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 Asymptomatic Carotid Surgery Trial (ACST-1).

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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).

Ethics Ref: to be applied for after sponsorship approval

Date and Version No: 18th November 2016 V6.2

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 _____**18/11/2016**

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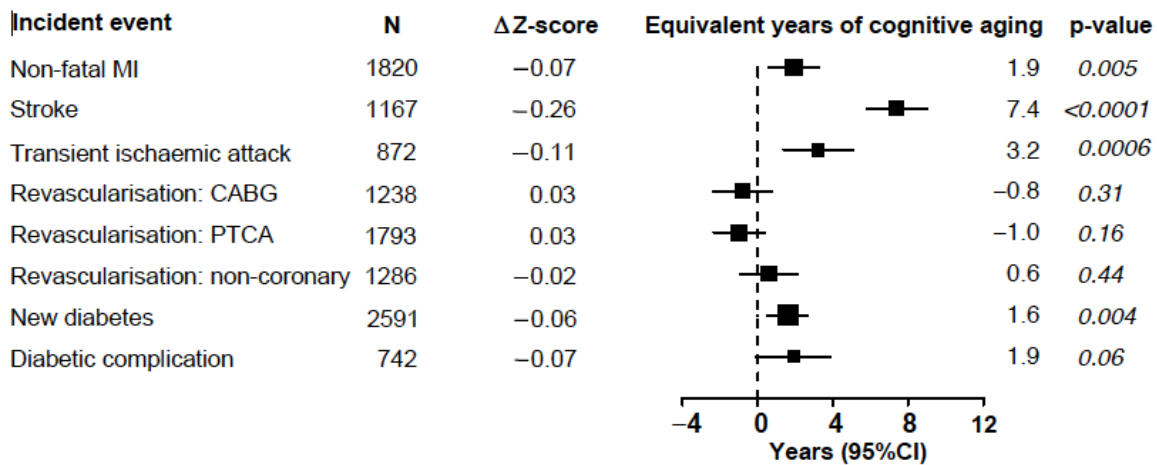| Study Title	Does surgery for asymptomatic carotid stenosis reduce the long-term risk of dementia, stroke, death and other important health outcomes? Extended post-trial follow-up of the first Asymptomatic Carotid Surgery Trial (ACST-1).	
Internal ref. no. / short title	PID: 12048/Extended post-trial follow-up of the Asymptomatic Carotid Surgery Trial (ACST-1)	

Study Design	Mixed methods study composed of two phases:
	
	    1) Extended post-trial follow up of a randomised trial via electronic health records and other routinely collected data.
	    2) Pre-specified relatives/friends of participants completing IQCODE dementia screening questionnaire on the participants. Living participants would be contacted for consent.
	
	This protocol outlines the 2 phases of the project but a detailed amendment of the protocol will be submitted for phase 2 once phase 1 has been substantially completed.	

Study Participants	UK and Swedish participants in ACST-1	
Planned Sample Size	1,601	
Planned period of research	5 years 2016-2020 (data acquisition will span 1993-present day)	
1st Phase of project	**Objectives**	**Outcome Measures**
1	To determine whether carotid endarterectomy reduces the long-term risk of dementia, after accounting for the competing risks of MI and stroke and deaths from other causes.	Dementia measured in ACST-1 records, hospital episode, death and other health records up to present day.
2	To determine whether carotid endarterectomy reduces the long-term risk of stroke (10 years +).	Incident stroke measured in ACST-1 and electronic health records measured up to present day.
3	To determine cause specific mortality in ACST-1 in UK and Sweden cohorts.	Cause-specific mortality recorded in national death registers up to present day.
4	To determine rates of hospitalisation, and other competing risks of stroke or dementia.	All HES (or Swedish equivalent) and death records to the present day.
2nd Phase of project		
1	To determine whether carotid endarterectomy reduces the long-term risk of dementia measured by completing IQCODE validated screening test questionnaire. This is completed by a relative or friend considering any change in cognition from 10 years ago to date in the living participant. In those who have died assessment will be made on cognition status before death.	Single assessment via IQCODE screening test questionnaire for dementia.

1. SYNOPSIS

2. ABBREVIATIONS

ACST-1	First asymptomatic carotid surgery trial
CMT	Contemporary Medical Treatment
CI	Chief Investigator
CEA	Carotid endarterectomy
CRF	Case Report Form
CONSORT	Consolidated Standards of Reporting Trials
CTRG	Clinical Trials & Research Governance, University of Oxford
GCP	Good Clinical Practice
GP	General Practitioner
HES	Hospital episode statistics
HSCIC	Health and Social Care Information Centre, England
HR	Hazard ratio
ICD	International Classification of Diseases
ICF	Informed Consent Form
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
ISD	Information and Statistics Division, NHS Scotland
K-M	Kaplan Meier
NHS	National Health Service
NRES	National Research Ethics Service
OR	Odds ratio
PI	Principal Investigator
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
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 the effect of

carotid endarterectomy, which reduces the risk of cerebral emboli leading to TIA or stroke, improves cerebral perfusion, and potentially reduces the risk of dementia, is of great interest. (See Figure 1)

Incident event	N	ΔZ-score	Equivalent years of cognitive aging	p-value
Non-fatal MI	1820	−0.07	1.9	0.005
Stroke	1167	−0.26	7.4	<0.0001
Transient ischaemic attack	872	−0.11	3.2	0.0006
Revascularisation: CABG	1238	0.03	−0.8	0.31
Revascularisation: PTCA	1793	0.03	−1.0	0.16
Revascularisation: non-coronary	1286	−0.02	0.6	0.44
New diabetes	2591	−0.06	1.6	0.004
Diabetic complication	742	−0.07	1.9	0.06

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).

Successful carotid endarterectomy (CEA) in asymptomatic patients halves the risk of future stroke, although the absolute risk reduction achieved is moderate.[7] Carotid atheroma can lead to embolization of atheromatous material or thrombus to the ipsilateral hemisphere, and may cause chronic cerebral hypoperfusion.[8] 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]).[8,9] There are a large number of small observational studies, some of which have reported improvement in cognition after carotid endarterectomy.[10–12] 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)] may provide answers to this question in the future, it will take many years and it may be harder for these studies to detect a proportional difference in dementia incidence because of better background management of cardiovascular risk. 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 very large randomised trial is an appealing method to determine the effect of carotid intervention on later dementia. We propose to follow-up 1601 participants allocated to carotid endarterectomy or control from the Asymptomatic Carotid Surgery Trial, ISRCTN26156392, (start date 01/04/1993: end date 31/12/2008)[7], to measure rates of dementia or cognitive impairment amongst those allocated to either CEA plus contemporary medical treatment versus contemporary medical treatment (CMT) alone.

Our proposed research is therefore an important test of the hypothesis that preventing cerebral emboli reduces the long-term risk of dementia.

ASCT-1 may be able to detect an effect of carotid intervention on dementia more reliably than any previous study. And, if it demonstrates a reduced risk of dementia in addition to a reduction in subsequent stroke in ACST-1 participants who had had endarterectomy, this would alter the perceived benefits and harms of surgery, and aid clinical decision making for patients with both asymptomatic and symptomatic carotid stenosis.

4. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure
1st Phase of project		
To determine whether carotid endarterectomy reduces the long-term risk of dementia	Dementia measured in electronic health records	Dementia measured in ACST-1 records, hospital episode, death and other health records up to present day
To determine whether carotid endarterectomy reduces the long-term risk of stroke (10 years +)	Incident stroke measured in electronic health records	Incident stroke measured in ACST-1 and electronic health records measured up to present day
To determine cause specific mortality in ACST-1 in UK and Sweden cohorts	Death recorded in national death registers	Cause-specific mortality recorded in national death registers up to present day
To determine the long-term rates of hospitalisation, and other competing risks for stroke or dementia	Hospitalisations and associated ICD-10 codes	All HES (or Swedish equivalent) and death records to the present day
2nd Phase of project		
To determine whether carotid endarterectomy reduces the long-term risk of dementia measured by completing IQCODE validated screening test questionnaire. This is completed by a relative or friend on the participant's behalf considering any change in cognition from 10 years ago to date in the living participant. In those who have died assessment will be made on cognition status before death.	Likelihood of dementia scored and used to augment dementia diagnosis from HES	Single assessment via IQCODE screening test questionnaire for dementia

TABLE 1 Objectives and outcomes of the study: Phase 1 and 2

5. STUDY DESIGN

Long-term follow-up of participants from a randomised trial using electronic health records. ACST-1 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.

This is a two-phase research proposal. We propose to follow-up 1601 participants in the UK and Sweden only, where long-term follow is possible with electronic records.

Phase 1: to link the UK participants from ACST-1 to data from electronic health records accessed via Health Episode Statistics (HES) and death records from HSCIC. We will gain information on the number of participants who have died and those coded for incident stroke, death and dementia. Data linkage will be made with corresponding registries for Swedish participants.

Phase 2: to contact participants and/or their relatives (named in the original consent for the trial) for completion of the IQCODE screening questionnaire for the potential diagnosis of dementia (see section 7.2 for further details)A detailed amendment of the protocol for phase 2 will be submitted to CTRG once phase 1 is underway. (see appendix A)

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

All participants randomised in ACST-1 in the UK and Sweden will be included in the post-trial extended follow-up study.

6.2. Inclusion Criteria

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.

For this study, all participants in the UK (1069) and Sweden (532) will be eligible for follow-up for data linkage in phase 1.The outcome of phase 1 will inform the point of contact of whether to contact participants if alive or if deceased their relative/friend in Phase 2 for both UK and Sweden.

Data Processing Agreement

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

7. STUDY PROCEDURES

Participant's 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, in addition to the contact details of two friends/relatives that the participant was asked to provide at the time of consent for ACST-1.

With the necessary approvals, we will follow up participants using outcomes in linked electronic health data through deterministic (where NHS numbers are available) and probabilistic linkage. Trial participants in the UK were followed for mortality with linkage to the General Registry Office, and this linkage will be used to inform the linkage to hospital episode statistics.

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

1st Phase of Research

7.1. Linked health data

We will measure three outcomes in linked electronic health data: dementia, stroke and death. In the UK, we will link UK participants with the following datasets:

1. Hospital episode statistics (HES), mental health and death statistics in England held by the Health and Social Care Information Centre
2. Scottish Morbidity Record (SMR) and death statistics in Scotland held by Information and Services Division, of NHS Scotland
3. Hospital activity statistics in Northern Ireland, Honest Broker Service, Northern Ireland Statistics and Research Agency (www.hscbusiness.hscni.net).

We will define stroke, myocardial infarction and dementia as follows:

Stroke: Admissions or death where stroke is recorded with the following:

 ICD-9 codes: I433, I434, or ICD-10 codes: I63, I64.[13]

Dementia: Hospitalisations or death, where dementia is recorded any position: episodes with the relevant ICD-10 and ICD-9 codes for dementia:

ICD-10: F01 (vascular dementia), F02 (other dementias), F03 (unspecified dementias), or G30 (Alzheimer's disease)

ICD-9: 290.1-290.4 – unspecified dementia, 331.0 (Alzheimer's dementia), 331.1 (Frontotemporal dementia), 331.2 (Senile degeneration), 331.9/294.9 (unspecified dementia)]; or where a patient is under the care of a mental health care team that predominantly cares for patients with dementia (see Mental Health minimum dataset below).

Myocardial infarction: Admissions or deaths: ICD-10 codes: I21-23, I46 (cardiac arrest)

Carotid endarterectomy or stenting: We will determine which patients have had a carotid endarterectomy with the ICD-9: 38.12 (carotid endarterectomy) and 00.40 (procedure on single vessel)

and ICD-10 03BK, O3BL (procedures on left or right internal carotid artery), ICD-9 39.50 (angioplasty or atherectomy of other non-coronary vessels), 00.61 (percutaneous angioplasty or atherectomy of precerebral vessel(s)), 00.63 (percutaneous insertion of carotid artery stent(s), 00.64 (percutaneous insertion of other precerebral (extracranial) artery stents))

In addition, we will use additional resources in the HSCIC datasets from England to define dementia:

- Mental health minimum dataset (under the care of a Young Onset Dementia team (A12), Memory Services/Clinic (use in relation to older people) (A16), Older People Community Mental Health Team – Organic (A17)
- Discharge destination to nursing home (although this may be a low quality surrogate marker for a diagnosis of dementia)
- Care Cluster Groups 19, 20, 21

Further datasets using ICD codes will be used to define stroke, myocardial infarction and dementia will be:
- Inpatient datasets
- Outpatient dataset
- Accident and emergency dataset
- Critical care dataset

In Sweden, we will use electronic health records with national datasets stored in the Socialstyrelsen, including prescriptions, death records, the national dementia register and hospital episode statistics.

Outline of Phase 2

7.2.   IQCODE screening questionnaire for dementia
We estimate 80% of participants may have died by 2016. By linking participants to electronic health records we can ascertain first how many are alive and how many have had a stroke or died. In our Phase 2 ethics amendment PPI groups from our funders (the Alzheimer's Society, Oxford University BRC and James Lind Alliance) will inform the optimal methods of contact with the living participants/relatives. We will ensure that this is compliant with the principles of conducting research with bereaved relatives using published guidelines.[14]

7.3. IQCODE Dementia questionnaire
At the time of recruitment, ACST-1 participants gave their consent for long-term follow-up, their contact details, and the details of two relatives or friends who could also be contacted for follow-up.

Phase 1 will identify those who have died. A participant information letter, including the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) questionnaire and consent, and a copy of the original ACST-1 patient consent will then be sent to the participant or to the relatives/friends if the participant had died.

The participant or relative/ friend will be informed about the purpose of the post-trial follow-up. The letter will explain what will happen if they decide to participate in this research study. It will be made clear in the written information provided that participation is completely voluntary. A self-addressed envelope will be provided for the completed questionnaire and consent to be returned.

The IQCODE is a validated screening tool, to assess cognition and is completed by the participant's relative/friend on their behalf.[15] A score of 3.6 or higher indicates cognitive impairment.

A telephone number for the study coordinator will be provided, in case assistance is needed to complete the form. Participants are free to withdraw from this research at any time during the study without giving a reason.

Previous experience with the IQCODE questionnaire suggests that informants find it reasonable and acceptable and we do not expect any significant risks associated with it. However, relatives /friends may need to ask questions about the study and may wish to discuss their responses to the questionnaire related to the health of the participant, especially in cases where the participant has died. There will be a dedicated phone number provided which will be manned by trained clinical research staff. They will give sufficient time to discuss such concerns sensitively.

A follow-up reminder letter will be sent if the questionnaire has not been returned within 1 month. Otherwise there will be no further contact.

If a score from the IQCODE suggests a surviving participant has cognitive impairment, we would contact the GP (but only with prior consent) to inform them of this finding to facilitate ongoing investigation/management.

7.4. Consent for this study (Phase 1 and Phase 2)

For the Phase 1 linkage study, we will not approach participants for further consent, but will seek permission of the Confidentiality Advisory Group of the Health Research Authority of NHS England (CAG 251) and the equivalent bodies in NHS Scotland and Northern Ireland. We will also inform local Stroke Association groups that we are performing the study.

We believe this is justified for the following reasons:

1. **Approaching participants for consent would be impracticable and lead to unreliable conclusions.**
   Many participants had died by last follow up in 2010: 486 out of 1069 UK participants had died and 188 participants out of 532 in Sweden (a total of 70% of participants over 75 years, and 40% under 75 years). We estimate that 80% of the randomised participants are likely to have died by 2016. Approaching living participants for consent would lead to such a bias in ascertainment that any conclusions from the linkage study would be unreliable (previous studies have demonstrated that non-responders are more likely to have dementia which would further bias this study.)
2. **The topic is an important one: the prevention of dementia is a current public health priority.**
   Any study that seeks to answer this question would need to be a sufficiently large trial and would be extremely expensive as well as not making the best use of existing information. Three PPI panels all agreed that this was a very important research question.
3. **We have consulted Patient and Public Involvement (PPI) panels.**
   The overwhelming majority of participants agreed that this use of data is justified and none expressed strong opposition to this research proposal providing that appropriate measures were in place to protect confidentiality. We have also received an Alzheimer's Society grant with excellent PPI feedback (see supporting documents).
4. **Participants have already consented to long-term follow-up.**
   At the time of recruitment, participants consented to allow access to their medical records by the trial team and yearly thereafter. Neither the consent form, not the information leaflet put a time

    limit on the last time that medical records would be inspected (for the purpose of evaluating the trial intervention).

5.   For the IQCODE questionnaire, we would want to ascertain how many participants have died by requesting a consent exemption (CAG 251 HSCIC), so not to cause undue distress to relatives/friends by contacting them unnecessarily. We know that 45% of participants had already died by 2008 and we estimate that this could be 80% by 2016.

7.5. Randomisation, blinding and code-breaking

There will be no randomisation in use during this study.

By use of minimised randomisation, the Clinical Trial Service Unit (CTSU; Oxford, UK) allocated patients equally to immediate CEA or deferral of any carotid surgery. Collaborating doctors telephoned or faxed the patients' identifiers and characteristics to the CTSU. Once these data were entered the patient was irrevocably in the trial, and the CTSU computer then generated a random allocation. All data processing and analysis relating to outcome ascertainment 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 randomly allocated 3120 participants with asymptomatic substantial carotid stenosis, judged suitable for surgery to a policy of immediate carotid endarterectomy plus medical management versus medical management alone until symptoms developed. Of those participants allocated to immediate endarterectomy, 92% had the procedure by 10 years after randomisation (90% within 1 year); of those allocated to deferral, 34% had the procedure by 10 years (7.5% within the first year). There is therefore some difference between the randomly allocated groupings in timing of endarterectomy and the proportion of participants who eventually had the procedure. It was expected that some of those allocated deferral might eventually require surgery.

In both the UK and Sweden, it is possible to link trial participants with national hospital admission records, and death records. Therefore, we will follow-up those participants who were from the UK (1,069) or Sweden (532). Baseline characteristics of participants from both countries were well balanced between randomised groups and are broadly representative of the rest of the trial.

In Scottish records, the hospital episode statistics have an approximately 50% sensitivity for dementia, which may be higher in admissions to psychiatric units and death certification (71%). The mean age of participants recruited to ACST-1 was 67 years, and 34% were women. The mean age of surviving participants is now 85 yrs. At the time of the last trial report (2010) mean follow-up was around 10 years (range 7-17 years) but with this study we would achieve an additional 10-20 years (mean 15 years) of follow-up.

We aim to follow up a total of 1601 participants. Assuming a 30% risk of diagnosed dementia (*Parish et al* unpublished data from meta-analyses of HPS, Search and Thrive) or other evidence of impaired cognitive function (which is plausible given the high cerebro-vascular risk population in ACST-1) and that our approaches are able to detect 50-60% of these, this would give about 265 cases detected. On this basis our study would have almost 90% power to detect a 30% reduction in dementia (at $p<0.05$) and about 70% power to detect a 25% reduction.

9.2. Analysis of Outcome Measures

For each participant, we will define the start date of dementia as the first record of dementia in any one of the linked datasets. Whilst dementia is an insidious process, and the date of onset cannot reliably be determined in electronic health records, Cox proportional hazards are a common method of analysis in dementia incidence studies, and are more easily explained than more complex statistical models.

Our analysis will compare participants in the treated group with those in the control group (deferred), defined by the ACST-1 randomised allocation.

9.3. Planned analyses, tables and figures

The main outcomes will be long-term rates of dementia, stroke and death amongst those allocated immediate CEA plus medical therapy versus those allocated medical therapy alone. Analyses will be by "intention to treat" and results will be displayed using Kaplan-Meier survival analyses. Log rank analyses will compare stroke rates and Cox-regression analysis will compare dementia rates between both treatment groups.

Events will be reviewed, centrally adjudicated (where necessary) and entered into the secure database held by Clinical Trial Service Unit (CTSU) (see 10.2) by members of the study team who are blind to original treatment allocation. A data analysis plan will be published prior to any un-blinded analyses via an open-access journal or on the CTSU website.

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

The data will be stored at the Clinical Trial Service Unit (CTSU), Richard Doll Building, University of Oxford. CTSU has successfully acquired analysed and appropriately stored data from HES for previous

large long-term studies such as HPS2-THRIVE and HPS3-REVEAL. 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.

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 form, information sheets and any proposed PPI material will be submitted to an appropriate Research Ethics Committee (REC), the Confidentiality Advisory Group (CAG) and host institution(s) for written approval.

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

12.4.   Reporting

The Chief Investigator shall submit once a year throughout the study or 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 Clinical Research Forms (CRFs) 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 also 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

Ethical issues to consider

The main ethical issues to be considered are as follows:

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 leads to a reduction in the risk of dementia, stroke or death in the longer term. This question is worth answering. If we demonstrate that treatments 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 make better decisions about their treatment.

This information is very hard to come by. It might come from: (i) very large, expensive long-term randomised trials but these are difficult (and would require many years to do.); (ii) from observational studies comparing the risk of dementia in participants who are offered endarterectomy with those who are not; the problem with these studies is 'confounding by indication', that is to say there are important differences between people who do and do not take medication, or have interventions, that probably also influence their risk of dementia; or (iii) the very long-term follow-up of older randomised controlled trials, as we propose.

CTSU has securely held participant information from the original ACST-1 trial with patient consent. All participants in the UK (1069) and Sweden (532) in Phase 1 will be eligible for follow-up data linkage in. The outcome of phase 1 will inform the point of contact for Phase 2.

For the linkage study, we will not approach participants for further consent, but will seek permission of the Confidentiality Advisory Group of the Health Research Authority of NHS England (CAG 251) and the equivalent bodies in NHS Scotland and Northern Ireland. As many of the randomised participants will have died by 2016, approaching survivors for consent would lead to such a bias in ascertainment that any conclusions from the linkage study would be unreliable. (Previous studies have demonstrated that non-responders are more likely to have dementia which would cause our study to have biased results).

For those who remain alive there is a process for dissent if they do not want their study data linked as proposed. Contact details for the process of withdrawal can be found on the current ACST-2 website www.acst-2.org, the Stroke Association forum www.stroke.org.uk/forum, and the Alzheimer's Society www.alzheimers.org.uk. The ISRCTN registry www.isrctn.com will be updated to include the process of dissent.

Phase 2 (IQCODE questionnaire) is important for this research question as the results of the dementia screening questionnaire will reliably validate the information provided from HES results and the other data sources used.

Risks, burdens and benefits

There would not be any direct benefit to the participants taking part in this study.

The study does not involve any additional physical risk to the participants. We believe that this study does not provide any risk in the loss of anonymity to the participants.

13. FINANCE AND INSURANCE

13.1.   Funding

Supported by an Alzheimer's Society project grant and CTSU core funding

13.2.   Insurance

The University of Oxford as study sponsor has a specialist insurance policy in place renewed annually which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

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.
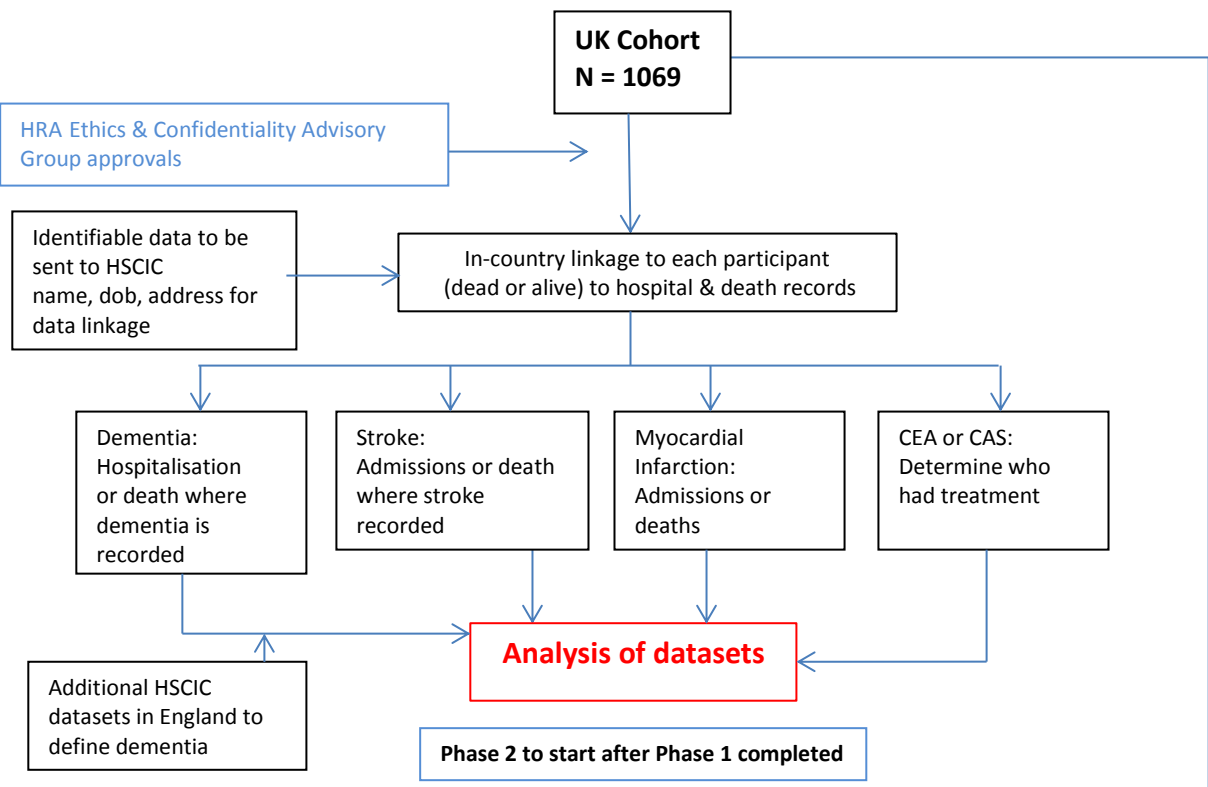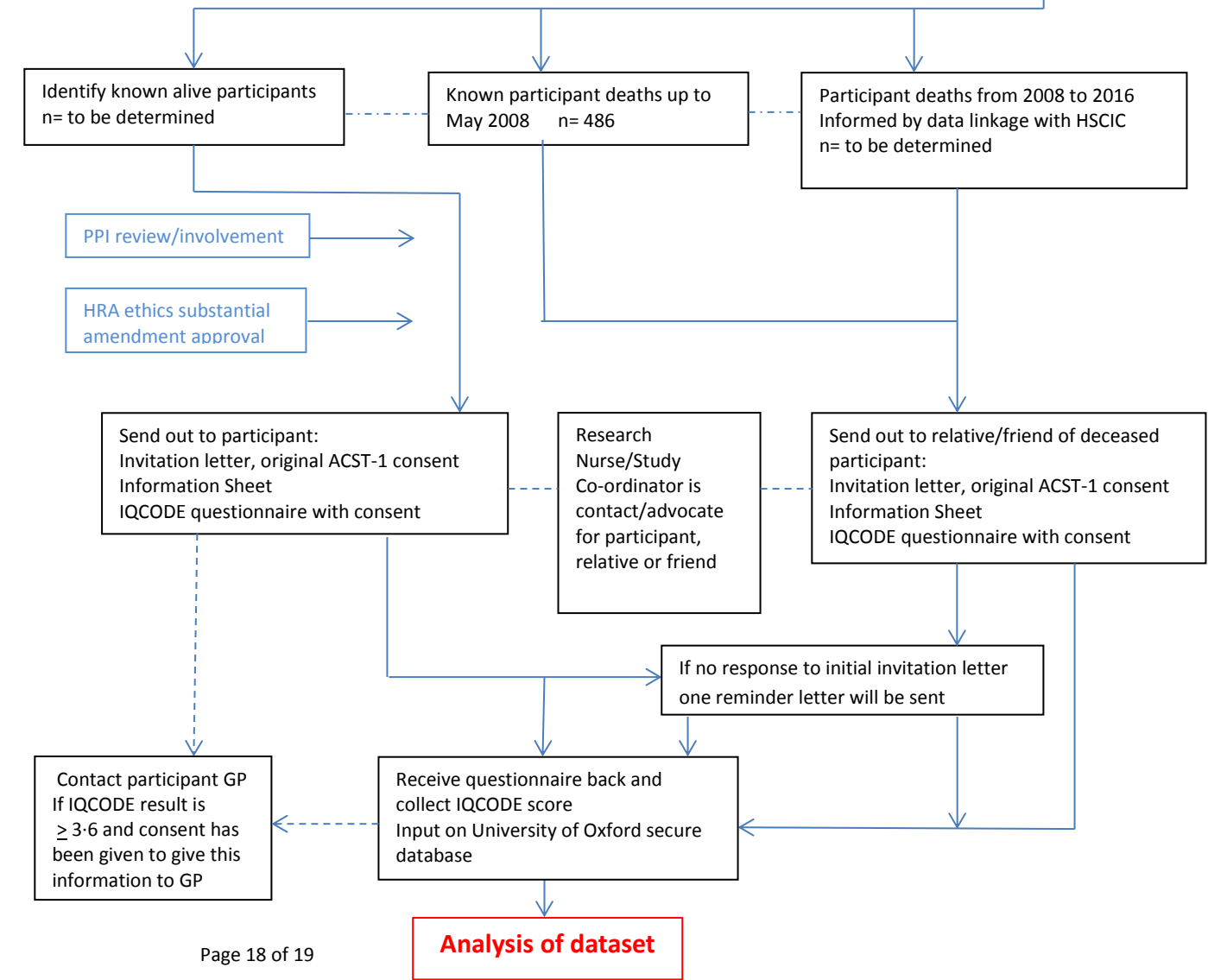
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16. APPENDIX A: Study Flow Chart for UK Phase 1-Data Linkage & Phase 2- IQCODE questionnaire

Phase 1: Data Linkage

UK Cohort
N = 1069

HRA Ethics & Confidentiality Advisory Group approvals

Identifiable data to be sent to HSCIC name, dob, address for data linkage

In-country linkage to each participant (dead or alive) to hospital & death records

Dementia: Hospitalisation or death where dementia is recorded

Stroke: Admissions or death where stroke recorded

Myocardial Infarction: Admissions or deaths

CEA or CAS: Determine who had treatment

Additional HSCIC datasets in England to define dementia

Analysis of datasets

Phase 2 to start after Phase 1 completed

Phase 2: IQCODE questionnaire

Identify known alive participants n= to be determined

Known participant deaths up to May 2008   n= 486

Participant deaths from 2008 to 2016 Informed by data linkage with HSCIC n= to be determined

PPI review/involvement

HRA ethics substantial amendment approval

Send out to participant: Invitation letter, original ACST-1 consent Information Sheet IQCODE questionnaire with consent

Research Nurse/Study Co-ordinator is contact/advocate for participant, relative or friend

Send out to relative/friend of deceased participant: Invitation letter, original ACST-1 consent Information Sheet IQCODE questionnaire with consent

If no response to initial invitation letter one reminder letter will be sent

Contact participant GP If IQCODE result is ≥ 3·6 and consent has been given to give this information to GP

Receive questionnaire back and collect IQCODE score Input on University of Oxford secure database

Analysis of dataset

17. APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	V 6.2 18th Nov 2016		Alison Halliday, Mary Sneade and the collaborative group	Page 1/19: Change of Collaborator in Sweden, Page 15/19, Section 12.6: added paragraph to refer to process of dissent for Phase 1, data linkage

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