The Active Brains Study Main Trial

PROTOCOL

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Lay Summary

We have made a new website called ‘Active Brains’ which aims to help older adults to look after their brain and body health. The aim is to help prevent problems with things like remembering, concentrating or reasoning (known as cognitive decline). The website will help older adults to make simple changes such as getting more active, playing brain training games and finding ways to eat more healthily.

This research will test how well the website works. We will be testing the website in two groups of people: 1) older adults with signs of cognitive decline, 2) older adults without any cognitive decline. Members of both these groups of people will be randomly put into one of three study groups: 1) care as they usually receive it from their GP practice, or 2) the Active Brains website, or 3) the Active Brains website plus a bit of support from a trained person (over the phone or by email). The study will last for five years. At the end of the first year we will compare people’s thinking (cognitive) skills in each of the three study groups. After five years we will compare the three study groups again and also check how many of the people in each study group went on to be diagnosed with dementia.

The findings of this study will mean that we can tell whether the Active Brains website helps the people who use it to avoid or delay cognitive decline.

Background

The prevalence of dementia is estimated to be between five and seven percent amongst those aged over 65 [1, 2] and although it has fallen slightly in the UK over the past 20 years [2] the absolute number of cases is likely to increase due to people living longer [3]. Over the next 30 years [3] 10-15 million cases are predicted in Europe, and more than 100 million in the world by 2050 [3, 4], with approximately 43% of prevalent cases needing high level care (equivalent to nursing home care)[3]. It has been estimated that if interventions could delay both disease onset and progression by a modest 1 year, there would be nearly 9.2 million fewer worldwide cases of the disease in 2050, with nearly the entire decline attributable to decreases in persons needing a high level of care [3].

Cognitive impairment in the absence of dementia is more common, but prevalence estimates vary considerably depending on definitions [5]. Mild Cognitive Impairment (MCI) is the most commonly used definition, conventionally defined as a deterioration in at least one non-memory cognitive domain in addition to memory impairment, without severe functional

impairment or loss of instrumental activities of daily living [5, 6]. The incidence of MCI is high in the over 65s [7-9] ranging from 51 to 76.8 per 1,000 person-years. There is no good evidence yet that screening for MCI is either effective or cost-effective [10], but a systematic review of cohort studies suggests that between 5 and 10% of MCI cases convert to dementia annually [11]. However, defining cognitive impairment solely in terms of MCI misses a large group of individuals who are at similar risk of developing dementia [12-14]. An alternative way of characterising cognitive impairment is Age Associated Cognitive Decline (AACD). AACD is defined as one standard deviation (SD) below normal cognitive functioning in any cognitive domain, with some investigators having an additional criterion (self-report of a gradual decline in memory present for at least 6 months) [5]. The estimated prevalence of AACD depends on how many cognitive domains are assessed, and whether additional criteria are used, which may explain the variable prevalence estimates – up to 20% of those aged over 60 in one population based study (additional criteria not used) [14], and lower in the UK Cognitive Functioning and Ageing Studies (additional criteria used: 2%) [5]. Progression to dementia is common whatever definition is used - with rates of conversion to dementia not much less than with MCI: 9% per annum in a population based study (additional criterion not used) [14], and 10% in Cognitive Functioning and Ageing Studies (additional criterion used) [12, 13]. Importantly, there is currently no diagnostic or treatment pathway for people with AACD. Given the scale of the problem, there are clearly insufficient resources currently on offer to help prevent cognitive decline or dementia in those with cognitive impairment, nor to prevent the development of cognitive impairment.

What could help prevent cognitive decline or dementia?

It's now widely recognised that proactive management of modifiable risk factors can either delay onset or slow progression of dementia [15]. There is mounting evidence that healthy behaviour change (particularly physical activity) and cognitive exercises improve cognitive functioning and activities of daily living, and a recent trial from other settings has demonstrated the potential effectiveness of combining healthy behaviour and cognitive interventions [16].

Healthy behaviours: Physical Activity and Healthy Eating

Several large cohort studies and systematic reviews indicate that leisure time physical activity even at moderate levels is protective, as are fish and fruit and vegetables, with increased risks shown for obesity and saturated fat intake [17-23]. The Caerphilly cohort is representative of the UK population and measured proposed protective factors (non-smoking; healthy BMI; fruit/vegetable intake; physical activity; moderate alcohol intake [23]) and after 30 years demonstrated markedly reduced risks of cognitive impairment (odds ratio

(OR) for having four to five protective risk factors = 0.36, and of dementia OR = 0.36). A trial of the Mediterranean diet over four years demonstrated beneficial effects on cognitive decline among those with no cognitive deficits at baseline: changes in cognitive z-scores were 0.04 (-0.09 to 0.18) for the Mediterranean diet plus olive oil, 0.09 (-0.05 to 0.23 vs controls) for the Mediterranean diet plus nuts, and - 0.17 (-0.32 to -0.01) for the control diet [24]. Physical activity is protective in the shorter term [25] with effects even at six months to a year on both cognitive decline, grey matter volume and atrophy [26-28]. The Population Attributable Risk (PAR) has been estimated for diabetes, hypertension, obesity, physical inactivity, depression, smoking, and low educational attainment, and the highest PAR was for physical inactivity (21.8%, 6.1–37.7) [29].

Cognitive exercises.

A systematic review of cognitive exercise trials [30] documented a strong effect size in cognitive performance (weighted mean difference (WMD) = 1.07, confidence interval (CI): 0.32–1.83, n = 3,194) with effects maintained after two years. A more recent systematic review of cognitive and memory training among those with MCI documented substantial heterogeneity of interventions [31], but a promising effect of cognitive exercises (effect sizes ranging from .10 to 1.21). The large ACTIVE study investigated the effect of training in several cognitive domains (memory, reasoning, speed of processing) [32]; the change in reasoning (effect size 0.26) was particularly important, resulting in significantly less functional decline in activities of daily living which was maintained over five years. Booster training produced additional improvement for reasoning performance (effect size 0.28) [32].

Feasibility of online delivery

Whilst there is good evidence that healthy behaviour changes can be protective against cognitive decline, behavioural interventions are complex and resource intensive if delivered by purely face-to-face methods. In contrast, the internet is now used extensively and successfully by older people for self-management [33, 34]. Although many individuals may benefit from a free standing intervention (without additional support), the additional impact of behavioural facilitation may be important in helping initiate and maintain behaviour change [35, 36] - and the effectiveness and cost-effectiveness of a more intensive intervention may vary with the risk of developing dementia.

Internet use amongst older adults

Recent UK government statistics demonstrate that the proportion of older adults using the internet is rapidly increasing. Amongst 55-64 year olds, 88.3% reported recent (in past three months) internet use. Between 2011 and 2016, the proportion of adults aged 75 and over

reporting recent internet use nearly doubled [37]. Although this proportion of frequent internet-users declines across age groups, this latter age-group have demonstrated the fastest growth.

The research team has extensive experience of ensuring intervention engagement and accessibility to encompass a range of user preferences [38] and have experience of successfully supporting older patients e.g. exercises for dizziness [39] and rehabilitation for stroke, and falls prevention [40]. The team can also draw upon existing experience of developing suitable interventions to ensure engagement and accessibility for people of all ages and computer abilities and lower health literacy [38, 41].

Internet delivered cognitive training amongst a cognitively impaired population

A large trial (n=2912) led by one of the research team's coinvestigators (CB) used an online cognitive training package in our target populations (ReaCT: Reasoning Cognitive Training package) with improvements after six months in Instrumental Activities of Daily Living, reasoning and verbal learning (standardised effect sizes respectively of 0.15, 0.42, and 0.18). There were very similar effect sizes among those with Age Associated Cognitive Decline (AACD). This suggests that a web based package is likely to be feasible and effective among those with cognitive decline. Although currently some of our target population are not internet users this proportion is rapidly declining [37], and so the findings of this study will be relevant to the large majority of the older population in future.

Intervening with non-cognitively impaired older adults

Intervening with non-cognitively impaired older adults may also prevent dementia. Whilst an intervention for non-cognitively impaired older adults may be expected to have a smaller effect, data from the above-mentioned large ReaCT trial led by CB suggests that this is not necessarily the case. Furthermore, the non-cognitively impaired are a substantially larger proportion of the population, so an intervention to target this group provides potential for many more of the older age population to be helped. The older age population are also very concerned about developing dementia: 80% of those aged 50 or more in a survey undertaken by Saga (n=9049) said they feared dementia, which was equivalent to fear of cancer, and 84% feared dementia in their partners, which was more than they feared cancer in their partners [42]. Fear of dementia, the need to improve dementia knowledge, and having adequate support for behavioural change rather than simply being told what to do are likely to be major motivators towards changing health behaviours in an older age general population group [43]. Thus it is plausible that a well-designed and engaging behavioural intervention to help prevent cognitive decline and dementia will be both well-received, and

effective, among an older age general population sample, and will be strongly supported by their partners.

Study aims and outcome measures

The primary aim of this study is to assess the effectiveness and cost-effectiveness of a digital intervention (Active Brains) to help support older adults (60-85 years) with and without cognitive impairment in making healthy changes (physical activity, brain training, diet) to maintain cognitive function and prevent cognitive decline.

Primary Research Objective:

Amongst older adults (60-85 years) both with and without cognitive impairment, the primary research objectives are:

1) to estimate the effectiveness and cost-effectiveness of the Active Brains digital intervention (compared with usual care) in maintaining cognitive functioning (assessed by verbal reasoning performance).

2) to estimate the effectiveness and cost-effectiveness of the Active Brains digital intervention (compared with usual care) in maintaining cognitive functioning (assessed by verbal reasoning performance) when supported as necessary by a trained behavioural facilitator.

The primary outcome (effectiveness) measure at one year is an online version of the Baddeley Verbal Reasoning task.

At the five year follow-up point*, a further primary objective is to estimate the effectiveness of the Active Brains digital intervention in delaying dementia. This will be determined in the following way:

1. If there is a notes diagnosis of dementia participants will be classed as having dementia.

As recording in notes is often sub-optimal, as sensitivity analyses, we will use the following methods to ascertain the dementia outcome:

2. Self-report item “Has a doctor or other medical worker ever said that you have dementia?” *(Y/N)* - as collected in baseline and year 1 and year 5 follow-up online/paper measures.

3. Evidence of significant decline in Baddeley (baseline to follow-up) **AND** evidence of functional deterioration (EITHER: a) significant change in self-report IQCODE (baseline to

follow-up) OR b) two self-report questions on difficulty in finance and planning*. These items are collected in year 5 online/paper measures.

* The items are:

Thinking about how you were ten years ago, how are you at:
a) handling your personal finances (banking, pension, etc)?
b) thinking about future events and planning ahead?
(Much improved/ A bit improved/ Not much change/ A bit worse/ Much worse)

Self-completed IQCODE will be used as it is likely to provide the most complete data. However, we will also explore the agreement between self-completed IQCODE and informant completed IQCODE among willing contacts (where provided), how these relate to other outcomes, and the implications of using self-completed or informant completed measures.

We will also explore the implications of using decrements in the other computerised tests (spatial working memory, attention, and verbal short-term memory) combined with IQCODE in indicating a diagnosis of dementia.

4. Self-report of difficulty in finance and planning alone.

* Funding for five year follow-up is contingent on evidence of effectiveness in changing behaviour and improving cognition at 1 year.

Secondary Research Objectives:

A key secondary research objective is to measure differences across trial arms in the change in the proportions of participants to a different category – either from no cognitive impairment to cognitive impairment (AACD or MCI), from AACD to MCI or severe cognitive impairment, or from MCI to severe cognitive impairment. The Baddeley verbal reasoning task will be used to indicate AACD (defined as scores more than 1 SD below the normative score*),MCI (defined as scores more than 1.5 SD below the normative score*) or severe cognitive impairment (defined as scores more than 2 SD below the normative score*). These are study specific definitions rather than formal diagnostic criteria.

*normative score determined by PROTECT database – large (n>15,000) cohort of older adults' data on battery of cognitive assessment tasks (https://www.protectstudy.org.uk/)

Additional secondary research objectives are to evaluate the effectiveness of the Active Brains digital intervention across a number of other key outcomes:

1. Instrumental Activities of Daily Living
2. Additional cognitive outcomes (including spatial working memory, attention, and verbal short-term memory)

3. Health-related quality of life
4. Patient enablement
5. Depression
6. Changes in the target behaviours (physical activity (including sedentary time), healthy eating, engagement with brain training games)
7. Mortality data

A complete list of measures is provided in table 2 at the end of the document.

Study design

Fully powered, definitive trials will test the effectiveness and cost-effectiveness of both the standalone Active Brains digital intervention and the Active Brains digital intervention plus support from a central facilitator to see if either of these interventions can maintain cognitive function and prevent cognitive decline (compared with usual care), in two groups of people: 1) older people who currently show signs of MCI or AACD, 2) older people who do not show any signs of cognitive decline.

Participants will be randomly allocated to one of three study groups:

1. Usual care
2. Access to the Active Brains website
3. Access to the Active Brains website with flexible human support from a central support facilitator

There are therefore two parallel trials with the same trial interventions: in one trial we will be recruiting a group of patients with cognitive decline and in the second trial a group without cognitive decline.

Sample Size Calculations

Cognitive decline trial

Baddeley reasoning test (Primary outcome)

We initially proposed an alpha of 0.025 for the primary outcome to adjust for multiplicity. However, where there are independent comparisons with control it is not mandatory to allow for multiplicity, as is currently the case with a host of platform trials and multi-drug trials which use a common control group - but where intervention groups are then compared as secondary comparisons multiplicity concerns become more important [44-46]. To make our approach consistent between outcomes we therefore assumed an alpha of 0.05 for

comparisons between each intervention group and control with the agreement of both the TSC and the funder. For the primary outcome of cognitive decline for 80% power to detect a standardised effect of 0.15 requires 698 per group for the MCI subgroup and the same again for the AACD subgroup or 4188 in total. Since the limiting factor in the sample size calculation is for the dementia outcome, the total sample size will provide more power for the primary outcome.

For primary outcome at one-year follow-up:

Assuming that 70% will be available to provide follow-up at 1 year, we will need 5983 in total.

For primary outcome at five-year follow-up:

Assuming that 60% will be available to provide follow-up within 5 years, this rises to 6980 in total.

Progression to dementia

Although the reduction in cognitive decline as assessed using the Baddeley reasoning test is the primary outcome at one-year, the limiting factor in the sample size calculation for those with cognitive impairment is the progression to dementia at five-years. We assume a 5% annual progression rate to dementia among those who are cognitively impaired. With alpha 0.05 and 80% power, we aim to detect a difference of 5% after 5 years (20% intervention and 25% control) in those with dementia (estimated as specified on pages 10-11). This means we would need 1094 in each of the MCI and AACD groups or a total of 2188. Assuming that 60% will be available to provide follow up in 5 years requires 3647 in each of the 3 study groups or 10940 in total.

Non-cognitive decline trial

Baddeley reasoning test (Primary outcome)

We assume few of those who have no cognitive impairment at baseline will develop dementia, and that we might find a smaller effect of the intervention. For the primary outcome of cognitive decline we assume an alpha of 0.05 and 90% power to detect a standardised mean difference of 0.1 in the Baddeley. This requires 2103 per group.

For primary outcome at one-year follow-up:

Assuming that 70% will be available to provide follow-up at 1 year, we will need 3004 per group, or 9013 in total.

For primary outcome at five-year follow-up:

Assuming that 60% will be available to provide follow-up within 5 years, that rises to 3505 per group or 10,515 in total.

- Therefore, in order to be powered to detect an effect at 5 year follow-up: In patients with cognitive decline we will recruit a minimum of 3647 patients to each of the three study groups (10,940 total); there will be a mixture of patients with MCI and AACD.
- In patients without cognitive decline we will recruit a minimum of 3505 patients to each of the three study groups (10,515 total).

This means our total sample size across both trials will be a minimum of 21,455 participants in the trials. Should we not continue to five-year follow-up (see page 10), we should have sufficient power to detect an effect at one year follow-up when we have recruited n=7260 into the cognitively impaired trial, and n = 9013 into the cognitively healthy trial; or total sample size of n = 16,273. Since the interventions are identical in both trials we will not only be able to analyse the two trials separately but also as a combined data set. These calculations are summarised in Table 1.

Table 1. Summary of sample size calculations for each trial and outcome

Cognitive decline trial		**Number of MCI/AACD participants per trial arm required**		**Total number of participants per trial arm**	**Total**
Primary outcome measures	**Cognitive Decline – Baddeley Verbal reasoning** (alpha = 0.05, 80% power to detect standardised mean difference of 0.15 in Baddeley)	698 of each		1396	4188
	Progression to Dementia at 5 years (Assuming 5% progression rate – alpha = 0.05, 80% power to detect 5% diff after 5 years)	1094 of each		2188	6564
For 1 Year Follow-up					

Baddeley verbal reasoning - assuming 70% follow-up	997 of each		1994	5983
For 5 Year Follow-up				
Baddeley Verbal reasoning – assuming 60% follow up	1163 of each		2327	6980
Progression to dementia – assuming 60% follow-up	1823 of each		3647	10940

Non-cognitive decline trial		**Total number of participants per trial arm**	**Total**
Primary outcome measure	**Cognitive Decline – Baddeley Verbal reasoning** (alpha = 0.05, 90% power to detect standardised mean difference of 0.1 in Baddeley)	2103	6309
For 1 Year Follow-up			
Baddeley verbal reasoning - assuming 70% follow-up		3005	9013
For 5 Year Follow-up			
Baddeley Verbal reasoning – assuming 60% follow up		3505	10515

Our ongoing feasibility trial (REC reference 18/NW/0341) has so far demonstrated that our proposed recruitment, screening and randomisation procedures have proven feasible and allowed us to recruit to target (n=360) within a three-month time frame (as planned). Furthermore, study recruitment materials proved accessible and acceptable amongst our participants.

Study participants

Identification and non-participation

Participants will be recruited via Primary Care. Recruitment will involve practice staff inviting patients from practice lists (GPs will screen practice lists to avoid inviting those who have an existing diagnosis of dementia, are terminally ill, seriously mentally ill or have/had long-COVID). Invitation letters, participant information sheets, and a 'getting started' sheet with instructions on how to log on to the website to start the study, will be sent from GP Practices. Reply slips (for those not interested to inform us why) will be included in these mail out packs for 5% of participating practices. Prospective participants can also contact the research team directly if they have any questions. GP practices will be asked to provide demographic data (gender and age) for all participants who are invited to the study. A sub-sample of practices will also be asked to provide Index of Multiple Deprivation (IMD)

anonymised data for all participants invited to the study. We will compare demographics and IMD data of those invited who do not participate to recruited participants to examine any differences between these two groups. This will help us to assess the likely generalisability of our findings.

Eligibility Criteria

When patients first register on the Active Brains study website they will answer a series of screening questions to make sure that they fit the study inclusion criteria below. Figure 1 outlines the participant identification and screening procedures.

To be eligible for inclusion, individuals with signs of cognitive decline will:

- Be aged between 60 and 85 years old inclusive
- Have cognitive impairment (AACD) defined as 1 SD below the norm on the Baddeley reasoning test [47]. A key subgroup is MCI, which will be defined simply as 1.5 SD below the norm on the Baddeley reasoning test. In statistical analysis we will also explore the impact in subgroups defined by alternative combinations of impairment in Baddeley reasoning, IADL and memory e.g. of MCI defined as 1.5SD below the norm in another non-memory cognitive domain plus memory impairment [5, 12, 13], and AACD defined as 1 SD below the norm for the Baddeley reasoning test [47] and IADL.
- Be willing and able to access the internet
- Not have an existing diagnosis of dementia at baseline
- Not report high levels of leisure time physical activity already (i.e. score 30 or more on the Godin Leisure Time Exercise Questionnaire (counting moderate or vigorous physical activity only)).
- Will not have a recorded diagnosis of long-COVID in their medical records at baseline

To be eligible for inclusion individuals without signs of cognitive decline will:

- Be aged between 60 and 85 years old inclusive
- Have normal cognitive function (i.e. do not meet criteria for cognitive impairment as defined above)
- Be willing and able to access the internet
- Not have an existing diagnosis of dementia at baseline

- Not report high levels of leisure time physical activity already (i.e. score 30 or more on the Godin Leisure Time Exercise Questionnaire (counting moderate or vigorous physical activity only)).
- Will not have a recorded diagnosis of long-COVID in their medical records at baseline

Randomisation

Patients will be randomised online using the study software. They will have an equal chance of being in each of the three groups in each of the two trials (the trial among those with cognitive impairment, and the trial among those with no cognitive impairment). Once randomised, participants will be informed of their group allocation (they will also be emailed this information). If participants are in one of the treatment arms they will be taken directly to Active Brains where they can begin the intervention. These participants can then use Active Brains as much as they would like to over the course of the study. The central facilitator will be notified by email when a participant is randomised to the support arm of the trial, so that they know to expect to provide support to the participant in the coming weeks.

Consent and Screening

Consent will be collected online (a method we have used successfully in our PRIMIT and CLASP trials [45]). Following consent participants will complete online screening to check that they meet the above eligibility criteria for the study. Those who are ineligible based on the screening measures will receive immediate feedback which thanks them for their time, advises that they are not eligible and explains the reason for this (e.g. that they are already very highly physically active).

Should participants' scores on the online cognitive assessment screening tools meet the threshold for cognitive impairment, they will be recruited to the cognitively impaired trial.

Those whose scores do not meet the threshold for cognitive impairment will not be excluded, as we are also aiming to recruit at least 10,515 participants to a trial of Active Brains amongst those who do not show signs of cognitive decline. However, given that we may not recruit participants to the two trials at an even rate, and the fact that a slightly larger number of participants with cognitive decline are required, it is possible we will reach our recruitment target for the non-cognitively impaired trial (n= 10,515) before recruitment into the cognitively impaired trial is complete. Once we have recruited a minimum of 10,515 people to the non-cognitively impaired trial, further participants without signs of impairment will be given the

opportunity to participate in a non-randomised cohort study which will provide the same digital intervention as in the full trial, with online self-completion of follow up only (we won't do a notes review or provide additional support from a centralised facilitator to this group). Whilst we don't expect it to be the case, in the unlikely event that we reach our recruitment target for the cognitively impaired trial first (n = 10,940), any additional individuals beyond this target would enter the cohort study. This would be instead of the cohort group being populated by over-recruitment from the non-cognitively impaired trial (which we think is more likely). After initial screening indicates that these participants are eligible, and that they are not needed for the randomised trial, these participants will be shown a different participant information sheet for a cohort study online and will complete a slightly different consent form. This procedure could be beneficial for participants without signs of impairment who will get access to the Active Brains intervention and will enable us to examine how the intervention might be implemented outside of a randomised trial (which will be more similar to the effects one might expect if implementing in clinical practice).

Based on our previous experience [48] (also, CB personal correspondence), there is no reason to suppose that those whose scores on the cognitive screening indicate possible cognitive impairment would not have capacity to consent. This is in accordance with the Mental Capacity Act (2005) [49] Code of Practice (2007) [50] which states that, unless otherwise demonstrated, all individuals should be assumed to have capacity. All participants will be community-dwelling older adults capable of reading and responding to the invite and participating in the screening prior to taking part. It is considered very unlikely that anyone who reaches this stage (i.e. who is able to complete the online consent and screening procedure) would be lacking capacity. Indeed, a 2014 review of the evidence on dementia and cognitive decline states that MCI "affects cognitive function to a greater extent than would be expected, but not to such extent that it precludes independent living" [51]. Whilst not practicable to assess continued capacity for the duration of the study, should we be made aware of confirmed loss of capacity (i.e. after assessment by participant's GP/other relevant medical professional), we would withdraw that participant from the study. We would collect/ retain any data from the period up until the confirmed loss of capacity.

The Active Brains intervention

The Active Brains digital intervention provides interactive, tailored support to encourage older adults to engage in behaviours beneficial for their cognitive and physical health. The intervention content utilises behaviour change techniques to motivate users to engage in, and maintain, evidence-based activities for sustaining cognitive health in later life. All intervention content has been iteratively developed with extensive input from the target user

group to ensure that it is highly accessible and engaging. For the first seven months, users will have access to the Active Brains 'Starter Section' which provides support for users to initiate changes to their lifestyle in line with the intervention's recommendations.

Active Brains Starter Section

Within the first section of Active Brains, three primary modules will become available to users sequentially. Within these modules, users will have access to: information addressing common concerns, instruction about recommended activities, facilities to set and review goals about their chosen activities, tailored motivational feedback about their progress, and reminder emails to motivate them to continue with their activities and to revisit intervention content as appropriate. Additional detail about each of the main modules is provided below.

Active Lives

The 'Active Lives' module supports users in gradually increasing their levels of physical activity in a manner that is most suited to their present physical capabilities and level of activity. Within this module, there are three sub-modules that users are directed to differentially depending on which is deemed to be most beneficial for them. The 'Getting Active' sub-module provides support and ideas about activities to try to increase individuals' overall levels of physical activity. The 'Breaks from Sitting' sub-module supports individuals in reducing sedentary behaviour by suggesting simple changes that can be made to daily routines. The 'Strength and Balance Training' module provides video demonstrations of simple strength and balance exercises and suggestions about how these can be built into daily activities. The level of exercise difficulty is tailored to the user and their progress. Whilst tailored recommendations will be made about which sub-module users may find most helpful, they will have access to all three sub-modules.

Brain Training

The Brain Training module follows on from Active Lives and is accessible to participants after four weeks. This module provides brief information about the rationale and evidence base for Brain Training tasks and how they are intended to work. The module initially provides participants with access to six online brain training games (via the existing PROTECT website) which they are encouraged to play between three and five times per week. Users are encouraged to set and review goals relating to their use of the brain training games. At regular intervals throughout the six month period of the starter session, six additional games are made available to users.

Eat for Health

The Eat for Health module follows on from Brain Training and becomes accessible to participants eight weeks after they first use the intervention. This module outlines the benefits of healthy eating for cognitive and physical health. It offers suggestions about specific foods and food groups that are beneficial for cognitive health. It also provides users with information and techniques to allow them to make healthy changes to their existing eating behaviours more generally (e.g. increasing fruit and vegetable consumption, cutting down on processed foods).

Active Brains Booster Section

After seven months, it is expected that the primary needs of intervention users will be somewhat different. It is likely that, with support from the Active Brains Starter Sessions, the recommended activities that users have chosen to engage with will have become more habitual behaviours. These users are, therefore, expected to have less need to rely on the intervention content so extensively. Accordingly, at this stage, users will be directed to access the Active Brains Booster section. This content will include access to all content from the Starter Section, as well as advice on a 'maintenance' schedule for brain training, and centralised links to external resources for additional support and to extend their progress with the behavioural changes made.

Our previous qualitative studies (REC reference SC/17/0463), explored the acceptability of Active Brains amongst target users. Analysis of our think aloud and semi-structured interviews (n=59) informed iterative changes to the intervention content throughout development and indicated that the intervention is acceptable to older adults with and without cognitive decline. This phase also sought extensive input from PPI representatives in the development of intervention content and participant recruitment materials. Our development phase qualitative work is currently being prepared for submission for publication.

Central Facilitator Support

Patients in the group receiving support from a central facilitator (in addition to the website) will be offered a brief (10 minute) telephone support call 2 weeks after they begin the study. In this support call they will discuss the cognitive/lifestyle changes that they are choosing to try. Patients will be offered two more support contacts by phone (up to 10 minutes) or email to support them in making behavioural changes. Should the participant not yet have

accessed Active Brains at the time of contact, the supporter will check whether the participant is having any technical difficulties and/or talk through any other barriers to getting started.

For patients who feel the need, up to 7 further email or phone contacts can be arranged. In the feasibility study only one participant requested additional contact beyond the three initial calls (n = 120 in support arm). In our previous studies only around 10-15% of patients have required this further support.

The central facilitator will use the CARE (Congratulate, Ask, Reassure, Encourage) approach to provide support to patients, which is based on Self-Determination Theory [52] and designed to promote autonomous motivation for making behavioural changes. The CARE approach has been used successfully in our previous trials and has been shown to be acceptable to patients and staff supporting patients [53]. Supporters will also provide brief technical website support to all participants as required throughout all contact points (e.g. advice on logging in problems). To maximise fidelity of support delivery, a 'checklist' of the CARE approach is provided in the supporter training materials that supporters are encouraged to use to guide their calls with participants. This will also include space to write notes about these interactions. As a means of fidelity check, supporters will be encouraged to share the completed checklists/notes from one or two of these anonymous interactions with the research team. A member of the research team with expertise in the CARE approach will provide feedback to the supporter as appropriate.

Usual Care

The comparison group will receive usual care from their GP practice, plus brief online advice about getting more active, improving diet and staying mentally active.

Measures

See table 2 for a full list of measures at each time point, for each study group.

Participants in both the randomised trials and cohort study will be followed-up every 12 months for the five year duration of the study. At years one and five, participants will be asked to complete a full set of follow-up measures. In years two, three and four participants will only be requested to complete a subset comprising the most important outcome measures. At the start of each follow-up time point, participants will receive three automated email reminders to complete follow-up measures, at one week intervals (cancelled if they complete the measures in the meantime). In follow-up years two, three and four, after this point we will not contact participants about completing measures any further. At years one

and five, if participants in the randomised trial (not cohort participants) do not complete follow-up measures after the three email reminders then we will contact them by post with a brief letter explaining the importance of completing measures online with instructions about how to login. If this is unsuccessful, we will subsequently contact them by phone to ask them to complete the most important outcome measures (reasoning [47], Instrumental Activities of Daily Living [54], quality of life with the EQ-5D [55]). The Baddeley verbal reasoning task can only be completed online, so if phone calls are required then they will be used to prompt/support (as required) the participant to complete this task online or to ascertain that the participant is no longer able to complete these measures. If the phone call is unsuccessful, a paper version of the measures that can be completed offline will be posted with a freepost return envelope. All of the participants will be contacted to complete follow-up measures, whether or not they have used the website. If the participant indicates that they would not be willing to complete any further measures at any point then no further contact will be made regarding the follow-ups.

To maximise outcome data, participants will have the option to nominate a contact person (a friend, relative, neighbour or colleague) at sign-up. The contact person will only be contacted by the research team if the participant does not complete the follow-up measures at the one and five year follow-up points (after all procedures to reach the participant have been tried: 3 emails, 1 postal contact, provision of paper questionnaires and 1 phone call). If a participant nominates a contact person, the nominated contact person will receive an email with a link to the Active Brains website where they will be able to read a participant information sheet explaining about the study and their potential role. If they decide to act as a contact person in this study they will give consent and provide their contact details (name, email address and telephone number). Should the contact person be needed at follow-up, they will either be asked to help put the research team in touch with the participant or to complete three short questionnaires about the participant (EQ5D5L-Proxy version 2, IADL proxy version, Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [56]).

Assuming progression to long term (5 year) follow-up, we will email participants who complete at least up to the self-report IQCODE questions within their 5 year follow-up, to ask if they would be willing for their existing contact person (if already nominated) or a new contact person of their choosing (if not nominated, or if the existing contact no longer suitable) could be contacted to complete the informant IQCODE questionnaire. This is to provide data to validate the self-report IQCODE as part of the sensitivity analysis for determination of the dementia outcome at five years. In this request, we will make it clear (in plain English language) that this is only for the purposes of answering a research question about the way the IQCODE questionnaire can be used, and would only happen with their

permission. If the participant is not happy for this to happen, no further action will be taken and no further requests would be made. If participants are happy to proceed, they will be asked to provide the name and contact details of an appropriate contact person, or to confirm that the existing one can be contacted. The contact person will then be emailed a participant information sheet, study team contact details, and a link to an online consent form to allow them to provide informed consent to provide the requested data. Should they consent by completing the online form, they will immediately be able to complete the informant IQCODE online. The contact person's name and contact details will not be available to, or saved, by the research team until after the point they have consented. If the contact person consents but does not complete the online IQCODE questionnaire, they will be sent one email prompt one week after the first request. After this, no further follow-up attempts will be made.

Statistical analysis

Intention to treat (ITT) analysis will be performed. If the assumptions for linear modelling are met, linear regression will be used to model the primary outcome and continuous secondary outcomes. If linear modelling assumptions are not met, another appropriate parametric distribution will be sought and a suitable regression model fitted. If no suitable parametric distribution fits the data, a non-parametric approach using quantile regression will be used.

Binary outcomes will be modelled using logistic regression and count outcomes with an appropriate distribution.

All regression models will control for baseline values. The estimates for the overall trial intervention cohorts compared with the control group will be provided with 95% confidence intervals.

Depending on the patterns of missing data, it is likely that we will be using multiple imputation methods for all outcome values that are missing at follow-up, using a chained equations approach to multiple imputation based on baseline data and any available follow up data from other time points. However, we will also include sensitivity analyses - where instead of allowing the model to predict the value of the outcome measure, we set it to a value representing either poor outcome or good outcome. We will also present a sensitivity analysis using complete cases only.

The study will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement. The primary analysis will analyse the two trials separately. We

will then explore as a secondary analysis whether both trial datasets can be combined for modelling, particularly for any pre-planned subgroup analyses.

Health economic analysis

The economic evaluation will be taken from an NHS and PSS perspective with a sensitivity analysis from a societal perspective taking employment status into account. The outcome will be expressed as incremental cost per improvement in cognitive functioning scores and per quality adjusted life year gained.

Personal out-of-pocket spending and informal care information will be collected through online questionnaires. We will record all resources required for interventions including staff support time, time using the internet, and the cost of maintaining the LifeGuide platform. Use of relevant primary/secondary care services will be extracted by notes review at years 1 and 5 of the trial. Health-related quality of life (HRQoL) questionnaires will be completed at baseline, and annually from year 1 to year 5. Personal resource usage questionnaires will be completed at years 1 and 5. All relevant resource items identified will be costed using appropriate local or national cost data (e.g. PSSRU, 2007), with informal care costed at the minimum wage level, NHS reference costs, and from participating Trusts where necessary.

EQ5D will be translated to utility score using the UK tariff. Area under the curve approach will be adopted to calculate quality adjust life years (QALYs) and discounted beyond one year for each individual.

We will follow the intention to treat principle. Generalised linear mixed models will be used to estimate the costs and QALYs difference by adjusting baseline characteristics including socioeconomic groups. Where appropriate we will estimate incremental cost-effectiveness ratios. We will estimate mean values and 95% percentiles using non-parametric bootstrapping, and use these to estimate cost-effectiveness acceptability curves. Major assumptions in the costing and analysis will be tested through sensitivity analyses. Missing value will be explored using multiple imputation and presented as sensitivity analyses.

A population dynamic model will be developed to consider prevalence, new incidence, and progression of cognitive impairment, using values informed by our literature review, data collected at feasibility stage and full trial results. We will extrapolate the trial findings to broader settings and test the cost effectiveness implications regarding different take-up rates, intensity of use, and socioeconomic variables.

Qualitative process studies

There will be two qualitative process studies, one with participants and one with central support facilitators. Interviews in both these studies may be carried out anytime between 2-12 months after participants begin the study. The most important role of these qualitative process studies will be to obtain an in-depth understanding of the perspective of participants and supporters and to reveal any influences on their experience and outcomes of the intervention and trial that had not been anticipated by the research team. Accordingly, all our qualitative research will commence with inductive data collection methods, using open-ended questions that allow participants to freely describe their experiences and views in their own way, and to focus on whatever is most salient to them. However, to ensure coverage of all potentially relevant aspects of the intervention and its implementation, we will then employ the constructs of our theoretical framework (represented in our logic model) as prompts in our topic guide. The Active Brains intervention logic model will be submitted for publication as part of our intervention planning work, in preparation.

Qualitative process study with participants

We will interview 12-18 participants from each of the intervention arms, employing purposive sampling to ensure a diverse range of participants in terms of demographic and clinical profiles, as well as website usage. Participants will have consented to be contacted by the research team throughout the study. Participants will be invited to participate by the research team (phone, email or by post) and asked if they would be willing to take part in a telephone interview. Participants will complete a separate consent form (online) prior to taking part in an interview. During the interview, open-ended questions will be used to explore participants' perceptions of the study, the website (if in one of the intervention groups) and the support they received from the central facilitator (if in the support group). Participants in the control group will also be asked about the brief advice they were given at baseline. Participants will be offered a £10 high street voucher as reimbursement for their time and effort.

Qualitative process study with central support facilitators

The second sub-study will use face-to-face or telephone interviews to explore central support facilitators' views of the study procedures, the website, the training they were provided and the support that they provided to patients (including perceptions of the CARE approach).

Analysis

Data from both qualitative process studies will be analysed, firstly, using inductive thematic analysis to identify themes emerging from and grounded in the data, to ensure that these represent participant perspectives and have the potential to challenge or extend our understanding of the factors and processes operating. Inter-rater agreement will be sought between team members. Following this, we will also examine the ways in which these inductively derived themes map onto, elaborate or diverge from our theoretical frameworks, so as to relate our context-specific insights to generalisable theoretical constructs. The findings will be discussed and interpretations agreed between the co-investigators (including PPI representatives).

Serious Adverse events

Definitions

For this study Serious Adverse Event (SAE) is defined as any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Other important medical events - based upon appropriate medical judgment; they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Causality

An SAE occurring to a research participant will be reported to the Active Brains study team where, in the opinion of the Principal Investigator at site, the event was related to administration of any of the research procedures, and was an unexpected occurrence. The causality assessment of the event should always be undertaken by a medically qualified doctor who is delegated to do so as indicated on the trial delegation log.

Expectedness

For the purposes of this trial no SAEs are considered expected.

Non serious AEs and exemptions

- Non-serious AEs will not be collected.
- SAEs NOT DIRECTLY related to the Trial are not required to be reported, this includes deaths and hospital admissions as assessed by PI at site as being not related to the trial website intervention. In such cases deaths will be reported using an End of Study form and will be sent directly to the trial team as per SOP.
- Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, elective procedures for a pre-existing condition will not be classed as an SAE unless deemed related to the trial. Hospital admissions that are not directly related to the trial do not need to be reported.

Reporting

GP Practices will inform the Active Brains Study Team of any SAEs considered to be related to the trial immediately but at least within 24 hours of becoming aware of the event occurring. SAEs should be reported using the trial specific SAE Report Form and completed in as much detail as possible and faxed/emailed to the Active Brains Study Team. Note that the initial report can be made by phone but this must be followed up as soon as possible with a paper report form.

The Active Brains Programme Manager will notify the appropriate REC should an SAE be considered related to the trial and unexpected within 15 days of the receipt of the report.

Follow Up

All SAEs will be followed up until resolved or an end of trial criteria is met (e.g. patient withdrew from study. All SAEs will also be sent to the PSC.

Table 2 – List of Measures

Measure		Baseline				Year 1 and Year 5 follow-up				Year 2, year 3 and Year 4 follow-up			
		Usual care	**Active Brains**	**AB + Support**	**Cohort group**	**Usual care**	**Active Brains**	**AB + Support**	**Cohort group**	**Usual care**	**Active Brains**	**AB + Support**	**Cohort group**
Patient Socio Demographic measures: (age, date of birth, gender, postcode (to estimate deprivation indices); internet experience, education level, work status, ethnicity, height, weight)		X	X	X	X								
Clinical/behavioural measures collected from patient report: , family history of dementia [b], smoking status, alcohol intake, BMI, potential dementia status.		X	X	X	X	X	X	X	X				
Health conditions and medications		X	X	X	X	X*	X*	X*					
Self-reported respiratory infections						X	X	X	X				
COVID-19 status		X	X	X	X	X	X	X	X				
Long-COVID status						X	X	X	X	X	X	X	X
Out of pocket expenditure						X	X	X	X				
Clinical measures from notes review (comorbidities, systolic blood pressure, cholesterol, frailty score[c])						X*	X*	X*					
Cognitive Performance Tasks	**Primary Outcome:** Reasoning (measured using the Baddeley reasoning test [47, 57])	X	X	X	X	X	X	X	X	X	X	X	X
	Spatial Working Memory (measured using the Self ordered search test)	X	X	X	X	X	X	X	X	X	X	X	X

	Digital Vigilance (attention - measured using the 'digit' span task [58])	X	X	X	X	X	X	X	X	X	X	X	X
	Verbal Short-term memory (measured using the paired associates learning [59])	X	X	X	X	X	X	X	X	X	X	X	X
Modified version of IQCODE SF (to allow self-report)		X	X	X	X	X	X	X	X	X	X	X	X
Instrumental Activities of Daily living [54]		X	X	X	X	X	X	X	X	X	X	X	X
The patient Enablement Scale [60]						X	X	X	X				
International Physical Activity Questionnaire (IPAQ) plus strength and balance items [61]		X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life (EQ5D) [55]		X	X	X	X	X	X	X	X	X	X	X	X
SWEMWBS [62]		X	X	X	X	X	X	X	X				
SF12 [63]		X	X	X	X	X	X	X	X				
Diagnosis of dementia						X*	X*	X*					
Mortality						X*	X*	X*					
Health economic analysis of cost effectiveness will require resource usage (meds, consultations, hospitalisation, A&E attendance, outpatient visits)						X*	X*	X*					
Dietary behaviour (food frequency questionnaire, with the addition of 2 items about nuts and oils) [64]		X	X	X	X	X	X	X	X	X	X	X	X
Brain training behaviours						X	X	X	X	X	X	X	X
Patient rated adherence to changes in behaviour and list of barriers they felt contributed to their adherence (measured with the PETS questionnaire) [65]							X	X	X				
Brief Geriatric Depression Scale [66, 67]		X	X	X	X	X[1]	X[1]	X[1]	X[1]				
Self-efficacy for exercise scale [68]		X	X	X	X	X	X	X	X				
mMOS Social Support Survey – 8 item [69, 70]		X	X	X	X								

Social Support for Exercise scale [71]						X	X	X				
Locus of Causation in Exercise [72]	X	X	X	X	X	X	X	X				
Technology Acceptance Model Perceived Ease of Use scale [73-75]						X	X	X				
Pedometer use/purchase					X	X	X	X				
Objective patient data												
Usage of the Active Brains website throughout (including what components viewed and any data entered online such as at goal reviews).		X	X	X		X	X	X		X	X	X
Objective supporter data												
Supporters' Usage of Active Brains website (throughout study)			X				X				X	
Emails sent to participants throughout study			X				X				X	
Qualitative data												
Interviews with patients about their experiences of the study and/or intervention					X[a]	X[a]	X[a]					
Interviews with Central Support Facilitators about their experiences of the study and intervention						X						
Proxy-Measures (not cohort group)												
	Baseline				Years 1 and 5				Years 2-4			
Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (short form) [56]						X						
Quality of Life (EQ5D5L-proxy version 2) to be completed by the nominated contact person (if necessary)						X						
IADL proxy version to be completed by the nominated contact person (if necessary)						X						

*=notes a measure collected at notes review at Year 1 **or** 5 (depending on when notes review conducted).

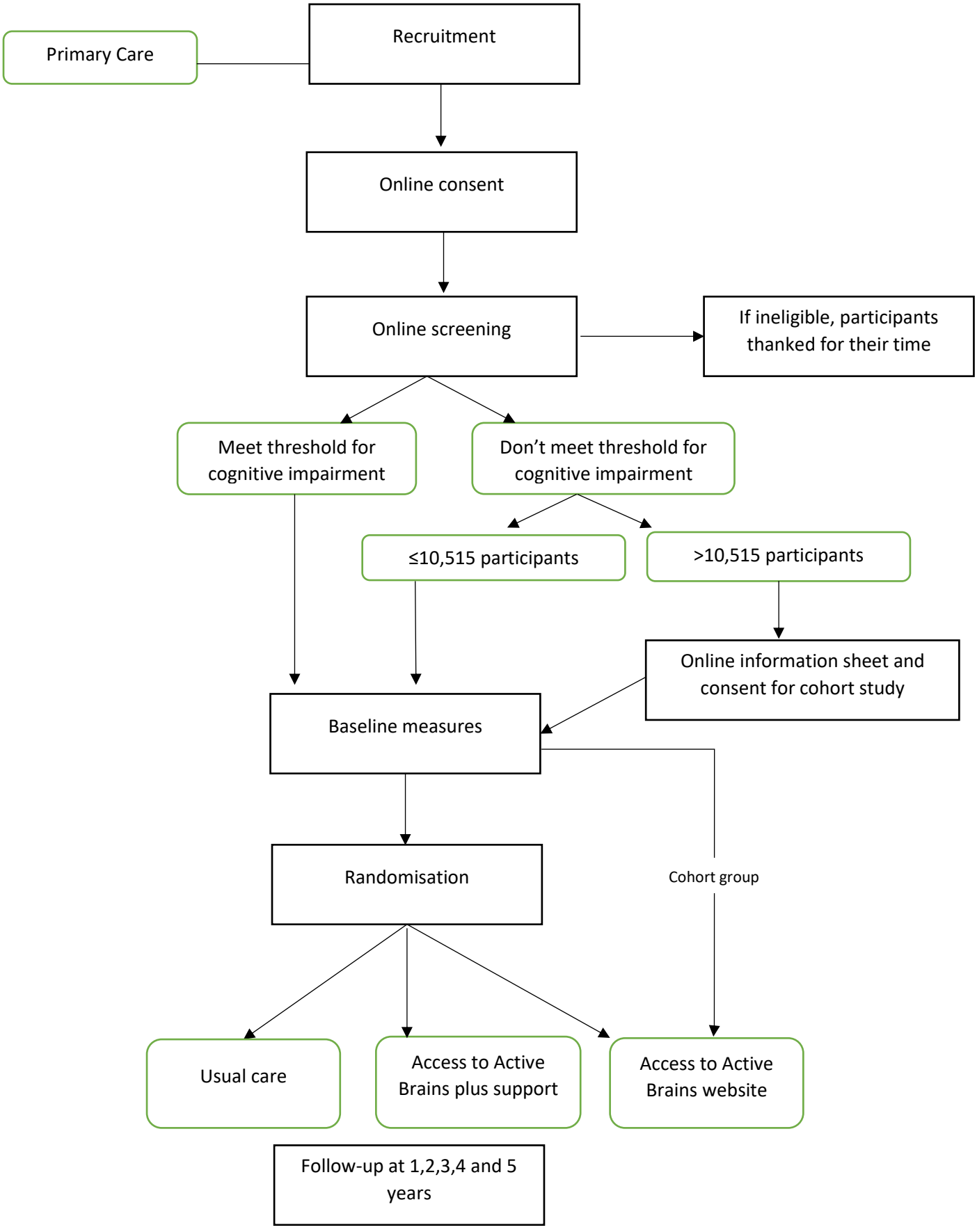
[1] = collected at year one only (not year five also)

[a] = Year 1 only; process interviews to be conducted 2-12 months after commencement of study

[b] = baseline only

[c] = Frailty estimated from IADL and comorbidity data

Figure 1 – Flow of participants through study



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