Does surgery for asymptomatic carotid stenosis reduce the long-term risk of dementia, stroke, death and other important health outcomes? Extended UK post-trial follow-up of the Asymptomatic Carotid Surgery Trial (ACST-1). PHASE 2

Short Title: ACST-1 follow-up study of memory and thinking function

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Study Title: Does surgery for asymptomatic carotid stenosis reduce the long- term risk of dementia, stroke, death and other important health outcomes? Extended post-trial follow-up of the first Asymptomatic Carotid Surgery Trial (ACST-1). PHASE 2

Short Title: ACST-1 follow-up study of memory and thinking function

Ethics Ref: 19/SC/0149 **CAG Ref:** 18/CAG/0195

Study Sponsor: University of Oxford

Date and Version No: 18th February 2019 V2.0

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

Chief Investigator

Prof. Alison Halliday _____ 18/02/2019

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1. SYNOPSIS

Study Title	Does surgery for asymptomatic carotid stenosis reduce the long-term risk of dementia, stroke, death and other important health outcomes? Extended UK post-trial follow-up of the first Asymptomatic Carotid Surgery Trial (ACST-1). Phase 2	
Internal ref. no. / short title	ACST-1 follow-up study of memory and thinking function	
Study Design	This Protocol outlines use of short IQCODE for surviving ACST-1 UK participants who would be contacted for consent to implement the short IQCODE dementia screening questionnaire to be completed by an 'informant' such as a relative or friend of the participant. The results of the IQCODE questionnaire is to supplement extended long-term follow-up through electronic data linkage of National health records for 1601 UK & Swedish ACST-1 participants that has already been completed with analysis ongoing.	
Study Participants	UK participants of ACST-1	
Planned Sample Size	~230 surviving participants of ACST-1	
Planned period of research	2019- 2020	
Qualitative study phase	**Objectives**	**Outcome Measures**
	To provide current cognition information in surviving ACST-1 UK participants to add to the information on dementia provided through the completed data linkage part of the study. The overall study (data linkage and IQCODE) may determine whether carotid endarterectomy reduces the long-term risk of dementia.	Single assessment by telephone via the short form of the **Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).** This is a validated screening assessment questionnaire for dementia completed by a relative or friend (informant) considering any change in cognition from 10 years to date of assessment in the surviving participant

2. ABBREVIATIONS

ACST-1	First Asymptomatic Carotid Surgery Trial
CAG	Confidentiality Advisory Group
CEA	Carotid endarterectomy
CI	Chief Investigator
CMT	Contemporary Medical Treatment
CTRG	Clinical Trials & Research Governance, University of Oxford
GCP	Good Clinical Practice
GP	General Practitioner
HES	Hospital Episode Statistics
HR	Hazard ratio
HRA	Health Research Authority
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly (short form)
K-M	Kaplan Meier
NHS	National Health Service
IQR	Interquartile Range
REC	Research Ethics Committee
SCR	Summary Care Records
SOP	Standard Operating Procedure

3. BACKGROUND AND RATIONALE

Of the 44 million people estimated to have dementia worldwide, 20% have dementia due to disease of the cerebral blood vessels ('vascular dementia'),[1] with a further 20-30% due to a mixture of vascular pathology and Alzheimer's disease.[2] A national consensus document between academics, politicians and public health physicians ('Blackfriars consensus') attributed a significant proportion of dementia to mid-life high blood pressure, hypercholesteraemia, hyperglycaemia, smoking and obesity.[3]

The mediators of the associations between these vascular risk factors and dementia may be stroke,[4] asymptomatic cerebral emboli,[5] cerebral small vessel disease (through changes in white matter, or cerebral hypo-perfusion), or perhaps an effect on the progression of Alzheimer's pathology.[6] Therefore carotid endarterectomy, which reduces the risk of cerebral emboli leading to TIA or stroke, improves

cerebral perfusion, may be of interest because of its potential to reduce the risk of later dementia. (Figure 1).

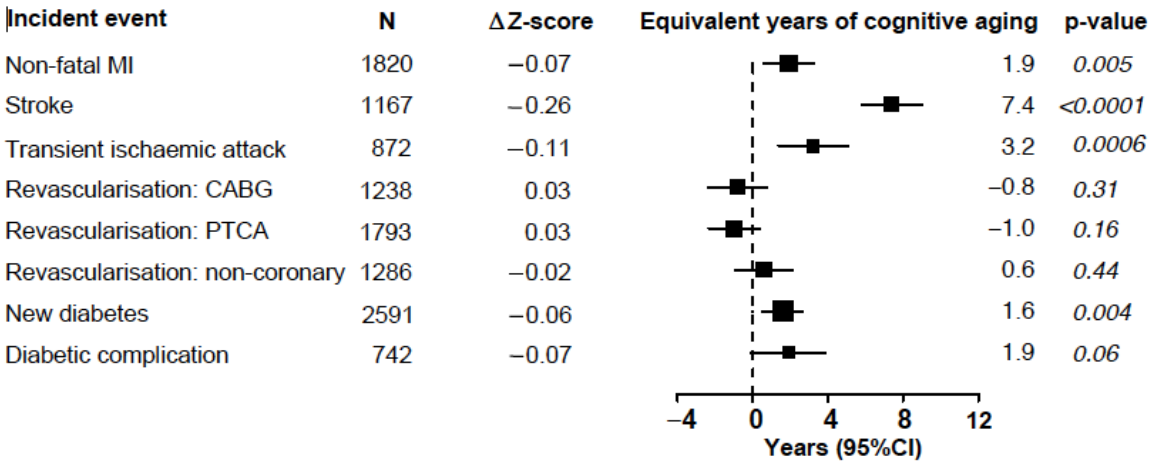

Figure 1: Cognitive aging associated with incident events (Cognitive aging and the incidence of cardiovascular events and diabetes: A meta-analysis of the HPS, SEARCH and HPS2-THRIVE studies, unpublished results, courtesy of Parish et al).

Carotid atheroma can lead to embolization of atheromatous material or thrombus to the ipsilateral hemisphere, and may cause stroke or even chronic cerebral hypoperfusion.[7] In observational studies, there is a modest association between carotid atheroma and impaired cognition, and between asymptomatic carotid atheroma and dementia (>75% stenosis OR for cognitive decline 2.6 [95%CI 1.1–6.3])[78] and several studies have reported improvement in cognition after carotid endarterectomy.[9-11] However, the effects of carotid endarterectomy on long-term cognitive outcomes and dementia have not been assessed in a trial that is: (a) sufficiently large to reduce the chance of random error, and (b) with random allocation of treatment and blinded assessment of outcome to reduce the risk of bias due allocation of treatment based on cognitive abilities or un-blinded measurement of dementia status.

We hypothesise that carotid endarterectomy could reduce the risk of cognitive decline by reducing the risk of stroke and asymptomatic cerebral embolization of thrombus and atheroma.

Dementia is an insidious condition that develops over many years. Therefore, long-term follow-up is necessary to determine the effect of carotid endarterectomy on cognitive decline or dementia. Although new trials of carotid endarterectomy versus contemporary medical management [e.g. 2nd European Carotid Surgery Trial www.ecst-2.com and CREST-2 http://www.crest2trial.org/] may provide answers to this question in the future, it will take many years and for definitive results to emerge. There are no long-term reports of cognitive impairment or dementia from randomised trials of carotid artery stenting or endarterectomy. Therefore, long-term follow-up of a large randomised trial is an appealing method to determine the effect of carotid intervention on later dementia.

Participants were eligible for ACST-1 if: (1) they had severe unilateral or bilateral carotid artery stenosis (generally carotid artery diameter reduction at least 60%, although there was no fixed minimum

percentage); (2) this stenosis had not caused stroke, transient cerebral ischaemia, or any other relevant neurological symptoms in the 6 months before recruitment; (3) no circumstance or condition precluded long-term follow-up; and (4) doctor and participant were both substantially uncertain whether to choose immediate CEA or deferral of any CEA until it seemed needed (e.g. if symptoms occurred).

Phase 1 of the study is now complete (Phase 1 protocol: ethics 16/SC/0406) and CAG (16/CAG/0122) approval for data linkage with National electronic health records held by NHS Digital in England and similar bodies in Scotland, Northern Ireland and Socialstyrelsen in Sweden) is now complete. See study flow chart (Appendix A).

Whilst linked data is a very important resource for the detection of dementia after carotid endarterectomy, it is likely that these datasets under ascertain dementia. Therefore it very important that we use overlapping methods to maximise ascertainment of dementia and significant cognitive impairment. Therefore for this part of the study we propose to follow-up 230 surviving UK participants allocated to carotid endarterectomy or control from the Asymptomatic Carotid Surgery Trial, ISRCTN26156392, (start date 01/04/1993: end date 31/12/2008)[12], measuring rates of dementia or cognitive impairment in those allocated to either CEA plus contemporary medical treatment or to contemporary medical treatment (CMT) alone.

This protocol is the final part of the research where we propose to complement the electronic data linkage already undertaken for dementia diagnosis with imformation from the short IQCODE questionnaire for UK survivors in ACST-1.

Our proposed research is therefore an important part of testing the hypothesis that, by undertaking CEA, cerebral embolization from carotid atheroma may be prevented, reducing later risk of dementia.

Patient numbers and the long follow-up in ASCT-1 may be sufficient to enable us to detect an effect of carotid intervention on dementia more reliably than any previous study. If a reduced risk of dementia is demonstrated in addition to the known reduction in subsequent stroke for participants who had endarterectomy, this would alter the perceived benefits and harms of surgery, and help future decision making for patients with carotid stenosis.

4. OBJECTIVES AND OUTCOME MEASURES FOR PHASE 2

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure
Primary Objective: To provide current cognition information in surviving ACST-1 UK participants to add to the information on dementia provided through the completed data linkage part of the study. The overall study may determine whether carotid endarterectomy reduces the long-term risk of dementia.	A cognitive impairment score to inform diagnosis of dementia and complementing data linkage with electronic health records	Single assessment by telephone via the short form of the **Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).** This is a validated screening assessment questionnaire for dementia by completed by a relative or friend (informant) determining changes in cognition from 10 years to the date of the assessment in the surviving participant.To be implemented Spring- 2019.

TABLE 1 Primary Objective and outcomes of the study: Phase 2

5. STUDY DESIGN

Long-term follow-up of participants from a randomised trial, ACST-1, which randomly allocated 3120 asymptomatic participants from 126 centres in 30 countries, by blinded minimised randomisation, to immediate CEA (median delay 1 month, IQR 0·3–2·5) or CMT with deferral of any carotid procedure. To provide current cognition information in surviving ACST-2 UK participants to complement the dementia information already provided through the data linkage that has already been completed.

For this final part of the study we will contact UK surviving participants (informed through data linkage with all-cause mortality electronic) for permission to undertake the single assessment short IQCODE screening informant questionnaire for the potential diagnosis of dementia (see section 7.2 for further details). Objective measurement of any cognitive decline from the short IQCODE questionnaire results will augment and complement dementia diagnoses from the electronic data linkage.

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

All surviving participants randomised in ACST-1 in the UK will be sent an invitation to participate in this follow-up by asking an informant (relative or friend of the participant) to complete a telephone questionnaire.

6.2. Inclusion Criteria

Randomisation of participants in ACST-1 was performed via Clinical Trial Service Unit (CTSU), University of Oxford with participant details and data stored securely at CTSU.

Inclusion criteria:

1. ACST-1 participant
2. Resident in UK
3. Known to be alive in March 2019
4. Consented to take part and nominated a relative or friend to complete the IQCODE questionnaire

Exclusion Criteria:

None

7. STUDY PROCEDURES

Participants' details from ACST-1 have been retained securely by University of Oxford as per Section 33 of the Data Protection Act (1998). This includes identifiable participant information, at the time of consent for ACST-1 and participant contact details updated if appropriate during the trial.

The Chief Investigator of ACST-1 will ensure that all data protection laws and their approval bodies in the UK will be adhered to as the data processor and that the secure copies of approvals will be made and stored in University of Oxford as data controller.

7.1. Implementation of Short IQCODE screening questionnaire for dementia

1. We will determine first which UK participants are known to be alive with linkage to mortality data already received (this is about 230 of 1069 original UK participants). As this is an elderly cohort, a second check for vital status will be made immediately prior to contact through the NHS Spine - NHS Summary Care Records (SCR).
2. We will also obtain up-to-date address from the NHS Summary Care Record. We will seek permission for access to the NHS Summary Care Record from the HRA Confidentiality Advisory Group (CAG) under the precedent set criteria, category 7, 'validity of consent' where contact details are held with consent but up-to-date details are required.
3. We will initially contact surviving UK participants by post. The mailing will include an invitation to take part with a participant information sheet,consent form and prepaid reply envelope. We would ask for the participant to consent to the proposed follow-up and for their named 'informant' (a relative or friend) to consent to be contacted by telephone to complete the IQCODE questionnaire. A prepaid address envelope will be provided for return of the consent form.

4. As sensitive information will be sent through the post e.g. name, address and participation in a trial, the mail out will be sent to the ACST-1 participant by recorded delivery marked 'private and confidential' as per University of Oxford guidelines. We will make every effort to contact the participants e.g. contacting a nursing home or hospital if they are found to be resident there. When the signed consent form is received in the ACST trials office the study coordinator (registered nurse) would then contact the participant's nominated relative or friend, 'the informant', tol complete with them the short IQCODE questionnaire over the telephone.
5. There will also be a dedicated contact telephone number for participants, the relative or friend, to contact the study coordinator (or the ACST research team in her absence) during office hours to answer any queries or concerns.

   As part of the informed consent, we have also included information on memory loss:

   https://www.alzheimers.org.uk/get-support/publications-and-factsheets/worried-about-your-memory

   https://www.nhs.uk/conditions/dementia/worried-someone-has-dementia/
6. A copy of the consent form would be made and sent back to the participant.
7. The participant will be informed that taking part is entirely voluntary and they can withdraw from the study at any time. There will also be an option on the consent form for the participant to actively decline to takin part in this follow-up and to send this back in the prepaid enevelope provided. They would then be removed from the follow-up IQCODE study database and they would not be contacted again.
8. If there is no response from a participant within 3 weeks after the initial mailing, we will resend the invitation to participate one more time. We will check participants' vital status and address again immediately prior to the posting out of the reminders in case there has been a change since the initial mailing. The reminder letters will also be sent recorded delivery and marked 'private and confidential'.
9. For non-responders to both mailings we will not follow-up further.
10. Data entry of short IQCODE scores into into the study database.

See Study Flow Chart (Appendix A)

7.2. Patient & Public Involvement (PPI)

We have sought Public and Patient Involvement (PPI) panels for the study through the Alzheimer's Society Research Network Volunteers (people living with dementia as relatives, friends or carers) and the Nuffield Department of Population Health (NDPH) Public Panel (eight members).

The study has two Alzheimer's society Research Network Volunteers who are working with us for the duration of the project. We have incorporated their feedback into our design and methodology.

We have also received excellent PPI feedback through the successful application process for an Alzheimer's Society grant (see supporting documents).
The long-term follow-up of ACST-1 has also a web page devoted to the purpose and methodology of the study for lay readers with links to and from the Alzheimer's Society website.
https://acst-2.org/acst1.html
PPI responses were overwhelmingly positive and there were no concerns with the study design.

We are re-contacting participants after a time lapse of up to 10-years but this is an engaged cohort that previously has completed annual questionnaires for up to 15 years. In addition, at present, there is no other randomised cohort of patients who have had treatment of carotid stenosis where extended long-term follow-up is possible to assess the risk of dementia. Prevention of dementia is a current health priority and a new trial would be extremely expensive whilst not making best use of existing information.

7.3. Consent

Participants have already consented to long-term follow-up**.** At the time of recruitment into
ACST-1, participants consented to allow access to their medical records by the trial team on a long-term basis.. Neither the consent form, nor the participant information leaflet put a time limit on the last time that medical records would be inspected (for evaluating the trial intervention).
For this study as part of the long-term follow-up, we will ask surviving UK ACST-1 participants, and their nominated informant (a relative or friend) to sign a consent form to to take part, including telephone contact details and return it to the coordinating centre using the prepaid envelope provided. We would assume capacity to understand what is intended in the study from return of the completed consent form, however this will also be determined by telephone contact with the informant. If there is any doubt over capacity we would not proceed with the questionnaire follow-up.

There is included on the consent form a yes/no option for participation so if they wish they can actively opt-out of this follow-up by selecting 'no' and returning in the prepaid enevelope provided. They would not then in this instance be sent a reminder and would be removed from the IQCODE study database.

Some participants will not, for whatever reason, be able to consent or name an informant. Most would likely in this case to be non-responders to the initial and reminder mailing and their name would be removed from the IQCODE study database, although their data would be kept for the followup into electronic health records.

In some instances it may be that, a relative might contact the study coordinator, having seen the study documents, and if applicable the coordinator may ask for and record any dementia, type (if known) and date of diagnosis of the ACST-1 participant.

7.4. Short IQCODE questionnaire for dementia

The short version of the 'Informant Questionnaire on Cognitive Decline in the Elderly' (IQCODE) is a validated screening tool which measures cognitive decline and is completed by an 'informant' (usually a relative or friend) nominated by the participant.[13,14]

The short IQCODE questionnaire has been widely used in previous postal and telephone studies of cognition and dementia and has been found to be acceptable to participants and informants and therefore we do not expect any significant risks associated with it.

7.5. Randomisation, blinding and code-breaking

There will be no randomisation in use during this long-term follow-up study of ACST-1 participants.

During the enrolment period of ACST-1 (1993-2003), randomisation was through the Clinical Trial Service Unit (CTSU; Oxford, UK) where patients were allocated equally to immediate CEA or deferral of any carotid surgery.

All data processing and analysis relating to outcome ascertainment for this follow-up study will be performed blind to the allocated group.

8. INTERVENTIONS

No further interventions are planned as part of this study.

In ACST-1 CEA was to be done as soon as routinely possible. Surgeons' normal operative techniques were used; shunting during surgery to maintain perfusion was optional, and anaesthetic technique was decided locally. Participants allocated to deferral were not to be treated unless they later developed carotid territory symptoms or some other indication for surgery (or unless the doctor or participant changed their mind). Both groups were to receive appropriate medical care.

9. STATISTICS AND ANALYSIS

9.1. The Number of Participants

Between 1993 and 2003, the ACST-1 trial included 3120 participants from 30 countries (n=1601 from UK and Sweden). Asymptomatic patients with substantial carotid stenosis, considered suitable for surgery were randomly allocated to a policy of immediate carotid endarterectomy plus contemporary medical management versus contemporary medical management alone. Of those allocated immediate endarterectomy, 90% had the procedure within 1 year after randomisation (92% by 10 years); of those

allocated to deferral, 7.5% had the procedure in the first year within the first year (34% by 10 years – as substantial numbers had developed symptoms during follow-up).

The median age of participants recruited to ACST-1 was 69 years, and 34% were women. The mean age of UK surviving participants is now 81 yrs. At the time of the last trial report (2010) median follow-up to 2008 was around 9 years (IQR 7-17 years) but with this study we would achieve an additional 10 years of follow-up.

For the short IQCODE questionnaire, the data linkage with UK National health records (n=1069) suggests the sample size for UK survivors is around 230, through all cause mortality The IQCODE score is subjective, as it comes from an 'informant' questionnaire, but the questionnaire has been validated and should not bias between-group comparisons. We would expect some loss of response rate from survivors, but could reasonably expect this loss to be similar in both groups. Results from the IQCODE scores will add to and complement dementia data from data linkage with National electronic health records. Additionally the IQCODE will prove a useful measurement of current cognition in this previously randomised cohort

9.2. Analysis of Outcome Measures

We will use the information obtained from the short IQCODE questionnaires to supplement the information gathered from National electronic health records.

Our analysis will compare participants in the treated (immediate CEA) group with those in the control group (deferred), as defined by the ACST-1 randomised allocation i.e. intention-to–treat analysis.

9.3. Planned analyses, tables and figures

The short IQCODE scores will supplement data obtained in the data linkage with electronic health records, chiefly through the detection of cognitive decline and the likelihood of dementia.

The main outcomes for the study (electronic data linkage and IQCODE follow-up) will be long-term rates of proven cognitive decline and proven dementia amongst those allocated immediate CEA plus medical therapy versus those allocated medical therapy alone. Cox proportional hazards will be used with Kaplan-Meier life-table analysis by "intention to treat". The analysis will compare dementia rates between treatment groups.

We will record IQCODE scores whether positive or negative for cognitive decline. The IQCODE score is calculated by adding the result for each question (Much improved = 1; A bit improved =2; Not much change

=3; A bit worse =4; Much worse =5) divided by the number of questions (16). The cut-off point for sensitivity and specificity for significant cognitive decline is $\geq$ 3.6.

10. DATA MANAGEMENT

10.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, appropriate regulatory bodies and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

10.2. Data Recording, Record Keeping and Data Security

CTSU researchers are experienced in handling confidential and participant sensitive data and have appropriate training in information governance.

The CTSU servers are protected against unauthorised external access by an appropriate strength firewall. Access to patient identifiable information is protected by the appropriate authentication procedures (user IDs and passwords.) Authentication is only given to personnel with a need to access the required data. Only personnel involved in the long-term follow-up study for ACST-1 study (processing and analysing data) will have access to this data. CTSU has a Corporate Level Security Policy that has been fully adopted by management and will apply fully to the long-term follow-up study. The data protection Registration Number is Z575783X.

Security Arrangements for the storage of data

CTSU is a secure building with access limited to employees and authorised visitors. The study servers are located in a climate controlled secure enclosure to which only system support staff have access. Offices will be routinely locked when not in use. Password protected screen savers will be routinely employed. IT equipment and media will be used within the manufacturer's environmental specifications. The data will be stored on secure servers at the Clinical Trial Service Unit (CTSU), University of Oxford. CTSU computers are in a secure building protected by a firewall. All CTSU employees agree to maintain confidentiality at all times as part of their employment contract with the University of Oxford and all University departments will have the similar clauses in their contracts. Access to study data will require a username and password combination and will be audited. Study staff only have access to data appropriate to their role. CTSU is subject to successful audit of computer security and similar audits.

11. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

12.2. Guidelines for Good Clinical Practice

The Chief Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

12.3. Approvals

The protocol, consent, participant information sheet, and proposed IQCODE questionnaire will be submitted to an appropriate HRA Research Ethics Committee (REC) the Confidentiality Advisory Group (CAG) and host institution for written approval.

The Chief Investigator will submit and, where necessary, obtain approval from the above for all substantial amendments to the original approved documents.

12.4. Reporting

The Chief Investigator shall submit once a year or more frequently on request, an annual progress report to the REC Committee, CAG, funder and Sponsor. In addition, an end of study notification and final report will be submitted to the same parties.

12.5. Participant Confidentiality

All information collected will be kept strictly confidential. The names of the interviewed participants and previous ACST-1 participants will only be available to the research staff via their unique study number. All study documentation including Consent forms will be kept in locked filing cabinets in a secure room and will be destroyed after 25 years. Files containing electronic data will be password protected and stored on a secure network and these files will be destroyed after 25 years. The Chief Investigator and research staff will be allowed access to the secure network and individuals will not be identified in any publications.

12.6. Other Ethical Considerations

Purpose and design

The prevention of dementia is a current public health priority. This research aims to address the question whether or not carotid endarterectomy in middle age may lead to a reduction in risk of dementia or stroke in the longer term. This question is worth answering. If we demonstrate that treatment that lower the risk of stroke also lower the risk of dementia, then this will increase the benefit of these treatments. In the long-term, this may lead to a reduction in the numbers of people who develop dementia over their lifetime and in the short term, it could help patients and their doctors make better decisions about their treatment.

This information isdifficult to obtain. It might come from: (i) very large, expensive long-term randomised trials but these are complex (and would require many years to undertake); (ii) from observational studies comparing risk of dementia in participants offered endarterectomy with those who are not; however a problem with 'confounding by indication' would then exist, as important differences between people who do and do not take medication, or have interventions, probably influence their risk ofstroke, which is the current indication for this surgery; or (iii) the very long-term follow-up of older randomised controlled trials, with large numbers of patient-years data, as we propose.

CTSU has, with patient consent securely held participant information from the original ACST-1 trial.

Implementing the short IQCODE screening questionnaire for UK participants will reliably complement the information on cognitive decline and dementia diagnosis already provided from the National electronic health records.

Risks, burdens and benefits

There are no direct benefits to the participants taking part in this study.

The study does not involve any additional physical risk to the participants and is one single questionnaire only. We are aware of the sensitive nature of implementing the IQCODE questionnaire in an elderly population but in our experience the questionnaire is acceptable to participants and informants and therefore we do not expect any significant risks associated with it.

13. FINANCE AND INSURANCE

13.1. Funding

Supported by an Alzheimer's Society project grant, Oxford Biomedical Research Centre (OBRC) and CTSU core funding.

13.2. Insurance

The University of Oxford maintains Public Liability and Professional Liability insurance which will operate in this respect.

14. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will also acknowledge the original funders of the ACST-1 trial. Authorship will be determined in accordance with the ICMJE guidelines and will be on behalf of the ACST-1 collaborative group. Other contributors will be acknowledged, particularly ACST-1 participants.

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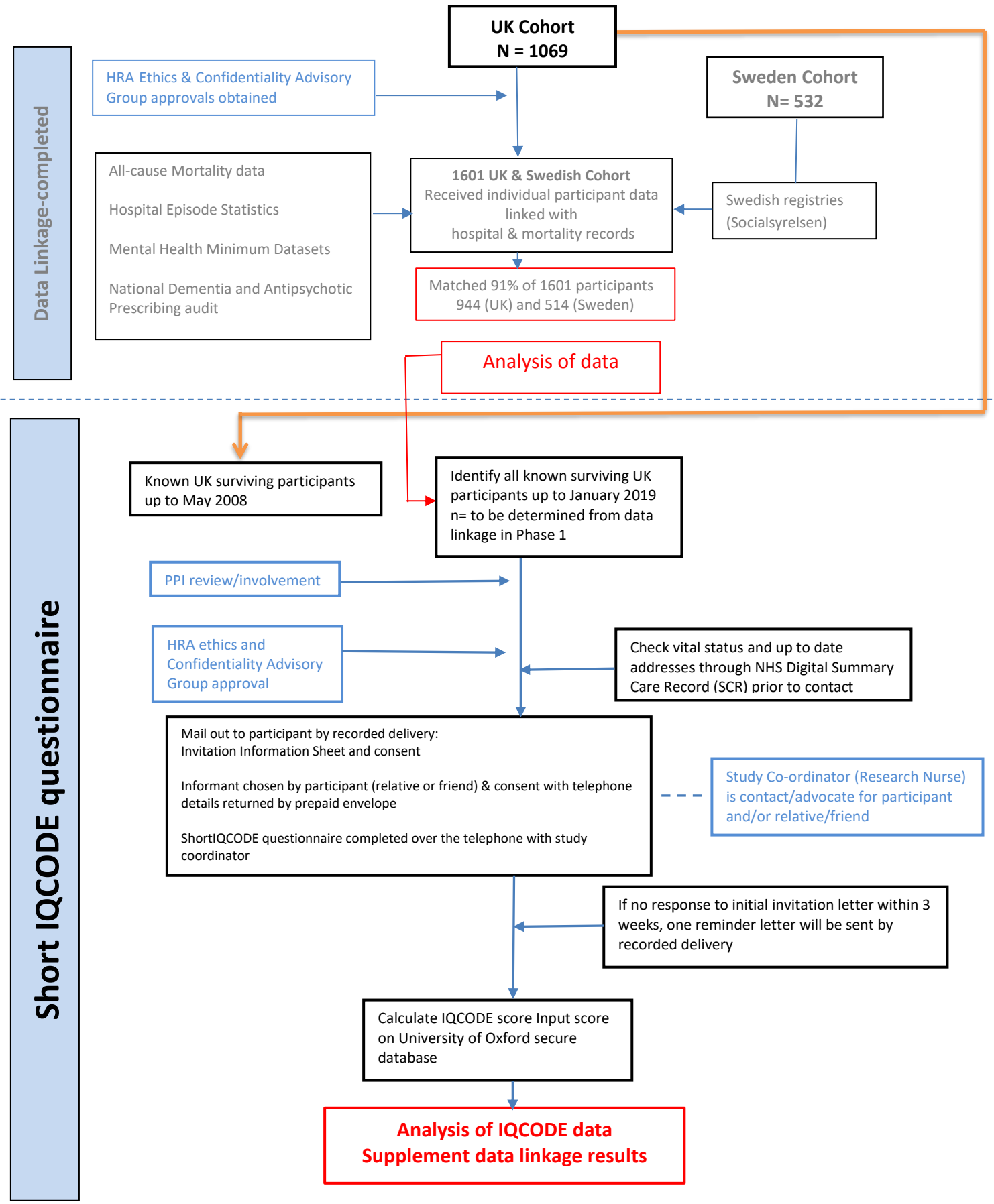
APPENDIX A: Flow Chart for use of Short IQCODE Questionnaire



APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	V2.0	18 February 2019	UK Collaborators on project (listed on page 1 of the protocol)	Changes to methodology from recommendations following Ethics and CAG review

List details of all protocol amendments here whenever a new version of the protocol is produced.