaflet has been given to the patient. It must be recorded in the medical notes when the participant information leaflet has been given to the participant. Patients will have at least 24 hours to consider the information before being telephoned or approached by a member of the research practitioner or member of research/clinical teams at the NHS site to see if they are interested in taking part in the trial. If they are, a convenient time will be arranged for them to meet a research staff member delegated by the CI to discuss the study, go through the information sheet, assess eligibility and answer any questions they may have and Informed consent will be obtained.

The investigator or designee will explain the patients are under no obligation to enter the investigation and that they can withdraw at any time during the Investigation, without having to give a reason.
No clinical investigation procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into investigation. A copy of the signed informed consent document will be given to the participant. The original signed form will be retained at the study site and a copy placed in the medical notes.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate.

A.9 Schedule of assessments and interventions by visit (see also Appendix 1)

Baseline (visit one): See section 7.6 for details of the procedure
Patients in the intervention group will be in telephone or email contact with the BP-monitoring team in Oxford throughout the trial. Completion of baseline eCRF and all enrolled participants will attend their local hospital clinic for one in person follow-up visit at 3 months and a final follow-up visit and an MRI scan at an average time of 1 year.

3 month follow-up (visit two): Completion of 3 month eCRF, BP recorded and completion of modified Montreal Cognitive assessment (appendix 2), EQ-5D questionnaire (appendix 3) and home blood pressure acceptability questionnaire (appendix 4). 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 eCRF, BP recorded, and completion of modified Montreal Cognitive assessment (appendix 2) and EQ-5D questionnaire (appendix 3). 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 (but not limited to):

- change in white matter hyperintensity volume
- change in white matter microstructure (DTI)
- change in the number of CMBs
- change in cerebral atrophy

A schedule of all trial assessments and procedures is set-out in Appendix 1. Where an in-person visit is not possible, every effort will be made to assess the participant by other means, including telephone, postal, email, or home visit contact.

A.9.1 Laboratory Assessments and Procedures

Translational research samples

Blood will be collected at baseline by a trained member of staff at the site. As soon as blood is collected, the member of the research team at the site will be responsible for sending the sample in a Safebox to the coordinating office, UCL. Blood samples will be stored for future research. An appropriate SOP will be in place for each site.

Sample storage and transfer

About 5-10mls of blood in EDTA plasma sampling tube will be collected from patients in accordance with the patient consent form and patient information sheet. The EDTA blood samples will be appropriately sent in a Safebox from the sites to Shahena Butt, the research coordinator; Stroke Research Centre, UCL Institute of Neurology, Russell Square House, 10-12 Russell Square, First Floor, London, WC1B 5EH for DNA extraction and storage.

The neurogenetics lab, UCL will process, store and dispose of EDTA blood samples in accordance with all applicable legal and regulatory requirements, including the Human Tissue Act 2004 and any amendments thereto.

The EDTA blood samples will not be transferred to any party not identified in this protocol and are not to be processed and/or transferred other than in accordance with the patients' consent. At the co-ordinating centre, DNA will be extracted and stored at -70 degrees C in the UCL Institute of Neurology.

A.10 Device accountability

The BP equipment will be purchased by the monitoring team in Oxford. The telemetric BP readings will be checked every working day by this team. In the absence of any readings, the monitoring team will troubleshoot the most common equipment problems over the telephone where possible, or arrange a

replacement where necessary. There will be a service contract in place to replace or mend any monitors that are not working.

A.11 Monitoring Plan

The sponsor will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.
The degree of monitoring will be proportionate to the risks associated with the trial.
A trial specific oversight and monitoring plan will be established for studies. The trial will be monitored in accordance with the agreed plan.

Low risk: central monitoring
Each site to email to the sponsor annually: delegation log, adverse event log, deviation log, minutes of Trial Steering Committee (or equivalent), annual progress report (lead site only) when sent to Ethics Committee.

a) Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998.
The electronic CRFs (eCRF) will not bear the participant's name or other personal identifiable data. The participant's year of birth and trial identification number, will be used for identification and this will be clearly explained to the patient in the Patient information sheet. Patient consent for this will be sought.
The team will ensure that their identities are protected from any unauthorised parties. Information with regards to study patients will be kept confidential and managed in accordance with the Data Protection Act, and Research Ethics Committee Approval. All participant identifiable information will be anonymised with regard to any report. The same standard will be followed if any patient information needs to be sent to a third party.

b) Record keeping and archiving

At the end of the trial, all essential documentation will be archived securely by the CI for a minimum of 20 years from the declaration of end of trial.
Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with all applicable regulatory requirements. The sponsor will notify sites when trial documentation can be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

A.12 Statistical Considerations

A.12.1 Primary Outcomes

(i) BP study:

1. The efficacy of telemetric BP monitoring to guide intensive BP treatment in ICH survivors; detection of a statistically significant reduction in BP in the intervention compared to the control arm at 3 months. We expect a 10 mm Hg difference in systolic BP between the intervention and control arms at 3 months (based on assessment of mean daytime BP on 24-hour ABPM at 3 months), and will be able to estimate this difference to within +/- 8 mm Hg with 112 patients if the standard deviation of systolic BP does not exceed 20 mm Hg (in either arm).

2. The feasibility and safety of telemetric BP lowering in ICH survivors
Feasibility criteria are:
(a) ≥50% of eligible participants agree to participate;
(b) <30% dropout from the intervention arm (discontinuation of home BP monitoring against the advice of the BP monitoring centre) prior to 1 month;
(c) Patient approval of the monitoring process in ≥70% of those randomised to the intervention arm.

Safety is measured by serious adverse events related to reducing BP in the intervention arm, cognitive function change over 1 year (modified Montreal Cognitive Assessment) and a composite of all recurrent major cerebrovascular and cardiovascular events.

(ii) Imaging study:

Previous studies have shown that WMH volume increases over time in both older community and hospital stroke populations.(38-42) Data of WMH progression in ICH are limited but one small study showed a progressive increase in white matter lesions in subjects with cererbral amyloid angiopathy over a year.(43) Because of the strong relationship between BP and WMH severity and progression;(36, 44) we hypothesise that lowering BP might reduce the increase in volume of WMH over 1 year. However, a key concern regarding intensive BP lowering is that this might reduce white matter perfusion and cause an increase in ischaemic injury to the brain. The primary imaging outcome is therefore the change in WMH volume (measured on 3T FLAIR images) at 1 year. We will develop and use an in-house automated volumetric lesion detection method,(45) but will also use validated progression scales including the Rotterdam and Schmidt progression scores; progression over 2 years has previously been demonstrated in only 20 scan pairs of patients with cerebral small vessel disease.(46) We will exclude WMH directly related to the index symptomatic ICH (i.e. close to the ICH in the ipsilateral hemisphere). We will investigate WMH progression in subgroups of ICH including lobar and deep categories, and probable or possible cerebral amyloid angiopathy.(47) WMH progression analyses will adjust for important predictors including baseline WMH and age.

A.12.2 Secondary outcomes

(i) BP study

1. Clinical outcomes including recurrent vascular events and cognition.
2. Number of BP-lowering drugs at 3 month and at 1 year follow-up visits.
3. Mean daytime BP at 1 year on 24-hour ABPM.

(ii) Imaging study

1. We will quantify white matter structure integrity using 1 year change in mean diffusivity (MD), fractional anisotropy (FA) and other 3T DTI metrics including tract-based spatial statistics.(48)
2. We hypothesise that intensive BP lowering will reduce the development of new haemorrhagic SVD-related brain injury. We will measure the proportion of patients developing new CMBs at 1 year (measured using a validated visual rating scale)(49) and the number of new CMBs in each participant. We will exclude CMBs adjacent to the index symptomatic ICH. A previous study showed that 48% (95% CI, 40–55) of 168 patients with ICH developed incident CMBs over a 3.4-year period.
3. Any new infarcts or intracerebral haemorrhage
4. 1 year change in cerebral blood flow (CBF) on 3T PCASL
5. 1 year change in total brain volume, white matter volume and grey matter volume on 3T T1 volumetric images
6. Composite neuroimaging measures (e.g summary SVD scores)(50)
7. We will investigate progression of neuroimaging markers in subgroups of ICH including lobar and deep ICH,(51) and probable or possible cerebral amyloid angiopathy.(47, 52)

A.12.3 Sample size calculation

(i) BP study

Our data will allow accurate sample size calculation for an adequately powered efficacy trial and the ability to estimate a difference in systolic BP between arms. We will assess 3-month BP based on both clinic measurements and separately on 3-month ABPM. Power will be least for the comparison of clinic BP measurements. If we expect an effect in one direction (i.e. BP lowering in the intervention group), sample size calculations based on a mean group difference in SBP of 10 mm Hg between the intervention and control arms (and standard deviations of 10 mm Hg and 15 mm Hg respectively) at 3 month gives:
One-tailed significance level = 0.05, power = 0.9, n in each group = 56. We will be able to estimate this difference to within +/- 8 mm Hg with 112 patients if the standard deviation of systolic BP does not exceed 20 mm Hg.

(ii) Imaging study

There are insufficient data on WMH progression in patients with ICH on which to base accurate power calculations, making formal sample size estimation challenging. One study in 26 patients (mean age 69.1) with probable or possible CAA scanned over about a year found a rapid median WMH growth of 0.5 mL per year (interquartile range 0.1-2.8 mL per year).(43) In a substudy of 192 participants in the

PROGRESS (Perindopril Protection Against Recurrent Stroke Study) trial the mean total volume of new WMHs was significantly reduced in the active treatment group (0.4 mm3 [SE=0.8]) compared with the placebo group (2.0 mm^3 [SE=0.7]; P=0.012).(53) This difference in WMH progression was greatest for patients with severe WMH at entry, 0.0 mm^3 (SE=0) in the active treatment group versus 7.6 mm^3 (SE=1.0) in the placebo group (P<0.0001). The BP reduction in the active arm compared with the placebo arm was 11.2 mm Hg for systolic BP and 4.3 mm Hg for diastolic BP. With 56 patients in each arm we would be able to estimate a similar difference in new WMH lesion volume (2.0mm^3 vs 0.4mm^3) (if the SD does not exceed 2.0 mm^3) to that shown overall in PROGRESS, with power 80% at an alpha significance level of P=0.05.

A.12.4 Planned recruitment rate

We plan a screening, randomisation and recruitment period of 12 months from beginning to last patient randomised. We will approach about 145 patients, given an expected consent rate for randomisation of 60%, hence achieving the goal of 112 patients), allowing the consent rate to be estimated to within +/- 7%.

Regarding dropouts from the intervention arm prior to 1 month, we expect less than 20% of individuals to drop out. With an intervention arm sample size of 56 the dropout rate can be estimated to within +/- 11%.

Regarding patient approval of intervention, we expect that 90% of individuals in the intervention arm will approve the monitoring process (based on a semi-structured questionnaire). With an intervention arm sample size of 56, this approval rate can be estimated to within +/- 8%.

Recruiting sites will be selected on their suitability to conduct the study and perform the necessary MR imaging, and site initiation visits will be completed by teleconference and online training tools with follow up by the study coordinators.

A.12.5 Randomisation methods

Patients will be randomised in a 1:1 group assignment ratio to intensive BP lowering or standard care using an online randomisation service (Sealed Envelope), available 24 hours a day. There will be equal allocation between treatment arms; a sample size of 112 will consist of patients randomised equally to the intervention and control groups (56 each).

We will use a web-based randomisation service with the following pre-specified features:

- Web-based randomisation is by random permuted blocks to active or control treatment in a 1:1 ratio
- The system is accessed via a secure internet connection (SSL). This connection encrypts data between the user's internet browser and the server

- Online randomisation is achieved by the user entering a patient identifier (text field - must be unique) and stratification information, confirming eligibility
- The patient is randomised to the next treatment or code and the chosen treatment group or code shown or texted to the user
- An email notification is generated displaying the chosen treatment group or code and sent to the email address given by the user randomising and the administrator email address. The administrator email address is the one provided when the system is set up (usually a trial coordinator or central trial email address)
- A list of all randomisations performed to date may be sent to the administrator email address by entering the password
- The randomisation list cannot be viewed through the system
- There is only one password and anyone with knowledge of the password can perform a randomisation
- Sealed Envelope will not edit or delete any data held by the system

A.12.6 Statistical analysis

In general, the most suitable statistical analysis consistent with the form of data will be used and the underlying assumptions of the statistical method will be verified. Baseline BP, modified MoCA and EQ5D will also be compared between randomised groups. Descriptive statistics, as appropriate (e.g. means and standard deviations for continuous variables; proportions for categorical variables), will be reported for variables measured at baseline. A consort flow diagram will be included.

A.12.6.1 Summary of baseline data and flow of participants

Age (SD), sex, vascular risk factors and other medical history, and 24-hour ABPM will be used for baseline comparability of the randomised groups.

A.12.6.2 Primary outcome analysis

Analysis will be performed according to the intention to treat and the per protocol principles.
Efficacy: The difference in BP (and the difference in change from baseline BP) between randomised groups at 3 months will be compared using t-tests. The change in white matter hyperintensity volume in the intervention and control groups will be compared using appropriate tests (e.g. t-tests or nonparametric tests) depending on whether the values are normally distributed. Automated analysis pipelines for WMH segmentation and quantification will be used to measure change.(45)
Feasibility: Proportions for the consent rate, drop-out rate and patient approval at 3 months will be calculated to determine if the required feasibility criteria were met.

Safety: Proportions of adverse events and recurrent events between randomised groups will be compared using Fisher's exact test. Randomised groups will be compared for cognitive impairment based on (1) the modified MoCA score as a continuous variable using the Mann-Whitney U-test and (2) numbers below cut-off thresholds of the modified MoCA score using Fisher's exact test. The change in modified MoCA score from baseline will also be compared between randomised groups similarly.

A.12.6.3 Secondary outcome analysis

Randomised groups will be compared for recurrent vascular events using Fisher's exact test and for the number of BP-lowering drugs at 3 month and at 1 year follow-up visits using the Chi-squared test. The mean daytime BP at 1 year on 24-hour ABPM will be analysed using a t-test to compare the intervention and control groups.

Changes in all neuroimaging measures (CMBs,(49) DTI measures,(48) atrophy, etc., measured using validated methods) will be compared between the intervention and control arms using appropriate statistical tests. Specific automated analysis pipelines will be developed for each measure.
The study sample size has been based on the primary efficacy outcome of a reduction in BP and may lack power for the secondary outcomes; therefore results will be interpreted in the light of these limitations.

A12.6.4 Sensitivity and other planned analyses

It may be necessary to address potential imbalances between randomised groups for influencing risk factors.

A.13 Data Management

When a person agrees to participate, demographic, contact and medical history information necessary to conduct the study will be recorded in accordance with the patient consent form, patient information sheet and section 7 of this protocol. Each participant will be allocated a unique trial number. This data will be collected on an eCRF, on a secure server; sealed envelope. Access to this data, will be granted to authorized research staff and representatives from the sponsor, host institution and regulatory authorities, by arrangement with the CI, to permit trial-related activities, monitoring and audit. All records will be kept securely and confidentially and the data will be pseudo-anonymised for analysis.
All records are the responsibility of the investigators and will be kept in secure conditions. They will ensure that patients' identities are protected from any unauthorised parties. Participants' information will be kept confidential and managed in accordance with the Data Protection Act and Research Ethics Committee Approval.

For BP data acquired via the Bluetooth-enabled telemetric BP monitors (A&D UA-767 BT), anonymised measures are transmitted securely to a server hosting a password-protected website for daily review (t+ Medical, Abingdon, UK). BP data are acquired from the secure server and are exported in .mat (Matlab) format before being stored for offline analysis within the Centre for Prevention of Stroke and Dementia (CPSD) along with the data securely downloaded from all 24-hour ABPM. All BP data will be stored only at the University of Oxford site in accordance to the data governance policy of the University of Oxford, and will be the responsibility of Professor Rothwell.

Neuroimaging data will be transferred from participating sites in an anonymised form, and then stored on secure servers within UCL accessible to the Stroke Research Centre. Any patient related documents will not be transferred to any unauthorised party and are will not be processed and/or transferred other than in accordance with the patients' consent.
All baseline, follow up data will be entered on an electronic CRF. The CI will manage and maintain the study database throughout the investigation. Information on the eCRF will, where relevant, be accepted as source data and transferred, in part, and as appropriate, to a sealed envelope database, password protected to defined users and with an audit trial managed from the study coordinating site at UCL. Direct access to data, source data and documents will be granted to authorized representatives, host institution and regulatory authorities, by arrangement with the CI, to permit trial-related monitoring and audit.

A.13.1 Procedures for data review, database cleaning, and issuing and resolving data queries.

Data entered on the eCRFs will be 100 % source verified by a sponsor representative trained on the CIP and who has current GCP training. Data Clarification Forms (DCF) will be issued to the investigator should a discrepancy be found between the source and eCRF. The investigator will be required to verify and correct all errors or provide an explanation for the discrepant data. Sponsor representatives will re-verify the corrected data and mark the clarification as resolved at the next monitoring visit.

A.13.2 Procedures for verification, validation and securing of electronic clinical data systems

All data from the examinations and investigations listed in Appendix 1 will be transferred to media provided by the sponsor and collected at the time of eCRF collection.

The CI will manage and maintain the study database throughout the investigation. At the conclusion of the investigation, the database will then be locked and data transferred for analysis. A final copy of the database will be provided to the study site. Where data is transferred electronically, this will be in accordance with the UK Data Protection Act 1998 as well as Trust Information Governance Policy. There will be a documented record of data transfer and measures in place for the recovery of original information after transfer.

The database maintained by the CI, shall be validated and secured according to the sponsor standard operating procedures. Access to the data shall be limited to sponsor representatives directly involved in the collection, analysis, maintenance or safety monitoring of the data. Any study data released shall be done according to the publication policy and in accordance with the UK Data Protection Act 1998.

A.13.3 Data retention

At the end of the trial, all essential documentation will be archived securely by the CI for a minimum of 20 years from the declaration of end of trial.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with all applicable regulatory requirements. The sponsor will notify sites when trial documentation can be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

A.13.4 Clinical quality assurance

The clinical investigators will meet every fortnight to discuss any issues with data quality and any concerns will be discussed with the sponsor.

A.13.5 Completion of electronic Case Report Forms

The local research team will be responsible for completion of an eCRF for each participant. This will be maintained by the local PI or delegated research staff. The eCRF will include participant's year of birth and unique trial number), medical history, visit details and dates, questionnaires and any related AEs and details of withdrawal from the study if appropriate.

The principal investigator will be responsible for the timing, accuracy and completeness of eCRF for each individual subject. All the data should be entered into sealed envelope, on the eCRF; access to this secure serve will be granted only to secure personnel. The personal data recorded on all documents will be regarded as confidential.

The principal investigator must record the subject's participation in this clinical investigation in the subject's hospital notes. In addition, the principal investigator must keep a separate list of all subjects entered into the clinical investigation showing each subject's name, date of birth and assigned subject number (for identification purposes). A subject identification log will also be provided in the investigation site file to record the subject's initials and assigned subject number.
All data will be handled in accordance with the UK Data Protection Act 1998.

A.13.6 Retention of Documentation

The principal investigator will retain all copies of the records for a period of 20 years from the discontinuation of the clinical investigation. In all cases, the principal investigator must contact the sponsor prior to disposing of any records related to the clinical investigation. Included in records to be maintained are the signed clinical investigation plan, , signed consent forms, ethics committee approval letters, product accountability records, correspondence concerning the clinical and any other documents to identify the subjects.

In addition, if the principal investigator moves/retires, etc., he should provide University College London with the name and address of the person who will look after and be responsible for the clinical investigation related records.

A.13.7 Training

During the initiation of the investigation site, the sponsor will ensure the investigators and the site study staff are trained on the device. The investigator is then responsible for ensuring that the investigation staff uses the device in the same way. All training will be documented in a Site Training Log.

The monitor will also ensure that the investigator and investigation site team have received and understood the requirements and content of:

* CIP (Clinical Investigation Plan)
* IB (Investigators Brochure)
* The informed consent forms
* eCRFs (electronic Case Report Forms)
* IFUs (Instructions For Use)
* All written clinical investigation agreements as appropriate

A.14 Amendments to the CIP

Amendments to this CIP may be necessary to protect the safety of the patients and integrity of the data. In collaboration with the Investigator(s), the CIP amendments will be documented and submitted for ethical and regulatory approval (as required) prior to implementation. All changes will be evaluated for impact per sponsor SOPs. Amendments will be considered implemented after all ethical and regulatory approvals (as required) are received and all key sponsor and site staff has been trained. This process does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

A.15 Deviations from clinical investigation plan

A deviation is considered a departure from the conditions and principles of GCP in connection with that investigation; or the CIP relating to that Investigation, as amended from time to time.

The investigator shall not deviate from this CIP except in situations that affect the subject's rights, safety and well-being, or the scientific integrity of the clinical investigation.

A.15.1 Procedures for recording, reporting and analysing CIP deviations

If possible, prior approval from the sponsor and REC, if appropriate, shall be obtained by the investigator. All spontaneous CIP deviations shall be recorded and reported to the sponsor as agreed. A deviation log shall be maintained by the study site. Deviations shall be reported to the REC and the regulatory authorities if required by national regulations. All deviations will be included, as required in the final study report.

Notification requirements and time frames.

Requests for deviations by the investigator will be responded to within 48 hours of receipt.

Corrective and preventive actions and principal investigator disqualification criteria.

Refer to the Monitoring Plan (as applicable) for corrective and preventative actions and principal investigator disqualification criteria.

A.15.2 Procedure for reporting any protocol deviations

Any deviation from the protocol that has not been previously approved by the sponsor (JRO at University College London), must be reported to the sponsor within 2 working days of the deviation occurrence. Any deviations from the clinical investigation plan that are identified during routine monitoring visits will be reported to the sponsor (JRO, University College London) within 24 hours of being identified.A.16 Statements of compliance

The clinical investigation shall be conducted in accordance with the ethical principles of the Declaration of Helsinki, ISO standard 14155 and all other applicable device and UK regulations.

The clinical investigation shall not commence recruitment until all REC, regulatory (if applicable) and local (NHS permission) is received. All additional requirements imposed by the REC or regulatory authority will be followed.

A.16 Insurance

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

A.17 Adverse events, adverse device effects and device deficiencies

a-c) Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. **Note 1:** This definition includes events related to the investigational medical device or the comparator **Note 2:** This definition includes events related to the procedures involved **Note 3:** For users or other persons, this definition is restricted to events related to investigational medical devices
Adverse Device Effect (ADE)	Adverse Event related to the use of an investigational device. **Note 1:** This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational device **Note 2:** This definition includes any event resulting from use error or from intentional misuse of the investigational medical device
Serious Adverse Event (SAE)	Any adverse event that: • Led to death, • Led to serious deterioration in the health of the subject, that either resulted in • a life-threatening illness or injury, or

	• a permanent impairment of a body structure or a body function, or • in-patient or prolonged hospitalisation, or • medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, • Led to foetal distress, foetal death or a congenital anomaly or birth defect

Serious Adverse Device Effect (SADE)	An ADE that has resulted in any of the consequences characteristic of an SAE
Unanticipated Serious Adverse Device Effect (USADE)	An SADE, which by its nature, incidence, severity or outcome, has not been identified in the current version of the risk analysis report.
Device Deficiency (DD)	Inadequately of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **Note 1:** this includes malfunctions, use errors, and inadequate labeling

An adverse event does not include:

- Medical or surgical procedures; the condition that leads to the procedure is an adverse event.
- Pre-existing disease, conditions, or laboratory abnormalities present at the start of the study that do not worsen in frequency or intensity.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic or elective surgery or social/convenience admissions);
- The disease being studied or signs/symptoms associated with the disease unless more severe than expected for the subject's condition.
- Expected post-operative course (see section x)

d) Reporting requirements and timelines

AEs and ADEs are not considered reportable.

Term	Reporter	Reported to	Reporting Timeline from awareness of the event
Adverse Event (AE)	Investigator	Sponsor	As agreed with sponsor. CI to record fully all AEs.
Adverse Device Effect (ADE)	Investigator	Sponsor/Manufacturer	As agreed with sponsor. CI to record fully all ADEs.

The following events are considered reportable events in accordance with Annex 7, section 2.3.5 and Annex X, section 2.3.5 of DIRECTIVES 90/385/EEC AND 93/42/EEC respectively.

Term	Reporter	Reported to	Reporting Timeline from awareness of the event
Serious Adverse Event (SAE)**/	Investigator	Sponsor	Immediately, but no more than 3 calendar days after becoming

Serious Adverse Device Effect (SADE)			aware of the event
	CI	MHRA aic@mhra.gsi.gov.uk	Immediately, but not later than 2* calendar days after awareness *For SAEs which indicate an imminent risk of death, serious injury, or serious illness and that require prompt remedial action for other patients/subjects, users or other persons All other events immediately but not later than 7 calendar days following date of awareness.
	CI	REC	N/A
Unanticipated Serious Adverse Device Effect (USADE)	Investigator	Sponsor	Immediately, but no more than 3 calendar days after becoming aware of the event
	CI	MHRA	Immediately, but not later than 2* calendar days after awareness *For SAEs which indicate an imminent risk of death, serious injury, or serious illness and that require prompt remedial action for other patients/subjects, users or other persons. All other events immediately but not later than 7 calendar days following date of awareness.
	CI	REC	Within 15 days of the chief investigator becoming aware of the event. Only reports of related and unexpected Serious Adverse Events (SAEs) should be submitted to the REC.

Term	**Reporter**	**Reported to**	**Reporting Timeline from awareness of the event**
Device Deficiency (DD)	Investigator	Sponsor	Immediately, no more than 24 hours of becoming aware of the event

	CI	MHRA	7 calendar days Only reportable if the event may have led to an SAE if; • suitable action had not taken • intervention had not been made • if circumstances had been less fortunate
Urgent Safety Measures	CI	REC	(i) Immediately-By telephone (ii) Within 3 days-Notice in writing setting out reasons for the USM and plan for further action

** **Note** Planned hospitalisation for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

e) Assessments of adverse events

Each adverse event will be assessed for the following criteria:

Severity

Category	Definition
Mild	The adverse event does not interfere with the subjects daily routine, and does not require intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the subjects routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health Note: A severity rating of severe does not necessarily categorise the event as an SAE.

Seriousness

Seriousness as defined for an SAE in section a) above. Causality

The assessment of relationship of adverse events to the study procedure and the investigational device will be a clinical decision based on all available information at the time of the completion of the eCRF. The following categories will be used to define the causality of the adverse event:

Category	Definition
Yes	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after procedure). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).
No	There is no evidence of any causal relationship.

Expectedness

Category	Definition
Expected	An adverse event that is consistent with the information about the device listed in the Investigator Brochure or clearly defined in this CIP.
Unexpected	An adverse event that is not consistent with the information about the device listed in the Investigator Brochure

The reference document to be used to assess expectedness against the intervention is the IB. The CIP will be used as the reference document to assess disease related and/or procedural expected events.

f) Procedures for recording and reporting Adverse Events and Device Deficiencies

Investigator responsibilities:

All adverse events and SAEs will be recorded in the medical records and eCRF following consent.

All serious adverse events will need to be reported to the sponsor on a SAE form (using MEDDEV form 2.7/3) unless stated in the CIP that some expected SAEs will not be reported to the sponsor, with a justification as to why they will not be reported.

For patients on the control arm of an Investigation, SAEs may not have to be reported to the sponsor but will be recorded in the eCRF and medical records.

The Chief or Principal Investigator will complete the serious adverse event form and the form will be emailed to the sponsor to add, within 3 working day of his/her becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

The Investigator will report to the MHRA and REC (as applicable) all reportable events within the specified timeframes as per section d above.

"All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the device, or an unrelated event".

"Only deaths that are assessed to be caused by the device will be reported to the sponsor. This report will be immediate".

"All deaths, including deaths deemed unrelated to the device, if they occur earlier than expected will be reported to the sponsor".

All SAEs and UADEs should be reported to the following;
e-mail: randd@uclh.nhs.uk

Reporting of all Adverse Events and Device Deficiencies: Investigator and Sponsor responsibilities

Any adverse incident involving a medical device should be reported to the manufacturer of the device. This is especially important where the incident has led to or, was it to occur again could lead to an event classified as serious. Other minor safety or quality problems should be reported along with incidents that appear to be caused by human error.
All adverse incidents involving the telemetric medical device must be reported to the device co-ordination site in Oxford, John Radcliffe Hospital, Centre for Prevention of Stroke and Dementia.
Incidents will be reported as soon as possible (usually within 24 hours).
Local trust reporting procedures may also need to be followed. It is the responsibility of the PI and trial site team to ensure they are aware of any specific local requirements for reporting device incidents.

Progress reports

Progress reports will be submitted to the REC as per the REC requirements. The chief investigator will prepare the annual progress reports.

A.18 Oversight Committees

Trial Management Group (TMG)
The TMG will include the Co-Chief Investigators and co-ordinating site trial staff. The TMG will be responsible for overseeing the trial. The group will meet regularly [approximately every month] in person, or by teleconference, and will send updates to local PIs and their teams. The TMG will review recruitment figures, SAEs and substantial amendments to the protocol prior to submission to the REC. All PIs will be kept informed of substantial amendments through their nominated responsible individuals. A Data Monitoring Committee (DMC) will regularly monitor outcome events including adverse events and will report to the TMG.

Trial Steering Committee (TSC)
The role of the TSC will provide overall supervision of the trial. The TSC will review the on-going of the trial and recommend any appropriate amendments/actions for the trial as necessary. The TSC will be determined by the TMG team, and will include members of the original grant application and other invitees with expertise relevant to the trial. The TSC is expected to meet either in person or by teleconference 1-2 times per year.

Independent Data Monitoring Committee (IDMC)
N/A

A.19 Vulnerable population

N/A

A.20 Suspension or premature termination of the clinical investigation

Both the Sponsor and the Principal investigator reserve the right to terminate the clinical investigation at any time. Should this be necessary, the procedures will be arranged on an individual basis after review and consultation by both parties. In terminating the clinical investigation, the JRO at University College London and the Principal investigator will assure that adequate consideration is given to the protection of the subject's interests.

A.20.1 Subject Withdrawals and Discontinuation

Participants who have consented to intervention, assessments, follow-up and data collection, their participation is voluntary and they are free to withdraw at any time and without their medical care or legal rights being affected. A participant may be withdrawn from trial whenever continued participation is no longer in the participant's best interests, and the reason for withdrawal will be recorded. Reasons for discontinuing the trial may include:

- intercurrent illness
- patients withdrawing consent
- persistent non-compliance to protocol requirements

The decision to withdraw a participant from treatment will be recorded in the eCRF and medical notes. If a participant explicitly states they do not wish to contribute further data to the trial their decision must be respected and recorded in the eCRF and medical notes.

A.21 Definition of End of Trial

The expected duration of the trial is 36 months from recruitment of the first participant.
The end of trial is the date of the last follow up of the last participant.

A.22 Publication policy

We plan to present the results of the study at scientific meetings and publish the results in scientific journals. All participant data will be anonymised for this purpose. Authorship of publications will be determined by the ICMJE criteria.

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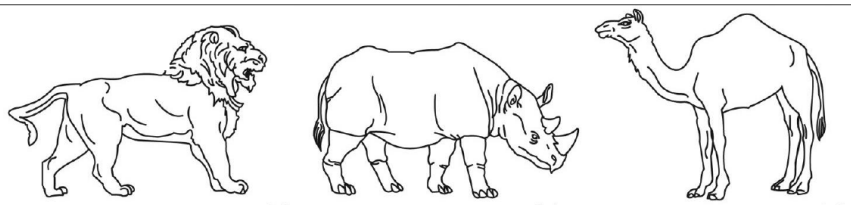
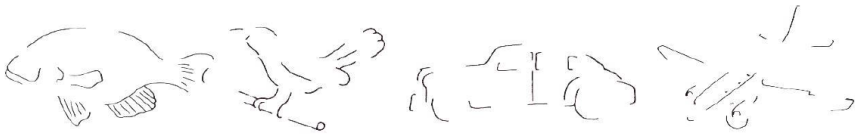
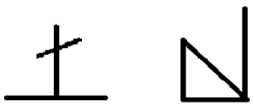
Appendix 1 - Schedule of assessments

	Screening (Pre-treatment assessment)	Intervention phase and Follow-ups	
	Baseline	3 Month follow-up	12 Month follow-up
Visit No:	1	2	Final Visit
Window of flexibility for timing of visits:		e.g. +/- 2 days	e.g. +/- 2 days
Informed Consent	X		
Medical History	X		
Eligibility confirmation	X		
Blood test	X		
MRI Scan (before randomisation)	X		X
Blood Pressure	X	X	X
24-hour ABPM	X	X	X
Cognitive assessment	X	X	X
Quality of life assessment (EQ-5D)	X	X	X
BP acceptability questionnaire		X	
Randomisation	X		
Adverse Events review	X	X	X

Appendix 2 - Cognitive functional change Assessment (modified Montreal Cognitive Assessment)

Name: DOB (Age): Hospital Number:
Place of Birth: Handedness: L / R Completion date:
Years of Education: Occupation:

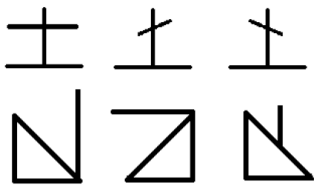
Orientation	[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City	**/6**
Attention + Executive functions	**Forward:** [ ] 3 2 9 7 **Backwards:** [ ] 2 5 **Forward:** [ ] 2 1 8 5 4 **Backwards:** [ ] 7 4 2 **Forward:** [ ] 7 2 9 5 8 4 **Backwards:** [ ] 4 9 7 5 **Tap A:** [ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B **Motor tapping:** 1 2 1 1 2 2 2 1 2 1 Congruent [ ] Incongruent [ ] **Three step Luria task:** Copy [ ] ≤ 2 trials [ ] > 2 trials [ ]	/2 **/2** /2 **/1** /2 /3
Language	**Repeat:** No ifs, ands or buts [ ] I only know that John is the one to help today. [ ] The cat always hid under the couch when dogs were in the room. [ ] **Command:** Touch your nose then open your mouth	/1 **/1** **/1** /1
Naming	 [ ] [ ] [ ]	**/3**
Perception		/4
Visual Memory -Immediate	 **COPY**	/2 /2
	RECALL	
Verbal Memory -Immediate		

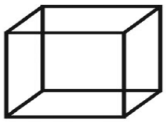
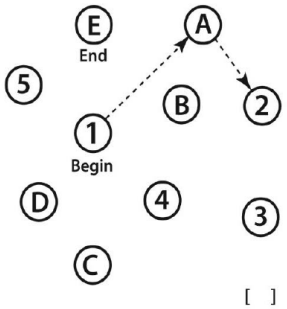
	Face	Velvet	Church	Daisy	Red	
1st trial						/5
2nd trial						/5

<table>
<tr><td>Processing Speed</td><td>Count Backwards: 30 – 1 [ ] (Time ≤ 25secs, 0 errors)
Months backwards: December – January [ ] (Time ≤ 24secs, 1 error)</td><td>/1
/1</td></tr>
<tr><td>Working memory</td><td>Subtract 7: [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0pt</td><td><u>/3</u></td></tr>
<tr><td>Executive functions</td><td>Fluency F: [ ] (N ≥ 11 Words)

Similarities: e.g. Banana – Orange = Fruit [ ] Train – Bicycle [ ] Watch – Ruler</td><td><u>/1</u>

<u>/2</u></td></tr>
<tr><td>Memory -Delayed</td><td>Verbal Recall:
<table>
<tr><th></th><th>Face</th><th>Velvet</th><th>Church</th><th>Daisy</th><th>Red</th></tr>
<tr><td>Free Recall</td><td>[ ]</td><td>[ ]</td><td>[ ]</td><td>[ ]</td><td>[ ]</td></tr>
<tr><td>Category Cue</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Multiple Choice</td><td></td><td></td><td></td><td></td><td></td></tr>
</table></td><td><u>/5</u>
/5
/5</td></tr>
<tr><td></td><td>Visual Recall:

Visual recognition:
  </td><td>/2
/2</td></tr>
<tr><td>Visuo-Executive</td><td>Draw Clock (Ten past eleven)

Copy cube
 
 

[ ] Contour [ ] Numbers [ ] Hands [ ] [ ]</td><td><u>/5</u></td></tr>
<tr><td></td><td>[ ] <12yrs Education: +1 ORIGINAL MoCA TOTAL:</td><td>/30</td></tr>
</table>

NOTES: e.g. dominant hand weakness? visual impairments? English 2nd language?

COMPLETED BY: _____

Appendix 3 – EQ-5D Questionnaire Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

We would like to know how good or bad your health is TODAY

This scale is numbered from 0 to 100

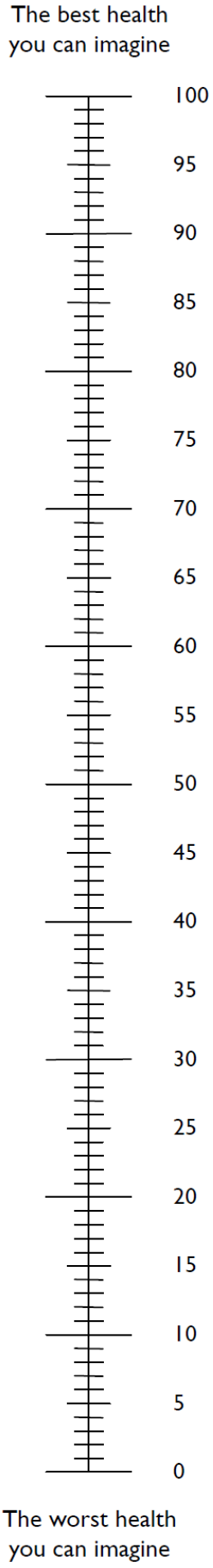
100 means the best health you can imagine.

0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 4 – Home BP monitoring participant acceptability questionnaire

HOME BLOOD PRESSURE MONITORING QUESTIONNAIRE

We would be very grateful if you could help us by answering some short questions about your experience using the home blood pressure monitor as part of the PROHIBIT-ICH study. Please tick the box that most closely matches your level of agreement with each of the following statements. Please give only one answer per line.

		Definitely agree	Moderately agree	Neither agree nor disagree	Moderately disagree	Definitely disagree
1	I liked the fact that the regular readings would provide better information about my blood pressure	☐	☐	☐	☐	☐
2	It reassured me to know that the equipment would transmit my readings directly to the hospital	☐	☐	☐	☐	☐
3	It was helpful to have a telephone number that I could call to discuss my blood pressure readings and treatment	☐	☐	☐	☐	☐
Measuring my blood pressure at home:						
4	was not uncomfortable	☐	☐	☐	☐	☐
5	was not too time consuming	☐	☐	☐	☐	☐
6	caused me no anxiety	☐	☐	☐	☐	☐
7	I found it very easy to remember to do it regularly	☐	☐	☐	☐	☐

Please rate your overall satisfaction with monitoring your blood pressure at home by marking a cross on the following line

0 25 50 75 100

Extremely satisfied **Extremely dissatisfied**

Has anyone helped you to fill in the questionnaire? (Please circle) **YES** or **NO**

Thank you very much for taking the time to complete this questionnaire.

Please return it to us in the attached prepaid envelope.

If you would like to make any additional comments please use the space provided below: