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OXFORD

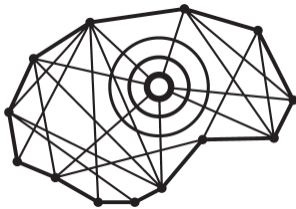


UCL

# PROHIBIT-ICH

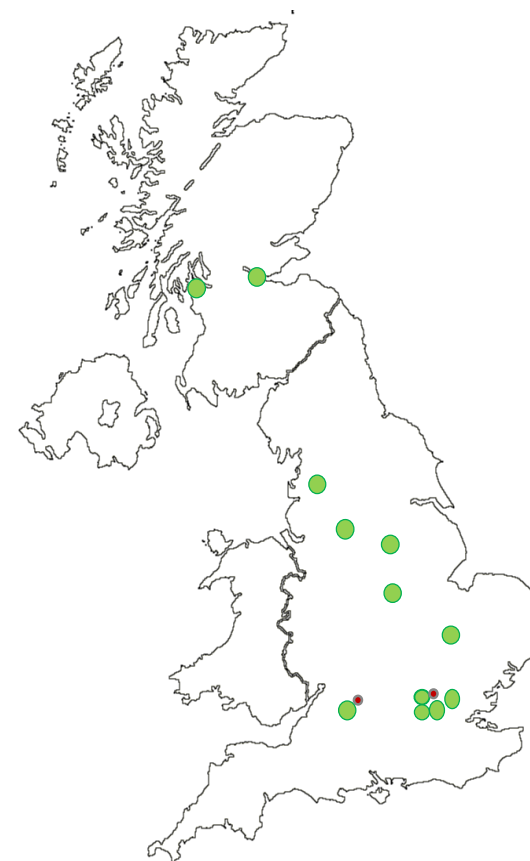
Prevention Of Hypertensive Injury to the Brain by  
Intensive Treatment in IntraCerebral Haemorrhage

## SITE INTIATION VISIT



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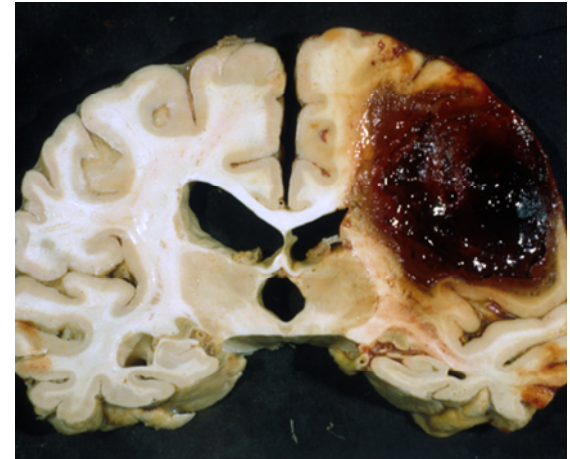
# AGENDA

1. Introduction to the Study and Scientific Background
2. Study protocol
  - Objectives
  - Primary and secondary outcomes
  - Inclusion and exclusion criteria
3. Trial Co-ordination from Oxford
  - Blood Pressure Device
  - Prescription Change
4. Trial Co-ordination from UCL
  - Clinical Data collection/Follow-up
  - Questionnaires and assessments
  - MRI Protocol

# Introduction to the Study and Scientific Background

# Importance of intracerebral haemorrhage

- About 10-20% of all strokes worldwide<sup>1</sup>
- Median 1 month case fatality 40%<sup>2</sup>
- ~ 60%-90% of survivors are dependent<sup>2</sup>
- Case fatality not improved 1980-2006<sup>2</sup>
- Incidence not declining in elderly populations despite better BP control<sup>3</sup>
  - especially antithrombotic related
  - ? related to CAA
- Few effective treatments



1. Lancet Neurol 2009;8:355-69
2. Lancet Neurol 2010;9:167-76
3. Lancet Neurol. 2007;6:487-93

- Hypertensive arteriopathy
- Cerebral amyloid angiopathy

- Arteriovenous malformation
- Aneurysm
- Cavernoma
- AV fistula

“macrovascular”

- Venous sinus thrombosis
- Clotting problems
- Tumour
- RCVS
- Vasculitis
- Endocarditis

“primary” ~80%

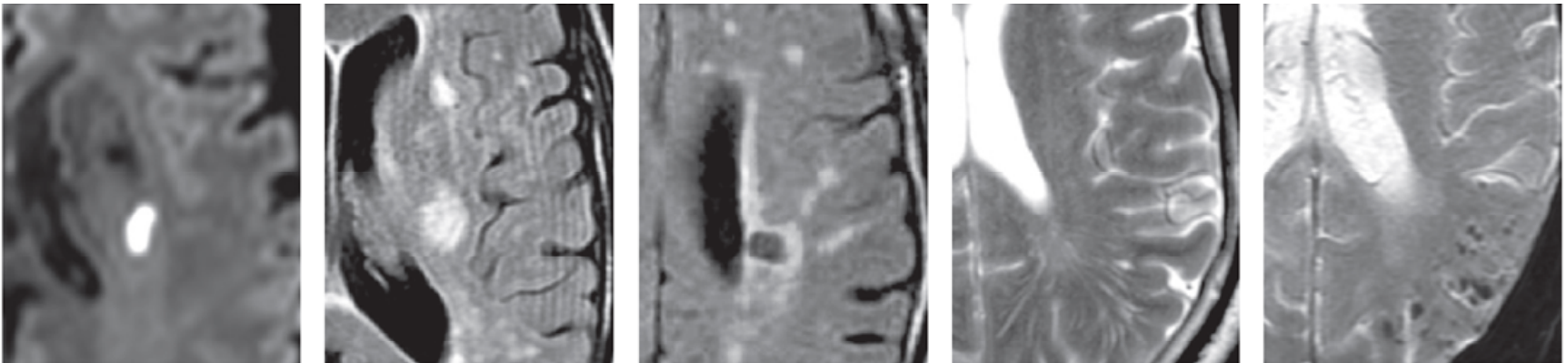
other causes ~20%



Also see SMASH-U (Structural lesion, Medication, Amyloid angiopathy, Systemic/other disease, Hypertension, Undetermined) for one suggested ICH classification scheme *Stroke*. 2012;43:2592-2597

## A definition of cerebral small vessel disease

*A group of pathologies affecting small perforating cerebral arterioles, capillaries (and venules), associated with a characteristic spectrum of clinical and imaging findings*



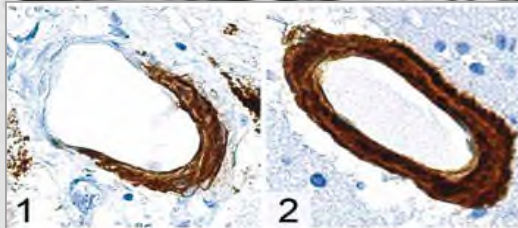


# small vessel networks of the brain

**CAA**



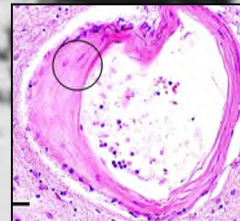
**cortical-  
leptomeningeal  
arterioles and  
arteries**



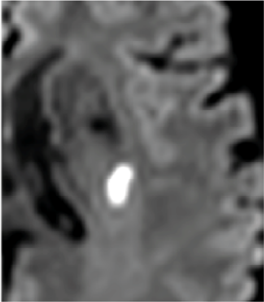



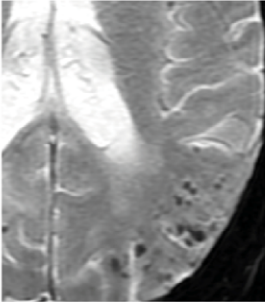
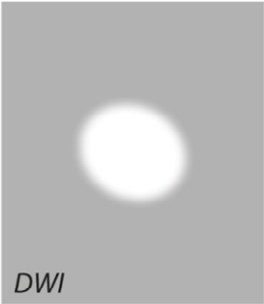

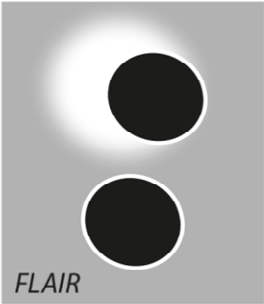
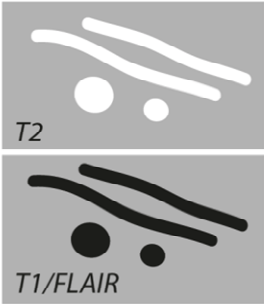
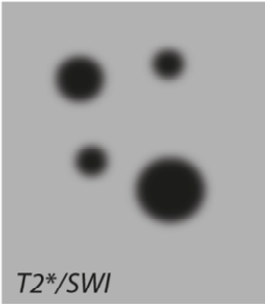
**deep perforators  
(white matter)**



**deep perforators  
(basal ganglia)**



***Arteriolosclerosis***

	Recent small subcortical infarct	White matter hyperintensity	Lacune	Perivascular space	Cerebral microbleeds
<b>Example image</b>					
<b>Schematic</b>					
<b>Usual diameter<sup>1</sup></b>	≤ 20 mm	variable	3-15 mm	≤ 2 mm	≤ 10 mm
<b>Comment</b>	best identified on DWI	located in white matter	usually have hyperintense rim	usually linear without hyperintense rim	detected on GRE seq., round or ovoid, blooming
<b>DWI</b>	↑	↔	↔/(↓)	↔	↔
<b>FLAIR</b>	↑	↑	↓	↓	↔
<b>T2</b>	↑	↑	↑	↑	↔
<b>T1</b>	↓	↔/(↓)	↓	↓	↔
<b>T2* / GRE</b>	↔	↑	↔ (↓ if haemorrhage)	↔	↓↓

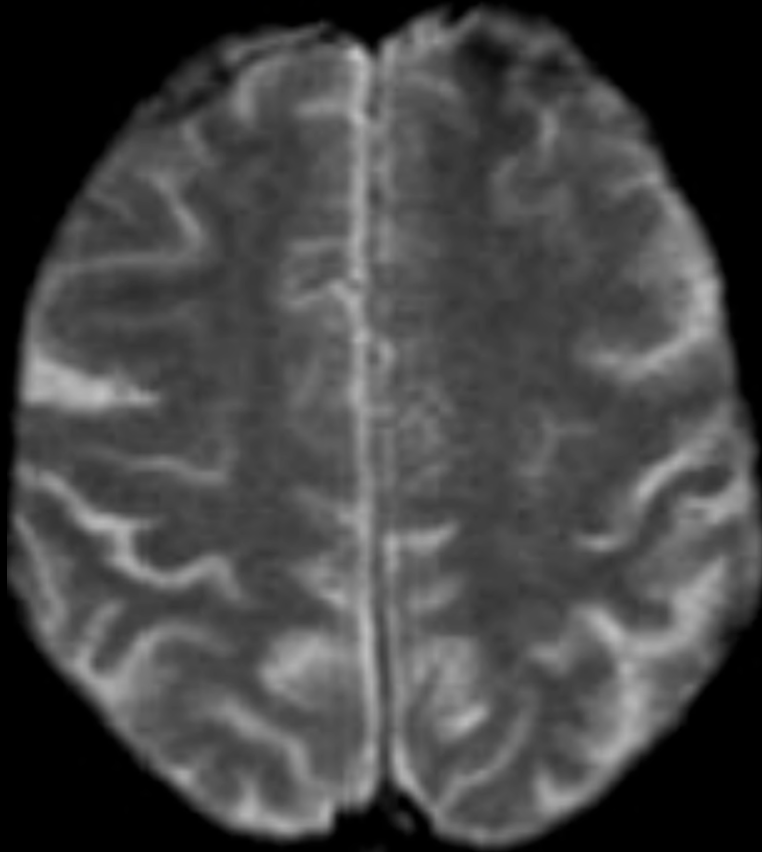
# Why use an SVD imaging biomarker?

- Can classify the underlying SVD causing ICH
- Reflect brain injury relevant to the adverse consequences of SVD, including cognitive impairment
- Evolve over time so can monitor progression
- 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 smaller number of participants in comparison to clinical event outcomes (e.g. recurrent stroke).

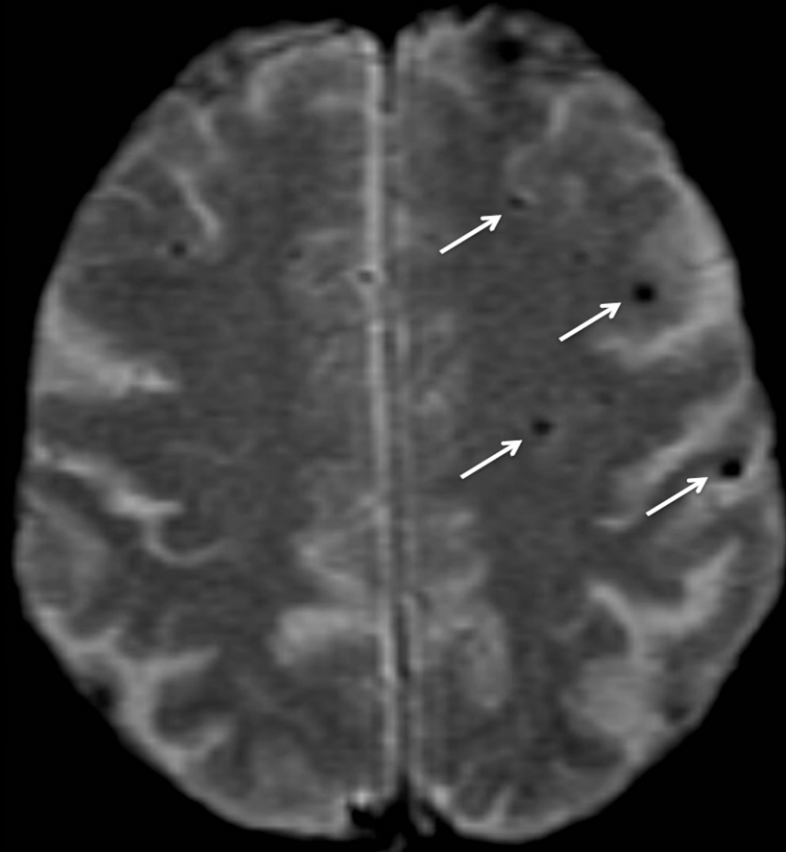
# The ideal biomarker for clinical studies

- Clinically meaningful
- Closely representative of the disease's underlying biological progression
- Efficient at detecting changes in response to treatment
- Reliably and reproducibly measurable
- Easily generalisable across many trial sites.

BASELINE

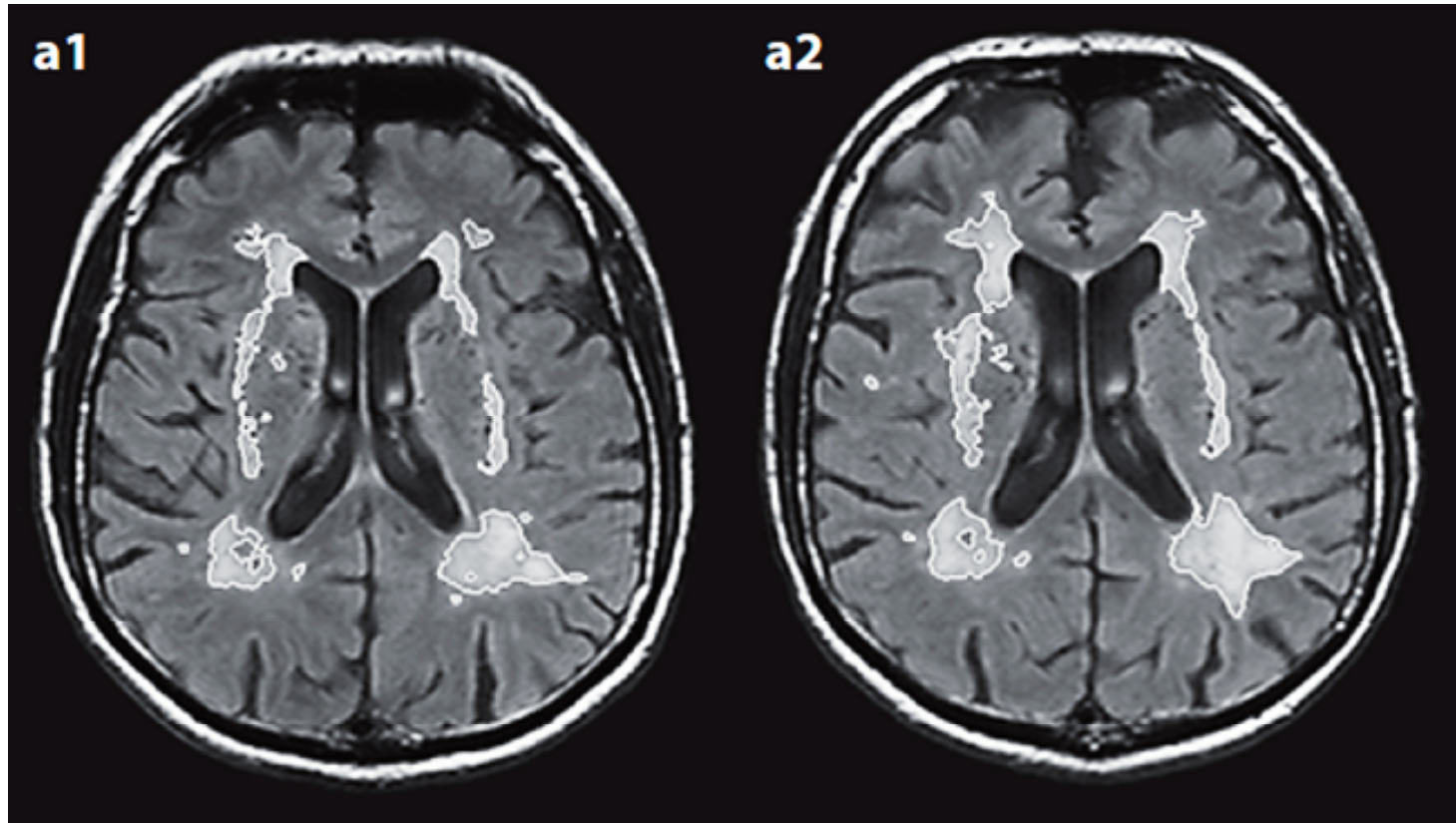


FOLLOW-UP



*The development of new CMBs was strongly related to baseline systolic BP (OR 1.28 per unit increase, 95%CI 1.23-1.33,  $p < 0.001$ ). Stroke. 2010 Jan;41(1):184-6.*





Cerebrovasc Dis  
2008;25:247–253

	Baseline	Follow-up	WMH progression
Volumetry, ml	24.6 (27.9)	29.2 (30.5)	4.6 (5.1)**
Fazekas Scale	4.3 (1.4)	4.6 (1.3)	0.3 (0.4)*
ARWMC Scale	12.3 (5.5)	13.2 (5.2)	0.9 (1.5)*
Scheltens Scale	22.7 (8.2)	24.1 (8.0)	1.4 (2.0)**
Schmidt Progression Scale	–	–	0.9 (0.6)***
Rotterdam Progression Scale	–	–	2.9 (2.9)***

# WMH volume increases over time

- Shown in older community and hospital stroke populations
- 26 patients (mean age 69.1) with probable or possible Cerebral Amyloid Angiopathy scanned over ~1yr found median WMH growth of 0.5 mL per year (IQR 0.1-2.8 mL per year)
- 192 participants in the PROGRESS trial mean total new WMH volume was significantly reduced in the active treatment group (0.4 mm<sup>3</sup> [SE=0.8]) compared with placebo group (2.0 mm<sup>3</sup> [SE=0.7]; P=0.012)
- With 56 patients in each arm we can detect a similar difference in new WMH lesion volume (2.0mm<sup>3</sup> vs 0.4mm<sup>3</sup>) (if the SD does not exceed 2.0 mm<sup>3</sup>) to that shown overall in PROGRESS, with power 80% at  $\alpha$  significance level of P=0.05.

## References

Stroke. 2008;39(5):1414-20.

Stroke 2008;39(10):2712-9.

Lancet. 2003;361(9374):2046-8.

Neurology. 1999;53(1):132-9.

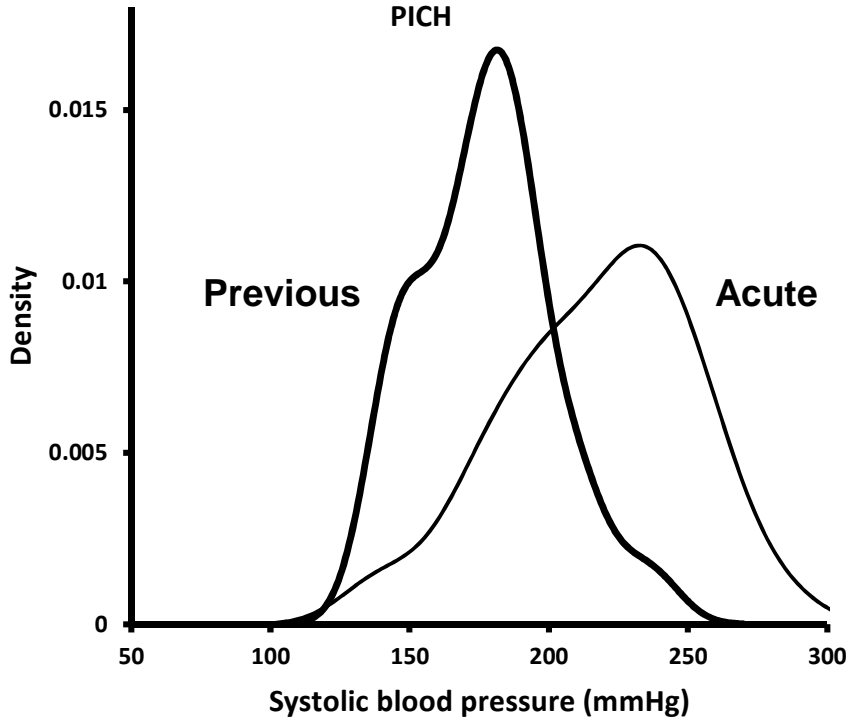
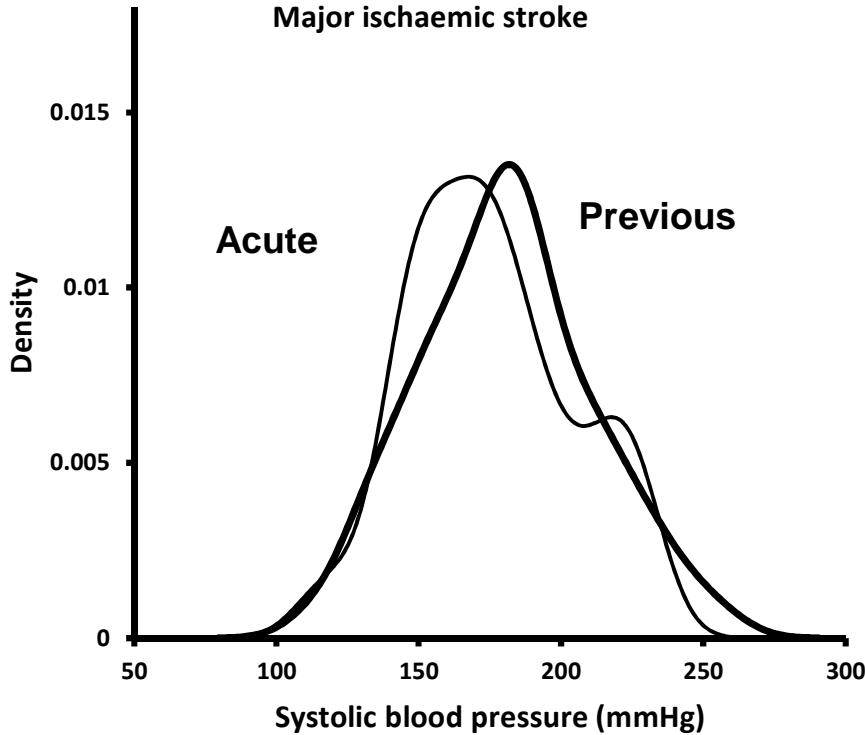
Trials. 2017;18(1):78.

Neurology. 2006;67(1):83-7.

Circulation. 2005;112(11):1644-50.

# Blood pressure in acute stroke

*Oxford Vascular Study*

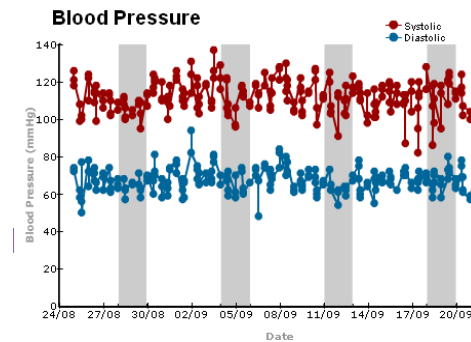
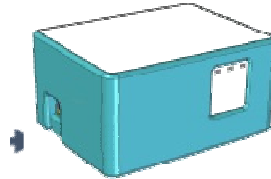


— Maximum post event SBP within 3 hours of stroke onset  
— Maximum premorbid SBP

— Maximum post event SBP within 3 hours of stroke onset  
— Maximum premorbid SBP

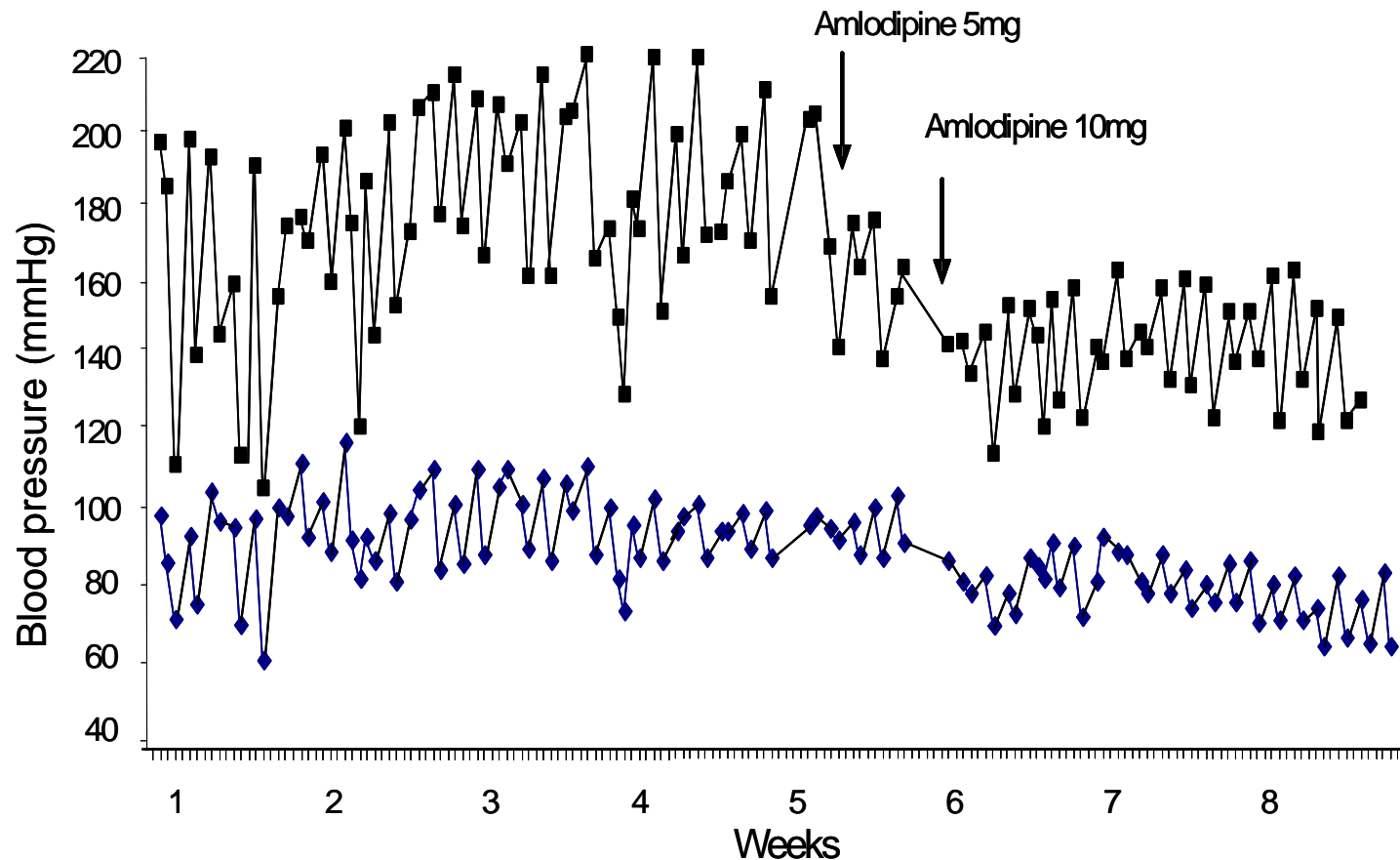


# Telemetric Bluetooth Home Monitoring



# COMMIT Study – OXVASC home monitoring

- 1200 patients; 2886 drug changes; 92% uptake



# Conclusions

- Telemetric home BP monitoring is feasible and well tolerated by patients with TIA and non-disabling stroke, irrespective of age, and is found to be helpful by GPs
- Monitoring detects high levels of masked hypertension, and informs titration of medication in the majority of patients
- Monitoring is associated with good BP-control and excellent longer-term compliance with medication
- Intensive BP-lowering titrated according to HBPM is reasonably safe in an elderly population prone to falls
- Residual hypertension detected on home-monitoring is of more prognostic value than on ABPM
- BUT - can it be rolled out across multiple centres?



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# Study Protocol

# Study Objectives

## Primary Objectives

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 SVD-related brain injury assessed on MRI compared with standard care?**

Including, but not limited to:

- White matter hyperintensities (WMH),
- White matter structural integrity,
- Incident cerebral microbleeds (CMBs),
- Brain atrophy

# Study Objectives

## Secondary Objectives

i). BP study:

1. Is it feasible in a multi-site setting?
2. Is it safe to intensively lower BP for an extended period of time following spontaneous ICH?
3. Is the intervention acceptable to participants?

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?

# Study Outcomes

## Primary Outcomes

### i). BP study:

1. **Efficacy:** the magnitude of difference in BP at 3 months in the intervention arm versus control arm
2. **Feasibility:** consent rate; dropout rate from the intervention prior to 1 month; patient approval of the monitoring process
3. **Safety:** serious adverse events related to reducing BP in intervention arm

### ii). Imaging study

1. **Efficacy:** the progression in MRI white matter hyperintensity (WMH) volume over 1 year

# Study Outcomes

## Secondary Outcomes

i). 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**

ii). 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)**



# Recruitment

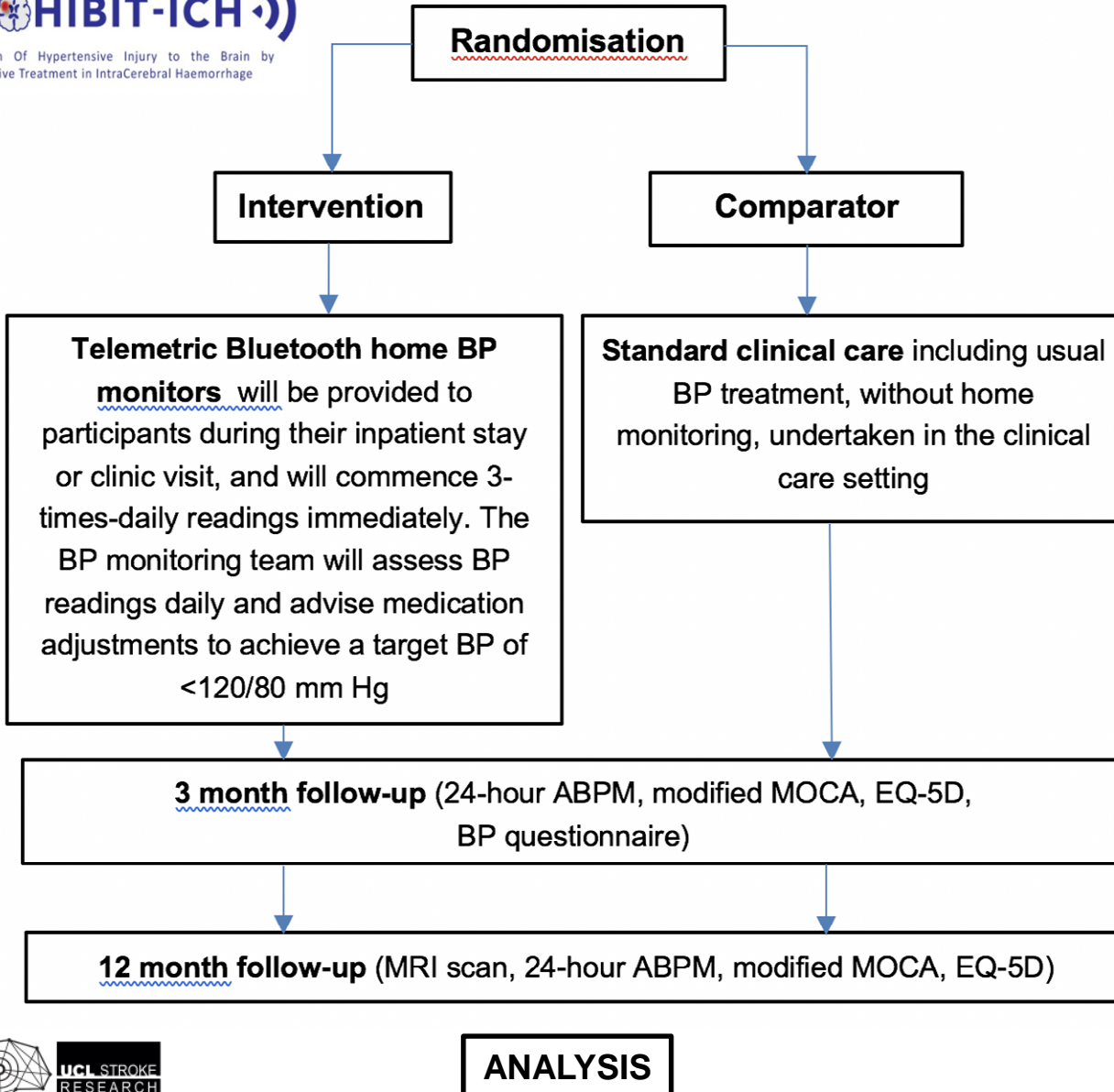
- Eligible patients will be identified by clinical staff from acute stroke units or high dependency units at participating hospitals, outpatient clinics (stroke, neurology, geriatric, neurosurgical) and from primary care centres
- Potentially eligible participants will be handed an information leaflet and a letter of invitation
- Patients will have at least 24 hours to consider the information before being telephoned or approached by a member of research/clinical team 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

# Inclusion Criteria

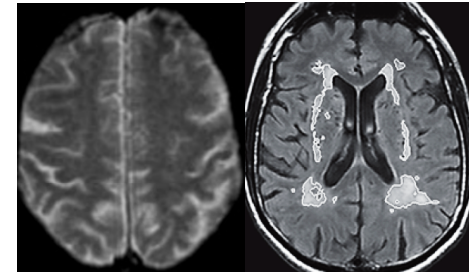
1. Adults ( $\geq 40$  years) with spontaneous primary ICH
2. BP control since the ICH is deemed not adequate AND the measured SBP prior to randomisation is  $\geq 130$  mm Hg
3. Recruitment soon after ICH is encouraged
4. Plan for home discharge (not to a nursing or care home)
5. Can undertake home BP measurements
6. Can complete an MRI scan
7. Can attend and complete the study assessments including cognitive screen
8. Can provide informed consent (or suitable consultee available)

# Exclusion Criteria

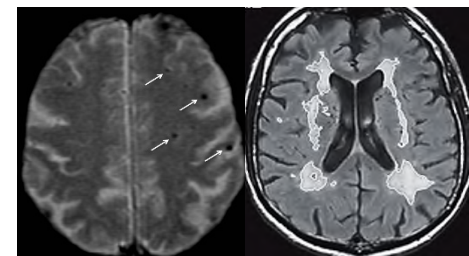
1. Inability to provide informed consent and lack of suitable consultee
  2. Evidence of a macrovascular or structural cause for ICH (e.g. AVM or tumour)
  3. Diagnosis of dementia
  4. Low Functional status (MRS  $\geq 4$ ) before or after ICH
  5. Life expectancy  $< 2$  years
  6. Taking more than 3 or more BP-lowering medications
  7. Consistently good BP control (below 130/80 mm Hg), judged not to require more intensive treatment
  8. Flow-restricting intracranial/extracranial large arterial stenosis
  9. Contraindication to MRI
  10. Absence of mobile phone coverage
- Contra-indication to BP treatments (e.g. symptomatic postural hypotension) is not an absolute exclusion criterion, but more information must be provided
  - Note that participation in other CTIMP or device trial is NOT an automatic exclusion criterion



**Baseline MRI before randomisation**



**Follow-up MRI at 12 months**



# Randomisation Procedure

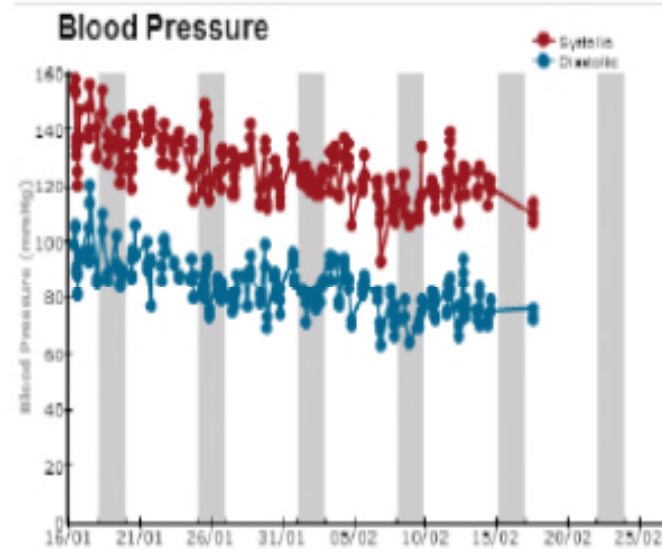
- Patients will be randomised in a 1:1 group assignment ratio to intensive BP lowering (intervention group) or standard care (control group) using an online randomisation service (Sealed Envelope)
- Baseline data collected (as described later)

# Blood Pressure Monitoring

## BP Measurement at Baseline

- 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

# Telemetric Home BP Monitor





# BP Treatment/Prescription changes

- The Oxford centre will directly advise patients on starting or adjusting BP medication
- 1st line treatment will usually be either combination therapy with perindopril and indapamide, or amlodipine 5mg daily
- Subsequent options will be likely to include the addition of spironolactone, an alpha-blocker and/or a beta-blocker
- The Oxford BP team will contact the patient directly to advise them on medication changes
- Changes will be notified to the GP and local research team
- The GP will provide prescriptions to patients

# BP Target

- $<120/80$  mm Hg
- If this is consistently achieved, monitors will be collected after a minimum of 1 month
- We expect most will be controlled by 3 months
- 3 month 24-hour ABPM
- Conventional monitors will be issued (weekly readings)

# Trial Coordination from UCL

**Shahena Butt**

# Coordination of PROHIBIT-ICH

- Clinical data collection
- Follow-up
- Questionnaires/Assessments
- MRI imaging
- MRI imaging upload and transfer

# Clinical Data Collection: eCRF

- Data collection
- Baseline
- 3 month follow-up
- 12 month follow-up



	Screening	Intervention phase and Follow-ups	
	Baseline	3 Month follow-up	12 Month follow-up
Visit No:	<b>1</b>	<b>2</b>	Final Visit
Informed Consent	<b>X</b>		
Medical History	<b>X</b>		
Eligibility confirmation	<b>X</b>		
Blood test	<b>X</b>		
MRI Scan (before randomisation)	<b>X</b>		<b>X</b>
Blood Pressure	<b>X</b>	<b>X</b>	<b>X</b>
24-hour ABPM	<b>X</b>	<b>X</b>	<b>X</b>
Cognitive assessment	<b>X</b>	<b>X</b>	<b>X</b>
Quality of life assessment (EQ-5D)	<b>X</b>	<b>X</b>	<b>X</b>
BP acceptability questionnaire		<b>X</b>	
Randomisation	<b>X</b>		

# Clinical Data Collection: eCRF

## ■ Data collection

- Electronically on sealed envelope
- Secure, authorised access



### PART A: PATIENT ELIGIBILITY

#### INCLUSION CRITERIA:

	YES	NO
Is the patient 40 years old or above?	<input type="checkbox"/>	<input type="checkbox"/>
Does the patient have spontaneous primary ICH? (i.e. without known underlying structural or macrovascular cause)	<input type="checkbox"/>	<input type="checkbox"/>
The patient's SBP > 140 mm Hg at the time of randomisation?	<input type="checkbox"/>	<input type="checkbox"/>
Is the patient planned for home discharge (not including nursing/care home) after their inpatient stay?	<input type="checkbox"/>	<input type="checkbox"/>
Is the patient willing (and demonstrate ability to) undertake home BP measurements, either unassisted or with the help of a relative, friend or carer?	<input type="checkbox"/>	<input type="checkbox"/>
Is the patient able and willing to complete an MRI scan?	<input type="checkbox"/>	<input type="checkbox"/>
Is the patient able and willing to attend and complete study assessments including cognitive screen?	<input type="checkbox"/>	<input type="checkbox"/>
Is the patient able and willing to provide informed consent?	<input type="checkbox"/>	<input type="checkbox"/>

If any of the above are checked "No", the patient is **NOT eligible** for the study - **STOP**

#### EXCLUSION CRITERIA:

	YES	NO
Is there evidence of a macrovascular or structural cause for ICH (e.g. AVM or tumour)?	<input type="checkbox"/>	<input type="checkbox"/>

# Clinical Data Collection: eCRF

## ■ Baseline

- Medical history
- Blood pressure medication
- 3 BP measurements
- 24-hour ABPM
- Blood test (venepuncture)
- MRI brain scan - **performed prior to randomisation.**
- Cognitive functional assessment (modified Montreal Cognitive Assessment)
- Completion of the EQ-5D questionnaire

### PAST MEDICAL HISTORY

	Y
Hypertension (on anti-hypertensive treatment pre-stroke or $\geq 140/90$ mmHg persisting 7 days after stroke or on two occasions before the stroke)	
Hypercholesterolemia (on treatment pre-stroke or cholesterol total $\geq 5.2$ mmol/L after stroke)	
Diabetes type I/II (pre-stroke diagnosis or $\geq 2$ random $\geq 11.1$ mmol/L or $\geq$ fasting $\geq 7$ mmol/L after stroke)	
Smoking History	
Alcohol: current drinker	
Ex-Alcohol drinker	
Recreational drug use	
Myocardial Infarction (MI)	
Revascularisation (Percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG))	
History of congestive heart failure	
History of arterial fibrillation	



# Blood Sample - Baseline

- About 5-10mls Blood will be taken from consenting patients
- EDTA blood sampling tube
- Stored at UCL Institute of Neurology, Queen Square for future genetic research.
- Sent in a Safebox from the sites to Shahena
- Royal Mail Safe Boxes will be provided



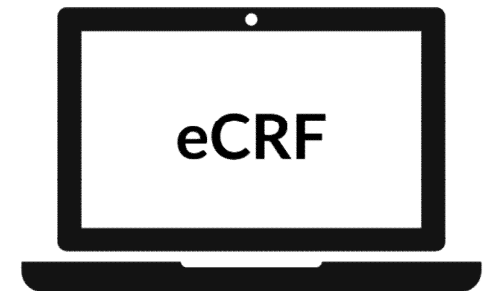
# Clinical Data Collection: eCRF

## ■ 3 month follow-up

- 3 month follow-up eCRF
- BP recorded
- modified Montreal Cognitive assessment
- EQ-5D questionnaire
- home blood pressure acceptability questionnaire
- 24-hour ABPM

## ■ 12 month follow-up

- 12 month follow-up eCRF
- As Above (minus: home blood pressure acceptability questionnaire)
- MRI Scan



# Questionnaires/Assessments

- Cognitive Assessment
  
- EQ-5D
  - Standardised instrument for use as a measure of health outcome
  - Two pages
  - EQ-5D descriptive system
  - EQ visual analogue scale

# MRI

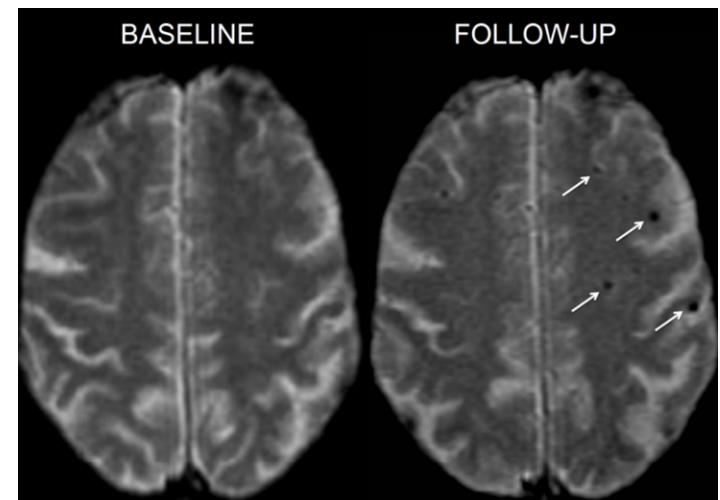
- Outcomes
- MRI Protocol
- Sequences
- MRI imaging upload and transfer



# MRI

## ■ Outcomes

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



# MRI

- **MRI Protocol and Manual**
  - For major MRI scanner manufacturer (Siemens, GE Philips)
  - Manual: how to upload a scan

# MRI protocol

## ■ Sequences

1. 3D T1 (5min)
  2. 3D FLAIR (5min)
  3. DTI (simplified) (5min)
  4. 3D SWI (5min)
  5. Axial T2 (2min)
- Total: 22min**
- Optional: Arterial Spin labelling (5min)
- Total: 27min**

# MRI Image upload and transfer

- Set- up: Password protected Log-in
  1. Name of person uploading the scans
  2. Email address

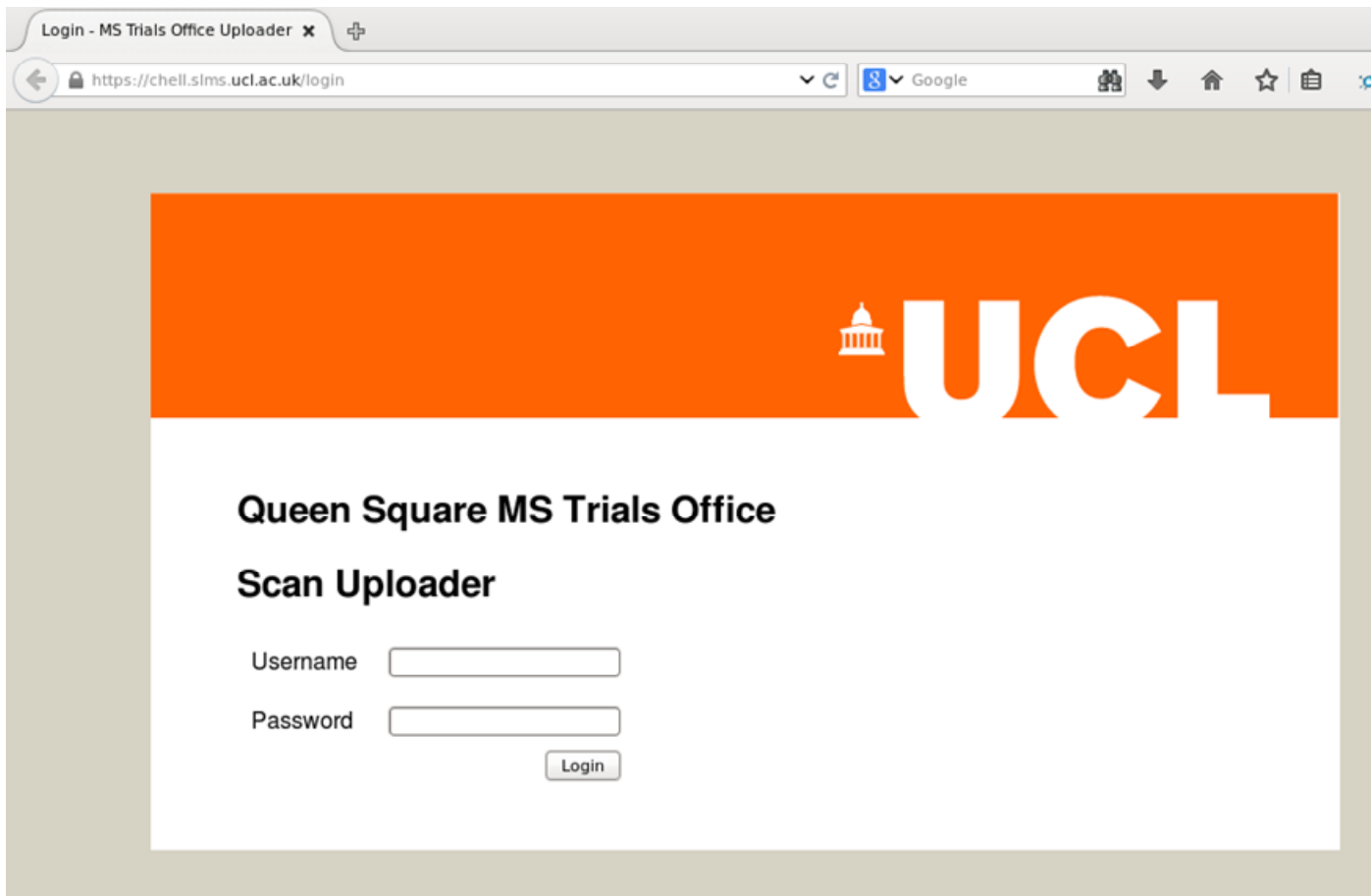
## Image file requirement:

- File needs to be compressed – Zip file



# MRI Image upload and transfer

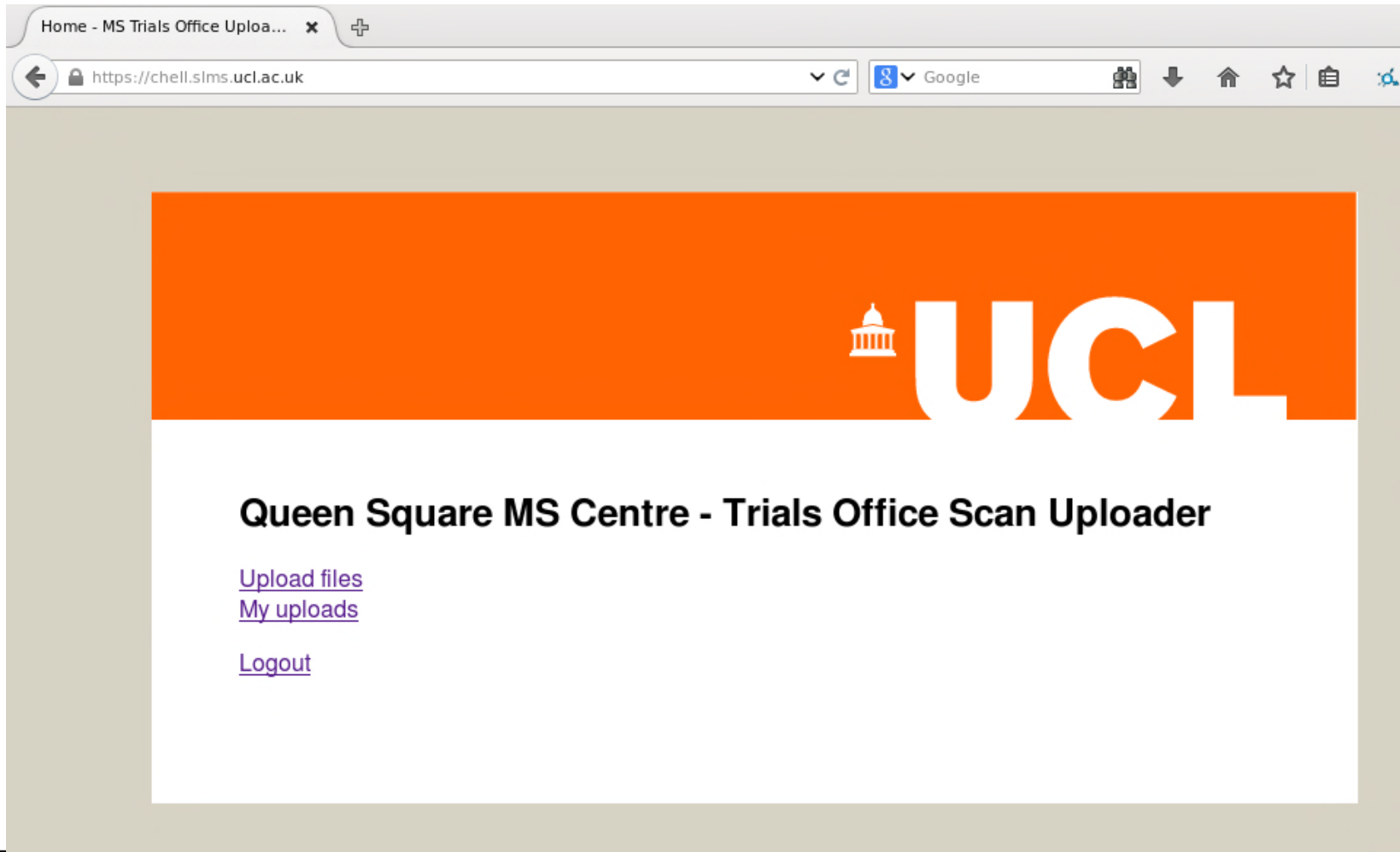
<http://qsmscentre.org.uk>



The screenshot shows a web browser window with the following elements:










- Browser tab: Login - MS Trials Office Uploader
- Address bar: <https://chell.sims.ucl.ac.uk/login>
- Search bar: Google
- Page header: UCL logo on an orange background.
- Section title: Queen Square MS Trials Office
- Section title: Scan Uploader
- Form fields: Username and Password.
- Button: Login.


# MRI Image upload and transfer



The screenshot shows a web browser window with the address bar displaying `https://chell.sims.ucl.ac.uk`. The page content features a large orange banner with the UCL logo. Below the banner, the title "Queen Square MS Centre - Trials Office Scan Uploader" is displayed. Three links are provided: "Upload files", "My uploads", and "Logout".

Home - MS Trials Office Uploa... x +

←  `https://chell.sims.ucl.ac.uk`   Google      



**Queen Square MS Centre - Trials Office Scan Uploader**

[Upload files](#)

[My uploads](#)

[Logout](#)

# MRI Image upload and transfer



## Upload scans

### Upload type

- Patient  
 Dummy

### Subject

#### Site

PROHIBIT 00

#### Subject number

#### Birth Date

dd / mm / yyyy

### Scan

#### Scan Date

dd / mm / yyyy

#### Visit

Baseline

### Comments

# MRI Image upload and transfer

ZIP FILE

Select files - MS Trials Office ... x +

https://chell.sims.ucl.ac.uk/select\_files

UCL

### Select files

Select Files

No files selected

0 files selected

[Start upload](#) [Cancel upload](#)

# MRI Image upload and transfer

https://chell.sims.ucl.ac.uk

UCL

## Queen Square MS Centre - Trials Office Scan Uploader

1 file(s) uploaded

[Upload files](#)  
[My uploads](#)  
[Admin](#)  
[Logout](#)

# Where Are We?

- Regulatory:
  - Ethical Approval
  - Final local R&D approval needed
- Operational:
  - Contact made with all sites
  - Gathering local study documentation
  - Creating local Site Files
- Site Initiation:
  - Study team

# If All Is In Place...

- LET'S GET STARTED!
- Dissemination via email
- All local study staff members will be included in the email
- Co-ordinator will action



# PROHIBIT-ICH

Prevention Of Hypertensive Injury to the Brain by  
Intensive Treatment in IntraCerebral Haemorrhage

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## THANK YOU

**Stroke**  
association