# Parallel randomised controlled feasibility trials of the ‘Active Brains’ digital intervention to protect cognitive health in adults aged 60-85.

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## Abstract

### Background and Objectives

Multidomain interventions to address modifiable risk factors for dementia are promising, but require more cost-effective, scalable delivery. This study investigated the feasibility of the ‘Active Brains’ digital behaviour change intervention and of its trial procedures.

### Research Design and Methods

Active Brains aims to reduce cognitive decline by promoting physical activity, healthy eating, and online cognitive training. We conducted 12-month parallel-design randomised controlled feasibility trials of ‘Active Brains’ amongst ‘lower cognitive scoring’ (n=180) and ‘higher cognitive scoring’ (n= 180) adults aged 60-85.

### Results

We collected 67.2% and 76.1% of our primary outcome (Baddeley verbal reasoning task) data for the ‘lower cognitive score’ and ‘higher cognitive score’ groups, respectively. Usage of ‘Active Brains’ indicated overall feasibility and satisfactory engagement with the physical activity intervention content (which did not require sustained online engagement), but engagement with online cognitive training was limited. Uptake of the additional brief telephone support was higher in the ‘lower cognitive score’ trial. Preliminary trends in the primary outcome data may indicate a protective effect of Active Brains against cognitive decline in both trials requiring further investigation in fully-powered trials.

### Discussion and Implications

Findings confirmed the feasibility of ‘Active Brains’ and identified minor modifications to procedures, particularly to improve online primary-outcome completion. These findings warrant further investigation of Active Brains to determine its efficacy in protecting cognitive performance amongst adults aged 60-85 with varied levels of existing cognitive performance.

## Keywords

Dementia prevention; behaviour change; physical activity; healthy eating; cognitive training

## Background

Dementia is a major cause of disability and dependency among older adults and places significant burden on the health and social care sector, accounting for costs of over US$ 1.3 trillion dollars globally in 2019 (WHO, 2021). Amongst adults over 60 between 12 and 18% are affected by mild cognitive impairment (MCI; Petersen, 2016), and up to 20% by age-associated cognitive decline (AACD; Ritchie et al., 2001). Up to 10% of MCI and AACD cases progress to dementia annually (Mitchell & Shiri-Feshki, 2009; Ritchie et al., 2001). Better preventative, diagnostic, therapeutic and social care solutions for dementia are public health priorities (WHO, 2021).

An estimated 40% of risk factors for dementia are modifiable, and, if managed proactively, could delay or slow disease onset (Livingston et al., 2020). People with physically active lifestyles, or those who follow a Mediterranean diet appear less likely to develop cognitive decline and dementia (Blondell et al., 2014; Wu & Sun, 2017). These behaviours also have positive effects on reducing the incidence of other risk factors including hypertension (Pescatello et al., 2019). Cognitive training interventions have also demonstrated potential, with reported moderate positive effects on cognitive function for healthy adults (Chiu et al., 2017) and small positive effects for those with MCI (Sherman et al., 2017).

The large ‘FINGER’ trial (n=1260) of a multidomain programme targeting diet, physical activity, cognitive training and vascular risk monitoring, demonstrated modest reductions in cognitive decline (Ngandu et al., 2015). Findings suggest that addressing multiple risk factors simultaneously offers a promising strategy. However, reaching large numbers with a face-to-face delivered programme such as this would prove prohibitively resource-intensive (Whitty et al., 2020). More scalable, cost-effective models of delivering multidomain interventions are required (Kivipelto et al., 2020).

Digital interventions may offer a feasible solution. A meta-analysis of effectiveness of web-based multidomain lifestyle programs aimed at optimising brain health in healthy adults concluded that these interventions show an overall small-to-medium effect on outcomes for brain health (Wesselman et al., 2019). Research in this area is still limited, and further exploration of the feasibility and efficacy of such multidomain digital interventions is needed (Wesselman et al., 2019).

Accordingly, we developed ‘Active Brains’, a multidomain web-based intervention for older adults aged 60-85 years with and without indications of existing cognitive impairment (Essery et al., 2021). Active Brains aims to reduce cognitive decline by promoting physical activity and healthy eating behaviours, and online cognitive training. This paper presents parallel feasibility randomised controlled trials (RCTs) of ‘Active Brains’ to determine the feasibility of both the intervention, and the procedures to test its efficacy and cost-effectiveness in fully powered trials.

### Objectives

Our main objective was to evaluate our ability to collect 80% of primary outcome data from both trial groups. The primary outcome measures were the Baddeley verbal reasoning score at one-year follow-up, and incidence of dementia diagnosis identified from medical notes review for the proposed five-year follow-up.

Additional objectives were to explore preliminary estimates of change in outcomes and to evaluate the feasibility and acceptability of: recruitment screening methods; trial procedures; recruitment and attrition rates; outcome measures; engagement with the Active Brains intervention; and engagement with the additional human support. We also assessed the feasibility and practicality of collecting key resource usage information, and the most suitable quality of life instruments for the full RCTs.

## Research Design and Methods

For further details about study design, measures and analysis, and a full description of ‘Active Brains’ see Smith et al. (2020).

### Study design

We conducted parallel-design 12-month randomised controlled feasibility trials of the Active Brains intervention. Active Brains was trialled amongst two groups of adults aged 60-85 years: 1) those with indications of existing cognitive impairment (‘lower cognitive score’; n=180); and 2) those with no indications of existing cognitive impairment (‘higher cognitive score’; n = 180). Trial allocation was determined by participants’ baseline scores on a computerised version of the Baddeley Verbal Reasoning Task (Baddeley, 1968). In line with existing definitions of AACD (Stephan et al., 2007), a score more than one standard deviation below the ‘normative score’ from the PROTECT database - a large (n>15,000) cohort of older adults (PROTECT Study Research Team, 2015) - determined allocation to the ‘lower cognitive score’ group. The ‘lower cognitive score’ and ‘higher cognitive score’ groups were treated as separate trials for randomisation and reporting. In each trial participants were randomised to one of three arms: 1) Active Brains; 2) Active Brains plus brief telephone/email support; or 3) Usual Care comprising a single-page advice sheet about activities to protect cognitive health.

### Study Setting and Recruitment

Between October 2018 and January 2019, 19 primary care practices in Hampshire, Dorset and Wiltshire completed a database search, screen and mailout in accordance with the study’s eligibility criteria. Participating practices recorded age, gender and postcode of all invitees. Mailout packs provided immediate access to the Active Brains study website where invitees could: sign up, provide online informed consent, complete additional screening (including the Baddeley Verbal Reasoning Task to determine trial assignment) and, if eligible, complete baseline measures and randomisation. Anyone whose score allocated them to the ‘higher cognitive score’ group after 180 participants had been allocated entered a non-randomised ‘cohort’ group with access to Active Brains. This paper focuses only on the randomised trial participants.

### Measures and data collection procedures

#### Baseline

At baseline, all measures were completed online after initial sign-up and online consent. The cognitive assessment tasks (comprising the Baddeley Verbal Reasoning task (Baddeley, 1968), the digit span task, the paired associates learning task and the self-ordered search task) were accessed via the PROTECT platform (Huntley et al., 2018). All other measures were completed via the Active Brains website by those eligible.

#### 12-month follow-up

All participants were contacted via email at one-year post-randomisation to invite them to complete online follow-up measures. Participants who had not completed the online cognitive assessment tasks, the Instrumental Activities of Daily Living (IADL; Landi et al., 2000) and the EQ-5D (Rabin & de Charro, 2001) measures after three weeks (including two additional reminder emails) were contacted by paper mail-out and, where necessary, by phone to prompt completion of the online or paper measures. The cognitive assessment tasks could only be completed online. If these measures remained incomplete after eight weeks with no participant contact, emails and phone calls were made to the participant’s nominated contact person if provided. These requested that the contact person prompted or supported the participant to complete the measures or, if not possible, for the contact person to complete the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; Jorm, 1994) and proxy versions of the IADL and EQ-5D.

#### Notes review

A medical notes review data collection form and accompanying instructions were shared with recruiting primary care practices. These asked practice staff to report for each of their randomised patients: major medical conditions diagnosed before and during the study period; family history of dementia; any record of cognitive impairment complaints; blood pressure and cholesterol readings; medications prescribed at baseline and medication changes during the study period; and healthcare use including primary care consultation, outpatient attendance, A & E visits and hospitalisation during the study period.

### Analysis

The completeness of the primary outcome data and the other key feasibility outcomes including: intervention uptake, adherence, attrition, retention and the number of participants recruited per practice, healthcare costs and quality of life were summarised descriptively. Baseline participant characteristics and trial outcomes were analysed as randomised, using number (%), mean (SD) or median (IQR) as appropriate. The pattern and frequency of missing data was also descriptively explored.

## Results

From 5475 study invitations, 1001 individuals (18.3%) completed online sign-up. Amongst those choosing not to participate, 18.5% (n=828) returned a reply slip indicating why. The most common reasons related to lack of access, or unwillingness to use computers or the internet, or commitments including work and caring responsibilities.

Of 1001 individuals who signed up, 2% (n=21) did not complete consent, and a further 7% (n=70) did not complete the online screening, leaving 910 individuals who were assessed for eligibility. Overall, 10.2% of invitees (n=560) participated.

Figure 1 illustrates participant flow through the trials.

*(Insert Figure 1 about here)*

### Sample Characteristics

Participant characteristics for each group (Table 1) were generally evenly distributed in each trial. Participants in the ‘higher cognitive score’ trial were slightly younger, with a larger proportion having Higher Education qualifications, compared to those in the ‘lower cognitive score’ trial. Samples were predominantly White (British, Irish or European), living with a partner and regular users of the internet.

*(Insert Table 1 about here)*

Participants were comparable to non-participants in terms of mean age (69.2 years vs 69.9 years respectively), demonstrated a similar gender balance (51.7% of participants vs. 49% invited were female), but areas of lower deprivation were over-represented (mean index of multiple deprivation (IMD) was 7.5 in participant group vs. 6.8 in non-participants; Office for National Statistics, 2019)

The remainder of the results section reports our findings relating to the acceptability and feasibility of: 1) the Active Brains intervention, and 2) the proposed trial procedures.

### Acceptability and feasibility of ‘Active Brains’ – uptake, usage and preliminary indications of change

#### Uptake and usage of Active Brains

Uptake of the intervention amongst those in the intervention arms (with or without support) was higher in the ‘lower cognitive score’ trial at 93.8%, compared to 86.4% in the ‘higher cognitive score’ trial. Usage of Active Brains is shown in table 2.

*(Insert Table 2 about here)*

Across both trials, and regardless of support provision, there was high initial use of Active Brains online content followed by a gradual decline over time. The three main components of Active Brains are released sequentially (Active Lives immediately, Brain Training after four weeks, Eat for Health after eight weeks), and approximately 50% of participants were still accessing Active Brains once all content was available. ‘Getting Active’ was the most accessed of the (simultaneously available) physical activity sub-modules. Access to ‘Breaks from Sitting’ (reducing sedentary time) was relatively low across all users but appeared higher in the supported group in the ‘lower cognitive score’ trial.

Larger proportions of the supported groups accessed the Strength and Balance and Brain Training modules - especially in the ‘lower cognitive score’ trial. Whilst the frequency of use of Brain Training games per participant was low overall, those in the supported groups accessed the games more frequently. Use of ‘Eat for Health’ was consistent across groups, with approximately 50% of users accessing this.

#### Uptake of, and adherence to, human support

Participants randomised to the support groups were offered up to three brief telephone support calls (or email support) with a trained facilitator during the first 12 weeks. These appointments only occurred if the participant contacted their designated supporter to arrange them. In addition, all support arm participants received automated emails from their designated supporter at three- and seven-weeks post-randomisation. These provided general encouragement and a reminder of the further support available. Uptake of these support opportunities is shown in table 3.

*(Insert Table 3 about here)*

More than half of all support arm participants contacted their supporter, and half had at least one telephone support appointment. Uptake of support was higher in the ‘lower cognitive score’ trial. Those in this trial were more likely to have multiple appointments. Feedback from supporters was collated via email and group discussion and is reported in supplementary materials 1.

#### Preliminary estimates of change

##### Primary outcome data

Although the feasibility trials were not powered to make statistical comparisons between groups, we can comment briefly on indicative patterns in the descriptive analysis of primary outcome data (Table 4).

*(Insert Table 4 about here)*

In the ‘lower cognitive score’ trial there was an overall indication of improved verbal reasoning scores at follow-up, as well as a smaller proportion of respondents meeting AACD/MCI criteria, across all trial arms. The change in proportion of respondents meeting the AACD criteria appears more pronounced in intervention arms compared to usual care.

In the ‘higher cognitive score’ trial, verbal reasoning scores remained consistent between baseline and follow-up in the two intervention arms and showed a small decline in the usual care group. Relatedly, the proportion of participants meeting the AACD/MCI criteria at follow-up increased more sharply in the usual care arm compared to the intervention arms.

An imputed analysis, including auxiliary variables and predictors of missing AACD outcome, gave similar estimates to the observed proportions. This assumes that missing outcomes are missing at random given the observed data.

##### Intervention-targeted behaviours

Reviewing the descriptive analysis of data relating to behaviours targeted by the intervention gives insight into trends to explore further in fully powered trials. Supplementary materials 2 and 3 report the brain training-related activity and healthy eating data respectively, which showed little indication of change or difference between groups. However, the physical activity data (table 5) appeared to indicate some change.

*(Insert Table 5 about here)*

The IPAQ-E data indicated high levels of physical activity amongst participants in both trials at baseline. At follow-up, in the ‘lower cognitive score’ trial there seemed to be a more apparent increase in all domains of activity in the Active Brains only group compared to either the supported group or usual care. In the ‘higher cognitive score’ trial there was a similar, but less pronounced pattern. Here the Active Brains group showed smaller increases across physical activity domains than in the ‘cognitively impaired’ trial, but still larger than in the support and usual care groups which demonstrated little change, or in some cases slight decline.

Uptake of a free pedometer from Active Brains was slightly higher in the ‘lower cognitive score’ trial (35%, n = 63) compared to the ‘higher cognitive score’ trial (29%, n = 52).

### Acceptability and feasibility of trial procedures

#### Collection of primary outcome data

##### Online Baddeley verbal reasoning task

Completion of the Baddeley verbal reasoning data was 76.1% in the ‘higher cognitive score’ trial and 67.2% in the ‘lower cognitive score’ trial. Completion of *some* outcome data regardless of whether the online primary outcome was completed, was 80% in both trials.

In both trials, there was greater primary outcome completion in the usual care groups compared to the intervention groups. Supplementary materials 5 provides a breakdown of primary outcome completion by trial and intervention group.

As our primary outcome completion fell short of the 80% target in both trials, we took measures to address identified issues (table 6).

*(Insert Table 6 about here)*

##### Notes review

We collected notes review data for 94.4% of participants across both trials. Data were analysed to inform any amendments required to the notes review data collection form and choice of instruments to measure quality of life (more detail in supplementary materials 6). We tested detailed collection of medication use both at baseline and follow up, but it proved difficult due to usability and practicality. We simplified the data form by collecting information only if any medication changes occurred during the study period.

We explored use of four quality life and wellbeing measures – SF12, EQ5D-5L, the Warwick-Edinburgh Mental Wellbeing Scale – short version (SWEMWBS; Ng Fat et al., 2017) and the Index of Capability for Older Adults (ICECAP-O; Coast et al., 2008); response rates were similar at both baseline and one-year follow-up. EQ5D-5L and SF12 were more sensitive to QoL variation compared with ICECAP-O and feedback from PPI that ICECAP-O’s items may be difficult or off-putting to answer led us to removing this measure. The EQ-5D-5L, SF12 and SWEMWBS were deemed sufficient to capture quality of life and wellbeing data in the trial population.

#### Evaluating trial procedures

We evaluated the acceptability of the study’s: screening methods, recruitment strategies, randomisation process, study materials, outcome measures, notes review process, and recruitment and attrition rates. Our screening methods appeared largely feasible to operationalise and were effective in recruiting eligible samples for each trial. Throughout the screening process, several minor issues were identified and addressed as described in supplementary materials 7.

Our key findings regarding trial procedures and the associated implications for the main trial are shown in table 7.

*(Insert Table 7 about here)*

## Discussion and Implications

This study provides insight into the uptake of, and engagement with, the Active Brains intervention; provides preliminary interpretations of trends in outcomes at one year, and evaluates the feasibility and acceptability of study procedures. These investigations were conducted amongst adults aged 60-85 with, and without, indications of existing AACD or MCI. The findings are important for determining the feasibility of planned future work to investigate the effectiveness of Active Brains.

### Uptake and engagement with Active Brains

The Active Brains usage data indicates that the intervention is feasible and acceptable for participants in both trials to access and use, with 50% still using it at two months. If the slightly higher proportion of ‘lower cognitive score’ participants accessing Active Brains overall (94% vs. 86% of the ‘higher cognitive score’ participants) reflects a real difference, this may indicate a greater perceived relevance of the intervention amongst this group. Previous research has demonstrated that self-perceived cognitive deficit predicts willingness to invest time in interventions to protect cognition (Harrell et al., 2019).

Usage of the online brain training element of Active Brains was low and did not reflect the intervention’s recommendations (3-5 times per week for an initial 6-month period). Across all groups, the median number of brain training sessions per user indicates lower usage than in a previous trial of the same cognitive training tasks which demonstrated a significant benefit for older adults’ cognitive function (Corbett et al., 2015). Our qualitative process data (to be reported elsewhere) indicated that many participants got bored of the games quite quickly which may explain low continued engagement. Whilst sufficient engagement with the brain training games is important, exactly what ‘sufficient engagement’ is in the context of a multi-domain intervention such as Active Brains is complex. For example, participants may have only accessed the components they were most interested in. Recent evidence from a study examining dose-response in a multi-domain dementia prevention intervention suggests that higher number of sessions engaged with was not necessarily optimal for cognitive outcomes (Belleville et al., 2022). Active Brains may also have prompted users to engage in brain training activities outside of the intervention – i.e. other online games, or pursuing ‘offline’ activities.

Despite this lower than anticipated engagement with the online brain training, the behavioural data suggests that physical activity recommendations may have been better engaged with. Whilst previous studies have recognised that the IPAQ-E can over-estimate time spent across all activity intensities and underestimate sedentary time amongst older adults (Ryan et al., 2018), inflation of physical activity estimates here are likely to be present at both baseline and follow-up and so any changes across time should indicate actual change. The IPAQ-E data indicated increases in physical activity behaviour in the Active Brains group – particularly in the ‘lower cognitive score’ trial. Active Brains was developed with the intention of minimising users’ need to regularly access online content and to instead build activity into daily routine and habits. Accordingly, sustained online engagement with the online content prompting physical activity was not considered necessary to support effective engagement with the intervention (Yardley et al., 2016). The suggestion of a possible increase in physical activity in the Active Brains groups is promising given that recent syntheses of the evidence about modifiable dementia risk factors indicate that interventions to enhance physical activity behaviour point towards small beneficial effects for cognition overall, whereas those for cognitive training are somewhat less conclusive (Livingston et al., 2020). The pattern of larger IPAQ-E increases in the Active Brains only groups compared to the supported groups indicates that brief human support may not be beneficial (or may even be detrimental) in relation to independently sustaining physical activity behaviour. These interpretations can be further explored in the fully powered trial.

About half of those offered additional support in each trial took up at least one telephone appointment. This is comparable to support uptake across a range of digital behaviour change interventions with similar models of brief additional support (Hallsworth et al., 2021; Santer et al., 2014). Those in the ‘lower cognitive score’ trial seemed to use the additional support more than those in the ‘higher cognitive score’ trial – particularly in terms of having multiple telephone appointments. This might be indicative of this group perceiving more need for the additional support. Regular telephone support has been advocated as an important strategy for maintaining engagement with complex interventions for those with cognitive impairment (Walton et al., 2020).

Differences in usage between the supported and non-supported groups, suggest that the support may have acted differently in the two trials. In the ‘lower cognitive score’ trial, a larger proportion of those in the support group accessed brain training compared to in the non-supported group, and also appeared to access the games more frequently. In the ‘higher cognitive score’ trial, although similar proportions of the supported and non-supported groups accessed brain training, individuals in the supported group seemed to access it more frequently. However, in both trials the additional support appeared to enhance engagement with brain training. Within the ‘lower cognitive score’ trial, those in the supported group also appeared more likely to access the full range of physical activity sub-sections than those in the non-supported group.

### Preliminary indications about intervention outcomes.

Patterns identified in the primary outcome data suggest that testing of Active Brains in fully powered effectiveness trials is warranted for both groups. In the ‘lower cognitive score’ trial, the indication of improved Baddeley verbal reasoning scores and fewer individuals meeting the AACD/MCI criteria at one year was seen in all trial arms including the usual care group. Whilst the improvement in the usual care group may suggest this improvement was not due to the intervention, this might be partly a consequence of the study procedures. All participants entering this trial were advised that their score on the baseline cognitive tests was slightly lower than the average. This may have prompted them to take action over the following year; those allocated to the usual care arm may have sought external advice or interventions beyond the brief advice sheet they were provided with, which may have led to improved scores. This message is no longer presented as it was not deemed acceptable by participants. In the ‘higher cognitive score’ trial, the minimal change in the Baddeley verbal reasoning scores and proportions meeting the AACD/MCI criteria in the intervention arms compared to indications of sharper decline in the usual care groups gives a provisional indication of a protective effect of Active Brains. It is possible that the higher withdrawal rates from the intervention arms in both trials may account for the patterns seen. However, assuming that the AACD outcomes are missing at random given the observed data, we would expect this apparent protective effect to remain. This would be reduced under the extreme assumption that all of those missing meet the AACD criteria.

### Feasibility and acceptability of study procedures

The findings indicated that the trial procedures were generally feasible, but also highlighted elements that required refining. Whilst there were imbalances of some participant characteristics between trial groups this is not unexpected given relatively small groups and should be overcome in larger main trial samples. Although successful in collecting 94% of the notes review data, our findings indicated that changes were required to facilitate sufficient response to the online Baddeley verbal reasoning task – particularly amongst those in the ‘lower cognitive score’ trial who may have found this more challenging. It is recognised that cognitive decline may detrimentally affect participant retention or follow-up within research given that it can make completion of research tasks more difficult, time consuming, and frustrating (Mody et al., 2008). In this case, the effect may be compounded by our primary outcome requiring online completion, therefore not offering the usual paper alternative. However, following recommendations by Mody et al. (2008), the subsequent changes to our materials and procedures offer participants more guidance and support about completing the online primary outcomes, and provide further explanation and encouragement. The greater completion of the primary outcome in the usual care groups compared to intervention groups likely reflects a combination of higher withdrawal rates in the intervention arms of both trials comparative to usual care, and possible fatigue with, or overlooking of, study emails within the intervention arms. The changes to automated emails and withdrawal process are anticipated to improve primary outcome completion in the intervention arms.

Retention of participants within the trials was another important factor in collecting sufficient follow-up data. Across both trials, withdrawal was relatively low, but disproportionately from the intervention arms. Those in the intervention arms naturally had more contact from the study team and therefore more opportunity to request withdrawal. After randomisation, the usual care participants were only contacted when their 12-month follow-up was due. However, the changes aimed to make it clearer and easier for participants to stop engaging with the intervention without leaving the trial, and also reassured them that completion of the primary outcome only was sufficient if that’s all they could manage.

### Strengths and limitations

The study’s parallel design allowed us to explore study objectives amongst older adults with and without existing indications of cognitive decline. This has allowed optimisation of the intervention and procedures amongst both groups. We can now trial the intervention to determine its effectiveness for both groups. In depth qualitative work conducted alongside these feasibility trials will be published separately providing further insight into participants’ engagement with Active Brains.

A key limitation was the lack of diversity in our sample with regards to ethnicity and deprivation. A predominantly white sample, largely from areas of low deprivation may not represent the outcomes or engagement we may have seen with a more diverse sample. Our recruitment region is likely to have contributed to both of these factors. The average IMD score of all invitees was 6.9, indicating lower than average levels of deprivation amongst all those invited. Furthermore, the South West region of England has the lowest proportion of non-White residents in the country (Office for National Statistics, 2012). For the main trials, we will employ a nationwide recruitment strategy to encourage invitation of more diverse groups in terms of both ethnicity and deprivation. Furthermore, we will consider other strategies to maximise recruitment of a diverse sample– for example, sending more invitations in areas with higher proportions of non-white residents and/or higher deprivation indices. We will also aim to engage with a wider group of PPI contributors with a more diverse range of characteristics, perspectives and experiences to ensure our recruitment strategies are accessible and engaging to a diverse audience.

### Conclusions

This study provides evidence that a multi-domain digital behaviour change intervention to protect cognitive health is feasible and acceptable amongst adults aged 60-85 both with and without existing indications of cognitive decline. The proposed trial procedures were largely feasible and confirmed that a nationwide primary care recruitment strategy should be a suitable approach. Minor modifications to recruitment and follow-up materials and procedures were important for providing participants with additional support and encouragement to complete the online primary outcome measures. Early indications from the primary outcome and behavioural data suggest Active Brains might offer protective benefits. Large-scale fully powered effectiveness trials amongst older adults with (n =10,940) and without (n=10,515) indications of existing cognitive decline will now investigate whether Active Brains is effective in reducing cognitive decline.

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## Tables and Figure captions

Figure 1. Recruitment and retention into the parallel trials; \* Cohort group data not presented within this paper

Table 1. Participant baseline characteristics in each trial

Table 2. Usage of Active Brains components by trial and trial arm

Table 3. Uptake and use of support provision

Table 4. Baddeley Verbal Reasoning task scores and number meeting AACD/MCI criteria

Table 5. Baseline and follow-up IPAQ-E (physical activity) data in each trial

Table 6. Issues with primary outcome collection and mitigating measures

Table 7. Acceptability of study processes - key findings and implications for trial



**Figure 1.**

**Table 1.**

|  |  |  |
| --- | --- | --- |
|  | **‘Lower cognitive score’ Trial** | **‘Higher cognitive score’ Trial** |
|  | **Active Brains** **n=53** | **AB + Support n=59** | **Usual Care** **n=68** | **Active Brains** **n=65** | **AB + Support n=60** | **Usual Care** **n=55** |
| **Female** | 34 (64.2%) | 33 (55.9%) | 43(63.2%) | 25 (38.5%) | 32 (53.3%) | 34(61.8%) |
| **Age (mean, SD)** | 71.1 (6.8) | 70.9 (5.5) | 70.8 (5.7) | 67.9 (5.3) | 67.8 (6.0) | 67.5 (5.1) |
| **Living situation** |
| On my own | 10 (18.9%) | 12 (20.3%) | 25 (36.8%) | 9 (13.8%) | 13 (21.7%) | 9 (16.4%) |
| With a spouse/partner | 40 (75.5%) | 45 (76.3%) | 39 (57.4%) | 54 (83.1%) | 45 (75.0%) | 45 (81.8%) |
| With a relative | 3 (5.7%) | 2 (3.4%) | 4 (5.9%) | 2 (3.1%) | 1 (1.7%) | 1 (1.8%) |
| With a friend | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (1.7%) | 0 (0.0%) |
| **Ethnic Group** |
| White | 53 (100.0%) | 58 (98.3%) | 68 (100.0%) | 64 (98.5%) | 59 (98.3%) | 55 (100.0%) |
| Mixed  | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (1.5%) | 1 (1.7%) | 0 (0.0%) |
| Asian | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Black | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Other  | 0 (0.0%) | 1 (1.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| **Education Level** |
| Secondary | 20 (37.7%) | 22 (37.3%) | 27 (39.7%) | 11 (16.9%) | 11 (18.3%) | 15 (27.3%) |
| Post-secondary | 9 (17.0%) | 9 (15.3%) | 10 (14.7%) | 10 (15.4%) | 11 (18.3%) | 9 (16.4%) |
| Vocational | 16 (30.2%) | 12 (20.3%) | 16 (23.5%) | 17 (26.2%) | 13 (21.7%) | 14 (25.5%) |
| Undergraduate | 6 (11.3%) | 11 (18.6%) | 10 (14.7%) | 17 (26.2%) | 17 (28.3%) | 13 (23.6%) |
| Post-graduate | 1 (1.9%) | 3 (5.1%) | 4 (5.9%) | 6 (9.2%) | 6 (10.0%) | 3 (5.5%) |
| Doctorate | 1 (1.9%) | 2 (3.4%) | 1 (1.5%) | 4 (6.2%) | 2 (3.3%) | 1 (1.8%) |
| **Internet Use** |
| Every day | 43 (81.1%) | 40 (67.8%) | 51 (75.0%) | 55 (84.6%) | 54 (90.0%) | 46 (83.6%) |
| A few times each week | 10 (18.9%) | 19 (32.2%) | 15 (22.1%) | 10 (15.4%) | 6 (10.0%) | 8 (14.5%) |
| A few times a month | 0 (0.0%) | 0 (0.0%) | 1 (1.5%) | 0 (0.0%) | 0 (0.0%) | 1 (1.8%) |
| Less often | 0 (0.0%) | 0 (0.0%) | 1 (1.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

**Table 2.**

|  |  |
| --- | --- |
|  | **% of people (and number) from each workstream and group who accessed at least once** |
| **Section**  | **Lower cognitive score (n=112)** | **Higher cognitive score (n=125)** | **Combined (n= 237)** |
|  | AB (n=53) | AB + S (n=59) | AB (n=65) | AB + S (n=60) | AB (n=118) | AB + S(n=119) |
| Overall uptake (any use) | 92.5% (49) | 94.9% (56) | 89.2% (58) | 83.3% (50) | 90.7%(107) | 89.1%(106) |
| Active Brains introduction | 92.5% (49) | 93.2% (55) | 87.7% (57) | 83.3% (50) | 89.8%(106) | 88.2%(105) |
| Active Lives (AL) intro | 84.9 % (45) | 84.7% (50) | 78.5% (51) | 75% (45) | 81.4% (96) | 79.8% (95) |
| AL: Getting Active | 56.6% (30) | 57.6% (34) | 61.5% (40) | 61.7% (37) | 59.3% (70) | 59.7% (71) |
| AL: Strength and Balance | 49.1% (26) | 61% (36) | 46.2% (30) | 50% (30) | 47.5% (56) | 55.5% (66) |
| AL: Breaks from Sitting | 32.1% (17) | 45.8% (27) | 40% (26) | 35% (21) | 36.4% (43) | 40.3% (48) |
| Brain Training (BT) | 58.5% (31) | 72.9% (43) | 58.5% (38) | 65% (39) | 58.5% (69) | 68.9% (82) |
| Number of BT sessionsa | 848 | 838 | 1113 | 1062 | 1961 | 1900 |
| Median BT sess. per user | 3 | 5 | 3 | 5 | 3 | 5 |
| Eat for Health | 52.8% (28) | 47.5% (28) | 46.2% (30) | 53.3% (32) | 49.2% (58) | 50.4% (60) |

aBT sessions = number of separate occasions Brain Training games were accessed

**Table 3.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Support type** | **Lower cognitive score support arm** **(n = 59)** | **Higher cognitive score support arm** **(n = 60)** | **Overall****(n= 119)** |
| **Participant made email contact** | 68% (40) | 53% (32) | **61% (72)** |
| **At least one phone appointment** | 54% (32) | 47% (28) | **50% (60)** |
| **At least two phone appointments** | 27% (16) | 13% (8) | **20% (24)** |
| **All three phone appointments** | 7% (4) | 0 | **3% (4)** |
| **Requested additional phone appointment** | 2% (1) | 0 | **1% (1)** |

**Table 4.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Lower cognitive score Trial** | **Active Brains (n=53)** | **Active Brains + Support (n=59)** | **Usual Care (n=68)** |
| **Baseline** | **Follow up**  | **Baseline** | **Follow up**  | **Baseline** | **Follow up**  |
| **Baddeley Verbal Reasoning score** Mean (SD) | 16.4 (4.9) | 18.7 (6.6) | 15.2 (5.8) | 19.1 (8.7) | 14.7 (5.8) | 19.45 (7.3) |
| **AACD flag** n (%)(1 SD below norm verbal reasoning) | 53 (100%) | 23/32 (71.9%) | 59 (100%) | 25/38 (65.8%) | 68 (100%) | 39/51 (76.5%) |
| **MCI flag** (1.5 SD below norm verbal reasoning) | 27(50.9%) | 13/32 (40.6%) | 35 (59.3%) | 15/38 (39.5%) | 45 (66.2%) | 20/51 (39.2%) |
| Missing score (n, %) | 0 (0.0%) | 21 (39.6%) | 0 (0.0%) | 21 (37.3%) | 0 (0.0%) | 17 (25.0%) |
| **Higher cognitive score Trial** | **Active Brains (n=65)** | **Active Brains + Support (n=60)** | **Usual Care (n=55)**  |
| **Baseline** | **Follow up**  | **Baseline** | **Follow up**  | **Baseline** | **Follow up** |
| **Baddeley Verbal Reasoning score** Mean (SD) | 31.4 (6.2) | 32.1 (8.1) | 31.6 (6.7) | 32.2 (8.1) | 30.4 (4.9) | 28.8 (7.8) |
| **AACD flag** (1 SD below norm verbal reasoning) | 0 (0.0%) | 5/48 (10.4%) | 0 (0.0%) | 5/40 (12.5%) | 0 (0.0%) | 12/49 (24.5%) |
| **MCI flag** (1.5 SD below norm verbal reasoning) | 0 (0.0%) | 1/48 (2.1%) | 0 (0.0%) | 1/40 (2.5%) | 0 (0.0%) | 5/49 (10.2%) |
| Missing score (n, %) | 0 (0.0%) | 17 (26.2%) | 0 (0.0%) | 20 (33.3%) | 0 (0.0%) | 6 (10.9%) |

**Table 5.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Lower cognitive score Trial** | **Active (n=53)**  | **AB + Support (n=59)** | **Usual Care (n=68)** |
| **Baseline** | **Follow up** | **Baseline** | **Follow up** | **Baseline** | **Follow up** |
| IPAQ mean (SD) MET minutes per week  | 4238.2 (2670.2) | 5414.9 (3475.6) | 3459.8 (2551.9) | 3656.2 (3121.8) | 4302.7 (2709.3) | 4577.4 (2676.2) |
| Mean (SD) minutes per week walking | 753.5 (423.3) | 825.1(444.8) | 604.9(372.0) | 617.7 (395.7) | 625.8 (389.9) | 671.2 (411.0) |
| Mean (SD) minutes per week moderate | 463.8 (371.0) | 632.7(441.4) | 379.1(265.6) | 429.0 (346.3) | 465.9 (335.6) | 461.6 (347.7) |
| Mean (SD) minutes per week vigorous | 137.8 (110.7) | 217.0(162.9) | 206.6(166.5) | 213.8 (166.2) | 220.3 (185.7) | 254.5 (201.5) |
| Mean (SD) minutes per week strength/balance a | 93.6 (54.7) | 247.5(306.0) | 107.6 (99.5) | 118.6 (148.4) | 149.3 (175.4) | 149.5 (118.4) |
| Missing IPAQ (n, %) | 0 (0.0%) | 25 (47.2%) | 0 (0.0%) | 29 (49.2%) | 0 (0.0%) | 20 (29.4%) |
| **Higher cognitive score Trial** | **Active Brains (n=65)** | **AB + Support (n=60)** | **Usual Care (n=55)** |
| **Baseline** | **Follow up** | **Baseline** | **Follow up** | **Baseline** | **Follow up** |
| IPAQ mean (SD) MET minutes per week | 3362.2 (1853.2) | 4157.0 (2944.8) | 3488.3 (2457.5) | 3607.2 (2052.9) | 4449.2 (2647.5) | 4004.1 (2413.7) |
| Mean (SD) minutes per week walking | 625.1 (389.6) | 673.0(393.0) | 612.0(401.5) | 588.3 (383.0) | 694.1 (432.8) | 647.7 (401.3) |
| Mean (SD) minutes per week moderate | 302.7 (238.3) | 396.0(310.4) | 339.4(327.5) | 366.3 (309.0) | 537.3 (415.2) | 390.6 (313.8) |
| Mean (SD) minutes per week vigorous | 155.6 (141.4) | 249.3(308.2) | 96.7 (65.5) | 94.3 (71.2) | 118.2 (80.4) | 194.7 (160.6) |
| Mean (SD) minutes per week strength/balance a | 93.5 (88.5) | 127.4(113.7) | 72.1 (43.6) | 123.5 (137.6) | 91.4 (54.3) | 101.6 (78.7) |
| Missing IPAQ (n, %) | 0 (0.0%) | 20 (30.8%) | 0 (0.0%) | 20 (33.3%) | 0 (0.0%) | 9 (16.4%) |

a An item relating to frequency and duration of strength and balance was added for the present study in the format of the IPAQ questionnaire but does not typically feature in the validated version of this survey.

**Table 6.**

|  |  |
| --- | --- |
| **Problem identified** | **Mitigation measures(s) implemented** |
| Less than 80% completion of online primary outcome task – especially amongst participants in ‘lower cognitive score’ trial.  | * Reordered follow-up process: moved phone call ahead of sending paper measures (to avoid completion of paper measures without primary outcome)
* Changed focus of call to prompting/supporting participants to complete online measures
* Added step to follow-up process between automated emails and phone call: postal reminder to complete follow-up online with detailed instructions about how to access and complete online tasks
 |
| Message possibly not clear that online tasks were the most important element and could be completed quickly | * Changes to PIS documents and automated email prompts to emphasise importance of completing online task even if no time for other parts
* Provided a time estimate for completion of tasks (10 minutes) to illustrate they could be completed quickly
* Adaptation of paper follow-up packs splitting into very brief ‘primary outcomes’ (IQCODE, IADL and EQ5D), plus additional longer pack of secondary measures. Accompanying letter stresses importance of online tasks, and signposts to this.
 |
| Possibility of automated emails being ignored/spam filtered so people miss request to complete online measures | * Amended emails to be sent from named email account; more clearly distinguishes them from other emails from Active Brains that don’t require action
 |
| Higher withdrawal rate from intervention groups limiting maximum possible follow-up | * Clarified existing ‘partial withdrawal’ (for participants wanting to cease use of Active Brains/ receiving intervention emails, but happy to be contacted to complete follow-up measures) option: made it clear to participants they can choose ‘partial withdrawal’ even if only happy to complete the online primary outcome task.
* Amended online system to allow participants more control over self- selecting level of withdrawal. Aim to maximise partial (primary) outcome data from those who would otherwise provide none.
 |

**Table 7.**

|  |  |
| --- | --- |
| **Key findings** | **Implications for main trial** |
| **Recruitment strategies** |
| * Primary care recruitment proved feasible to recruit to target (n=360) within timeframe (3 months)
* Practices reported database search criteria easy to operationalise
* Practices identified screening process as the most resource intensive aspect, and determinant of maximum mailout size.
* Average mailout size = 288
* Average number of participants recruited per practice = 29
* Alternative routes explored (e.g. Join Dementia Research, Dementia Platforms UK, poster recruitment) not feasible for various reasons:
* no clear pathway to access participants’ medical notes for review at the end of the study;
* administrative procedures required far too resource intensive at the scale required;
* screening out ineligible invitees not possible/easy
 | Primary care recruitment only feasibleBased on need to recruit n =21,455 across both trials, will need to recruit approx. 740 GP practices |
| **Randomisation** |
| * Pure randomisation
* Performed automatically ‘behind the scenes’ by the Active Brains website, allowing participants seamless transition from baseline measures to notification of group allocation
* Resulted in relatively evenly balanced groups even in small sample
* No reported issues with randomisation
 | Randomisation method will be taken forward to main trial unchanged |
| **Study materials** |
| * Participant facing materials and instructional documents for GP practices generally accessible and easy to follow
* Clarifications required to information sheet/ follow-up questionnaires/ cover letter to maximise completion of online primary outcome
 | Modifications to participant facing documentation detailed in Table 5 |
| **Outcome measures** |
| * Overall good completion – 80% in both trials provided some follow-up data
* Little missing data due to online completion automatically flagging missed responses
* Slightly lower than hoped completion of primary outcome – particularly in ‘lower cognitive score’ trial
* Some issues identified with IPAQ-E and IADL measures – further details provided in supplementary materials 8.
 | Modifications to participant facing documentation detailed in Table 5 to facilitate improved completion of primary outcomeContinued use of IPAQ-E to measure physical activity – further detail in supplementary materials 8.Minor modifications to IADL measure – further detail in supplementary materials 8. |
| **Notes review** |
| * Highly successful in collecting required data – 94.4% of whole sample notes review data collection; 100% of the data requested
* Instructional document ensured form was easy to complete, but practice staff expressed concerns that it was too time consuming per patient, especially re. medical conditions and medications.
 | Removed baseline medications and medical conditions questions and only record any changes/ additions since baseline. Added questions on these items to participants’ baseline measures. |
| **Recruitment and attrition rates** |
| * 10.2% randomisation rate – 560 participants from 5475 invites
* 92.2% retention rate – 28 withdrew, 14 from each trial
* Across both trials, withdrawal rate from intervention substantially higher than Usual Care - 0.8%; Active Brains - 10.2%, Active Brains Plus Support - 12.6%
* Loss to follow-up (i.e. no completion of primary outcome amongst those who remained in the study) higher in ‘lower cognitive score’ trial (24.4%) than in ‘higher cognitive score’ trial (16.1%)
 | Confirms need for 730-740 GP practices.Amendments to ensure: 1) clear to participants they could withdraw from use of the intervention without leaving the trial; and 2) participants could more easily self-action withdrawal via the website.Changes to follow-up materials to facilitate completion of primary outcome online documented in Table 5. |

## Supplementary Materials