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1. Overview of study design

CROMIS-2 consists of two studies: Study I (AF) and Study II (ICH). Participating centres can take part in Study I, Study II or both.

1.1. **CROMIS-2: Study I (AF)** is a prospective, multicentre, inception cohort study in 1000 patients with ischaemic stroke due to AF started on oral anticoagulation. Patients will have standardized MRI including GRE at baseline, with central follow-up by postal questionnaires (and clinical assessment or medical records surveillance after suspected events). We will compare the rate of symptomatic ICH between CMB and CMB-free patients. We aim to develop and validate a risk model to predict symptomatic ICH following best practice oral anticoagulation to prevent recurrent ischaemic stroke due to AF.

1.1.1 **Recruitment for Study I: (AF)** - We will recruit a total of 1,000 patients from UK centres in the Stroke Research Network over 36 months. All eligible patients with first or recurrent ischaemic stroke and TIA in whom it is decided that best practice oral anticoagulant treatment is to be commenced (without any prior use or contraindications to oral anticoagulation) will be invited to participate from acute stroke units and outpatient stroke clinics. We anticipate that each centre will be able to recruit at least 8 patients per year.

1.2 **CROMIS-2: Study II (ICH)** is a multicentre observational study of the clinical and radiological risk factors associated with spontaneous and anticoagulant-related ICH. We will recruit 600 patients with spontaneous ICH (target >300 anticoagulant-related).

1.2.1 **Recruitment for Study II: (ICH)** - We will recruit a total of 600 patients admitted to participating hospitals with ICH during the study period (300 patients will have an anticoagulation-related ICH). Patients with a history of ICH seen in outpatient clinics will also be recruited. Of an estimated 60 patients with ICH admitted per centre per
year. We expect each participating hospital to recruit as many spontaneous ICH cases as possible (at least 2-3 patients with anticoagulation-associated ICH per year). In both studies, DNA will be stored for future analysis in collaboration with the International Stroke Genetics Consortium.

1.3 Expected outcomes

A successful predictive model for ICH risk after best practice oral anticoagulation for AF will help to determine whether genetic or CMB screening should be used in clinical practice and future trials. New genetic, clinical and radiological risk factors associated with anticoagulant-related ICH will be identified.
2. Co-ordination of the Study

2.1 Central Co-ordination
The study is coordinated by the CROMIS-2 Coordinating Centre, University College Hospital and The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, where full time study staff will be based.

CROMIS-2 Co-ordinating Centre
Department of Brain Repair and Rehabilitation
Stroke Research Group, Box 6
The National Hospital for Neurology and Neurosurgery
Queen Square
London, WC1N 3BG
United Kingdom

Tel: + 44 (0)207 676 2194
Fax: + 44 (0)207 837 9632
Email: c.shakeshaft@ion.ucl.ac.uk

2.2 Local Co-ordination
The study has been adopted as a multicentre study by the Stroke Research Network, allowing research nurses/practitioners to provide service support for the study. In each participating Stroke Unit, there is a Local Co-ordinating team consisting of a research practitioner/nurse(s) and a Principal Investigator. Local co-ordination in participating sites is the responsibility of a lead clinician in the participating hospital who is responsible for ensuring the smooth running of the CROMIS-2 study in their unit.

2.2.1 Responsibilities of the local research team
The specific responsibility of the local research team will be to:

- be familiar with the study
- liaise with the Central Co-ordinating Centre
• ensure that all medical and nursing staff involved in the care of patients are well informed about the study
• ensure that mechanisms for recruitment of eligible patients (including information material) are in place, monitor their effectiveness, and discuss reasons for the non-recruitment of any eligible patients with relevant staff
• ensure that supplies of case report forms (CRFs) are always available, that the patient information section is completed and returned to the Study Office promptly, and to deal with any queries arising
• ensure all data is entered electronically via the website secure log in, in a timely manner
• ensure all study documentation is kept up to date in the Study Site File
• assist with recruitment and taking consent
• take blood samples required for the study and ensure they are sent to UCH for analysis in a timely manner
• organise the MRI scan necessary for the study
• ensure consent forms are completed and returned to the Study office
• investigate medical notes if the coordinating centre has been notified by a positive event by the patient in follow up or by their GP
• conduct telephone interviews if required due to non return of postal questionnaire data, as this data collection is to be undertaken by SRN research nurses/practitioners
• ensure all members taking consent at the site are properly trained and on the delegation log
• facilitate other aspects of local collaboration as appropriate
• make all data available for verification, audit and inspection purposes as necessary
• put in place systems for the follow-up for all patients recruited
2.2.2 Which hospitals are able to recruit patients to the study?

All recruiting sites will be within the UK Stroke Research Network. We expect a total of approximately 50 hospitals to take part in the study.

3. Study documentation

All of the documentation necessary for CROMIS-2 is stored in the CROMIS-2 site file and CROMIS-2 study documentation box, and Data Collection File, all to be kept in the Stroke unit at each participating site. The Research Practitioners are responsible for ensuring copies of all relevant paperwork are present and kept up to date in the site file. All blank copies of consent forms and study documents should be kept in the Study Documents File provided. All completed paperwork for patients should be kept in the Data Collection File.

The study documentation consists of:

- Consent forms for study I (AF) and study II (ICH)
- Patient Information Leaflets study I (AF) and study II (ICH)
- Baseline case report forms for Study I (AF) and Study II (ICH) - electronic and hard copies
- Patient Information Form
- CROMIS-2 protocol
- CROMIS-2 researcher handbook
- CROMIS-2 CRF guidelines
- CROMIS-2 guide to taking consent
- Labels for patient’s notes
- FREEPOST envelopes
- Documents and Consumables Request form
3.1 Completion of data collection forms

- All blank data collection forms are kept in the CROMIS-2 Study Documentation Box, if you are running low on stock re-order more using the Documents & Consumables Request Form (see Figure 1 below) and fax or send back to CROMIS-2 Co-ordinating Centre.

![Documents and consumables request form](image)

**Figure 1. Documents and consumables request form**

- Electronic copies of all the data collection forms are also kept on the CROMIS-2 website (www.ucl.ac.uk/cromis-2) and can be downloaded and printed.

There are 3 data collection forms that should be completed for all patients in the study:

1. **Consent Form**
2. **Patient Information Details form**
3. **CRF (baseline)** – this should be completed electronically, a paper copy is also available with copies of all scales needed to be completed by researcher/ next of kin/ patient.
There is a further data collection form in the Documentation Box that may be needed for some patients:

4. Study withdrawal

3.2 Specific points to remember about each data collection form

3.2.1 Consent Form
The localised consent form must be signed and 4 copies made - two must be returned to the Co-ordinating Centre, one copy to be given to the patient, one copy to be filed in the patient’s notes, and the final copy to be filed in the site Data Collection File.

3.2.2 Case Report Form
Complete the eligibility criteria on the form of the form prior to study allocation number from the website (to ensure patient is eligible to be recruited to the study). Be sure to complete the necessary scales and patient information details on the paper copy, and send with the consent from. Complete the whole form on line, and return the consent
form and patient information form to the Co-ordinating Centre **within 7 days of study entry.**

**Please see separate ‘CRF completion guide’ for step by step instructions**

3.2.3 **Patient Information Form**
This form (within the CRF) provides details of the patient’s name, address, next of kin details, and GP details. This MUST be completed for each patient to send to the Co-ordinating centre, so we have their details to obtain follow up. When the consent forms and Patient Information form are both completed please send to the Co-ordinating Centre (using a Freepost envelope provided in the CROMIS-2 Documentation Box). This information is ONLY needed for the Co-ordinating Centre, and is not inputted into the electronic database, therefore a paper copy MUST be completed.

3.2.4 **Study withdrawal form**
To be completed and signed by the Principal Investigator or delegated deputy for any patient who is totally withdrawn from the study. It is **important that you clarify** with the patient and record on the form whether, they would agree to retention and use of the data already collected, for data collection to continue to completion. Depending on the wishes of the patient, further data collection and form completion maybe required.
4. Who can be recruited to CROMIS-2?

4.1 Eligibility criteria
Patients are eligible to be recruited to CROMIS-2 if they fulfil the following criteria:

4.1.1 Study I: CROMIS-2 (AF)

**Inclusion criteria:**
- Adult (≥18y; no upper limit) patients with a clinical diagnosis of non-valvular AF (verified by ECG) with intention to treat with best practice oral anticoagulants (e.g. warfarin)
- Previous ischaemic stroke or TIA diagnosed by treating clinician
- All patients must be able to have GRE MRI before (or within 1 week) of starting best practice oral anticoagulant

**Exclusion criteria:**
- Any MRI contraindications
- Previous use of oral anticoagulation
- Definite contra-indication to oral anticoagulation
- Serious head injury (resulting to loss of consciousness)

4.1.2 Study II: CROMIS-2 (ICH)

**Inclusion criteria:**
- Adult (>18y) patients treated at participating centres with confirmed ICH (confirmed on CT or MRI scans) with or without a history of anticoagulant use at the time of the ICH

**Exclusion criteria:**
- Known underlying structural cause for ICH (e.g arteriovenous malformation, tumour, cavernoma, intracranial aneurysm, haemorrhagic transformation of an infarct)
- Major head trauma (causing loss of consciousness and though to be sufficient to have caused the ICH) in previous 24 hours
The consent form must be signed and photocopied 4 times:

- **Original** copy AND one further copy to the CROMIS-2 Study office using a FREE POST envelope provided in the CROMIS-2 documentation box (the white copy is for the study master file; the second copy will be sent to the GP with a cover letter and copy of the Patient Information Sheet).
- One copy to the CROMIS-2 Data collection file (filed under Study I or Study II as appropriate).
- One copy to the patient/consultee.
- One copy to the patient’s medical notes together with a copy of the Patient Information Leaflet (PIL).

### 4.2 If patient is not able to consent

If the patient is not deemed eligible to consent when they are eligible to join CROMIS-2, consent may be sought by a consultee. The consultee consent form must be signed and photocopied 4 times; The **original** copy AND one further copy to the CROMIS-2 Study office using a FREE POST envelope provided in the CROMIS-2 documentation box (the white copy is for the study master file; the yellow copy will be sent to the GP with a cover letter and copy of the PIS); the green copy to the CROMIS-2 Data collection file; the pink copy to the patient/consultee.; the blue copy to the patient’s medical notes together with a copy of the Patient Information Leaflet (PIL).

### 4.3 Study Withdrawal

If it is felt that a patient has been consented to CROMIS-2 inappropriately, the clinical team caring for the patient must decide whether or not to continue with participating in the CROMIS-2 study. Regardless of what decision is made, the a patient will remain part of CROMIS-2 study and data should be collected and recorded on the CRF by the Research Practitioner, although no follow up will take place. A withdrawal form should be completed and returned to the Co-ordinating Centre.

If the patient is transferred on to another hospital then please telephone the CROMIS-2 Co-ordinating Centre on +44 (0)207 676 2194 [during UK office hours].

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4.4 After consent has been obtained
When a patient is eligible to join the CROMIS-2 study and consent has been obtained:

1. Check that the patient is eligible by filling in the eligibility criteria (i.e. answers to questions 1 to 5 on the Case Report Form (CRF) are as required to be ‘Yes’).
2. If eligible, complete the remainder of the questions of the CRF.
3. Complete the Patient information form and send, with the consent form, to the co-ordinating centre. No personal details will be completed on the electronic form, in compliance with the Data Protection Act. However, follow up requires patient details in order for the Co-ordinating centre to contact patients, a patient information form (paper copy) must be sent with the consent form to the co-ordinating study.
4. This data will be entered electronically onto a separate secure database; that does not link patient medical information to their identifiers.
5. Go to the online eCRF on the CROMIS-2 website. Type in your log in details. Enter the details to obtain a study number. The first two numbers will be your site number (e.g. UCH is site 01).
6. Place the CROMIS-2 patient label found in your study documentation box on the front of the patient’s notes so that all personnel will know that this patient is participating in CROMIS-2, and can inform the co-ordinating centre should an event occur that is relevant to the study.
4.5 Study consent procedures: A step by step guide to the CROMIS-2 study

1. Identifying patients who are eligible – please see Eligibility criteria
2. On admission: When a patient is admitted to hospital, they should be given a copy of the leaflet “Information for Patients”.
3. Ensure they are aware that consent is being sought for their participation in an observational study
4. Ensure they are aware that participation in the study is voluntary and declining to enter the study will not affect the quality of the medical care they receive that follow up questionnaires will be required at 3 months after their event, and every 6 months for 2 years.
5. Ensure they are aware that they are free to withdraw from the study, but any data collected up to the point of withdrawal can be used, if appropriate, to contribute to the outcome of the study.
6. What will happen to patients who enter the study?

6.1 Study I (AF):

6.1.1 At recruitment in hospital after consenting to the study:
- Participants will have a bedside assessment of their cognitive function using a questionnaire.
- All participants will have a blood sample taken for genetic and/or biomarker analysis.
- They will also have an MRI scan of the brain including specific sequences to detect microbleeds.
- Some patients may be invited to have fundoscopy and retinal photography, a straightforward, non-invasive procedure that will take about 15 to 30 minutes.
- Participants will then be treated according to standard clinical care, with no additional procedures as part of the study.
- Information about best practice oral anticoagulant control will be recorded in the CRF whilst in hospital by the study team.

6.1.2 Follow up:
- Patients will be followed up at 3, 6, 12, 18 and 24 months by a postal questionnaire sent from the co-ordinating centre at UCL.
- After discharge from hospital, patients (or carers/consultees) will be asked to send information about any blood tests of best practice oral anticoagulant control that they have to the central study team. This will be done by postal questionnaire.
- Patients will also be asked to contact their local study team if they are admitted to hospital for any reason or suffer any bleeding complications related to best practice oral anticoagulant. This information will then be sent to the central study team by the local research team.
- Planned follow up will be every 6 months for up to 2 years, using structured questionnaire to assess for any further stroke or TIA events or other clinical or
medication changes. Patients will be contacted by postal questionnaire, or if this is not possible, will be contacted for a brief telephone interview. The follow up will be carried out by the co-ordinating centre.

- INR values will also be requested from the patient’s GP and/or anticoagulant clinic by the Study Co-ordinator.

6.2 Study II (ICH)

6.2.1 At recruitment in hospital after consenting to the study:
- Participants will have a bedside assessment of their cognitive function using a questionnaire.
- All participants will have a blood sample taken for genetic and/or biomarker analysis.
- Participants will then be treated according to standard clinical care (which may include a brain scan), but with no additional procedures as part of the study.

6.2.2 Follow up:
- Patients will be followed up by postal questionnaire at 6 months and 1 year.

7. How baseline data will be collected?

7.1 Case Report Form
Baseline data for Study I and Study II will be entered by the local study team into an electronic case report form (CRF) and submitted to the central study co-ordinating centre at UCL. Researchers will have their own personal log in user name and password, which will allow them to log on to a secure part of the study’s website – www.ucl.ac.uk/cromis-2.

A paper copy of the baseline Case Report form is also available for researchers to use and enter data if they wish. The paper copy, if used, can be kept in the Data collection file at site; it does not need to be sent to the Co-ordinating Centre.
7.2 Imaging data: MRI

7.2.1 Study I: CROMIS-2 (AF)

Procedure:

- All patients should have a baseline scan taken either before or after randomisation.
- The MRI scan must be requested in accordance with the procedure for each individual participating hospital (please refer to individual hospital guidelines).
- All patients must have T2* GRE MRI (with standardized sequence parameters recommended by the central study team) at baseline, as soon as possible after stroke or TIA attributed to AF (before or within < 1 week after anticoagulation is started).
- Other vascular MRI sequences (Axial T1, Axial T2 FSE, Coronal FSE Flair and DWI) should be done, if possible (this will have been agreed with individual sites).

7.2.1.2 Study II: CROMIS-2 (ICH)

All brain imaging undertaken as part of standard clinical care will be collected. We expect that MRI including GRE T2* will be obtained in many cases as a routine investigation in the diagnosis of spontaneous ICH, but MRI imaging is NOT essential for this study. Computed tomography (CT) data where available will also be included. The CT scan should be a plain, non contrast brain scan in DICOM format. If an MRI is carried out, please refer to guidelines above with regards to sending the scan to the Co-ordinating Centre.

7.2.1.3 How do I transfer the scan to the Co-ordinating centre?

- The scan will need to be on a CD produced by the PACS team/Radiology.
- Viewing software should not be added to the CD.
- If there is more than one series of scans then please request that each series be saved in a separate folder.
• Please ensure an anonymised CD is sent to us. We will need written confirmation that this method is consistent with your trust’s policy of sending electronic data.
• Although the CD is anonymised please do not delete the following fields, as they are required to ensure that the scan is matched to the correct patient:
  ▪ Age at stroke (or date of birth)
  ▪ Sex
  ▪ Study and content date and time.
  ▪ Please ensure study patient ID either replaces name or is written on the CD.

7.2.1.4 Posting Scans
Please post using a secure courier where a signature is required upon receipt. Please send the scans to:

CROMIS-2 Co-ordinating Centre
Stroke Research Office
Department of Brain Repair and Rehabilitation
Box 6
The National Hospital for Neurology and Neurosurgery
Queen Square
London
WC1N 3BG
7.3 Other study data to be collected:

7.3.1 ECG
ECG should always be done as routine care at all participating sites. A copy should be filed in the patient’s hospital notes. A copy is **NOT** required to be sent to the Co-ordinating Centre; however a copy should be available should it be requested by the coordinating centre.

7.3.2 Echocardiography (ECHO)
ECHO is not essential but they are often done in practice. A copy should be filed in the patient’s hospital notes. A copy is **NOT** required to be sent to the Co-ordinating Centre; however a copy should be available should it be requested.

7.3.3 Genetics data
Blood will be taken and DNA and extracted from consenting patients at baseline and stored in a repository at UCL Institute of Neurology, Queen Square. Blood samples should be taken as per routine standard care. 2 X 4.7ml Purple top (EDTA) blood tubes will be collected and transported to the co-ordinating centre by post. Once taken, please complete the CROMIS-2 blood sample form (provided in the Study Documentation Box), completing all details on the form. Put the form and the blood into a Royal Mail Safebox™, provided by the Co-ordinating centre.

7.3.4 Step by step guide to taking and sending blood samples:
- 2 x vial required for study blood samples
- Ensure both tubes are filled to the top
- Ensure the patient’s study number is written on the side of both tubes.
- Fill out the CROMIS-2 Blood sample form, found in the study documentation box, ensuring all information requested is provided, this is vital for the UCH laboratory to process the samples.
- Place the completed form and the blood inside the Safebox™.
- The sample must be packaged appropriately according to the directions of the Safebox™ (see step by step guide – applicable to all sites except UCH).
• The sample should be sent to UCH on the same day the blood sample was taken. If, for any reason, this is not possible, the sample MUST be sent to UCH WITHIN 7 days.

NB. Ensure the sample is stored at room temperature.

7.3.5 SAFE BOX instructions (applicable to all sites except UCH)

1. Place sample securely in a leak-proof container.
2. Wrap the containers in absorbent material and place in the plastic self-seal bag, sealing it and putting the whole package in the clear plastic compartment.
3. Place the form in the other compartment.
4. Once the pack is closed, it can't be re-opened without destroying it, so carefully check all contents you want to send are inside the package before closing.
5. Remove the cardboard separator, place the lid over the top of the container and firmly press shut.
6. Peel the outer backing from the self-adhesive label and wrap around the Safebox™.
7. Make sure the package is addressed correctly and the return address has been completed in full.
8. If you have a First Class Safebox™, simply put it in the post, or take it to a Post Office®.

The sample should be sent to the Co-ordinating Centre ON THE SAME DAY the blood sample was taken. However, if for any reason this is not possible, the sample may remain at ambient temperature for up to 1 week before arriving at Queen Square; if a longer delay is anticipated the sample must be frozen prior to transfer. At the co-ordinating centre, DNA will be extracted from each patient and the DNA stored at -70 °C.
EDTA plasma, citrated plasma and serum may also be taken for biomarker substudies and which can be kept for up to 4 weeks at -40°C and indefinitely at -70°C, prior to transport to the co-ordinating centre. Please refer to a separate SOP if you are taking part in the sub studies. This is NOT a requirement of the basic study.

7.3.6 Outstanding data/queries
Outstanding data will be monitored by the central research team, who will contact the local study team to chase missing data. Researcher Practitioners/nurses will also be able to monitor their data input via their electronic log in on the website. For further details please see the separate ‘Guide to CRF completion’.
8. Follow up

The central co-ordinating centre at UCL will be responsible for all initial routine follow up.

8.1 Study I (AF)
Follow up will take place at 3, 6, 12, 18 and 24 months by postal questionnaires sent to patient. All follow up information and processes can be found in the Study Protocol.

8.2 Study II (ICH)
Follow up at 6 and 12 months by postal questionnaire sent to patient. All follow up information and processes can be found in the Study Protocol.

The central co-ordinating centre will also contact the GP to inform them of their patient’s participation in the study.

The local research team will be asked to obtain and return further information if patients are readmitted or a new event is notified. The local research team will also be asked to chase up outstanding data if this cannot be obtained by the co-ordinating centre (usually after two reminders).
9. Who funds the study?

The BHF/Stroke Association fund this study, and it has been adopted as a multicentre study by the Stroke Research Network, allowing research practitioners to provide service support for the study, including assisting with recruitment, blood taking, organising MRI and follow-up.

Funding to support the research costs of this locally has been allocated for study I MRI costs.