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**Cognitive Training and Neuroplasticity in Mild Cognitive Impairment (COG-IT):  
Clinical Rationale and Study Design  
A two-site, blinded, randomized, controlled treatment trial.**

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Manuscripts

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3 **Cognitive Training and Neuroplasticity in Mild Cognitive Impairment (COG-IT):**  
4 **Clinical Rationale and Study Design**  
5 **A two-site, blinded, randomized, controlled treatment trial.**  
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## ABSTRACT

*Introduction:* Mild cognitive impairment (MCI) is common in older adults and represents a high-risk group for progression to Alzheimer's disease (AD). Medication trials in MCI have generally failed, but new discoveries with brain plasticity in aging have led to the study of cognitive training as a potential treatment to improve cognitive abilities. Computerized Cognitive Training (CCT) involves computerized cognitive exercises that target specific cognitive abilities and neural networks to potentially improve cognitive functioning through neuroplasticity.

*Methods and Analysis:* In a two-site study (New York State Psychiatric Institute/Columbia University Medical Center and Duke University Medical Center) we will randomize 100 patients with MCI (WMS-III Logical Memory II score 0-11; MMSE  $\geq$  23) to home-based CCT (suite of exercises: memory, matching, spatial recognition, processing speed) or a home-based active control condition (computerized crossword puzzle training; CPT) with 12 weeks of intensive training followed by regular booster sessions up to 78 weeks. All patients will receive standard neuropsychological and functional assessments in clinic as well as structural/functional brain MRI scans at study entry and endpoint. We will test if CCT, versus CPT, leads to improved cognitive functioning, transfers to functional ability and tasks of everyday life, and impacts hippocampal volume changes and changes in the default mode network (DMN) of the brain measured by resting-state fMRI.

*Ethics:* The study will be conducted following ethics approval and written informed consent will be obtained from all subjects.

*Dissemination/Significance:* Study results will be disseminated via publication, [clinicaltrials.gov](http://clinicaltrials.gov), media and conference presentations. This will be the first controlled long-term trial to evaluate the effects of home-based computerized cognitive training versus computerized crossword puzzle training on not only cognitive abilities, but also functional measures and neural outcomes as determined by MRI indices in patients with MCI. Positive results from this pilot trial may support further development of home-based cognitive training in people at risk for dementia.

*Trial Registration:* ClinicalTrials.gov Identifier: NCT03205709.

## ARTICLE SUMMARY

### Strengths and Limitations of this Study

- The study will improve upon limitations of most previous studies by including an “active” control condition, rather than waitlist or control conditions that do not account for engagement and motivation.
- This study will evaluate performance on traditional cognitive and functional assessments (e.g., ADAS-Cog 11, UPSA) in addition to performance on a self-administered, computerized cognitive test, the NeuroCognitive Performance Test (NCPT), which consists of 10 subtests that are online adaptations of widely used neuropsychological tests.
- The trial will utilize a remote internet-based CCT intervention that can be done at home; compared to most existing treatments under investigation, it is easily accessible, relatively inexpensive, non-invasive, and scaled to the skill level of each individual.
- The trial will include evaluation of clinically relevant genetic, brain network, and neuronal loss markers as moderators of outcome; this will be one of the first trials to examine long-term effects on cognition, daily functioning, and neuroplastic changes in DMN with CCT in MCI.
- As our trial will be restricted to English-speaking participants because the online training platform is only available in English, we are unsure how this will generalize to non-English speaking individuals.
- In addition, the inclusion criteria state that the participant must have an at-home desktop or laptop computer, which, in low socioeconomic class homes, is not always available.

## INTRODUCTION

Alzheimer's disease (AD) is a major public health concern affecting over 40 million people worldwide and there is an urgent need to develop new treatment modalities to prevent or delay the onset of dementia. Mild cognitive impairment (MCI) is common in older adults and represents a high-risk group for AD, but medication trials in MCI have generally failed. There is no FDA-approved treatment for MCI or to prevent the progression of MCI to AD.

There is growing evidence that a cognitively active lifestyle may reduce rates of dementia. A systematic review of 22 population-based studies found that mental activities may reduce overall incident dementia risk by 46% over a median 7-year period [1]. Computerized Cognitive Training (CCT) provides a novel strategy to improve cognitive performance in MCI by establishing a more cognitively active lifestyle. CCT involves computerized cognitive exercises that target specific abilities to improve cognitive functioning, and this effect is likely to be mediated by neuroplasticity. CCT has been used successfully to improve cognitive functioning in healthy adult populations [2, 3, 4, 5]. In particular, two studies in older healthy controls have garnered much attention. The ACTIVE trial is the first ever large-scale, randomized trial to show evidence of transfer from cognitive training to improved daily function, but only in participants who completed reasoning or speed of processing focused training, and not memory training [6]. In this ten-year follow up study with 2,832 healthy adults (average age = 73.6), participants were randomized to one of three intervention groups (memory, reasoning, or speed of processing) or a no-contact control group. Booster sessions occurred for 39% of participants in all active groups at 11 and 35 months after initial training, but the cognitive effects of the memory training did not persist over the ten-year follow up period [6]. In addition, a large online cognitive training study was originally considered to be negative in terms of cognitive gains. However, in an examination of an older subsample, training was effective in improving cognitive abilities and instrumental activities of daily living [7].

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3 In a recent meta-analysis examining CCT in older adults with MCI or dementia, the overall  
4 efficacy of cognitive outcomes in MCI was moderate and statistically significant [8]. This pattern  
5 was also found for global cognition, verbal learning and memory, nonverbal learning, working  
6 memory, attention, and psychosocial functioning (e.g. depression, quality of life,  
7 neuropsychiatric symptoms). However, for the efficacy of cognitive outcomes in patients with  
8 dementia, the overall effect was found to be small, though statistically significant.  
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15 Early interventions at the stage of MCI, and not dementia, may be more helpful for improving  
16 cognition. In fact, Hill et al. [8] concluded that CCT is a feasible intervention for improving  
17 cognition in patients with MCI. Transfer effects have also been found in studies evaluating CCT  
18 in healthy older adults, supporting the potential for transfer of CCT benefits to daily life [6, 9]. In  
19 this study, we will assess for transfer effects by administering the following functional  
20 assessments at specific timepoints: Functional Activity Questionnaire (FAQ) and University of  
21 California Performance-Based Skills Assessment (UPSA).  
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29 Although CCT has received more support in the past few years as a viable treatment option for  
30 older adults with MCI, the brain mechanisms underlying the observed cognitive changes remain  
31 elusive. Many studies of CCT that include imaging components have only been conducted with  
32 healthy older adults [10, 11, 12, 13]. CCT may have neuroplastic effects in the brain, including  
33 in the hippocampus, a key region that supports memory [13, 14, 15, 16]. Additional research  
34 needs to be done that evaluates both structural and functional data within a rigorously-conducted  
35 clinical trial. In this study, patients will undergo a structural MRI and fMRI at both study entry  
36 and exit to assess for changes in hippocampal volume and the default mode network.  
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44 The default mode network (DMN) of the brain is crucial to evaluate in patients with MCI as  
45 dysfunction in the DMN has been implicated in the progression of MCI to AD [17]. The DMN is  
46 a resting state neural network of several highly interconnected cortical hubs, including the  
47 posteromedial parietal, anteromedial frontal, and inferolateral parietal cortices. We have shown  
48 that impaired deactivation and functional connectivity in the DMN may be a significant predictor  
49 in MCI of poor memory and transition to dementia over a 2-3 year follow-up period [18].  
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55 Neuronal dysfunction precedes structural atrophy in AD, and functional magnetic resonance  
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3 imaging (fMRI) offers the potential for identifying specific patterns of disruption in the memory  
4 networks affected early in MCI and AD.  
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8 Limitations of prior CCT trials include the inconsistent demonstration of transfer to everyday  
9 functioning, reliance on waitlist control conditions as opposed to active control conditions, and  
10 lack of long-term follow-up. Most studies have not assessed transfer of cognitive improvement  
11 to everyday function or quality of life [19, 20, 21, 22, 23]. While CCT may produce transfers to  
12 untrained cognitive domains, the few studies that evaluate transfer to everyday functioning have  
13 reported mixed findings [24, 25, 26-29]. This is particularly important given the strong  
14 association between cognitive decline and functional disability [30]. Many studies use waitlist  
15 control conditions or control conditions that do not account for engagement and motivation in the  
16 task [22]. Such designs are biased in favor of the treatment condition because waitlisted subjects  
17 are not receiving any form of cognitive treatment and, therefore, may be more likely to drop out  
18 of such studies due to lack of engagement and motivation. In the current study, patients will be  
19 assigned to one of two cognitively stimulating exercises, computerized cognitive training (suite  
20 of exercises) or crossword puzzle training (crossword puzzles). Since one of the purposes of  
21 CCT in patients with MCI is to reduce the risk of progression to dementia, longer follow-up  
22 times are necessary to be able to accurately capture patient progression. However, most studies  
23 have only used no follow-up or short-term follow-ups, with the notable exception of the  
24 ACTIVE trial [6, 31-33].  
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39 Overall, recent findings in the field suggest that computerized cognitive training could benefit  
40 patients at risk for dementia. The current study will build on these findings by implementing a  
41 study design with an active control group, a longer trial duration, an increased intensity of  
42 computerized cognitive training, examination of generalizability to functional abilities beyond  
43 cognitive training skills, structural and functional MRI assessment, and rigorously blinded  
44 methodology.  
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## 51 **METHODS AND ANALYSIS**

### 52 **Study Design Features and Rationale**

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3 One-hundred patients clinically diagnosed with mild cognitive impairment (MCI) will be  
4 randomized. There will be two sites: New York State Psychiatric Institute/Columbia University  
5 Medical Center in New York, NY (NYSPI as lead coordinating site) and Duke University  
6 Medical Center in Durham, NC. Patients will be randomized to one of two computerized  
7 cognitively stimulating exercises: crossword puzzle training (CPT) or a suite of exercises (CCT;  
8 memory tasks, matching tasks, spatial recognition tasks, processing speed tasks). These patients  
9 will be randomized by MCI type (early MCI or late MCI), age (70 and below or 71 and above),  
10 and site (NYSPI/CUMC or DUMC) as the stratification factors and will be followed for 78-  
11 weeks. The randomization sequences will be balanced in blocks of random size (2, 4) to prevent  
12 clinicians from guessing what the next patient's treatment might be.  
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22 In order to maintain neutrality and mitigate expectancy bias among patients, the informed  
23 consent form signed by all patients during the screening visit will not indicate which group is  
24 the active group (suite of exercises) or the control group (crosswords). Rather, it will indicate  
25 that the patient may be assigned to one of two cognitively stimulating exercises, CCT or CPT.  
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### 31 **Role of Sponsor**

32 The study is funded entirely by a National Institute on Aging grant and supervised by a Data  
33 Safety Monitoring Board. Using Lumosity, a web-based gaming platform from Lumos Labs, we  
34 customized a specific set of CCT and CPT training modules for participants to use in this trial.  
35 After a comprehensive review of several CCT modules on the market, we chose these modules  
36 from Lumosity due to their large selection of games tailored to specific cognitive domains, their  
37 research specific platform, availability of active control condition, availability of an online self-  
38 administered neuropsychological test battery (NCPT), and our previous pilot data in the elderly  
39 with this platform; see figures 1 and 2 for examples of the Lumosity platform. Aside from  
40 providing the research platform and technical support at no cost, Lumos Labs provides no  
41 financial support for this study and their staff have no significant role in the final study design,  
42 study conduct, data interpretation or publication. Patients will not be required to pay for the  
43 platform and will not have a post-study commitment to the platform. None of the study team has  
44 any financial conflicts with Lumos Labs.  
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## Recruitment, Eligibility, Consent

Patients will be recruited from the current patient caseload of the investigators, referral by neurology, psychiatry, primary care, public health (inner city) and geriatric medical clinics affiliated with the centers and supplemented by advertisement.

### Inclusion/Exclusion Criteria.

Detailed inclusion/exclusion criteria are described in Table 1. Notable inclusion criteria will be age range restriction 55-95 years, subjective cognitive complaints (i.e., memory or other cognitive complaints, e.g., naming/language), Wechsler Memory Scale-III (WMS-III) Logical Memory Story A delayed recall score 0-11, Folstein Mini Mental State Examination (MMSE) score  $\geq 23$  out of 30, availability of an informant, and access to a home desktop or laptop computer with full access to the internet for the study duration. Patients who have a history of major psychiatric or neurological illness, a dementia diagnosis of any type, contraindication to MRI scan, lack of English-speaking ability, or have been defined as regular online brain training or regular crossword puzzle users ( $\geq 2$  times per week in the past year) will be excluded.

Depression will be assessed using the 15-item Geriatric Depression Scale (GDS); a diagnosis of Major Depressive Disorder is exclusionary.

**Table 1. Inclusion/Exclusion Criteria**

<b>Inclusion Criteria</b>
1. Males and females 55 to 95 years of age (inclusive) at the time of informed consent.
2. Subjective cognitive complaints, i.e., memory or other cognitive complaints, e.g., naming/language.
3. Meets criteria for cognitive impairment (CI) defined as scores $>1$ SD below standardized norms on memory function as identified by the Wechsler Memory Scale (WMS) III Logical Memory delayed recall score.
4. Folstein Mini Mental State (MMSE) score $\geq 23$ out of 30.
5. A family member or other individual who is in contact with the patient and consents to serve as informant during the study; this could be a telephone informant in case of patients who do not have a live-in informant or close significant other.
6. Access to a home desktop or laptop computer at acceptable speed for the study duration.
<b>Exclusion Criteria</b>
1. Diagnosis of dementia of any type.
2. Current clinical evidence of schizophrenia, schizoaffective disorder, major depression, psychosis, or bipolar I disorder (DSM-IV TR criteria).
3. Active suicidal ideation or plan.
4. Current or recent (past 6 months) alcohol or substance use disorder (DSM-5 criteria).

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5. Clinical stroke with residual neurological deficits. While we will not exclude patients with cerebrovascular disease, we will not include patients who have had a stroke with residual clinical deficits because it is not clear that this type of patient is similar to the MCI patient generally, and clear-cut neurological impairment, e.g., hemiplegia/hemiparesis or speech impairment, may compromise the patient's ability to do the CCT or active control procedures and to complete the neuropsychological tests.
  6. Use of medications known to have a negative impact on cognition: benzodiazepines in lorazepam equivalents  $\geq 1$  mg daily, narcotics, anticholinergics. Other patients receive medications that may be associated with cognitive impairment but are rarely considered the likely etiology, e.g., theophylline, nifedipine, beta blockers; they will not be excluded. Patients receiving other psychotropic medications not expected to have a material impact on cognition, e.g., SSRIs and SNRIs will be eligible.
  7. Presence of any of the following disorders: a) CNS infection, with CSF evidence of meningitis, encephalitis, or other infectious process; b) dementia of any type; c) Huntington's disease; d) Multiple sclerosis; e) Parkinson's disease; f) Other neurologic disorders with focal signs, e.g., amyotrophic lateral sclerosis; g) Mental retardation.
  8. Acute, severe unstable medical illness. For cancer, acutely ill patients (including those with metastases) will be excluded, but past history of successfully treated cancer will not result in exclusion.
  9. Contraindication to MRI scan: pacemaker, metal implants following surgery, any other contraindication to MRI. Eligibility for the MRI scan is a requirement for the study.
  10. UPSIT exclusions: current smoker  $> 1$  pack daily, current upper respiratory infection (retested as soon as the infection clears). UPSIT scores are reduced in schizophrenia, Parkinson's disease and Parkinson's related conditions; these disorders are exclusion criteria for this study. Patients with UPSIT exclusions will not receive the UPSIT but will continue to participate in all other aspects of the study.
  11. Patients lacking English-speaking ability as determined by self-report and clinical evaluation.
  12. Regular online brain training or regular crossword puzzle user, defined as doing these procedures at a frequency of twice weekly or greater during the year prior to screening. Eligible participants who join the trial are instructed not to do these procedures on their own during the trial, i.e., independent of the study.
  13. Participation in another intervention trial for cognitive impairment.
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### *Mild Cognitive Impairment Criteria*

Mild cognitive impairment (MCI) and type of MCI (early MCI or late MCI) will be assessed by the delayed recall score of WMS-III Logical Memory and by the score on the Folstein Mini Mental Status Examination (MMSE). On Logical Memory II Story A, a score from 0-11 will indicate cognitive impairment, per the Alzheimer's Disease Neuroimaging Initiative (ADNI) criteria. MCI type will be determined from this score combined with years of education of the patient. Early MCI (eMCI) will be defined as a delayed recall score of 3-6 with 0-7 years of education, score of 5-9 with 8-15 years of education, and score of 9-11 with 16 or more years of education. Late MCI (lMCI) will be defined as a delayed recall score of  $\leq 2$  with 0-7 years of education, score of  $\leq 4$  with 8-15 years of education, and score of  $\leq 8$  with 16 or more years of education. For both eMCI and lMCI, everyday function must be well preserved for study inclusion. A MMSE score  $\geq 23$  will also be required to indicate mild cognitive impairment, and this is required for study inclusion.

### **Length of Clinical Trial**

Most transitions from MCI to AD typically occur by three years of follow-up after the diagnosis of MCI is made [34]. We chose 18-months as the length of this clinical trial to decrease dropouts that can occur in a very long controlled trial. Thus, we will conduct a follow-up visit one year after the last study visit, which is a total duration of 2.5 years of participation. Since this study is considered low risk, we do not anticipate participants to suffer harm from trial participation.

### **Treatment Regimen**

Enrolled participants will come to the clinic for five scheduled visits (Weeks 0, 12, 32, 52, and 78) and will receive at least three scheduled phone calls with research staff (Weeks 20, 42, and 64). Participants will be enrolled into the study after screening for eligibility and consent is signed. The randomization will be assigned by the statistician and then carried out by the unblinded research coordinator, with individuals stratified by MCI type, age group, and site. The term “control” will not be used in the consent form in order to reduce the participant’s expectancy bias.

Randomization.

The blinded research coordinator (at NYSPI or Duke) will complete the Training Group Randomization Form to indicate the following information for the patient: site, age, and MCI type. This form will be verified by the unblinded research coordinator at NYSPI, who will then assign a study ID to that patient, using a pre-populated form from the statistician’s randomization assignment. The order of the study ID assignment will determine which study condition the patient will receive: CPT or CCT. The Lumosity account information will be generated after the MRI has been completed and quality checked. Lumosity account credentials will include a research-specific COGIT ID email address and password, which will enable users to log into an account specific to their study condition. The unblinded research coordinator at NYSPI will then send the login credentials to the blinded research coordinator at the appropriate site.

Randomization will be complete when the patient logs into his/her account for the first time at the baseline visit and sees which condition he/she is in. At this visit, patients will be trained by unblinded study staff in their assigned training condition. Eighteen modules were selected to

target various cognitive domains: (A) Memory (Tidal Treasures, Familiar Faces, Memory Matrix) (B) Processing Speed (Speed Match) (C) Response Inhibition (Color Match) (D) Verbal Fluency/Vocabulary Proficiency (Word Bubbles, Word Snatchers, Editor's Choice, Continuum) (E) Planning/Divided Attention (Train of Thought, Brain Shift, Trouble Brewing, Disillusion) (F) Visual Interference (Lost in Migration, Ebb and Flow, Masterpiece) (G) Identification (River Ranger) (H) Visualization (Speed Pack). These cognitive domains were chosen as they are areas that are often impaired in patients with MCI and thus represent areas that can be targeted for improvement [35]. Each CCT session will consist of a random selection of six modules. Each module will require the use of various cognitive abilities and will scale in difficulty with the patient's progress. The Lumosity platform will scale difficulty by using the patient's Lumosity Performance Index (LPI). The LPI will consider the following areas for each patient: Game Performance Index, Cognitive Area Performance Index, and overall Cognitive Performance Index. The Game Performance Index will be determined by reviewing score distributions for each game. The Cognitive Area Performance Index (speed, memory, attention, flexibility and problem solving) will be calculated using a weighted average of the Game Performance Index. Lastly, the overall Cognitive Performance Index will be calculated using a weighted average of the Game Performance Indices from all cognitive areas. A complete list of selected CCT games and the associated cognitive abilities being tested are described in Table 2. There should be no case in which an emergency unblinding will need to take place, as the blinded intervention is a computerized intervention.

**Table 2. Complete list of CCT game battery and associated cognitive domains (provided by Lumos Labs)**

Game Name	Cognitive Domain
Tidal Treasures	Working Memory i.e., delayed, non-matching to sample; self-ordered pointing
Speed Match	Processing Speed
Color Match	Response Inhibition
Word Bubbles	Verbal Fluency
Train of Thought	Planning Divided Attention Multiple attractions
Familiar Faces	Episodic Memory
Memory Matrix	Episodic Memory; Visuospatial memory
Lost in Migration	Visual Interference

Brain Shift	Task Switching
Trouble Brewing	Multitasking, divided attention, sustained attention, planning, working memory
Ebb and Flow	Task switching, semantic and visual interference
Masterpiece	Mental rotation; visualization; spatial reasoning
River Ranger	Identification
Word Snatchers	Vocabulary proficiency
Speed Pack	Visualization
Disillusion	Task Switching
Editor's Choice	Vocabulary Proficiency
Continuum	Vocabulary Proficiency

Participants in the computerized cognitive training group and the crossword puzzle training group will spend the same amount of time on the platform during the intensive training phase, which will consist of four 30-minute training sessions per week for 12 weeks. For both groups, responses will be entered via mouse and keyboard. For the crossword puzzle training group, questions will not need to be completed in order and there will not be any feedback for the accuracy of the response at the time of entry by the participant. Upon completion of the CCT suite of exercises after 30 minutes, participants will receive a score. Similarly, after 30 minutes the crossword training will automatically end. If a participant were to finish an entire crossword puzzle before the 30-minute cutoff, they would be directed to another puzzle to ensure they complete a total of 30 minutes. Global automated feedback will be given in a similar manner for both groups.

Following the intensive training phase of 12 weeks, participants will be instructed to complete six booster sessions. Each booster session will consist of four computerized cognitive training/crossword puzzle training sessions. Booster sessions will be completed at weeks 20, 32, 42, 52, 64, and 78. At weeks 32, 52, and 78, patients will be instructed to complete three booster sessions at home and to complete the fourth session in-clinic with research staff. At weeks 20, 42, and 64, patients will be instructed to complete all four booster sessions at home. Generally, in previous cognitive training studies, booster sessions have been limited. For instance, the ACTIVE trial had two booster sessions, each consisting of four 75-minute trainings at 11 and 35 months. During the course of the trial, booster sessions included a total of 8 trainings, for a total of 10 hours [6]. In contrast, COGIT will have six booster sessions (24 total training sessions each lasting 30 minutes) over 15 months. Thus, COGIT will include 12 hours total for booster

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3 sessions during the trial. The ACTIVE trial only required compliant participants to complete the  
4 booster sessions, whereas all participants will complete booster sessions in the COGIT study [6].  
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8 Clinic Based Cognitive, Functional, and Smell Assessments.  
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10 At baseline (week 0) The Alzheimer's Disease Assessment Scale-Cognition Subscale 11  
11 (ADAS-Cog 11) will be administered, in addition to the following neuropsychological test  
12 battery: WAIS-III Block Design (to assess visuospatial skills), Digit Symbol Substitution Test  
13 (to assess attention), Trail Making A & B (to assess attention and executive function), Verbal  
14 Fluency and 15-item Boston Naming Test (to assess language), Auditory-Verbal Learning Test  
15 (to assess verbal learning and memory), and WMS-III Visual Reproduction Test (to assess  
16 nonverbal learning and memory). In addition, the University of California Performance-Based  
17 Skills Assessment (UPSA) and University of Pennsylvania Smell Identification Test (UPSIT)  
18 will be administered. The Functional Activity Questionnaire will be administered to the patient's  
19 informant, either during the study visit or shortly after the visit over the phone.  
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29 Self-Administered Cognitive Test Battery.

30 Another unique aspect of the study is the use of an online self-administered test, the  
31 NeuroCognitive Performance Test (NCPT), which will be self-administered via computer. It  
32 will test various cognitive domains outlined in the Study Measures section. The NCPT will allow  
33 us to examine the efficacy of a self-administered test, in combination with standardized, clinic-  
34 based neuropsychological tests.  
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### 41 **Timeline of Longitudinal Assessments**

42 At subsequent in-clinic visits (weeks 12, 52, and 78), the same neuropsychological battery of  
43 testing will be completed. At the week 12 and week 78 visits, patient will be asked to complete  
44 the User Engagement Scale, which will be adapted to capture usage of a computerized platform.  
45 This scale will measure aspects of engagement, usability, and satisfaction with the computerized  
46 platform on a 5-point Likert scale. Week 20 will be a phone interview between study  
47 physician/neuropsychologist and patient to follow-up on how the patient has been doing, and to  
48 remind the patient to complete a booster session of computerized training.  
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### **Blinded Training Procedure**

The blinded research coordinator will administer the full neuropsychological test battery, including the UPSA and FAQ. The blinded clinician will complete the Diagnosis Form and the Contributing Features to MCI form after clinical interview and review of the neuropsychological testing. The unblinded research coordinator will be responsible for administering the initial computerized training and all subsequent booster sessions of training to patients in the clinic. Each week, the unblinded research coordinator will review the compliance of all patients. Over any two week period, a patient must be 50% compliant with the computerized training sessions. If the participant does not demonstrate this level of compliance, the unblinded research coordinator will call the patient to ensure high compliance rates and to provide assistance with technical problems.

### **Hypotheses**

See Figure 3 for a Conceptual Model of specific study aims and outcome measures. The primary aim of the study is to assess change in cognitive and functional status over 18 months in MCI patients comparing the CCT and CPT groups. Hypothesis 1: MCI patients randomized to CCT will show better cognitive outcomes on the ADAS-Cog 11 (primary outcome measure), Neuropsychological Testing Composite score (secondary outcome measure), and NeuroCognitive Performance Test (exploratory outcome measure) compared to active control (CPT). Hypothesis 2: MCI patients randomized to CCT will show better functional outcomes as assessed by the UPSA (primary functional outcome) and the FAQ (secondary functional outcome) by the end of the 18-month trial compared to active control. Hypothesis 3: brain pathology (smaller hippocampal volumes, lower odor identification scores on the UPSIT, ApoE e4 allele present) will moderate the relationship between treatment assignment and cognitive and functional outcomes.

The secondary aim of the study is to examine the effects of CCT on resting-state DMN connectivity as well as other networks modulated by CCT effects. Hypothesis 1: MCI patients randomized to CCT will demonstrate greater change in an index of DMN functional connectivity compared to patients randomized to active control. Hypothesis 2: indicators of brain pathology (smaller hippocampal volumes, lower odor identification scores on the UPSIT, ApoE e4 allele



present) will moderate the relationship between change in the DMN and treatment assignment (see Figure 4 [36]).

The tertiary aim of the study is to examine differences in rates of progression to dementia and AD in the two randomized treatment groups, recognizing that if progression to these outcomes is uncommon there will be insufficient statistical power. Hypothesis 1: the proportion converting to dementia will be lower in the CCT group compared to active control.

### Study Measures

Study measures with time-points of administration are listed in Table 3. The MMSE will be administered at screen and each subsequent in-clinic visit using five different versions of the three-word recall item to reduce practice effects [37]. The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) and The Framingham Stroke Risk Scale will be completed by the study physician at screen and week 78 to assess for cardiovascular disease risk factors and other medical conditions.

**Table 3. Table of Study Procedures**

Measure	Screen	Baseline	12 Weeks	20 Weeks Phone Interview	32 Weeks	42 Weeks	52 Weeks	64 Weeks	78 Weeks
ADAS-Cog11		X	X				X		X
APOE & blood test	X								
CIRS-G	X								X
Cognitive Reserve Index	X								
Cognitive Training or Control training booster session			X	X	X	X	X	X	X
Contributing Features to MCI		X			X				X
Demographics History (Patient Tracking Form)	X								
Diagnosis Form			X		X				X
Digit Symbol Substitution Test		X	X				X		X
Expectancy Scale (Participant & Informant)		X			X				X
Family History FAQ	X	X	X	X	X		X		X
Framingham Stroke Risk	X								X
Geriatric Depression Scale	X		X		X		X		X
History of Game Use Questionnaire	X		X						X
Inclusion/ Exclusion Form	X								
Informed Consent	X								

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3	Medications (Chart List & Database List)	X	X	X	X	X
4						
5	MMSE	X	X	X	X	X
6	MRI Scan of Brain	X				X
7	NCPT online cognitive performance test		X	X		X
8	Neuropsychological Battery: AVLT, Block Design, Verbal Fluency, Visual Reproduction, Boston Naming Test, Trails A & B		X	X	X	X
9						
10	Physical Activity Assessment	X				
11						
12	UPSA		X	X		X
13	UPSIT		X			X
14	User Engagement Scale			X		X
15	WMS-III Logical Memory I & II	X				
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The Geriatric Depression Scale will be administered at screen and each subsequent in-clinic visit to assess for depression. If GDS is greater than 5 at any visit, the patient will be evaluated by a psychiatrist and an appropriate clinical referral will be made, if needed, for treatment of depression. The Cognitive Reserve Index is a brief questionnaire that will be administered by the research coordinator at screen and will evaluate the cognitive reserve of an individual by means of the compilation of information as it relates to his/her adult life.

At screen, the research coordinator will be responsible for administering the History of Game Use Questionnaire, Physical Activity Assessment, and WMS-III Logical Memory I & II. The History of Game Use Questionnaire will be administered again at weeks 12 and 78 to ensure that patients are not partaking in any other types of cognitive training games while in the study.

At screen and week 78, patients will undergo an MRI scan of the brain. The MRI scan will include the following sequences: Localizer, high-resolution T1-weighted IR prepped 3DSPGR, and T2 FLAIR, and GE-EPI resting-state fMRI scans.

At weeks 0 and 78, the UPSIT will be completed by the patient, which is a 40-item scratch and sniff multiple-choice olfactory identification test.

At each in-clinic visit, apart from week 32, the ADAS-Cog 11 and full neuropsychological test battery will be administered. The NCPT will be administered at weeks 0, 12, and 78. The NCPT

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3 is a brief, unsupervised, online battery of cognitive assessments developed by Lumosity. The  
4 cognitive domains measured by the NCPT are memory (visuo-spatial working memory, short-  
5 term memory), processing speed (visual search, psychomotor speed), problem solving (logical  
6 reasoning, numerical calculation), attention (selective, divided), and flexibility (response  
7 inhibition, task-switching). The assessments, 10 total “subtests,” are online adaptations of widely  
8 used neuropsychological tests whose test properties are not affected by shifting to computerized  
9 administration [38].  
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17 The neuropsychological test battery includes: WAIS-III Block Design, Digit Symbol  
18 Substitution Test, Trail Making A & B, Verbal Fluency and 15-item Boston Naming Test,  
19 Auditory-Verbal Learning Test, and WMS-III Visual Reproduction Test. The UPSA will be  
20 administered only at weeks 0, 32, and 78 due to the high tendency for practice effects. It is a  
21 performance-based measure of functional abilities that includes measures of simulated real-world  
22 activities; for example, planning a trip to the beach, remembering documents to bring to a  
23 medical appointment, and dialing a phone number.  
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31 At screen and weeks 12, 32, 52, and 78 the participant will meet with the study physician or the  
32 neuropsychologist to assess for illness progression and adverse events. Adverse events that are  
33 spontaneously reported to research coordinators at any clinic visit will be discussed with the  
34 study physician or the neuropsychologist in order to determine how to proceed. Adverse events  
35 and subsequent steps to deal with the adverse events will be documented in the patient chart and  
36 serious adverse events will be reported to the Data Safety and Monitoring Board and study  
37 sponsor, National Institute on Aging.  
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45 Additionally, the research coordinator will conduct an interview with the informant at, or shortly  
46 after, each visit to complete the Functional Activity Questionnaire.  
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### 50 **Criteria for Early Discontinuation**

51 We expect early discontinuation to occur because of one or more of the following reasons: (1)  
52 the patient’s decision not to continue the computerized training (CCT or CPT) due to lack of  
53 interest, motivation, or available time; (2) unavoidable circumstances, e.g., moving residence and  
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3 unwillingness to return for in-person evaluations; (3) investigator decision to terminate; (4) death  
4 or prolonged hospitalization for medical reasons. We will not terminate participation for non-  
5 adherence because even if the patient is non-adherent to the protocol, we will document level of  
6 adherence (done electronically in this computerized training protocol) and still include the  
7 patient's data in the analyses based on the intent-to-treat principle.  
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### 13 **Data Management**

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15 Data entry will be completed by Program Managers, Clinical Research Coordinators, and  
16 Research Assistants on the study protocol. Data entry/cleaning will be done throughout the  
17 project. The data collected in this study will be monitored by the Data Coordinating Center at  
18 NYSPI. The unit will work closely with the research assistant/coordinator and the Principal  
19 Investigator to facilitate independent auditing of primary subject records. The database will  
20 provide reports indicating all modifications that have been made in the database together with  
21 paper communications (fax, e-mail) confirming and authorizing these modifications. Access to  
22 the data system is available only to authorized users, with multiple levels of security including  
23 user id/password authentication via MS Active Directory overseen by experienced IT personnel.  
24 Other authorized users with direct access to the data system will be Data Coordinating Center  
25 (DCC) staff. DCC data-related operations and the SIR/Citrix system have been certified by  
26 Columbia University's Information Security Office. The dataset will not be published in a data  
27 repository.  
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### 39 **Genetic Testing**

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41 Apolipoprotein E (ApoE) genetic analysis on a blood sample will be done through the laboratory  
42 of the Human Genetics Resources Core (HGRC) at Columbia University Medical Center. We  
43 will assess the ApoE  $\epsilon$ 4 allele as potentially associated with response to CCT; a prior trial found  
44 an association between the  $\epsilon$ 4 allele and cognitive improvement on donepezil [39].  
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### 50 **Concomitant Medications**

51 Putative cognitive enhancers, narcotics, all classes of psychotropic medications, and over 20  
52 other classes of commonly prescribed and over the counter (and alternative) medications will be  
53 documented in a rating form at screen and subsequent in-clinic visits. An exclusion criterion will  
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3 be daily use of medications known to have a negative impact on cognition: high-dose narcotics,  
4 anticholinergics, and benzodiazepines in lorazepam equivalents  $\geq 1$  mg daily. During the first 12  
5 weeks of the study, the intensive cognitive training phase, patients are encouraged not to change  
6 any of their medications, unless clinically indicated.  
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## 10 11 **Statistical Analysis and Sample Size**

12 Outcome Measures (Primary and Secondary Hypotheses Testing).

13 *Aim 1 Hypothesis 1 and 2.* MCI patients on CCT will show a lower rate of cognitive and  
14 functional decline compared to MCI patients on active control by the end of the 18-month trial.  
15 We will use generalized linear mixed effects models of cognitive and functional measures  
16 collected repeatedly across the 78 weeks according to the schedule (see Table 3). For example,  
17 cognitive measure $_{ik} = \beta_0 + \beta_1 \text{Time}_{ik} + \beta_2 \text{Group}_i + \beta_3 (\text{Group}_i \times \text{Time}_{ik}) + v_{0i} + v_{1i} \text{Time}_{ik} + \varepsilon_{ik}$   
18 where  $\text{Group}_i$  indicates treatment group for subject  $i$  ( $\text{Group} = 1$  CCT, 0 for control),  $k = \text{time}$   
19 (baseline, 12 weeks, 20 weeks, 52 weeks, 78 weeks), and  $v_{0i}$  is a subject-specific random  
20 intercept. Time will be treated as categorical if linearity is not plausible and group effects at 18  
21 months can be tested by forming contrasts from the fitted model. Potential site differences will  
22 be evaluated using descriptive statistics and site will be included in all analyses as a covariate, as  
23 will other stratification variables including age group and MCI type at baseline.  
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36 *Aim 2 Hypothesis 1.* MCI patients randomized to CCT will demonstrate either more of an  
37 increase or less of a decrease in DMN connectivity (goodness-of-fit [GOF] index scores)  
38 compared to patients randomized to active control. To test this hypothesis, we will use a repeated  
39 measures Analysis of Covariance (ANCOVA) with time (baseline vs. post treatment) as the  
40 repeated measure, DMN connectivity as an outcome, treatment condition (CCT vs CPT) as a  
41 predictor, and site, age, and MCI status at baseline as covariates.  
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48 *Moderating Effects in Aim 1 Hypothesis 3 and Aim 2 Hypothesis 2.* As a part of our exploratory  
49 analyses, we will examine specific potential moderators: Apolipoprotein E  $\epsilon 4$  allele, MRI  
50 indices, UPSIT. To show, for example, that baseline hippocampal volume is a moderator, we  
51 will test its interactive effect with treatment on outcomes. Moderator and moderator-interaction  
52 terms can be easily accommodated in the mixed effects regression models described in Aim 1,  
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3 Hypotheses 1 and 2. A similar approach will be used by adding moderator and moderator x  
4 Group interactions to the ANCOVA described in Aim 2 Hypothesis 1. The results must be  
5 interpreted with the caveat that there may not be enough power to assess these interactions,  
6 especially for moderators with low prevalence.  
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12 *Aim 3 Hypothesis 1.* The proportion diagnosed with dementia during follow-up will be lower in  
13 the CCT group compared to active control. Logistic regression will be used to test the binary  
14 outcome of dementia status at 18 months predicted by treatment group controlling for site, age  
15 group, and MCI type at baseline.  
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### 20 **Sample Size.**

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22 A power analysis was conducted using the RMASS program for longitudinal studies, which  
23 determined that a total sample size of 100 participants will provide a sufficient effect size to  
24 evaluate our hypotheses.  
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### 27 **Patient and Public Involvement**

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29 Patients will first be involved in the research after study design is finalized by the study  
30 investigators. At this stage, patients will be referred by physicians or self-referred from online  
31 and newspaper advertisements for their initial screening visit. The patients will not be involved  
32 in study design, study recruitment or conduct, or dissemination of study results. We will assess  
33 the burden of the trial intervention on patients using the User Engagement Scale and the  
34 Participant/Informant Expectancy Scales. Patients will not be invited to comment on the study  
35 design and were not consulted to develop patient relevant outcomes or interpret the results.  
36 Patients will not be invited to contribute to the writing or editing of this document for readability  
37 or accuracy.  
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## 45 **ETHICS**

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48 This study has been approved by NYSPI IRB, Duke University IRB, and Queens College IRB.  
49 All COGIT patients at entry will be required to have the capacity to provide informed consent  
50 and sign the IRB-approved informed consent form. Local IRB and state regulations for consent  
51 will be followed. Patient confidentiality as it pertains to potential and enrolled participants  
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3 before, during, and after the trial will be collected, shared, and maintained strictly according to  
4 HIPAA law.  
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8 Important protocol modifications will be communicated to the Data Safety and Monitoring  
9 Board, NYSPI IRB and Duke University IRB, and updated online for trial registries.  
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13 The research data on specific moderators, including UPSIT and apolipoprotein E genotyping,  
14 will not be not released to the patient, and this will be specified in the consent form. The  
15 cognitive testing results and clinical reading of the MRI scan will be released to the patient (and  
16 the patient's primary physician, if requested); the MRI research volumetric ratings and fMRI  
17 findings will not be released.  
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#### 24 **Data Safety and Monitoring Board (DSMB)**

25 Three independent experts with expertise in conducting clinical trials in mild cognitive  
26 impairment will form the DSMB. All serious adverse events (SAEs) will be reported to the  
27 DSMB. The DSMB will audit the trial conduct, review all SAEs, participate in a teleconference  
28 twice a year to determine if the study should continue, and then will provide an actionable report  
29 to the Principal Investigator. This process will be independent from the investigators.  
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#### 36 **DISSEMINATION**

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39 The study results will be disseminated through publications and conference presentations as well  
40 as on public websites, including clinicaltrials.gov. Researchers will be eligible for authorship  
41 after consideration by the principal investigators; no professional writers will be utilized.  
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#### 46 **SIGNIFICANCE**

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49 This will be one of the first controlled long-term trials to evaluate the effects of home-based  
50 computerized cognitive training versus computerized crossword puzzle training on cognitive,  
51 functional, hippocampal and default mode network connectivity neural outcomes in MCI.  
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3 Positive results from this pilot trial may support the further development of home based  
4 cognitive training and self-assessments in people at risk for dementia.  
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8 The results will help inform the design of a more powerful RCT in many ways: determine  
9 sample size for a multicenter trial, identify subgroups more likely to benefit, identify subdomains  
10 and exercises most likely to improve, optimize training dose and duration, learn how subjects  
11 engage, identify gender effects, model slopes and long-term benefits, assess value of a self-  
12 administered cognitive test, understand brain networks affected, and examine the potential  
13 moderating role of apolipoprotein E ε4 status on CCT outcome.  
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### 20 **AUTHOR CONTRIBUTIONS**

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23  
24 DPD, PMD, JRP, and JRS conceived and designed the study and obtained funding. All other  
25 authors assisted with elements of study design, database, and conduct. HA contributed to  
26 statistics design and JRP to design of MRI component. DPD is the overall study PI and PMD is  
27 the PI at the Duke site. JLD and LSP did the initial draft of the paper and all authors contributed  
28 to manuscript edits and revisions.  
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### 34 **FUNDING STATEMENT**

35  
36  
37 This work is supported by National Institute on Aging, National Institutes of Health, grant  
38 number 1R01AG052440-01A1. We thank Lumos Labs for providing the gaming platform at no  
39 cost; however, they will not have any involvement in the final design, conduct, or analyses of the  
40 study.  
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### 45 **COMPETING INTERESTS**

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48 JLD, LSP, TEG, SNR, SNT, EP, JRP, CAH, HFA, JRS, NAK have no competing interests.  
49 PMD has received research grants and advisory fees from several companies in this field for  
50 other studies, and owns shares in several companies whose products are not discussed here. DPD  
51 serves as a consultant on the advisory board to Acadia, Avanir, and Eisai.  
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**Table 1. Inclusion/Exclusion Criteria**

<b>Inclusion Criteria</b>
1. Males and females 55 to 95 years of age (inclusive) at the time of informed consent.
2. Subjective cognitive complaints, i.e., memory or other cognitive complaints, e.g., naming/language.
3. Meets criteria for cognitive impairment (CI) defined as scores >1 SD below standardized norms on memory function as identified by the Wechsler Memory Scale (WMS) III Logical Memory delayed recall score.
4. Folstein Mini Mental State (MMSE) score $\geq$ 23 out of 30.
5. A family member or other individual who is in contact with the patient and consents to serve as informant during the study; this could be a telephone informant in case of patients who do not have a live-in informant or close significant other.
6. Access to a home desktop or laptop computer at acceptable speed for the study duration.
<b>Exclusion Criteria</b>
1. Diagnosis of dementia of any type.
2. Current clinical evidence of schizophrenia, schizoaffective disorder, major depression, psychosis, or bipolar I disorder (DSM-IV TR criteria).

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3. Active suicidal ideation or plan.
  4. Current or recent (past 6 months) alcohol or substance use disorder (DSM-5 criteria).
  5. Clinical stroke with residual neurological deficits. While we will not exclude patients with cerebrovascular disease, we will not include patients who have had a stroke with residual clinical deficits because it is not clear that this type of patient is similar to the MCI patient generally, and clear-cut neurological impairment, e.g., hemiplegia/hemiparesis or speech impairment, may compromise the patient's ability to do the CCT or active control procedures and to complete the neuropsychological tests.
  6. Use of medications known to have a negative impact on cognition: benzodiazepines in lorazepam equivalents  $\geq 1$  mg daily, narcotics, anticholinergics. Other patients receive medications that may be associated with cognitive impairment but are rarely considered the likely etiology, e.g., theophylline, nifedipine, beta blockers; they will not be excluded. Patients receiving other psychotropic medications not expected to have a material impact on cognition, e.g., SSRIs and SNRIs will be eligible.
  7. Presence of any of the following disorders: a) CNS infection, with CSF evidence of meningitis, encephalitis, or other infectious process; b) dementia of any type; c) Huntington's disease; d) Multiple sclerosis; e) Parkinson's disease; f) Other neurologic disorders with focal signs, e.g., amyotrophic lateral sclerosis; g) Mental retardation.
  8. Acute, severe unstable medical illness. For cancer, acutely ill patients (including those with metastases) will be excluded, but past history of successfully treated cancer will not result in exclusion.
  9. Contraindication to MRI scan: pacemaker, metal implants following surgery, any other contraindication to MRI. Eligibility for the MRI scan is a requirement for the study.
  10. UPSIT exclusions: current smoker  $> 1$  pack daily, current upper respiratory infection (retested as soon as the infection clears). UPSIT scores are reduced in schizophrenia, Parkinson's disease and Parkinson's related conditions; these disorders are exclusion criteria for this study. Patients with UPSIT exclusions will not receive the UPSIT but will continue to participate in all other aspects of the study.
  11. Patients lacking English-speaking ability as determined by self-report and clinical evaluation.
  12. Regular online brain training or regular crossword puzzle user, defined as doing these procedures at a frequency of twice weekly or greater during the year prior to screening. Eligible participants who join the trial are instructed not to do these procedures on their own during the trial, i.e., independent of the study.
  13. Participation in another intervention trial for cognitive impairment.
- 

**Table 2. Complete list of CCT game battery and associated cognitive domains (provided by Lumos Labs)**

Game Name	Cognitive Domain
Tidal Treasures	Working Memory i.e., delayed, non-matching to sample; self-ordered pointing
Speed Match	Processing Speed
Color Match	Response Inhibition
Word Bubbles	Verbal Fluency
Train of Thought	Planning Divided Attention Multiple attractions
Familiar Faces	Episodic Memory
Memory Matrix	Episodic Memory; Visuospatial memory

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3	Lost in Migration	Visual Interference
4	Brain Shift	Task Switching
5	Trouble Brewing	Multitasking, divided attention, sustained attention, planning, working
6		memory
7	Ebb and Flow	Task switching, semantic and visual interference
8	Masterpiece	Mental rotation; visualization; spatial reasoning
9	River Ranger	Identification
10	Word Snatchers	Vocabulary proficiency
11	Speed Pack	Visualization
12	Disillusion	Task Switching
13	Editor's Choice	Vocabulary Proficiency
14	Continuum	Vocabulary Proficiency
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**Table 3. Table of Study Procedures**

Measure	Screen	Baseline	12 Weeks	20 Weeks Phone Interview	32 Weeks	42 Weeks	52 Weeks	64 Weeks	78 Weeks
ADAS-Cog11		X	X				X		X
APOE & blood test	X								
CIRS-G	X								X
Cognitive Reserve Index	X								
Cognitive Training or Control training booster session			X	X	X	X	X	X	X
Contributing Features to MCI		X			X				X
Demographics History (Patient Tracking Form)	X								
Diagnosis Form			X		X				X
Digit Symbol Substitution Test		X	X				X		X

Expectancy Scale (Participant & Informant)		X			X		X
Family History	X						
FAQ		X	X	X	X	X	X
Framingham Stroke Risk	X						
Geriatric Depression Scale	X		X		X	X	X
History of Game Use Questionnaire	X		X				X
Inclusion/ Exclusion Form	X						
Informed Consent	X						
Medications (Chart List & Database List)	X		X		X	X	X
MMSE	X		X		X	X	X
MRI Scan of Brain	X						X
NCPT online cognitive performance test		X	X				X
Neuropsychological Battery: AVLT, Block Design, Verbal Fluency, Visual Reproduction, Boston Naming Test, Trails A & B		X	X			X	X
Physical Activity Assessment	X						
UPSA		X			X		X
UPSIT		X					X
User Engagement Scale			X				X
WMS-III Logical Memory I & II	X						

**Table 3 Legend:** ADAS-Cog 11 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 11. ApoE = Apolipoprotein E gene. CIRS-G = Cumulative Illness Rating Scale for Geriatrics. MCI = Mild Cognitive Impairment. FAQ = Functional Assessment Questionnaire. MMSE = Mini Mental Status Examination. MRI = Magnetic Resonance Imaging. NCPT = NeuroCognitive Performance Test. AVLT = Auditory Verbal Learning Test. UPSA = UCSD Performance-Based Skills Assessment. UPSIT = University of Pennsylvania Smell Identification Test. WMS-III = Wechsler Memory Scale-III.

### Figure 1. Example of Crossword Puzzle Training Condition

This figure is a snapshot of the crossword puzzle training platform. This is an example of the interface a patient in this treatment arm works on to complete training sessions.

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For peer review only

**Figure 2. Example of Computerized Cognitive Training Condition**

This figure is a snapshot from the computerized cognitive training platform. This is an example of the interface a patient in this treatment arm works on to complete training sessions. The picture game is entitled Trouble Brewing.

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### Figure 3. Conceptual Model

In the intervention phase patients are randomly assigned to either CCT or CPT. To evaluate cognitive status, the primary outcome measure will be the ADAS-Cog 11, the secondary outcome measure will be the Neuropsychological Testing Composite Score, and the exploratory outcome measure will be the NeuroCognitive Performance Test. To evaluate functional status, the primary outcome measure will be the UPSA and the secondary outcome measure will be the FAQ. To evaluate changes in the default mode network, the primary outcome measures will include hippocampal volume (MRI) and DMN connectivity (fMRI).

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**Figure 4. Model of CCT Impact on Neural Circuits [36].**

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### Today's Crossword Training

**Across**

1. Holy building

7. Writing tablet

10. Bluegrass singer Krauss

11. "\_\_\_ got my eye on you!"

12. With 24-across, classic Beach Boys song

14. Child

15. Mao \_\_\_-tung

16. Pie \_\_\_ mode

18. No friend

20. Chomps down on

22. Filled with moisture, as a meadow in

**Down**

1. \_\_\_ on (added)

2. "Seinfeld" role

3. Gross growth in the shower

4. Greek letter

5. Ambitious, as goals

6. "Dukes of Hazzard" deputy

7. One of ten in a bowling lane

8. What 26-acrosses do

9. Casino employee

13. Fight back

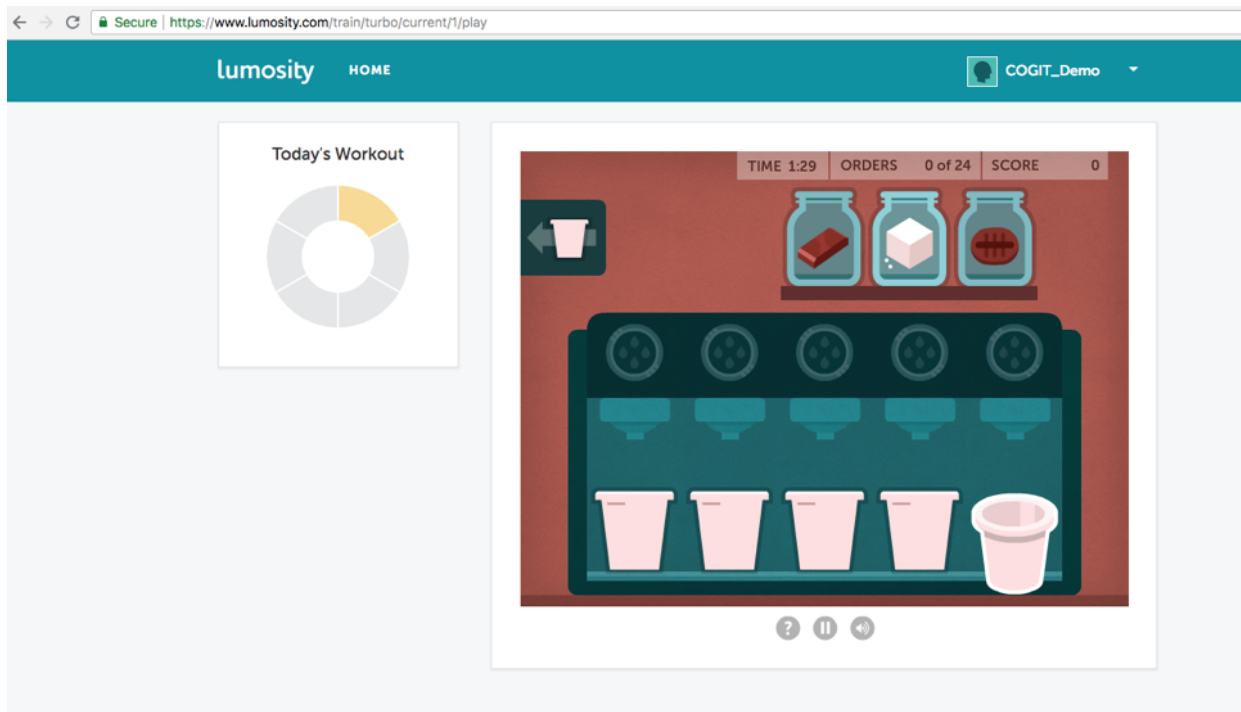
17. Jawbone of an \_\_\_

19. "Goodness gracious!"

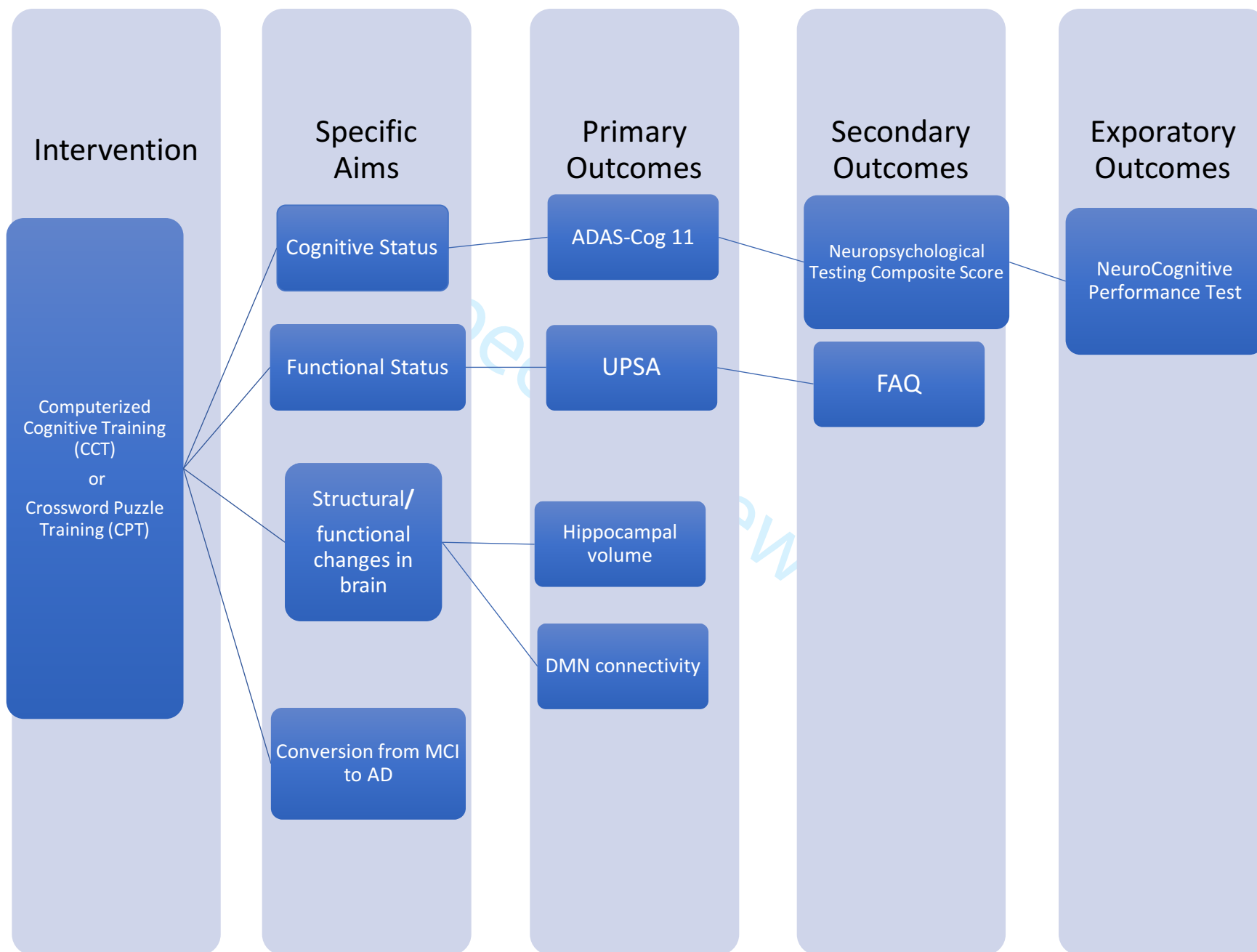
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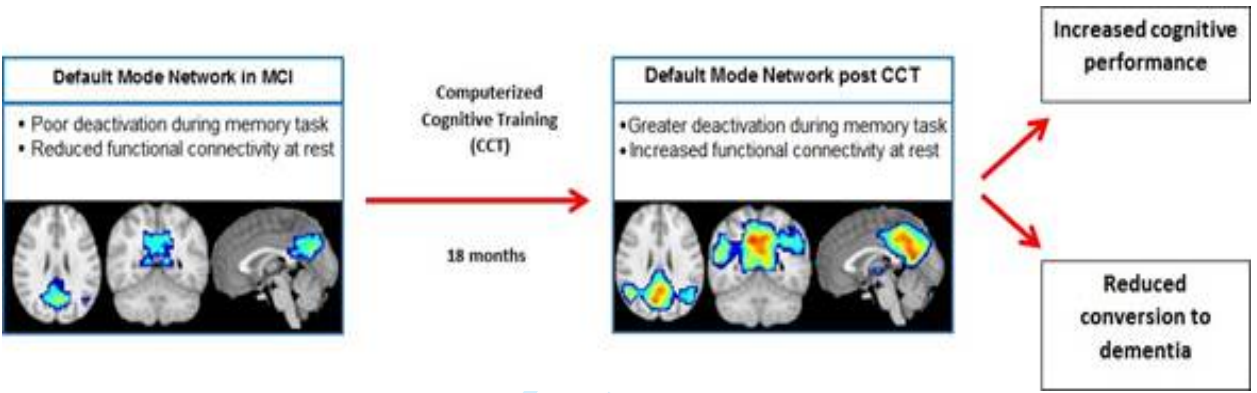


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# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	7; 22
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1;22
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	1



1	sponsor contact			
2	information			
3				
4	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	7;22
5	responsibilities:		collection, management, analysis, and interpretation of data;	
6	sponsor and funder		writing of the report; and the decision to submit the report for	
7			publication, including whether they will have ultimate authority	
8			over any of these activities	
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12	Roles and	#5d	Composition, roles, and responsibilities of the coordinating centre,	18;21
13	responsibilities:		steering committee, endpoint adjudication committee, data	
14	committees		management team, and other individuals or groups overseeing the	
15			trial, if applicable (see Item 21a for data monitoring committee)	
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19	Background and	#6a	Description of research question and justification for undertaking	4-6
20	rationale		the trial, including summary of relevant studies (published and	
21			unpublished) examining benefits and harms for each intervention	
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24	Background and	#6b	Explanation for choice of comparators	4-6
25	rationale: choice of			
26	comparators			
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29	Objectives	#7	Specific objectives or hypotheses	14-15
30				
31				
32	Trial design	#8	Description of trial design including type of trial (eg, parallel	6-19
33			group, crossover, factorial, single group), allocation ratio, and	
34			framework (eg, superiority, equivalence, non-inferiority,	
35			exploratory)	
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39	Study setting	#9	Description of study settings (eg, community clinic, academic	6-7
40			hospital) and list of countries where data will be collected.	
41			Reference to where list of study sites can be obtained	
42				
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44	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	8-9
45			eligibility criteria for study centres and individuals who will	
46			perform the interventions (eg, surgeons, psychotherapists)	
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49	Interventions:	#11a	Interventions for each group with sufficient detail to allow	6-14
50	description		replication, including how and when they will be administered	
51				
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53	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for	17-18
54	modifications		a given trial participant (eg, drug dose change in response to	
55			harms, participant request, or improving / worsening disease)	
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1	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any	14
2	adherence		procedures for monitoring adherence (eg, drug tablet return;	
3			laboratory tests)	
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6	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or	18-19
7	concomitant care		prohibited during the trial	
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10	Outcomes	#12	Primary, secondary, and other outcomes, including the specific	See note
11			measurement variable (eg, systolic blood pressure), analysis metric	1
12			(eg, change from baseline, final value, time to event), method of	
13			aggregation (eg, median, proportion), and time point for each	
14			outcome. Explanation of the clinical relevance of chosen efficacy	
15			and harm outcomes is strongly recommended	
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20	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins	13; 15-
21			and washouts), assessments, and visits for participants. A	17
22			schematic diagram is highly recommended (see Figure)	
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25	Sample size	#14	Estimated number of participants needed to achieve study	20
26			objectives and how it was determined, including clinical and	
27			statistical assumptions supporting any sample size calculations	
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30	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach	8
31			target sample size	
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34	Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer-	7; 10-11
35	generation		generated random numbers), and list of any factors for	
36			stratification. To reduce predictability of a random sequence,	
37			details of any planned restriction (eg, blocking) should be provided	
38			in a separate document that is unavailable to those who enrol	
39			participants or assign interventions	
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44	Allocation	#16b	Mechanism of implementing the allocation sequence (eg, central	10-12
45	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
46	mechanism		describing any steps to conceal the sequence until interventions are	
47			assigned	
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51	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	10-12
52	implementation		participants, and who will assign participants to interventions	
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55	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial	10-12;14
56			participants, care providers, outcome assessors, data analysts), and	
57			how	
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1	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible,	11
2	emergency		and procedure for revealing a participant's allocated intervention	
3	unblinding		during the trial	
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6	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and	15-17
7			other trial data, including any related processes to promote data	
8			quality (eg, duplicate measurements, training of assessors) and a	
9			description of study instruments (eg, questionnaires, laboratory	
10			tests) along with their reliability and validity, if known. Reference	
11			to where data collection forms can be found, if not in the protocol	
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16	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up,	17-18
17	retention		including list of any outcome data to be collected for participants	
18			who discontinue or deviate from intervention protocols	
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21	Data management	#19	Plans for data entry, coding, security, and storage, including any	18
22			related processes to promote data quality (eg, double data entry;	
23			range checks for data values). Reference to where details of data	
24			management procedures can be found, if not in the protocol	
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28	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes.	See note
29			Reference to where other details of the statistical analysis plan can	2
30			be found, if not in the protocol	
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33	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted	19-20
34	analyses		analyses)	
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37	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	19-20
38	population and		adherence (eg, as randomised analysis), and any statistical	
39	missing data		methods to handle missing data (eg, multiple imputation)	
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43	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary of	21
44	formal committee		its role and reporting structure; statement of whether it is	
45			independent from the sponsor and competing interests; and	
46			reference to where further details about its charter can be found, if	
47			not in the protocol. Alternatively, an explanation of why a DMC is	
48			not needed	
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52	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	21
53	interim analysis		including who will have access to these interim results and make	
54			the final decision to terminate the trial	
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1	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17; 21
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6	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	21
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11	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	20
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15	Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	20-21
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22	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7-8; 20
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26	Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	18
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30	Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20-21
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35	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
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39	Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
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44	Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10
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48	Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
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56	Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	21
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1	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	18; 20
2	reproducible research		participant-level dataset, and statistical code	
3				
4				
5	Informed consent	#32	Model consent form and other related documentation given to	10
6	materials		participants and authorised surrogates	
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9	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	18
10			biological specimens for genetic or molecular analysis in the	
11			current trial and for future use in ancillary studies, if applicable	
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## Author notes

1. 14-15; 19-20

2. 14-15;19-20

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# BMJ Open

**Cognitive Training and Neuroplasticity in Mild Cognitive Impairment (COG-IT): Protocol for a two-site, blinded, randomized, controlled treatment trial.**

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3 **Cognitive Training and Neuroplasticity in Mild Cognitive Impairment (COG-IT):**  
4 **Protocol for a two-site, blinded, randomized, controlled treatment trial.**  
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**ABSTRACT**

*Introduction:* Mild cognitive impairment (MCI) is common in older adults and represents a high-risk group for progression to Alzheimer's disease (AD). Medication trials in MCI have generally failed, but new discoveries with brain plasticity in aging have led to the study of cognitive training as a potential treatment to improve cognitive abilities. Computerized Cognitive Training (CCT) involves computerized cognitive exercises that target specific cognitive abilities and neural networks to potentially improve cognitive functioning through neuroplasticity.

*Methods and Analysis:* In a two-site study (New York State Psychiatric Institute/Columbia University Medical Center and Duke University Medical Center) we will randomize 100 patients with MCI (WMS-III Logical Memory II score 0-11; MMSE  $\geq$  23) to home-based CCT (suite of exercises: memory, matching, spatial recognition, processing speed) or a home-based active control condition (computerized crossword puzzle training; CPT) with 12 weeks of intensive training followed by regular booster sessions up to 78 weeks. All patients will receive standard neuropsychological and functional assessments in clinic as well as structural/functional brain MRI scans at study entry and endpoint. We will test if CCT, versus CPT, leads to improved cognitive functioning, transfers to functional ability and tasks of everyday life, and impacts hippocampal volume changes and changes in the default mode network (DMN) of the brain measured by resting-state fMRI.

*Ethics:* The study will be conducted following ethics approval and written informed consent will be obtained from all subjects.

*Dissemination/Significance:* Study results will be disseminated via publication, clinicaltrials.gov, media and conference presentations. This will be the first controlled long-term trial to evaluate the effects of home-based computerized cognitive training versus computerized crossword puzzle training on not only cognitive abilities, but also functional measures and neural outcomes as determined by MRI indices in patients with MCI. Positive results from trial may support further development of home-based CCT.

*Trial Registration:* ClinicalTrials.gov Identifier: NCT03205709.

## ARTICLE SUMMARY

### Strengths and Limitations of this Study

- The study will improve upon limitations of most previous studies by including an “active” control condition, rather than waitlist or control conditions that do not account for engagement and motivation.
- This study will evaluate performance on traditional cognitive and functional assessments (e.g., ADAS-Cog 11, UPSA) in addition to performance on a self-administered, computerized cognitive test, the NeuroCognitive Performance Test (NCPT), which consists of 10 subtests that are online adaptations of widely used neuropsychological tests.
- The trial will utilize a remote internet-based CCT intervention that can be done at home; compared to most existing treatments under investigation, it is easily accessible, relatively inexpensive, non-invasive, and scaled to the skill level of each individual.
- The trial will include evaluation of clinically relevant genetic, brain network, and neuronal loss markers as moderators of outcome; this will be one of the first trials to examine long-term effects on cognition, daily functioning, and neuroplastic changes in DMN with CCT in MCI.
- As our trial will be restricted to English-speaking participants because the online training platform is only available in English, we are unsure how this will generalize to non-English speaking individuals.
- In addition, the inclusion criteria state that the participant must have an at-home desktop or laptop computer, which, in low socioeconomic class homes, is not always available.

## INTRODUCTION

Alzheimer's disease (AD) is a major public health concern affecting over 40 million people worldwide and there is an urgent need to develop new treatment modalities to prevent or delay the onset of dementia. Mild cognitive impairment (MCI) is common in older adults and represents a high-risk group for AD, but medication trials in MCI have generally failed. There is no FDA-approved treatment for MCI or to prevent the progression of MCI to AD.

There is growing evidence that a cognitively active lifestyle may reduce rates of dementia. A systematic review of 22 population-based studies found that mental activities may reduce overall incident dementia risk by 46% over a median 7-year period [1]. Computerized Cognitive Training (CCT) provides a novel strategy to improve cognitive performance in MCI by establishing a more cognitively active lifestyle. CCT involves computerized cognitive exercises that target specific abilities to improve cognitive functioning, and this effect is likely to be mediated by neuroplasticity. CCT has been used successfully to improve cognitive functioning in healthy adult populations [2, 3, 4, 5]. In particular, two studies in older healthy controls have garnered much attention. The ACTIVE trial was the first large-scale, randomized trial to show evidence of transfer from cognitive training to improved daily function, but only in participants who completed reasoning or speed of processing focused training, and not memory training [6]. In this ten-year follow up study of 2,832 healthy adults (average age = 73.6), participants were randomized to one of three intervention groups (memory, reasoning, or speed of processing) or a no-contact control group. Booster sessions occurred for 39% of participants in all active groups at 11 and 35 months after initial training, but the cognitive effects of the memory training did not persist over the ten-year follow up period [6]. In a second large, well-publicized online cognitive training study, findings were originally considered to be negative in terms of cognitive gains. However, in an examination of an older subsample, training was effective in improving cognitive abilities and instrumental activities of daily living [7].

In a recent meta-analysis examining CCT in older adults with MCI or dementia, the overall efficacy of cognitive outcomes in MCI was moderate and statistically significant [8]. This pattern was also found for global cognition, verbal learning and memory, nonverbal learning, working

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3 memory, attention, and psychosocial functioning (e.g. depression, quality of life,  
4 neuropsychiatric symptoms). However, for the efficacy of cognitive outcomes in patients with  
5 dementia, the overall effect was found to be small, though statistically significant.  
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10 Early interventions at the stage of MCI, and not dementia, may be more helpful for improving  
11 cognition. In fact, Hill et al. [8] concluded that CCT is a feasible intervention for improving  
12 cognition in patients with MCI. Transfer effects have also been found in studies evaluating CCT  
13 in healthy older adults, supporting the potential for transfer of CCT benefits to daily life [6, 9]. In  
14 this study, we will assess for transfer effects by administering the following functional  
15 assessments at specific timepoints: Functional Activities Questionnaire (FAQ) and University of  
16 California San Diego Performance-Based Skills Assessment (UPSA).  
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24 Although CCT has received more support in the past few years as a viable treatment option for  
25 older adults with MCI, the brain mechanisms underlying the observed cognitive changes remain  
26 elusive. Many studies of CCT that include imaging components have only been conducted with  
27 healthy older adults [10, 11, 12, 13]. CCT may promote neuroplasticity in the brain, including in  
28 the hippocampus, a key region that supports memory [13, 14, 15, 16]. Additional research needs  
29 to be done that evaluates both structural and functional data within a rigorously-conducted  
30 clinical trial. In this study, patients will undergo a structural MRI and fMRI at both study entry  
31 and exit to assess for changes in hippocampal volume and the default mode network (DMN). The  
32 latter is crucial to evaluate in patients with MCI as dysfunction in the DMN has been implicated  
33 in the progression of MCI to AD [17]. The DMN is a resting state neural network of several  
34 highly interconnected cortical hubs, including the posteromedial parietal, anteromedial frontal,  
35 and inferolateral parietal cortices. We have shown that impaired deactivation and functional  
36 connectivity in the DMN may be a significant predictor in MCI of poor memory and transition to  
37 dementia over a 2-3 year follow-up period [18]. Neuronal dysfunction precedes structural  
38 atrophy in AD, and functional magnetic resonance imaging (fMRI) offers the potential for  
39 identifying specific patterns of disruption in the memory networks affected early in MCI and  
40 AD.  
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3 Limitations of prior CCT trials include the inconsistent demonstration of transfer to everyday  
4 functioning, reliance on waitlist control conditions as opposed to active control conditions, and  
5 lack of long-term follow-up. Most studies have not assessed transfer of cognitive improvement to  
6 everyday function or quality of life [19, 20, 21, 22, 23]. While CCT may produce transfers to  
7 untrained cognitive domains, the few studies that evaluate transfer to everyday functioning have  
8 reported mixed findings [24, 25, 26-29]. This is particularly important given the strong  
9 association between cognitive decline and functional disability [30]. Many studies use waitlist  
10 control conditions or control conditions that do not account for engagement and motivation in the  
11 task [22]. Such designs are biased in favor of the treatment condition because waitlisted subjects  
12 are not receiving any form of cognitive treatment and, therefore, may be more likely to drop out  
13 of such studies due to lack of engagement and motivation. In the current study, patients will be  
14 assigned to one of two cognitively stimulating exercises, computerized cognitive training (suite  
15 of exercises) or crossword puzzle training (crossword puzzles). Since one of the purposes of  
16 CCT in patients with MCI is to reduce the risk of progression to dementia, longer follow-up  
17 times are necessary to be able to accurately capture patient progression. However, most studies  
18 have only used no follow-up or short-term follow-ups, with the notable exception of the  
19 ACTIVE trial [6, 31-33].  
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34 Overall, recent findings in the field suggest that computerized cognitive training could benefit  
35 patients at risk for dementia. The current study will build on these findings by implementing a  
36 study design with an active control group, a longer trial duration, an increased intensity of  
37 computerized cognitive training, examination of generalizability to functional abilities beyond  
38 cognitive training skills, structural and functional MRI assessment, and rigorously blinded  
39 methodology.  
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## 46 METHODS AND ANALYSIS

### 47 Study Design Features and Rationale

48 One hundred patients clinically diagnosed with mild cognitive impairment (MCI) will be  
49 randomized. There will be two sites: New York State Psychiatric Institute/Columbia University  
50 Medical Center in New York, NY (NYSPI as lead coordinating site) and Duke University  
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3 Medical Center in Durham, NC. Patients will be randomized to one of two computerized  
4 cognitively stimulating exercises: crossword puzzle training (CPT) or a suite of exercises (CCT;  
5 memory tasks, matching tasks, spatial recognition tasks, processing speed tasks). These patients  
6 will be further randomized by MCI type (early MCI or late MCI), age (70 and below or 71 and  
7 above), and site (NYSPI/CUMC or DUMC) as the stratification factors and will be followed for  
8 78-weeks. The randomization sequences will be balanced in blocks of random size (2, 4) to  
9 prevent clinicians from guessing what the next patient's treatment might be. The term "control"  
10 will not be used in the consent form in order to reduce the participant's expectancy bias.  
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19 In order to maintain neutrality and mitigate expectancy bias among patients, the informed  
20 consent form signed by all patients during the screening visit will not indicate which group is the  
21 active group (suite of exercises) or the control group (crosswords). Rather, it will indicate that  
22 the patient may be assigned to one of two cognitively stimulating exercises, CCT or CPT.  
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### 27 **Role of Sponsor**

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29 The study is funded entirely by a National Institute on Aging grant and supervised by a Data  
30 Safety Monitoring Board. Using Lumosity, a web-based gaming platform from Lumos Labs, we  
31 customized a specific set of CCT and CPT training modules for participants to use in this trial.  
32 After a comprehensive review of several CCT modules on the market, we chose these modules  
33 from Lumosity due to their large selection of games tailored to specific cognitive domains, their  
34 research specific platform, availability of active control condition, availability of the online self-  
35 administered NeuroCognitive Performance Test (NCPT), and our previous pilot data in the  
36 elderly with this platform. Aside from providing the research platform and technical support at  
37 no cost, Lumos Labs provides no financial support for this study and their staff have no  
38 significant role in the final study design, study conduct, data interpretation or publication.  
39 Patients will not be required to pay for the platform and will not have a post-study commitment  
40 to the platform. None of the study team has any financial conflicts with Lumos Labs.  
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### 51 **Recruitment, Eligibility, Consent**

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3 Patients will be recruited from the current patient caseload of the investigators, referral by  
4 neurology, psychiatry, primary care, public health and geriatric medical clinics affiliated with the  
5 centers and supplemented by advertisement.  
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#### 10 Inclusion/Exclusion Criteria.

11 Detailed inclusion/exclusion criteria are described in Table 1. Notable inclusion criteria will be  
12 age range restriction 55-95 years, subjective cognitive complaints (i.e., memory or other  
13 cognitive complaints, e.g., naming/language), Wechsler Memory Scale-III (WMS-III) Logical  
14 Memory Story A delayed recall score 0-11, Folstein Mini Mental State Examination (MMSE)  
15 score  $\geq 23$  out of 30, availability of an informant, and access to a home desktop or laptop  
16 computer with full access to the internet for the study duration. Patients who have a history of  
17 major psychiatric or neurological illness including motor disorders like Parkinson's disease, a  
18 dementia diagnosis of any type, contraindication to MRI scan, lack of English-speaking ability,  
19 or have been defined as regular online brain training or regular crossword puzzle users ( $\geq 2$  times  
20 per week in the past year) will be excluded. Depression will be assessed using the 15-item  
21 Geriatric Depression Scale (GDS); a diagnosis of Major Depressive Disorder is exclusionary.  
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#### 32 *Mild Cognitive Impairment Criteria*

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34 Mild cognitive impairment (MCI) and type of MCI (early MCI or late MCI) will be assessed by  
35 the delayed recall score of WMS-III Logical Memory and by the score on the MMSE. On  
36 Logical Memory II Story A, a score from 0-11 will indicate cognitive impairment, per the  
37 Alzheimer's Disease Neuroimaging Initiative (ADNI) criteria. MCI type will be determined from  
38 this score combined with years of education of the patient. Early MCI (eMCI) will be defined as  
39 a delayed recall score of 3-6 with 0-7 years of education, score of 5-9 with 8-15 years of  
40 education, and score of 9-11 with 16 or more years of education. Late MCI (lMCI) will be  
41 defined as a delayed recall score of  $\leq 2$  with 0-7 years of education, score of  $\leq 4$  with 8-15 years  
42 of education, and score of  $\leq 8$  with 16 or more years of education. For both eMCI and lMCI,  
43 everyday function must be well preserved for study inclusion. A MMSE score  $\geq 23$  will also be  
44 required to indicate mild cognitive impairment, and this is required for study inclusion.  
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#### 55 **Length of Clinical Trial**

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3 Most transitions from MCI to AD typically occur within three years of follow-up after the  
4 diagnosis of MCI is made [34]. We chose 18-months as the length of this clinical trial to  
5 decrease dropouts that can occur in a very long controlled trial. Since this study is considered  
6 low risk, we do not anticipate participants to suffer harm from trial participation.  
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## 10 11 12 **Treatment Regimen**

13 Enrolled participants will come to the clinic for five scheduled visits (Weeks 0, 12, 32, 52, and  
14 78) and will receive at least three scheduled phone calls with research staff (Weeks 20, 42, and  
15 64). Participants will be enrolled into the study after screening for eligibility and consent is  
16 signed. The randomization will be assigned by the statistician and then carried out by the  
17 unblinded research coordinator, with individuals stratified by MCI type, age group, and site.  
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24 Randomization.

25 The blinded research coordinator (at NYSPI or Duke) will complete the Training Group  
26 Randomization Form to indicate the following information for the patient: site, age, and MCI  
27 type. This form will be verified by the unblinded research coordinator at NYSPI, who will then  
28 assign a study ID to that patient, using a pre-populated form from the statistician's randomization  
29 assignment. The order of the study ID assignment will determine which study condition the  
30 patient will receive: CPT or CCT. The Lumosity account information will be generated after the  
31 MRI has been completed and quality checked. Lumosity account credentials will include a  
32 research-specific COGIT ID email address and password, which will enable users to log into an  
33 account specific to their study condition.  
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43 Randomization will be complete when the patient logs into his/her account for the first time at  
44 the baseline visit and sees which condition he/she is in. At this visit, patients will be trained by  
45 unblinded study staff in their assigned training condition. Eighteen modules were selected to  
46 target various cognitive domains: (A) Memory (Tidal Treasures, Familiar Faces, Memory  
47 Matrix) (B) Processing Speed (Speed Match) (C) Response Inhibition (Color Match) (D) Verbal  
48 Fluency/Vocabulary Proficiency (Word Bubbles, Word Snatchers, Editor's Choice, Continuum)  
49 (E) Planning/Divided Attention (Train of Thought, Brain Shift, Trouble Brewing, Disillusion)  
50 (F) Visual Interference (Lost in Migration, Ebb and Flow, Masterpiece) (G) Identification (River  
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3 Ranger) (H) Visualization (Speed Pack). These cognitive domains were chosen as they are areas  
4 that are often impaired in patients with MCI and thus represent areas that can be targeted for  
5 improvement [35]. Verbal Fluency and Vocabulary Proficiency tasks were included to promote  
6 verbal learning in the CCT group. Each CCT session will consist of a random selection of six  
7 modules. Participants in the CCT condition are not allowed to choose the games, and are not  
8 allowed to skip over or change the suite of games. The Lumosity platform will scale difficulty by  
9 using the patient's Lumosity Performance Index (LPI). The LPI will consider three areas for  
10 each patient. The Game Performance Index will be determined by reviewing score distributions  
11 for each game. The Cognitive Area Performance Index (speed, memory, attention, flexibility and  
12 problem solving) will be calculated using a weighted average of the Game Performance Index.  
13 Thirdly, the overall Cognitive Performance Index will be calculated using a weighted average of  
14 the Game Performance Indices from all cognitive areas. A complete list of selected CCT games  
15 are described in Table 2. Crosswords engage primarily verbal abilities and perhaps, executive  
16 and attentional mechanisms. The Lumosity games target different cognitive domains, such as  
17 speed of processing and memory, as well as verbal abilities. The effect that these different  
18 trainings have on the so-called far transfer problem will of course be of major interest. There  
19 should be no case in which an emergency unblinding will need to take place, as the blinded  
20 intervention is a computerized intervention.  
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36 Participants in the computerized cognitive training group and the crossword puzzle training  
37 group will spend the same amount of time on the platform during the intensive training phase,  
38 which will consist of four 30-minute training sessions per week for 12 weeks. Participants are  
39 not required to have any particular level of computer skills for study inclusion; however, at the  
40 initial baseline training, all participants will be trained on how to successfully access the training  
41 platform, and how they could obtain help both from research staff and their informant throughout  
42 the study. For both groups, responses will be entered via mouse and keyboard. For the crossword  
43 puzzle training group, questions will not need to be completed in order and there will not be any  
44 feedback for the accuracy of the response at the time of entry by the participant. Upon  
45 completion of the CCT suite of exercises after 30 minutes, participants will receive a score.  
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53 Similarly, after 30 minutes the crossword training will automatically end. If a participant were to  
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3 finish an entire crossword puzzle before the 30-minute cutoff, they would be directed to another  
4 crossword puzzle to ensure they complete a total of 30 minutes.  
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8 Following the intensive training phase of 12 weeks, participants will be instructed to complete  
9 six booster sessions. Each booster session will consist of four CCT/CPT sessions. Booster  
10 sessions will be completed at weeks 20, 32, 42, 52, 64, and 78. At weeks 32, 52, and 78, patients  
11 will complete three booster sessions at home and complete the fourth session in-clinic with  
12 research staff. At weeks 20, 42, and 64, patients will complete all four booster sessions at home.  
13 Generally, in previous cognitive training studies, booster sessions have been limited. For  
14 instance, the ACTIVE trial had two booster sessions, each consisting of four 75-minute trainings  
15 at 11 and 35 months. During the course of the trial, booster sessions included a total of 8  
16 trainings, for a total of 10 hours [6]. In contrast, COGIT will have six booster sessions (24 total  
17 training sessions each lasting 30 minutes) over 15 months. Thus, COGIT will include 12 hours  
18 total for booster sessions during the trial. The ACTIVE trial only required compliant participants  
19 to complete the booster sessions, whereas all participants will complete booster sessions in the  
20 COGIT study [6].  
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### 32 Clinic Based Cognitive, Functional, and Smell Assessments.

34 At baseline (week 0) The Alzheimer's Disease Assessment Scale-Cognition Subscale 11  
35 (ADAS-Cog 11) will be administered, in addition to the following neuropsychological test  
36 battery: WAIS-III Block Design (to assess visuospatial skills), Digit Symbol Substitution Test  
37 (DSST) (to assess attention), Trail Making A & B (to assess attention and executive function),  
38 Verbal Fluency and 15-item Boston Naming Test (to assess language), Auditory-Verbal  
39 Learning Test (to assess verbal learning and memory), and WMS-III Visual Reproduction Test  
40 (to assess nonverbal learning and memory). In addition, the UPSA and University of  
41 Pennsylvania Smell Identification Test (UPSIT) will be administered. Testing fatigue is  
42 mitigated by allowing participants to take breaks during the testing. If there is missing data from  
43 one time point, the study team will attempt to bring the participant back to the clinic within the  
44 allowed window to complete missing measures. The FAQ will be administered to the patient's  
45 informant, either during the study visit or shortly after the visit over the phone.  
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3 Self-Administered Cognitive Test Battery.

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5 Another unique aspect of the study is the use of the NCPT, an online, computerized, self-  
6 administered battery developed by Lumosity. It will test various cognitive domains outlined in  
7 the Study Measures section. The NCPT will allow us to examine the efficacy of a self-  
8 administered test, in combination with standardized, clinic-based neuropsychological tests.  
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### 13 **Timeline of Longitudinal Assessments**

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15 At in-clinic visits (baseline and weeks 12, 52, and 78), the same neuropsychological battery of  
16 testing will be completed. At the week 12 and week 78 visits, the patient will be asked to  
17 complete the User Engagement Scale, which will be adapted to capture usage of a computerized  
18 platform. This scale will measure aspects of engagement, usability, and satisfaction with the  
19 computerized platform on a 5-point Likert scale. Week 20 will be a phone interview between  
20 study physician/neuropsychologist and patient to follow-up on how the patient has been doing,  
21 and to remind the patient to complete a booster session.  
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### 29 **Blinded Training Procedure**

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31 The blinded research coordinator will administer the full neuropsychological test battery,  
32 including the UPSA and FAQ. The blinded clinician will complete the Diagnosis Form and the  
33 Contributing Features to MCI form after clinical interview and review of the neuropsychological  
34 testing. The unblinded research coordinator will administer the initial computerized training and  
35 all subsequent booster sessions to patients in the clinic. To track type of games/crossword  
36 puzzles and amount of time that the subject spends doing the games/crossword puzzles, only  
37 unblinded study coordinators receive reports from Lumosity each week. If the Lumosity reports  
38 of computer games/crosswords access do not match the subject's assigned instructions, the  
39 unblinded coordinator then contacts the subject to guide and ensure adherence to the protocol.  
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### 48 **Hypotheses**

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50 See Figure 1 for a Conceptual Model of specific study aims and outcome measures. The primary  
51 aim of the study is to assess change in cognitive and functional status over 18 months in MCI  
52 patients comparing the CCT and CPT groups. Hypothesis 1: MCI patients randomized to CCT  
53 will show better cognitive outcomes on the ADAS-Cog 11 (primary outcome measure),  
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3 Neuropsychological Testing Composite score (secondary outcome measure), and NCPT  
4 (exploratory outcome measure) compared to active control (CPT). Hypothesis 2: MCI patients  
5 randomized to CCT will show better functional outcomes as assessed by the UPSA (primary  
6 functional outcome) and FAQ (secondary functional outcome) by the end of the 18-month trial  
7 compared to active control. Hypothesis 3: brain pathology (smaller hippocampal volumes, lower  
8 odor identification scores on the UPSIT, ApoE e4 allele present) will moderate the relationship  
9 between treatment assignment and cognitive and functional outcomes.  
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17 The secondary aim of the study is to examine the effects of CCT on resting-state DMN  
18 connectivity as well as other networks modulated by CCT effects. Hypothesis 1: MCI patients  
19 randomized to CCT will demonstrate greater change in an index of DMN functional connectivity  
20 compared to patients randomized to active control. Hypothesis 2: indicators of brain pathology  
21 (smaller hippocampal volumes, lower odor identification scores on the UPSIT, ApoE e4 allele  
22 present) will moderate the relationship between change in the DMN and treatment assignment.  
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29 The tertiary aim of the study is to examine differences in rates of progression to dementia and  
30 AD in the two randomized treatment groups, recognizing that if progression to these outcomes is  
31 uncommon there will be insufficient statistical power. Hypothesis 1: the proportion converting to  
32 dementia will be lower in the CCT group compared to active control.  
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### 38 **Study Measures**

39 Study measures with time-points of administration are listed in Table 3. The MMSE will be  
40 administered at screen and each subsequent in-clinic visit using five different versions of the  
41 three-word recall item to reduce practice effects [36]. The Cumulative Illness Rating Scale for  
42 Geriatrics (CIRS-G) and The Framingham Stroke Risk Scale will be completed by the study  
43 physician at screen and week 78 to assess for cardiovascular disease risk factors and other  
44 medical conditions.  
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51 The Geriatric Depression Scale will be administered at screen and each subsequent in-clinic visit  
52 to assess for depression. If GDS is greater than 5 at any visit, the patient will be evaluated by a  
53 psychiatrist and an appropriate clinical referral will be made, if needed, for treatment of  
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3 depression. The Cognitive Reserve Index is a brief questionnaire that will be administered by the  
4 research coordinator at screen and will evaluate the cognitive reserve of an individual by means  
5 of the compilation of information as it relates to his/her adult life.  
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10 At screen, the research coordinator will be responsible for administering the History of Game  
11 Use Questionnaire, Physical Activity Assessment, and WMS-III Logical Memory I & II. The  
12 History of Game Use Questionnaire will be administered again at weeks 12 and 78 to ensure that  
13 patients are not partaking in any other types of cognitive training games while in the study.  
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18 At screen and week 78, patients will undergo an MRI scan of the brain. The MRI scan will  
19 include the following sequences: Localizer, high-resolution T1-weighted IR prepped 3DSPGR,  
20 and T2 FLAIR, and GE-EPI resting-state fMRI scans.  
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25 At weeks 0 and 78, the UPSIT will be completed by the patient, which is a 40-item scratch and  
26 sniff multiple-choice olfactory identification test.  
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30 At each in-clinic visit, apart from week 32, the ADAS-Cog 11 and full neuropsychological test  
31 battery will be administered. The NCPT will be administered at weeks 0, 12, and 78. The  
32 cognitive domains measured by the NCPT are memory (visuo-spatial working memory, short-  
33 term memory), processing speed (visual search, psychomotor speed), problem solving (logical  
34 reasoning, numerical calculation), attention (selective, divided), and flexibility (response  
35 inhibition, task-switching). The assessments, 10 total “subtests,” are online adaptations of widely  
36 used neuropsychological tests whose test properties are not affected by shifting to computerized  
37 administration [37].  
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46 The neuropsychological test battery includes: WAIS-III Block Design, Digital Symbol  
47 Substitution (DSST), Trail Making A & B, Verbal Fluency and 15-item Boston Naming Test,  
48 Auditory-Verbal Learning Test (AVLT), and WMS-III Visual Reproduction Test. For word  
49 learning lists, the neuropsychological testing materials provide different but parallel word lists,  
50 so as to avoid practice effects in MMSE and ADAS-Cog, but not for AVLT. With respect to the  
51 latter we did not adopt this approach because we were concerned that different forms have not  
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3 been established as equivalent in difficulty level. The UPSA will be administered only at weeks  
4 0, 32, and 78 due to the high tendency for practice effects. It is a performance-based measure of  
5 functional abilities that includes measures of simulated real-world activities; for example,  
6 planning a trip to the beach, remembering documents to bring to a medical appointment, and  
7 dialing a phone number. When a participant wears corrective lenses during the testing battery,  
8 this is documented in the participant's research chart.  
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15 At screen and weeks 12, 32, 52, and 78 the participant will meet with the study physician or the  
16 neuropsychologist to assess for illness progression and adverse events. Adverse events that are  
17 spontaneously reported to research coordinators at any clinic visit will be discussed with the  
18 study physician or the neuropsychologist in order to determine how to proceed. Adverse events  
19 and subsequent steps to deal with the adverse events will be documented in the patient chart and  
20 serious adverse events will be reported to the Data Safety and Monitoring Board and study  
21 sponsor, National Institute on Aging.  
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29 Additionally, the research coordinator will conduct an interview with the informant at, or shortly  
30 after, each visit to complete the FAQ.  
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### 34 **Criteria for Early Discontinuation**

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36 We expect early discontinuation to occur because of one or more of the following reasons: (1)  
37 the patient's decision not to continue the computerized training (CCT or CPT) due to lack of  
38 interest, motivation, or available time; (2) unavoidable circumstances, e.g., moving residence and  
39 unwillingness to return for in-person evaluations; (3) investigator decision to terminate; (4) death  
40 or prolonged hospitalization for medical reasons. We will not terminate participation for non-  
41 adherence because even if the patient is non-adherent to the protocol, we will document level of  
42 adherence (done electronically in this computerized training protocol) and still include the  
43 patient's data in the analyses based on the intent-to-treat principle.  
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### 51 **Data Management**

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53 Data entry will be completed by Program Managers, Clinical Research Coordinators, and  
54 Research Assistants on the study protocol. Data entry/cleaning will be done throughout the  
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3 project. The data collected in this study will be monitored by the Data Coordinating Center at  
4 NYSPI. The unit will work closely with the research assistant/coordinator and the Principal  
5 Investigator to facilitate independent auditing of primary subject records. The database will  
6 provide reports indicating all modifications that have been made in the database together with  
7 paper communications (fax, e-mail) confirming and authorizing these modifications. Access to  
8 the data system is available only to authorized users, with multiple levels of security including  
9 user id/password authentication via MS Active Directory overseen by experienced IT personnel.  
10 Other authorized users with direct access to the data system will be Data Coordinating Center  
11 (DCC) staff. DCC data-related operations and the SIR/Citrix system have been certified by  
12 Columbia University's Information Security Office. The dataset will not be published in a data  
13 repository.  
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### 24 **Genetic Testing**

25 Apolipoprotein E (ApoE) genetic analysis on a blood sample will be done through the laboratory  
26 of the Human Genetics Resources Core (HGRC) at Columbia University Medical Center. We  
27 will assess the ApoE  $\epsilon 4$  allele as potentially associated with response to CCT; a prior trial found  
28 an association between the  $\epsilon 4$  allele and cognitive improvement on donepezil [38].  
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### 34 **Concomitant Medications**

35 Putative cognitive enhancers, narcotics, all classes of psychotropic medications, and over 20  
36 other classes of commonly prescribed and over the counter (and alternative) medications will be  
37 documented in a rating form at screen and subsequent in-clinic visits. An exclusion criterion will  
38 be daily use of medications known to have a negative impact on cognition: high-dose narcotics,  
39 anticholinergics, and benzodiazepines in lorazepam equivalents  $\geq 1$  mg daily. During the first 12  
40 weeks of the study, the intensive cognitive training phase, patients are encouraged not to change  
41 any of their medications, unless clinically indicated.  
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### 50 **Statistical Analysis and Sample Size**

51 We powered our trial to detect an effect size at 18 months of  $d=.58$  (80% power). This effect size  
52 is more conservative than published treatment changes associated with CCT (for instance, see  
53 [39]). We assume that dropout is distributed uniformly across waves of follow-up assessments  
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(with 5% attrition between each consecutive pair of the 5 major time-points, i.e. 20% by 18 months).

Outcome Measures (Primary and Secondary Hypotheses Testing).

*Aim 1 Hypothesis 1 and 2.* MCI patients on CCT will show a lower rate of cognitive and functional decline compared to MCI patients on active control by the end of the 18-month trial. We will use generalized linear mixed effects models of cognitive and functional measures collected repeatedly across the 78 weeks according to the schedule (see Table 3). For example, cognitive measure<sub>ik</sub> =  $\beta_0 + \beta_1 \text{Time}_{ik} + \beta_2 \text{Group}_i + \beta_3 (\text{Group}_i \times \text{Time}_{ik}) + v_{0i} + v_{1i} \text{Time}_{ik} + \varepsilon_{ik}$  where Group<sub>i</sub> indicates treatment group for subject i (Group = 1 CCT, 0 for control), k = time (baseline, 12 weeks, 20 weeks, 52 weeks, 78 weeks), and v<sub>0i</sub> is a subject-specific random intercept. Time will be treated as categorical if linearity is not plausible and group effects at 18 months can be tested by forming contrasts from the fitted model. Potential site differences will be evaluated using descriptive statistics and site will be included in all analyses as a covariate, as will other stratification variables including age group and MCI type at baseline.

*Aim 2 Hypothesis 1.* MCI patients randomized to CCT will demonstrate either more of an increase or less of a decrease in DMN connectivity (goodness-of-fit [GOF] index scores) compared to patients randomized to active control. To test this hypothesis, we will use a repeated measures Analysis of Covariance (ANCOVA) with time (baseline vs. post treatment) as the repeated measure, DMN connectivity as an outcome, treatment condition (CCT vs CPT) as a predictor, and site, age, and MCI status at baseline as covariates.

*Moderating Effects in Aim 1 Hypothesis 3 and Aim 2 Hypothesis 2.* As a part of our exploratory analyses, we will examine specific potential moderators: Apolipoprotein E  $\epsilon$ 4 allele, MRI indices, UPSIT. To show, for example, that baseline hippocampal volume is a moderator, we will test its interactive effect with treatment on outcomes. Moderator and moderator-interaction terms can be easily accommodated in the mixed effects regression models described in Aim 1. Hypotheses 1 and 2. A similar approach will be used by adding moderator and moderator x Group interactions to the ANCOVA described in Aim 2 Hypothesis 1. The results must be



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3 interpreted with the caveat that there may not be enough power to assess these interactions,  
4 especially for moderators with low prevalence.  
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8 *Aim 3 Hypothesis 1.* The proportion diagnosed with dementia during follow-up will be lower in  
9 the CCT group compared to active control. Logistic regression will be used to test the binary  
10 outcome of dementia status at 18 months predicted by treatment group controlling for site, age  
11 group, and MCI type at baseline.  
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17 Missing data is managed statistically through use of mixed model repeated measures analyses.  
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### 20 **Sample Size.**

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22 A power analysis was conducted using the RMASS program for longitudinal studies, which  
23 determined that a total sample size of 100 participants will provide a sufficient effect size to  
24 evaluate our hypotheses. We have two primary outcome measures (i.e., multiple outcome  
25 measures), namely ADAS-Cog and the UPSA. For multiple outcome measures, statistical  
26 significance on any one measure is meaningful and there is no need to correct for multiple  
27 comparisons (unlike co-primary outcome measures). All other outcome measures are secondary  
28 and exploratory.  
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### 36 **Patient and Public Involvement**

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38 Patients will first be involved in the research after study design is finalized by the study  
39 investigators. At this stage, patients will be referred by physicians or self-referred from online  
40 and newspaper advertisements for their initial screening visit. The patients will not be involved  
41 in study design, study recruitment or conduct, or dissemination of study results. We will assess  
42 the burden of the trial intervention on patients using the User Engagement Scale and the  
43 Participant/Informant Expectancy Scales. Patients will not be invited to comment on the study  
44 design and were not consulted to develop patient relevant outcomes or interpret the results.  
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49 Patients will not be invited to contribute to the writing or editing of this document for readability  
50 or accuracy.  
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## 55 **ETHICS**

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5 This study has been approved by NYSPI IRB, Duke University IRB, and Queens College IRB.  
6 All COGIT patients at entry will be required to have the capacity to provide informed consent  
7 and sign the IRB-approved informed consent form. Local IRB and state regulations for consent  
8 will be followed. Patient confidentiality as it pertains to potential and enrolled participants  
9 before, during, and after the trial will be collected, shared, and maintained strictly according to  
10 HIPAA law.  
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17 Important protocol modifications will be communicated to the Data Safety and Monitoring  
18 Board, NYSPI IRB and Duke University IRB, and updated online for trial registries.  
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22 The research data on specific moderators, including UPSIT and apolipoprotein E genotyping,  
23 will not be not released to the patient, and this will be specified in the consent form. The  
24 cognitive testing results and clinical reading of the MRI scan will be released to the patient (and  
25 the patient's primary physician, if requested); the MRI research volumetric ratings and fMRI  
26 findings will not be released.  
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### 32 **Data Safety and Monitoring Board (DSMB)**

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34 Three NIA-approved independent experts with expertise in conducting clinical trials in mild  
35 cognitive impairment will form the DSMB. All serious adverse events (SAEs) will be reported to  
36 the DSMB. The DSMB will audit the trial conduct, review all SAEs, participate in a  
37 teleconference twice a year to determine if the study should continue, and then will provide an  
38 actionable report to the Principal Investigator. This process will be independent from the  
39 investigators.  
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## 46 **DISSEMINATION**

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49 The study results will be disseminated through publications and conference presentations as well  
50 as on public websites, including [clinicaltrials.gov](http://clinicaltrials.gov). Researchers will be eligible for authorship  
51 after consideration by the principal investigators; no professional writers will be utilized.  
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## SIGNIFICANCE

This will be one of the first investigator-blinded and controlled long-term trials to evaluate the effects of home-based computerized cognitive training versus computerized crossword puzzle training on cognitive, functional, hippocampal and default mode network connectivity neural outcomes in MCI. Positive results from this pilot trial may support the further development of home based cognitive training and self-assessments in people at risk for dementia.

The results will help inform the design of a more powerful RCT in many ways: determine sample size for a multicenter trial, identify subgroups more likely to benefit, identify subdomains and exercises most likely to improve, optimize training dose and duration, learn how subjects engage, identify gender effects, model slopes and long-term benefits, assess value of a self-administered cognitive test, understand brain networks affected, and examine the potential moderating role of apolipoprotein E  $\epsilon$ 4 status on CCT outcome.

## AUTHOR CONTRIBUTIONS

DPD, PMD, JRP, and JRS conceived and designed the study and obtained funding. All other authors assisted with elements of study design, database, and conduct. HA contributed to statistics design and JRP to design of MRI component. DPD is the overall study PI and PMD is the PI at the Duke site. JLD and LSP did the initial draft of the paper and all authors contributed to manuscript edits and revisions.

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## COMPETING INTERESTS

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5 JLD, LSP, TEG, SNR, SNT, EP, JRP, CAH, HFA, JRS, NAK have no competing interests.

6 PMD has received research grants and advisory fees from several companies in this field for  
7 other studies, and owns shares in several companies whose products are not discussed here. DPD  
8 serves as a consultant on advisory boards to Acadia, Avanir, Genentech, Eisai, and Neuronix.  
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**Table 1. Inclusion/Exclusion Criteria**

<b>Inclusion Criteria</b>
1. Males and females 55 to 95 years of age (inclusive) at the time of informed consent.
2. Subjective cognitive complaints, i.e., memory or other cognitive complaints, e.g., naming/language.
3. Meets criteria for cognitive impairment (CI) defined as scores >1 SD below standardized norms on memory function as identified by the Wechsler Memory Scale (WMS) III Logical Memory delayed recall score.
4. Folstein Mini Mental State (MMSE) score $\geq$ 23 out of 30.
5. A family member or other individual who is in contact with the patient and consents to serve as informant during the study; this could be a telephone informant in case of patients who do not have a live-in informant or close significant other.
6. Access to a home desktop or laptop computer at acceptable speed for the study duration.
<b>Exclusion Criteria</b>
1. Diagnosis of dementia of any type.
2. Current clinical evidence of schizophrenia, schizoaffective disorder, major depression, psychosis, or bipolar I disorder (DSM-IV TR criteria).
3. Active suicidal ideation or plan.
4. Current or recent (past 6 months) alcohol or substance use disorder (DSM-5 criteria).
5. Clinical stroke with residual neurological deficits. While we will not exclude patients with cerebrovascular disease, we will not include patients who have had a stroke with residual clinical deficits because it is not clear that this type of patient is similar to the MCI patient generally, and clear-cut neurological impairment, e.g., hemiplegia/hemiparesis or speech impairment, may compromise the patient's ability to do the CCT or active control procedures and to complete the neuropsychological tests.
6. Use of medications known to have a negative impact on cognition: benzodiazepines in lorazepam equivalents $\geq$ 1 mg daily, narcotics, anticholinergics. Other patients receive medications that may be associated with cognitive impairment but are rarely considered the likely etiology, e.g., theophylline, nifedipine, beta blockers; they will not be excluded. Patients receiving other psychotropic medications not expected to have a material impact on cognition, e.g., SSRIs and SNRIs will be eligible.
7. Presence of any of the following disorders: a) CNS infection, with CSF evidence of meningitis, encephalitis, or other infectious process; b) dementia of any type; c) Huntington's disease; d) Multiple sclerosis; e) Parkinson's disease; f) Other neurologic disorders with focal signs, e.g., amyotrophic lateral sclerosis; g) Mental retardation.
8. Acute, severe unstable medical illness. For cancer, acutely ill patients (including those with metastases) will be excluded, but past history of successfully treated cancer will not result in exclusion.
9. Contraindication to MRI scan: pacemaker, metal implants following surgery, any other contraindication to MRI. Eligibility for the MRI scan is a requirement for the study.
10. UPSIT exclusions: current smoker > 1 pack daily, current upper respiratory infection (retested as soon as the infection clears). UPSIT scores are reduced in schizophrenia, Parkinson's disease and Parkinson's related conditions; these disorders are exclusion criteria for this study. Patients with UPSIT exclusions will not receive the UPSIT but will continue to participate in all other aspects of the study.
11. Patients lacking English-speaking ability as determined by self-report and clinical evaluation.
12. Regular online brain training or regular crossword puzzle user, defined as doing these procedures at a frequency of twice weekly or greater during the year prior to screening. Eligible participants who join the trial are instructed not to do these procedures on their own during the trial, i.e., independent of the study.
13. Participation in another intervention trial for cognitive impairment.

**Table 2. Complete list of CCT game battery and associated cognitive domains (provided by Lumos Labs)**

<b>Game Name</b>	<b>Cognitive Domain</b>
Tidal Treasures	Working Memory i.e., delayed, non-matching to sample; self-ordered pointing
Speed Match	Processing Speed
Color Match	Response Inhibition
Word Bubbles	Verbal Fluency
Train of Thought	Planning Divided Attention Multiple attractions
Familiar Faces	Episodic Memory
Memory Matrix	Episodic Memory; Visuospatial memory
Lost in Migration	Visual Interference
Brain Shift	Task Switching
Trouble Brewing	Multitasking, divided attention, sustained attention, planning, working memory
Ebb and Flow	Task switching, semantic and visual interference
Masterpiece	Mental rotation; visualization; spatial reasoning
River Ranger	Identification
Word Snatchers	Vocabulary proficiency
Speed Pack	Visualization
Disillusion	Task Switching
Editor's Choice	Vocabulary Proficiency
Continuum	Vocabulary Proficiency

**Table 3. Table of Study Procedures**

Measure	Screen	Baseline	12 Weeks	20 Weeks Phone Interview	32 Weeks	42 Weeks	52 Weeks	64 Weeks	78 Weeks
ADAS-Cog11		X	X				X		X
ApoE & blood test	X								
CIRS-G	X								X
Cognitive Reserve Index	X								
Cognitive Training or Control training booster session			X	X	X	X	X	X	X
Contributing Features to MCI		X			X				X
Demographics History (Patient Tracking Form)	X								
Diagnosis Form			X		X				X
Digit Symbol Substitution Test		X	X				X		X
Expectancy Scale (Participant & Informant)		X			X				X
Family History FAQ	X	X	X	X	X		X		X
Framingham Stroke Risk	X								
Geriatric Depression Scale	X		X		X		X		X
History of Game Use Questionnaire	X		X						X
Inclusion/Exclusion Form	X								
Informed Consent	X								
Medications (Chart List & Database List)	X		X		X		X		X
MMSE	X		X		X		X		X
MRI Scan of Brain	X								X
NCPT online cognitive performance test		X	X						X
Neuropsychological Battery: AVLT, Block Design, Verbal Fluency, Visual Reproduction, Boston Naming Test, Trails A & B		X	X				X		X
Physical Activity Assessment	X								
UPSA		X			X				X
UPSIT		X							X
User Engagement Scale			X						X
WMS-III Logical Memory I & II	X								

**Table 3 Legend:** ADAS-Cog 11 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 11. ApoE = Apolipoprotein E gene. CIRS-G = Cumulative Illness Rating Scale for Geriatrics. MCI = Mild Cognitive Impairment. FAQ = Functional Assessment Questionnaire. MMSE = Mini Mental Status Examination. MRI = Magnetic Resonance Imaging. NCPT = NeuroCognitive Performance Test. AVLT = Auditory Verbal Learning Test. UPSA = UCSD Performance-Based Skills Assessment. UPSIT = University of Pennsylvania Smell Identification Test. WMS-III = Wechsler Memory Scale-III.

### Figure 1. Conceptual Model

In the intervention phase patients are randomly assigned to either CCT or CPT. To evaluate cognitive status, the primary outcome measure will be the ADAS-Cog 11, the secondary outcome measure will be the Neuropsychological Testing Composite Score, and the exploratory outcome measure will be the NeuroCognitive Performance Test. To evaluate functional status, the primary outcome measure will be the UPSA and the secondary outcome measure will be the FAQ. To evaluate changes in neural circuitry, the primary outcome measures will include hippocampal volume (MRI) and DMN connectivity (fMRI).

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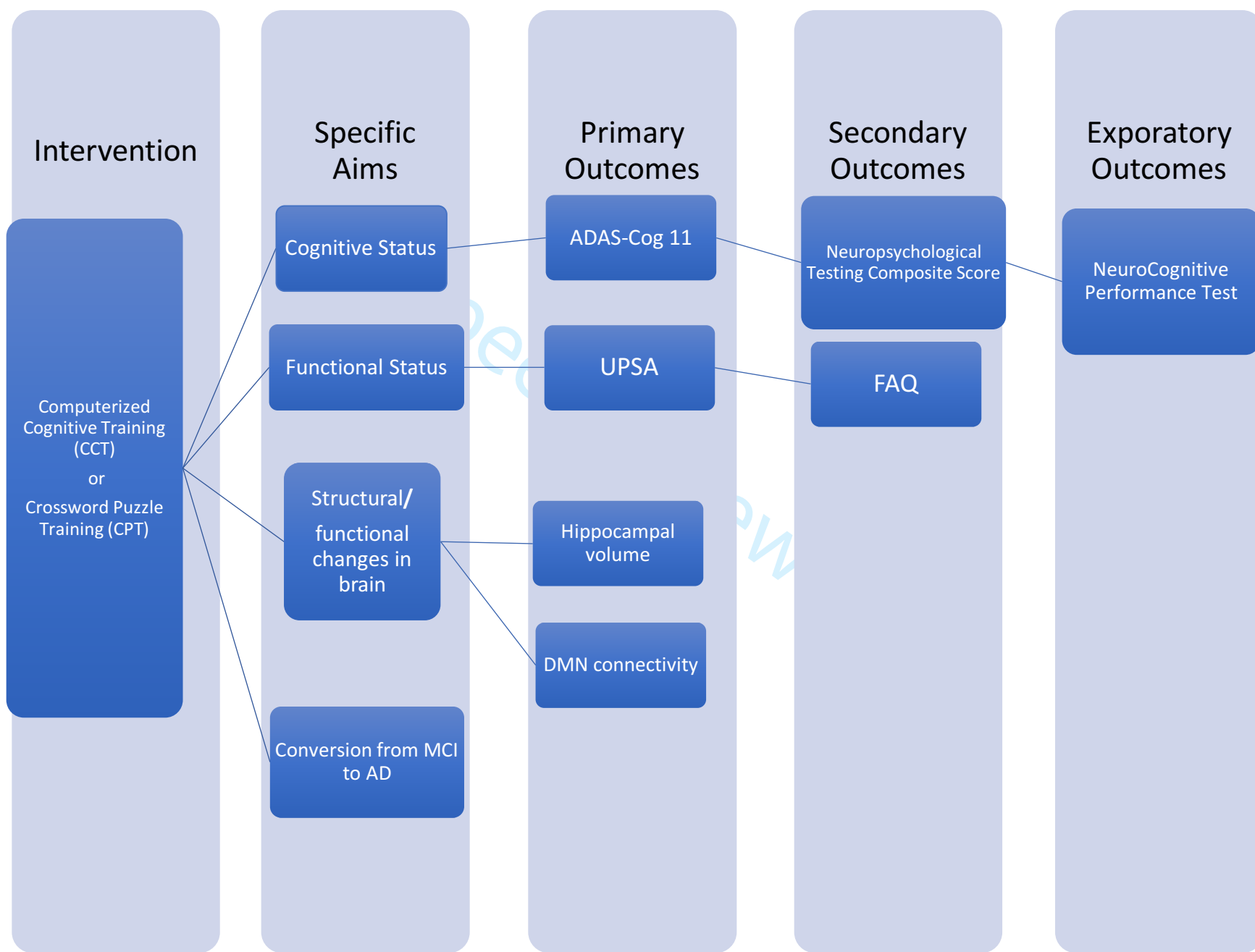


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# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	7; 20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1;20

1	Roles and	#5b	Name and contact information for the trial sponsor	1
2	responsibilities:			
3	sponsor contact			
4	information			
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8	Roles and	#5c	Role of study sponsor and funders, if any, in study	7;20
9	responsibilities:		design; collection, management, analysis, and	
10	sponsor and funder		interpretation of data; writing of the report; and the	
11			decision to submit the report for publication, including	
12			whether they will have ultimate authority over any of	
13			these activities	
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18	Roles and	#5d	Composition, roles, and responsibilities of the	18-19
19	responsibilities:		coordinating centre, steering committee, endpoint	
20	committees		adjudication committee, data management team, and	
21			other individuals or groups overseeing the trial, if	
22			applicable (see Item 21a for data monitoring committee)	
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27	Background and	#6a	Description of research question and justification for	4-6
28	rationale		undertaking the trial, including summary of relevant	
29			studies (published and unpublished) examining benefits	
30			and harms for each intervention	
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34	Background and	#6b	Explanation for choice of comparators	4-6
35	rationale: choice of			
36	comparators			
37				
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39	Objectives	#7	Specific objectives or hypotheses	12-13, 16-17
40				
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43	Trial design	#8	Description of trial design including type of trial (eg,	6-16
44			parallel group, crossover, factorial, single group),	
45			allocation ratio, and framework (eg, superiority,	
46			equivalence, non-inferiority, exploratory)	
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50	Study setting	#9	Description of study settings (eg, community clinic,	6-7
51			academic hospital) and list of countries where data will	
52			be collected. Reference to where list of study sites can	
53			be obtained	
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1	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
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8	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-14
9	description			
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13	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	15
14	modifications			
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20	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11-12
21	adherence			
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26	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16
27	concomitant care			
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30	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13, 16-17
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42	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13-15, 23
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49	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16-18
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56	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7, 16
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1	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	9
2	generation		computer-generated random numbers), and list of any	
3			factors for stratification. To reduce predictability of a	
4			random sequence, details of any planned restriction	
5			(eg, blocking) should be provided in a separate	
6			document that is unavailable to those who enrol	
7			participants or assign interventions	
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13	Allocation	#16b	Mechanism of implementing the allocation sequence	9-12
14	concealment		(eg, central telephone; sequentially numbered, opaque,	
15	mechanism		sealed envelopes), describing any steps to conceal the	
16			sequence until interventions are assigned	
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20	Allocation:	#16c	Who will generate the allocation sequence, who will	9-12
21	implementation		enrol participants, and who will assign participants to	
22			interventions	
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25	Blinding (masking)	#17a	Who will be blinded after assignment to interventions	9, 12
26			(eg, trial participants, care providers, outcome	
27			assessors, data analysts), and how	
28				
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31	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	10, 12
32	emergency		permissible, and procedure for revealing a participant's	
33	unblinding		allocated intervention during the trial	
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36	Data collection plan	#18a	Plans for assessment and collection of outcome,	13-17
37			baseline, and other trial data, including any related	
38			processes to promote data quality (eg, duplicate	
39			measurements, training of assessors) and a description	
40			of study instruments (eg, questionnaires, laboratory	
41			tests) along with their reliability and validity, if known.	
42			Reference to where data collection forms can be found,	
43			if not in the protocol	
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50	Data collection plan:	#18b	Plans to promote participant retention and complete	11, 13-
51	retention		follow-up, including list of any outcome data to be	15
52			collected for participants who discontinue or deviate	
53			from intervention protocols	
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57	Data management	#19	Plans for data entry, coding, security, and storage,	15
58			including any related processes to promote data quality	
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(eg, double data entry; range checks for data values).

Reference to where details of data management procedures can be found, if not in the protocol

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6	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-17
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13	Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17
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17	Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
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24	Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15, 19
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36	Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	19
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43	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14-15; 19
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50	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
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55	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18
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1 2 3 4 5 6 7 8	Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	18-19
9 10 11 12 13 14	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 9
15 16 17 18 19	Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
20 21 22 23 24 25 26 27	Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
28 29 30 31	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
32 33 34 35 36	Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
37 38 39 40 41 42	Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
43 44 45 46 47 48 49 50	Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
51 52 53 54	Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19-20
55 56 57 58 59 60	Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A

1	Informed consent	#32	Model consent form and other related documentation	N/A
2	materials		given to participants and authorised surrogates	
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5	Biological	#33	Plans for collection, laboratory evaluation, and storage	16
6	specimens		of biological specimens for genetic or molecular	
7			analysis in the current trial and for future use in ancillary	
8			studies, if applicable	
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## Author notes

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# BMJ Open

## **Cognitive Training and Neuroplasticity in Mild Cognitive Impairment (COG-IT): Protocol for a two-site, blinded, randomized, controlled treatment trial.**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-028536.R2
Article Type:	Protocol
Date Submitted by the Author:	17-Jun-2019
Complete List of Authors:	D'Antonio, Jessica; New York State Psychiatric Institute, Division of Geriatric Psychiatry Simon-Pearson, Laura; New York State Psychiatric Institute, Division of Geriatric Psychiatry Goldberg, Terry; New York State Psychiatric Institute, Division of Geriatric Psychiatry; Columbia University Medical Center, Department of Psychiatry Sneed, Joel; New York State Psychiatric Institute, Division of Geriatric Psychiatry; Queens College, City University of New York, Rushia, Sara; The Graduate Center, City University of New York; Queens College, City University of New York, Kerner, Nancy; Columbia University Medical Center, Department of Psychiatry Andrews, Howard; Columbia University Medical Center, Department of Biostatistics, Mailman School of Public Health Hellegers, Caroline; Duke University Medical Center, Psychiatry Tolbert, Sierra; Duke University Medical Center, Psychiatry Perea, Elena; Duke University Medical Center, Psychiatry Petrella, Jeffrey; Duke University Medical Center, Radiology Doraiswamy, Murali; Duke University Medical Center, Psychiatry Devanand, Davangere; Columbia University Medical Center, Department of Psychiatry; New York State Psychiatric Institute, Division of Geriatric Psychiatry
<b>Primary Subject Heading</b>:	Neurology
Secondary Subject Heading:	Geriatric medicine, Research methods
Keywords:	Dementia < NEUROLOGY, Delirium & cognitive disorders < PSYCHIATRY, Magnetic resonance imaging < RADIOLOGY & IMAGING, Clinical trials < THERAPEUTICS

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3 **Cognitive Training and Neuroplasticity in Mild Cognitive Impairment (COG-IT):**  
4 **Protocol for a two-site, blinded, randomized, controlled treatment trial.**  
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26 **Article Type:** Study Protocol

27 **Protocol version date:** November 14, 2018

28 **Trial Sponsor Contact Information:**

29 National Institute on Aging  
30 Building 31, Room 5C27  
31 31 Center Drive, MSC 2292  
32 Bethesda, MD 20892

33 **Keywords:** dementia, delirium and cognitive disorders, magnetic resonance imaging, clinical trials

34 **Word count:** 6,157

**ABSTRACT**

*Introduction:* Mild cognitive impairment (MCI) is common in older adults and represents a high-risk group for progression to Alzheimer's disease (AD). Medication trials in MCI have generally failed, but new discoveries with brain plasticity in aging have led to the study of cognitive training as a potential treatment to improve cognitive abilities. Computerized Cognitive Training (CCT) involves computerized cognitive exercises that target specific cognitive abilities and neural networks to potentially improve cognitive functioning through neuroplasticity.

*Methods and Analysis:* In a two-site study (New York State Psychiatric Institute/Columbia University Medical Center and Duke University Medical Center) we will randomize 100 patients with MCI (WMS-III Logical Memory II score 0-11; MMSE  $\geq$  23) to home-based CCT (suite of exercises: memory, matching, spatial recognition, processing speed) or a home-based active control condition (computerized crossword puzzle training; CPT) with 12 weeks of intensive training followed by regular booster sessions up to 78 weeks. All patients will receive standard neuropsychological and functional assessments in clinic as well as structural/functional brain MRI scans at study entry and endpoint. We will test if CCT, versus CPT, leads to improved cognitive functioning, transfers to functional ability and tasks of everyday life, and impacts hippocampal volume changes and changes in the default mode network (DMN) of the brain measured by resting-state fMRI.

*Ethics:* The study will be conducted following ethics approval and written informed consent will be obtained from all subjects.

*Dissemination/Significance:* Study results will be disseminated via publication, [clinicaltrials.gov](http://clinicaltrials.gov), media and conference presentations. This will be the first controlled long-term trial to evaluate the effects of home-based computerized cognitive training versus computerized crossword puzzle training on not only cognitive abilities, but also functional measures and neural outcomes as determined by MRI indices in patients with MCI. Positive results from trial may support further development of home-based CCT.

*Trial Registration:* ClinicalTrials.gov Identifier: NCT03205709.

## ARTICLE SUMMARY

### Strengths and Limitations of this Study

- The study will improve upon limitations of most previous studies by including an “active” control condition, rather than waitlist or control conditions that do not account for engagement and motivation.
- This study will evaluate performance on traditional cognitive and functional assessments (e.g., ADAS-Cog 11, UPSA) in addition to performance on a self-administered, computerized cognitive test, the NeuroCognitive Performance Test (NCPT), which consists of 10 subtests that are online adaptations of widely used neuropsychological tests.
- The trial will utilize a remote internet-based CCT intervention that can be done at home; compared to most existing treatments under investigation, it is easily accessible, relatively inexpensive, non-invasive, and scaled to the skill level of each individual.
- The trial will include evaluation of clinically relevant genetic, brain network, and neuronal loss markers as moderators of outcome; this will be one of the first trials to examine long-term effects on cognition, daily functioning, and neuroplastic changes in DMN with CCT in MCI.
- As our trial will be restricted to English-speaking participants because the online training platform is only available in English, we are unsure how this will generalize to non-English speaking individuals.
- In addition, the inclusion criteria state that the participant must have an at-home desktop or laptop computer, which, in low socioeconomic class homes, is not always available.



## INTRODUCTION

Alzheimer's disease (AD) is a major public health concern affecting over 40 million people worldwide and there is an urgent need to develop new treatment modalities to prevent or delay the onset of dementia. Mild cognitive impairment (MCI) is common in older adults and represents a high-risk group for AD, but medication trials in MCI have generally failed. There is no FDA-approved treatment for MCI or to prevent the progression of MCI to AD.

There is growing evidence that a cognitively active lifestyle may reduce rates of dementia. A systematic review of 22 population-based studies found that mental activities may reduce overall incident dementia risk by 46% over a median 7-year period [1]. Computerized Cognitive Training (CCT) provides a novel strategy to improve cognitive performance in MCI by establishing a more cognitively active lifestyle. CCT involves computerized cognitive exercises that target specific abilities to improve cognitive functioning, and this effect is likely to be mediated by neuroplasticity. CCT has been used successfully to improve cognitive functioning in healthy adult populations [2, 3, 4, 5]. In particular, two studies in older healthy controls have garnered much attention. The ACTIVE trial was the first large-scale, randomized trial to show evidence of transfer from cognitive training to improved daily function, but only in participants who completed reasoning or speed of processing focused training, and not memory training [6]. In this ten-year follow up study of 2,832 healthy adults (average age = 73.6), participants were randomized to one of three intervention groups (memory, reasoning, or speed of processing) or a no-contact control group. Booster sessions occurred for 39% of participants in all active groups at 11 and 35 months after initial training, but the cognitive effects of the memory training did not persist over the ten-year follow up period [6]. In a second large, well-publicized online cognitive training study, findings were originally considered to be negative in terms of cognitive gains. However, in an examination of an older subsample, training was effective in improving cognitive abilities and instrumental activities of daily living [7].

In a recent meta-analysis examining CCT in older adults with MCI or dementia, the overall efficacy of cognitive outcomes in MCI was moderate and statistically significant [8]. This pattern was also found for global cognition, verbal learning and memory, nonverbal learning, working

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3 memory, attention, and psychosocial functioning (e.g. depression, quality of life,  
4 neuropsychiatric symptoms). However, for the efficacy of cognitive outcomes in patients with  
5 dementia, the overall effect was found to be small, though statistically significant.  
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10 Early interventions at the stage of MCI, and not dementia, may be more helpful for improving  
11 cognition. In fact, Hill et al. [8] concluded that CCT is a feasible intervention for improving  
12 cognition in patients with MCI. Transfer effects have also been found in studies evaluating CCT  
13 in healthy older adults, supporting the potential for transfer of CCT benefits to daily life [6, 9]. In  
14 this study, we will assess for transfer effects by administering the following functional  
15 assessments at specific timepoints: Functional Activities Questionnaire (FAQ) and University of  
16 California San Diego Performance-Based Skills Assessment (UPSA).  
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24 Although CCT has received more support in the past few years as a viable treatment option for  
25 older adults with MCI, the brain mechanisms underlying the observed cognitive changes remain  
26 elusive. Many studies of CCT that include imaging components have only been conducted with  
27 healthy older adults [10, 11, 12, 13]. CCT may promote neuroplasticity in the brain, including in  
28 the hippocampus, a key region that supports memory [13, 14, 15, 16]. Additional research needs  
29 to be done that evaluates both structural and functional data within a rigorously-conducted  
30 clinical trial. In this study, patients will undergo a structural MRI and fMRI at both study entry  
31 and exit to assess for changes in hippocampal volume and the default mode network (DMN). The  
32 latter is crucial to evaluate in patients with MCI as dysfunction in the DMN has been implicated  
33 in the progression of MCI to AD [17]. The DMN is a resting state neural network of several  
34 highly interconnected cortical hubs, including the posteromedial parietal, anteromedial frontal,  
35 and inferolateral parietal cortices. We have shown that impaired deactivation and functional  
36 connectivity in the DMN may be a significant predictor in MCI of poor memory and transition to  
37 dementia over a 2-3 year follow-up period [18]. Neuronal dysfunction precedes structural  
38 atrophy in AD, and functional magnetic resonance imaging (fMRI) offers the potential for  
39 identifying specific patterns of disruption in the memory networks affected early in MCI and  
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3 Limitations of prior CCT trials include the inconsistent demonstration of transfer to everyday  
4 functioning, reliance on waitlist control conditions as opposed to active control conditions, and  
5 lack of long-term follow-up. Most studies have not assessed transfer of cognitive improvement to  
6 everyday function or quality of life [19, 20, 21, 22, 23]. While CCT may produce transfers to  
7 untrained cognitive domains, the few studies that evaluate transfer to everyday functioning have  
8 reported mixed findings [24, 25, 26-29]. This is particularly important given the strong  
9 association between cognitive decline and functional disability [30]. Many studies use waitlist  
10 control conditions or control conditions that do not account for engagement and motivation in the  
11 task [22]. Such designs are biased in favor of the treatment condition because waitlisted subjects  
12 are not receiving any form of cognitive treatment and, therefore, may be more likely to drop out  
13 of such studies due to lack of engagement and motivation. In the current study, patients will be  
14 assigned to one of two cognitively stimulating exercises, computerized cognitive training (suite  
15 of exercises) or crossword puzzle training (crossword puzzles). Since one of the purposes of  
16 CCT in patients with MCI is to reduce the risk of progression to dementia, longer follow-up  
17 times are necessary to be able to accurately capture patient progression. However, most studies  
18 have only used no follow-up or short-term follow-ups, with the notable exception of the  
19 ACTIVE trial [6, 31-33].  
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34 Overall, recent findings in the field suggest that computerized cognitive training could benefit  
35 patients at risk for dementia. The current study will build on these findings by implementing a  
36 study design with an active control group, a longer trial duration, an increased intensity of  
37 computerized cognitive training, examination of generalizability to functional abilities beyond  
38 cognitive training skills, structural and functional MRI assessment, and rigorously blinded  
39 methodology.  
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## 46 METHODS AND ANALYSIS

### 47 Study Design Features and Rationale

48 One hundred patients clinically diagnosed with mild cognitive impairment (MCI) will be  
49 randomized. There will be two sites: New York State Psychiatric Institute/Columbia University  
50 Medical Center in New York, NY (NYSPI as lead coordinating site) and Duke University  
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3 Medical Center in Durham, NC. Patients will be randomized to one of two computerized  
4 cognitively stimulating exercises: crossword puzzle training (CPT) or a suite of exercises (CCT;  
5 memory tasks, matching tasks, spatial recognition tasks, processing speed tasks). These patients  
6 will be further randomized by MCI type (early MCI or late MCI), age (70 and below or 71 and  
7 above), and site (NYSPI/CUMC or DUMC) as the stratification factors and will be followed for  
8 78-weeks. The randomization sequences will be balanced in blocks of random size (2, 4) to  
9 prevent clinicians from guessing what the next patient's treatment might be. The term "control"  
10 will not be used in the consent form in order to reduce the participant's expectancy bias.  
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19 In order to maintain neutrality and mitigate expectancy bias among patients, the informed  
20 consent form signed by all patients during the screening visit will not indicate which group is the  
21 active group (suite of exercises) or the control group (crosswords). Rather, it will indicate that  
22 the patient may be assigned to one of two cognitively stimulating exercises, CCT or CPT.  
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### 27 **Role of Sponsor**

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29 The study is funded entirely by a National Institute on Aging grant and supervised by a Data  
30 Safety Monitoring Board. Using Lumosity, a web-based gaming platform from Lumos Labs, we  
31 customized a specific set of CCT and CPT training modules for participants to use in this trial.  
32 After a comprehensive review of several CCT modules on the market, we chose these modules  
33 from Lumosity due to their large selection of games tailored to specific cognitive domains, their  
34 research specific platform, availability of active control condition, availability of the online self-  
35 administered NeuroCognitive Performance Test (NCPT), and our previous pilot data in the  
36 elderly with this platform. Aside from providing the research platform and technical support at  
37 no cost, Lumos Labs provides no financial support for this study and their staff have no  
38 significant role in the final study design, study conduct, data interpretation or publication.  
39 Patients will not be required to pay for the platform and will not have a post-study commitment  
40 to the platform. None of the study team has any financial conflicts with Lumos Labs.  
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### 51 **Recruitment, Eligibility, Consent**

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3 Patients will be recruited from the current patient caseload of the investigators, referral by  
4 neurology, psychiatry, primary care, public health and geriatric medical clinics affiliated with the  
5 centers and supplemented by advertisement.  
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#### 10 Inclusion/Exclusion Criteria.

11 Detailed inclusion/exclusion criteria are described in Table 1. Notable inclusion criteria will be  
12 age range restriction 55-95 years, subjective cognitive complaints (i.e., memory or other  
13 cognitive complaints, e.g., naming/language), Wechsler Memory Scale-III (WMS-III) Logical  
14 Memory Story A delayed recall score 0-11, Folstein Mini Mental State Examination (MMSE)  
15 score  $\geq 23$  out of 30, availability of an informant, and access to a home desktop or laptop  
16 computer with full access to the internet for the study duration. Patients who have a history of  
17 major psychiatric or neurological illness including motor disorders like Parkinson's disease, a  
18 dementia diagnosis of any type, contraindication to MRI scan, lack of English-speaking ability,  
19 or have been defined as regular online brain training or regular crossword puzzle users ( $\geq 2$  times  
20 per week in the past year) will be excluded. Depression will be assessed using the 15-item  
21 Geriatric Depression Scale (GDS); a diagnosis of Major Depressive Disorder is exclusionary.  
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#### 32 *Mild Cognitive Impairment Criteria*

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34 Mild cognitive impairment (MCI) and type of MCI (early MCI or late MCI) will be assessed by  
35 the delayed recall score of WMS-III Logical Memory and by the score on the MMSE. On  
36 Logical Memory II Story A, a score from 0-11 will indicate cognitive impairment, per the  
37 Alzheimer's Disease Neuroimaging Initiative (ADNI) criteria. MCI type will be determined from  
38 this score combined with years of education of the patient. Early MCI (eMCI) will be defined as  
39 a delayed recall score of 3-6 with 0-7 years of education, score of 5-9 with 8-15 years of  
40 education, and score of 9-11 with 16 or more years of education. Late MCI (lMCI) will be  
41 defined as a delayed recall score of  $\leq 2$  with 0-7 years of education, score of  $\leq 4$  with 8-15 years  
42 of education, and score of  $\leq 8$  with 16 or more years of education. For both eMCI and lMCI,  
43 everyday function must be well preserved for study inclusion. A MMSE score  $\geq 23$  will also be  
44 required to indicate mild cognitive impairment, and this is required for study inclusion.  
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#### 55 **Length of Clinical Trial**

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3 Most transitions from MCI to AD typically occur within three years of follow-up after the  
4 diagnosis of MCI is made [34]. We chose 18-months as the length of this clinical trial to  
5 decrease dropouts that can occur in a very long controlled trial. Since this study is considered  
6 low risk, we do not anticipate participants to suffer harm from trial participation.  
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## 10 11 12 **Treatment Regimen**

13 Enrolled participants will come to the clinic for five scheduled visits (Weeks 0, 12, 32, 52, and  
14 78) and will receive at least three scheduled phone calls with research staff (Weeks 20, 42, and  
15 64). Participants will be enrolled into the study after screening for eligibility and consent is  
16 signed. The randomization will be assigned by the statistician and then carried out by the  
17 unblinded research coordinator, with individuals stratified by MCI type, age group, and site.  
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24 Randomization.

25 The blinded research coordinator (at NYSPI or Duke) will complete the Training Group  
26 Randomization Form to indicate the following information for the patient: site, age, and MCI  
27 type. This form will be verified by the unblinded research coordinator at NYSPI, who will then  
28 assign a study ID to that patient, using a pre-populated form from the statistician's randomization  
29 assignment. The order of the study ID assignment will determine which study condition the  
30 patient will receive: CPT or CCT. The Lumosity account information will be generated after the  
31 MRI has been completed and quality checked. Lumosity account credentials will include a  
32 research-specific COGIT ID email address and password, which will enable users to log into an  
33 account specific to their study condition.  
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43 Randomization will be complete when the patient logs into his/her account for the first time at  
44 the baseline visit and sees which condition he/she is in. At this visit, patients will be trained by  
45 unblinded study staff in their assigned training condition. Eighteen modules were selected to  
46 target various cognitive domains: (A) Memory (Tidal Treasures, Familiar Faces, Memory  
47 Matrix) (B) Processing Speed (Speed Match) (C) Response Inhibition (Color Match) (D) Verbal  
48 Fluency/Vocabulary Proficiency (Word Bubbles, Word Snatchers, Editor's Choice, Continuum)  
49 (E) Planning/Divided Attention (Train of Thought, Brain Shift, Trouble Brewing, Disillusion)  
50 (F) Visual Interference (Lost in Migration, Ebb and Flow, Masterpiece) (G) Identification (River  
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3 Ranger) (H) Visualization (Speed Pack). These cognitive domains were chosen as they are areas  
4 that are often impaired in patients with MCI and thus represent areas that can be targeted for  
5 improvement [35]. Verbal Fluency and Vocabulary Proficiency tasks were included to promote  
6 verbal fluency in the CCT group. Further, the episodic memory task, Familiar Faces, targets  
7 verbal memory and learning. With this, it is acknowledged that episodic memory training may be  
8 somewhat limited in the selected battery of modules provided by Lumosity. Each CCT session  
9 will consist of a random selection of six modules. Participants in the CCT condition are not  
10 allowed to choose the games, and are not allowed to skip over or change the suite of games. The  
11 Lumosity platform will scale difficulty by using the patient's Lumosity Performance Index  
12 (LPI). The LPI will consider three areas for each patient. The Game Performance Index will be  
13 determined by reviewing score distributions for each game. The Cognitive Area Performance  
14 Index (speed, memory, attention, flexibility and problem solving) will be calculated using a  
15 weighted average of the Game Performance Index. Thirdly, the overall Cognitive Performance  
16 Index will be calculated using a weighted average of the Game Performance Indices from all  
17 cognitive areas. A complete list of selected CCT games are described in Table 2. Crosswords  
18 engage primarily verbal abilities and perhaps, executive and attentional mechanisms. The  
19 Lumosity games target different cognitive domains, such as speed of processing and memory, as  
20 well as verbal abilities. The effect that these different trainings have on the so-called far transfer  
21 problem will of course be of major interest. There should be no case in which an emergency  
22 unblinding will need to take place, as the blinded intervention is a computerized intervention.  
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39 Participants in the computerized cognitive training group and the crossword puzzle training  
40 group will spend the same amount of time on the platform during the intensive training phase,  
41 which will consist of four 30-minute training sessions per week for 12 weeks. Participants are  
42 not required to have any particular level of computer skills for study inclusion; however, at the  
43 initial baseline training, all participants will be trained on how to successfully access the training  
44 platform, and how they could obtain help both from research staff and their informant throughout  
45 the study. For both groups, responses will be entered via mouse and keyboard. For the crossword  
46 puzzle training group, questions will not need to be completed in order and there will not be any  
47 feedback for the accuracy of the response at the time of entry by the participant. Upon  
48 completion of the CCT suite of exercises after 30 minutes, participants will receive a score.  
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3 Similarly, after 30 minutes the crossword training will automatically end. If a participant were to  
4 finish an entire crossword puzzle before the 30-minute cutoff, they would be directed to another  
5 crossword puzzle to ensure they complete a total of 30 minutes.  
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10 Following the intensive training phase of 12 weeks, participants will be instructed to complete  
11 six booster sessions. Each booster session will consist of four CCT/CPT sessions. Booster  
12 sessions will be completed at weeks 20, 32, 42, 52, 64, and 78. At weeks 32, 52, and 78, patients  
13 will complete three booster sessions at home and complete the fourth session in-clinic with  
14 research staff. At weeks 20, 42, and 64, patients will complete all four booster sessions at home.  
15 Generally, in previous cognitive training studies, booster sessions have been limited. For  
16 instance, the ACTIVE trial had two booster sessions, each consisting of four 75-minute trainings  
17 at 11 and 35 months. During the course of the trial, booster sessions included a total of 8  
18 trainings, for a total of 10 hours [6]. In contrast, COGIT will have six booster sessions (24 total  
19 training sessions each lasting 30 minutes) over 15 months. Thus, COGIT will include 12 hours  
20 total for booster sessions during the trial. The ACTIVE trial only required compliant participants  
21 to complete the booster sessions, whereas all participants will complete booster sessions in the  
22 COGIT study [6].  
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#### 34 Clinic Based Cognitive, Functional, and Smell Assessments.

35 At baseline (week 0) The Alzheimer's Disease Assessment Scale-Cognition Subscale 11  
36 (ADAS-Cog 11) will be administered, in addition to the following neuropsychological test  
37 battery: WAIS-III Block Design (to assess visuospatial skills), Digit Symbol Substitution Test  
38 (DSST) (to assess attention), Trail Making A & B (to assess attention and executive function),  
39 Verbal Fluency and 15-item Boston Naming Test (to assess language), Auditory-Verbal  
40 Learning Test (to assess verbal learning and memory), and WMS-III Visual Reproduction Test  
41 (to assess nonverbal learning and memory). In addition, the UPSA and University of  
42 Pennsylvania Smell Identification Test (UPSIT) will be administered. Testing fatigue is  
43 mitigated by allowing participants to take breaks during the testing. If there is missing data from  
44 one time point, the study team will attempt to bring the participant back to the clinic within the  
45 allowed window to complete missing measures. The FAQ will be administered to the patient's  
46 informant, either during the study visit or shortly after the visit over the phone.  
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5 Self-Administered Cognitive Test Battery.

6 Another unique aspect of the study is the use of the NCPT, an online, computerized, self-  
7 administered battery developed by Lumosity. It will test various cognitive domains outlined in  
8 the Study Measures section. The NCPT will allow us to examine the efficacy of a self-  
9 administered test, in combination with standardized, clinic-based neuropsychological tests.  
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### 15 **Timeline of Longitudinal Assessments**

16 At in-clinic visits (baseline and weeks 12, 52, and 78), the same neuropsychological battery of  
17 testing will be completed. At the week 12 and week 78 visits, the patient will be asked to  
18 complete the User Engagement Scale, which will be adapted to capture usage of a computerized  
19 platform. This scale will measure aspects of engagement, usability, and satisfaction with the  
20 computerized platform on a 5-point Likert scale. Week 20 will be a phone interview between  
21 study physician/neuropsychologist and patient to follow-up on how the patient has been doing,  
22 and to remind the patient to complete a booster session.  
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### 31 **Blinded Training Procedure**

32 The blinded research coordinator will administer the full neuropsychological test battery,  
33 including the UPSA and FAQ. The blinded clinician will complete the Diagnosis Form and the  
34 Contributing Features to MCI form after clinical interview and review of the neuropsychological  
35 testing. The unblinded research coordinator will administer the initial computerized training and  
36 all subsequent booster sessions to patients in the clinic. To track type of games/crossword  
37 puzzles and amount of time that the subject spends doing the games/crossword puzzles, only  
38 unblinded study coordinators receive reports from Lumosity each week. If the Lumosity reports  
39 of computer games/crosswords access do not match the subject's assigned instructions, the  
40 unblinded coordinator then contacts the subject to guide and ensure adherence to the protocol.  
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### 50 **Hypotheses**

51 See Figure 1 for a Conceptual Model of specific study aims and outcome measures. The primary  
52 aim of the study is to assess change in cognitive and functional status over 18 months in MCI  
53 patients comparing the CCT and CPT groups. Hypothesis 1: MCI patients randomized to CCT  
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3 will show better cognitive outcomes on the ADAS-Cog 11 (primary outcome measure),  
4 Neuropsychological Testing Composite score (secondary outcome measure), and NCPT  
5 (exploratory outcome measure) compared to active control (CPT). Hypothesis 2: MCI patients  
6 randomized to CCT will show better functional outcomes as assessed by the UPSA (primary  
7 functional outcome) and FAQ (secondary functional outcome) by the end of the 18-month trial  
8 compared to active control. Hypothesis 3: brain pathology (smaller hippocampal volumes, lower  
9 odor identification scores on the UPSIT, ApoE e4 allele present) will moderate the relationship  
10 between treatment assignment and cognitive and functional outcomes.  
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19 The secondary aim of the study is to examine the effects of CCT on resting-state DMN  
20 connectivity as well as other networks modulated by CCT effects. Hypothesis 1: MCI patients  
21 randomized to CCT will demonstrate greater change in an index of DMN functional connectivity  
22 compared to patients randomized to active control. Hypothesis 2: indicators of brain pathology  
23 (smaller hippocampal volumes, lower odor identification scores on the UPSIT, ApoE e4 allele  
24 present) will moderate the relationship between change in the DMN and treatment assignment.  
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31 The tertiary aim of the study is to examine differences in rates of progression to dementia and  
32 AD in the two randomized treatment groups, recognizing that if progression to these outcomes is  
33 uncommon there will be insufficient statistical power. Hypothesis 1: the proportion converting to  
34 dementia will be lower in the CCT group compared to active control.  
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### 40 **Study Measures**

41 Study measures with time-points of administration are listed in Table 3. The MMSE will be  
42 administered at screen and each subsequent in-clinic visit using five different versions of the  
43 three-word recall item to reduce practice effects [36]. The Cumulative Illness Rating Scale for  
44 Geriatrics (CIRS-G) and The Framingham Stroke Risk Scale will be completed by the study  
45 physician at screen and week 78 to assess for cardiovascular disease risk factors and other  
46 medical conditions.  
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52 The Geriatric Depression Scale will be administered at screen and each subsequent in-clinic visit  
53 to assess for depression. If GDS is greater than 5 at any visit, the patient will be evaluated by a  
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3 psychiatrist and an appropriate clinical referral will be made, if needed, for treatment of  
4 depression. The Cognitive Reserve Index is a brief questionnaire that will be administered by the  
5 research coordinator at screen and will evaluate the cognitive reserve of an individual by means  
6 of the compilation of information as it relates to his/her adult life.  
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11 At screen, the research coordinator will be responsible for administering the History of Game  
12 Use Questionnaire, Physical Activity Assessment, and WMS-III Logical Memory I & II. The  
13 History of Game Use Questionnaire will be administered again at weeks 12 and 78 to ensure that  
14 patients are not partaking in any other types of cognitive training games while in the study.  
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20 At screen and week 78, patients will undergo an MRI scan of the brain. The MRI scan will  
21 include the following sequences: Localizer, high-resolution T1-weighted IR prepped 3DSPGR,  
22 and T2 FLAIR, and GE-EPI resting-state fMRI scans.  
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27 At weeks 0 and 78, the UPSIT will be completed by the patient, which is a 40-item scratch and  
28 sniff multiple-choice olfactory identification test.  
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32 At each in-clinic visit, apart from week 32, the ADAS-Cog 11 and full neuropsychological test  
33 battery will be administered. The NCPT will be administered at weeks 0, 12, and 78. The  
34 cognitive domains measured by the NCPT are memory (visuo-spatial working memory, short-  
35 term memory), processing speed (visual search, psychomotor speed), problem solving (logical  
36 reasoning, numerical calculation), attention (selective, divided), and flexibility (response  
37 inhibition, task-switching). The assessments, 10 total “subtests,” are online adaptations of widely  
38 used neuropsychological tests whose test properties are not affected by shifting to computerized  
39 administration [37].  
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48 The neuropsychological test battery includes: WAIS-III Block Design, Digital Symbol  
49 Substitution (DSST), Trail Making A & B, Verbal Fluency and 15-item Boston Naming Test,  
50 Auditory-Verbal Learning Test (AVLT), and WMS-III Visual Reproduction Test. For word  
51 learning lists, the neuropsychological testing materials provide different but parallel word lists,  
52 so as to avoid practice effects in MMSE and ADAS-Cog, but not for AVLT. With respect to the  
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3 latter we did not adopt this approach because we were concerned that different forms have not  
4 been established as equivalent in difficulty level. The UPSA will be administered only at weeks  
5 0, 32, and 78 due to the high tendency for practice effects. It is a performance-based measure of  
6 functional abilities that includes measures of simulated real-world activities; for example,  
7 planning a trip to the beach, remembering documents to bring to a medical appointment, and  
8 dialing a phone number. When a participant wears corrective lenses during the testing battery,  
9 this is documented in the participant's research chart.  
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17 At screen and weeks 12, 32, 52, and 78 the participant will meet with the study physician or the  
18 neuropsychologist to assess for illness progression and adverse events. Adverse events that are  
19 spontaneously reported to research coordinators at any clinic visit will be discussed with the  
20 study physician or the neuropsychologist in order to determine how to proceed. Adverse events  
21 and subsequent steps to deal with the adverse events will be documented in the patient chart and  
22 serious adverse events will be reported to the Data Safety and Monitoring Board and study  
23 sponsor, National Institute on Aging.  
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31 Additionally, the research coordinator will conduct an interview with the informant at, or shortly  
32 after, each visit to complete the FAQ.  
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### 36 **Criteria for Early Discontinuation**

37 We expect early discontinuation to occur because of one or more of the following reasons: (1)  
38 the patient's decision not to continue the computerized training (CCT or CPT) due to lack of  
39 interest, motivation, or available time; (2) unavoidable circumstances, e.g., moving residence and  
40 unwillingness to return for in-person evaluations; (3) investigator decision to terminate; (4) death  
41 or prolonged hospitalization for medical reasons. We will not terminate participation for non-  
42 adherence because even if the patient is non-adherent to the protocol, we will document level of  
43 adherence (done electronically in this computerized training protocol) and still include the  
44 patient's data in the analyses based on the intent-to-treat principle.  
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### 53 **Data Management**

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3 Data entry will be completed by Program Managers, Clinical Research Coordinators, and  
4 Research Assistants on the study protocol. Data entry/cleaning will be done throughout the  
5 project. The data collected in this study will be monitored by the Data Coordinating Center at  
6 NYSPI. The unit will work closely with the research assistant/coordinator and the Principal  
7 Investigator to facilitate independent auditing of primary subject records. The database will  
8 provide reports indicating all modifications that have been made in the database together with  
9 paper communications (fax, e-mail) confirming and authorizing these modifications. Access to  
10 the data system is available only to authorized users, with multiple levels of security including  
11 user id/password authentication via MS Active Directory overseen by experienced IT personnel.  
12 Other authorized users with direct access to the data system will be Data Coordinating Center  
13 (DCC) staff. DCC data-related operations and the SIR/Citrix system have been certified by  
14 Columbia University's Information Security Office. The dataset will not be published in a data  
15 repository.  
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### 27 **Genetic Testing**

28 Apolipoprotein E (ApoE) genetic analysis on a blood sample will be done through the laboratory  
29 of the Human Genetics Resources Core (HGRC) at Columbia University Medical Center. We  
30 will assess the ApoE  $\epsilon$ 4 allele as potentially associated with response to CCT; a prior trial found  
31 an association between the  $\epsilon$ 4 allele and cognitive improvement on donepezil [38].  
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### 38 **Concomitant Medications**

39 Putative cognitive enhancers, narcotics, all classes of psychotropic medications, and over 20  
40 other classes of commonly prescribed and over the counter (and alternative) medications will be  
41 documented in a rating form at screen and subsequent in-clinic visits. An exclusion criterion will  
42 be daily use of medications known to have a negative impact on cognition: high-dose narcotics,  
43 anticholinergics, and benzodiazepines in lorazepam equivalents  $\geq 1$  mg daily. During the first 12  
44 weeks of the study, the intensive cognitive training phase, patients are encouraged not to change  
45 any of their medications, unless clinically indicated.  
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### 53 **Statistical Analysis and Sample Size**

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3 We powered our trial to detect an effect size at 18 months of  $d=.58$  (80% power). This effect size  
4 is more conservative than published treatment changes associated with CCT (for instance, see  
5 [39]). We assume that dropout is distributed uniformly across waves of follow-up assessments  
6 (with 5% attrition between each consecutive pair of the 5 major time-points, i.e. 20% by 18  
7 months).  
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13 Outcome Measures (Primary and Secondary Hypotheses Testing).

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15 *Aim 1 Hypothesis 1 and 2.* MCI patients on CCT will show a lower rate of cognitive and  
16 functional decline compared to MCI patients on active control by the end of the 18-month trial.  
17 We will use generalized linear mixed effects models of cognitive and functional measures  
18 collected repeatedly across the 78 weeks according to the schedule (see Table 3). For example,  
19 cognitive measure $_{ik} = \beta_0 + \beta_1 \text{Time}_{ik} + \beta_2 \text{Group}_i + \beta_3 (\text{Group}_i \times \text{Time}_{ik}) + v_{0i} + v_{1i} \text{Time}_{ik} + \varepsilon_{ik}$   
20 where  $\text{Group}_i$  indicates treatment group for subject  $i$  (Group = 1 CCT, 0 for control),  $k$  = time  
21 (baseline, 12 weeks, 20 weeks, 52 weeks, 78 weeks), and  $v_{0i}$  is a subject-specific random  
22 intercept. Time will be treated as categorical if linearity is not plausible and group effects at 18  
23 months can be tested by forming contrasts from the fitted model. Potential site differences will  
24 be evaluated using descriptive statistics and site will be included in all analyses as a covariate, as  
25 will other stratification variables including age group and MCI type at baseline.  
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37 *Aim 2 Hypothesis 1.* MCI patients randomized to CCT will demonstrate either more of an  
38 increase or less of a decrease in DMN connectivity (goodness-of-fit [GOF] index scores)  
39 compared to patients randomized to active control. To test this hypothesis, we will use a repeated  
40 measures Analysis of Covariance (ANCOVA) with time (baseline vs. post treatment) as the  
41 repeated measure, DMN connectivity as an outcome, treatment condition (CCT vs CPT) as a  
42 predictor, and site, age, and MCI status at baseline as covariates.  
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49 *Moderating Effects in Aim 1 Hypothesis 3 and Aim 2 Hypothesis 2.* As a part of our exploratory  
50 analyses, we will examine specific potential moderators: Apolipoprotein E  $\epsilon 4$  allele, MRI  
51 indices, UPSIT. To show, for example, that baseline hippocampal volume is a moderator, we  
52 will test its interactive effect with treatment on outcomes. Moderator and moderator-interaction  
53 terms can be easily accommodated in the mixed effects regression models described in Aim 1.  
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3 Hypotheses 1 and 2. A similar approach will be used by adding moderator and moderator x  
4 Group interactions to the ANCOVA described in Aim 2 Hypothesis 1. The results must be  
5 interpreted with the caveat that there may not be enough power to assess these interactions,  
6 especially for moderators with low prevalence.  
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12 *Aim 3 Hypothesis 1.* The proportion diagnosed with dementia during follow-up will be lower in  
13 the CCT group compared to active control. Logistic regression will be used to test the binary  
14 outcome of dementia status at 18 months predicted by treatment group controlling for site, age  
15 group, and MCI type at baseline.  
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20 Missing data is managed statistically through use of mixed model repeated measures analyses.  
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### 23 **Sample Size.**

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25 A power analysis was conducted using the RMASS program for longitudinal studies, which  
26 determined that a total sample size of 100 participants will provide a sufficient effect size to  
27 evaluate our hypotheses. We have two primary outcome measures (i.e., multiple outcome  
28 measures), namely ADAS-Cog and the UPSA. For multiple outcome measures, statistical  
29 significance on any one measure is meaningful and there is no need to correct for multiple  
30 comparisons (unlike co-primary outcome measures). All other outcome measures are secondary  
31 and exploratory.  
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### 39 **Patient and Public Involvement**

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41 Patients will first be involved in the research after study design is finalized by the study  
42 investigators. At this stage, patients will be referred by physicians or self-referred from online  
43 and newspaper advertisements for their initial screening visit. The patients will not be involved  
44 in study design, study recruitment or conduct, or dissemination of study results. We will assess  
45 the burden of the trial intervention on patients using the User Engagement Scale and the  
46 Participant/Informant Expectancy Scales. Patients will not be invited to comment on the study  
47 design and were not consulted to develop patient relevant outcomes or interpret the results.  
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49 Patients will not be invited to contribute to the writing or editing of this document for readability  
50 or accuracy.  
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## ETHICS

This study has been approved by NYSPI IRB, Duke University IRB, and Queens College IRB. All COGIT patients at entry will be required to have the capacity to provide informed consent and sign the IRB-approved informed consent form. Local IRB and state regulations for consent will be followed. Patient confidentiality as it pertains to potential and enrolled participants before, during, and after the trial will be collected, shared, and maintained strictly according to HIPAA law.

Important protocol modifications will be communicated to the Data Safety and Monitoring Board, NYSPI IRB and Duke University IRB, and updated online for trial registries.

The research data on specific moderators, including UPSIT and apolipoprotein E genotyping, will not be not released to the patient, and this will be specified in the consent form. The cognitive testing results and clinical reading of the MRI scan will be released to the patient (and the patient's primary physician, if requested); the MRI research volumetric ratings and fMRI findings will not be released.

### **Data Safety and Monitoring Board (DSMB)**

Three NIA-approved independent experts with expertise in conducting clinical trials in mild cognitive impairment will form the DSMB. All serious adverse events (SAEs) will be reported to the DSMB. The DSMB will audit the trial conduct, review all SAEs, participate in a teleconference twice a year to determine if the study should continue, and then will provide an actionable report to the Principal Investigator. This process will be independent from the investigators.

## DISSEMINATION



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3 The study results will be disseminated through publications and conference presentations as well  
4 as on public websites, including [clinicaltrials.gov](http://clinicaltrials.gov). Researchers will be eligible for authorship  
5 after consideration by the principal investigators; no professional writers will be utilized.  
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## 10 **SIGNIFICANCE**

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13 This will be one of the first investigator-blinded and controlled long-term trials to evaluate the  
14 effects of home-based computerized cognitive training versus computerized crossword puzzle  
15 training on cognitive, functional, hippocampal and default mode network connectivity neural  
16 outcomes in MCI. Positive results from this pilot trial may support the further development of  
17 home based cognitive training and self-assessments in people at risk for dementia.  
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24 The results will help inform the design of a more powerful RCT in many ways: determine  
25 sample size for a multicenter trial, identify subgroups more likely to benefit, identify subdomains  
26 and exercises most likely to improve, optimize training dose and duration, learn how subjects  
27 engage, identify gender effects, model slopes and long-term benefits, assess value of a self-  
28 administered cognitive test, understand brain networks affected, and examine the potential  
29 moderating role of apolipoprotein E  $\epsilon$ 4 status on CCT outcome.  
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## 36 **AUTHOR CONTRIBUTIONS**

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39 DPD, PMD, JRP, and JRS conceptualized and designed the study and obtained funding. JLD and  
40 LSP drafted the initial manuscript. HFA contributed to statistics design and JRP to design of  
41 MRI component. TEG, SNR, NAK, CAH, SNT, EP assisted with elements of study design,  
42 database, and conduct. DPD is the overall study PI and PMD is the PI at the Duke site. All  
43 authors (JLD, LSP, TEG, JRS, SNR, NAK, HFA, CAH, SNT, EP, JRP, PMD, DPD) contributed  
44 to manuscript edits and revisions and approved the final manuscript as submitted. All authors  
45 agree to be accountable for all aspects of the work.  
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## FUNDING STATEMENT

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## COMPETING INTERESTS

JLD, LSP, TEG, JRS, SNR, NAK, HFA, CAH, SNT, EP, JRP have no competing interests. PMD has received research grants and advisory fees from several companies in this field for other studies, and owns shares in several companies whose products are not discussed here. DPD serves as a consultant on advisory boards to Acadia, Avanir, Genentech, Eisai, and Neuronix.

**Table 1. Inclusion/Exclusion Criteria**

<b>Inclusion Criteria</b>
1. Males and females 55 to 95 years of age (inclusive) at the time of informed consent.
2. Subjective cognitive complaints, i.e., memory or other cognitive complaints, e.g., naming/language.
3. Meets criteria for cognitive impairment (CI) defined as scores >1 SD below standardized norms on memory function as identified by the Wechsler Memory Scale (WMS) III Logical Memory delayed recall score.
4. Folstein Mini Mental State (MMSE) score $\geq$ 23 out of 30.
5. A family member or other individual who is in contact with the patient and consents to serve as informant during the study; this could be a telephone informant in case of patients who do not have a live-in informant or close significant other.
6. Access to a home desktop or laptop computer at acceptable speed for the study duration.
<b>Exclusion Criteria</b>
1. Diagnosis of dementia of any type.
2. Current clinical evidence of schizophrenia, schizoaffective disorder, major depression, psychosis, or bipolar I disorder (DSM-IV TR criteria).
3. Active suicidal ideation or plan.
4. Current or recent (past 6 months) alcohol or substance use disorder (DSM-5 criteria).
5. Clinical stroke with residual neurological deficits. While we will not exclude patients with cerebrovascular disease, we will not include patients who have had a stroke with residual clinical deficits because it is not clear that this type of patient is similar to the MCI patient generally, and clear-cut neurological impairment, e.g., hemiplegia/hemiparesis or speech impairment, may compromise the patient's ability to do the CCT or active control procedures and to complete the neuropsychological tests.
6. Use of medications known to have a negative impact on cognition: benzodiazepines in lorazepam equivalents $\geq$ 1 mg daily, narcotics, anticholinergics. Other patients receive medications that may be associated with cognitive impairment but are rarely considered the likely etiology, e.g., theophylline, nifedipine, beta blockers; they will not be excluded. Patients receiving other psychotropic medications not expected to have a material impact on cognition, e.g., SSRIs and SNRIs will be eligible.
7. Presence of any of the following disorders: a) CNS infection, with CSF evidence of meningitis, encephalitis, or other infectious process; b) dementia of any type; c) Huntington's disease; d) Multiple sclerosis; e) Parkinson's disease; f) Other neurologic disorders with focal signs, e.g., amyotrophic lateral sclerosis; g) Mental retardation.
8. Acute, severe unstable medical illness. For cancer, acutely ill patients (including those with metastases) will be excluded, but past history of successfully treated cancer will not result in exclusion.
9. Contraindication to MRI scan: pacemaker, metal implants following surgery, any other contraindication to MRI. Eligibility for the MRI scan is a requirement for the study.
10. UPSIT exclusions: current smoker > 1 pack daily, current upper respiratory infection (retested as soon as the infection clears). UPSIT scores are reduced in schizophrenia, Parkinson's disease and Parkinson's related conditions; these disorders are exclusion criteria for this study. Patients with UPSIT exclusions will not receive the UPSIT but will continue to participate in all other aspects of the study.
11. Patients lacking English-speaking ability as determined by self-report and clinical evaluation.
12. Regular online brain training or regular crossword puzzle user, defined as doing these procedures at a frequency of twice weekly or greater during the year prior to screening. Eligible participants who join the trial are instructed not to do these procedures on their own during the trial, i.e., independent of the study.
13. Participation in another intervention trial for cognitive impairment.

**Table 2. Complete list of CCT game battery and associated cognitive domains (provided by Lumos Labs)**

<b>Game Name</b>	<b>Cognitive Domain</b>
Tidal Treasures	Working Memory i.e., delayed, non-matching to sample; self-ordered pointing
Speed Match	Processing Speed
Color Match	Response Inhibition
Word Bubbles	Verbal Fluency
Train of Thought	Planning Divided Attention Multiple attractions
Familiar Faces	Episodic Memory; verbal memory and learning
Memory Matrix	Episodic Memory; Visuospatial memory
Lost in Migration	Visual Interference
Brain Shift	Task Switching
Trouble Brewing	Multitasking, divided attention, sustained attention, planning, working memory
Ebb and Flow	Task switching, semantic and visual interference
Masterpiece	Mental rotation; visualization; spatial reasoning
River Ranger	Identification
Word Snatchers	Vocabulary proficiency
Speed Pack	Visualization
Disillusion	Task Switching
Editor's Choice	Vocabulary Proficiency
Continuum	Vocabulary Proficiency

**Table 3. Table of Study Procedures**

Measure	Screen	Baseline	12 Weeks	20 Weeks Phone Interview	32 Weeks	42 Weeks	52 Weeks	64 Weeks	78 Weeks
ADAS-Cog11		X	X				X		X
ApoE & blood test	X								
CIRS-G	X								X
Cognitive Reserve Index	X								
Cognitive Training or Control training booster session			X	X	X	X	X	X	X
Contributing Features to MCI		X			X				X
Demographics History (Patient Tracking Form)	X								
Diagnosis Form			X		X				X
Digit Symbol Substitution Test		X	X				X		X
Expectancy Scale (Participant & Informant)		X			X				X
Family History FAQ	X	X	X	X	X		X		X
Framingham Stroke Risk	X								
Geriatric Depression Scale	X		X		X		X		X
History of Game Use Questionnaire	X		X						X
Inclusion/Exclusion Form	X								
Informed Consent	X								
Medications (Chart List & Database List)	X		X		X		X		X
MMSE	X		X		X		X		X
MRI Scan of Brain	X								X
NCPT online cognitive performance test		X	X						X
Neuropsychological Battery: AVLT, Block Design, Verbal Fluency, Visual Reproduction, Boston Naming Test, Trails A & B		X	X				X		X
Physical Activity Assessment	X								
UPSA		X			X				X
UPSIT		X							X
User Engagement Scale			X						X
WMS-III Logical Memory I & II	X								

**Table 3 Legend:** ADAS-Cog 11 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 11. ApoE = Apolipoprotein E gene. CIRS-G = Cumulative Illness Rating Scale for Geriatrics. MCI = Mild Cognitive Impairment. FAQ = Functional Assessment Questionnaire. MMSE = Mini Mental Status Examination. MRI = Magnetic Resonance Imaging. NCPT = NeuroCognitive Performance Test. AVLT = Auditory Verbal Learning Test. UPSA = UCSD Performance-Based Skills Assessment. UPSIT = University of Pennsylvania Smell Identification Test. WMS-III = Wechsler Memory Scale-III.

### Figure 1. Conceptual Model

In the intervention phase patients are randomly assigned to either CCT or CPT. To evaluate cognitive status, the primary outcome measure will be the ADAS-Cog 11, the secondary outcome measure will be the Neuropsychological Testing Composite Score, and the exploratory outcome measure will be the NeuroCognitive Performance Test. To evaluate functional status, the primary outcome measure will be the UPSA and the secondary outcome measure will be the FAQ. To evaluate changes in neural circuitry, the primary outcome measures will include hippocampal volume (MRI) and DMN connectivity (fMRI).

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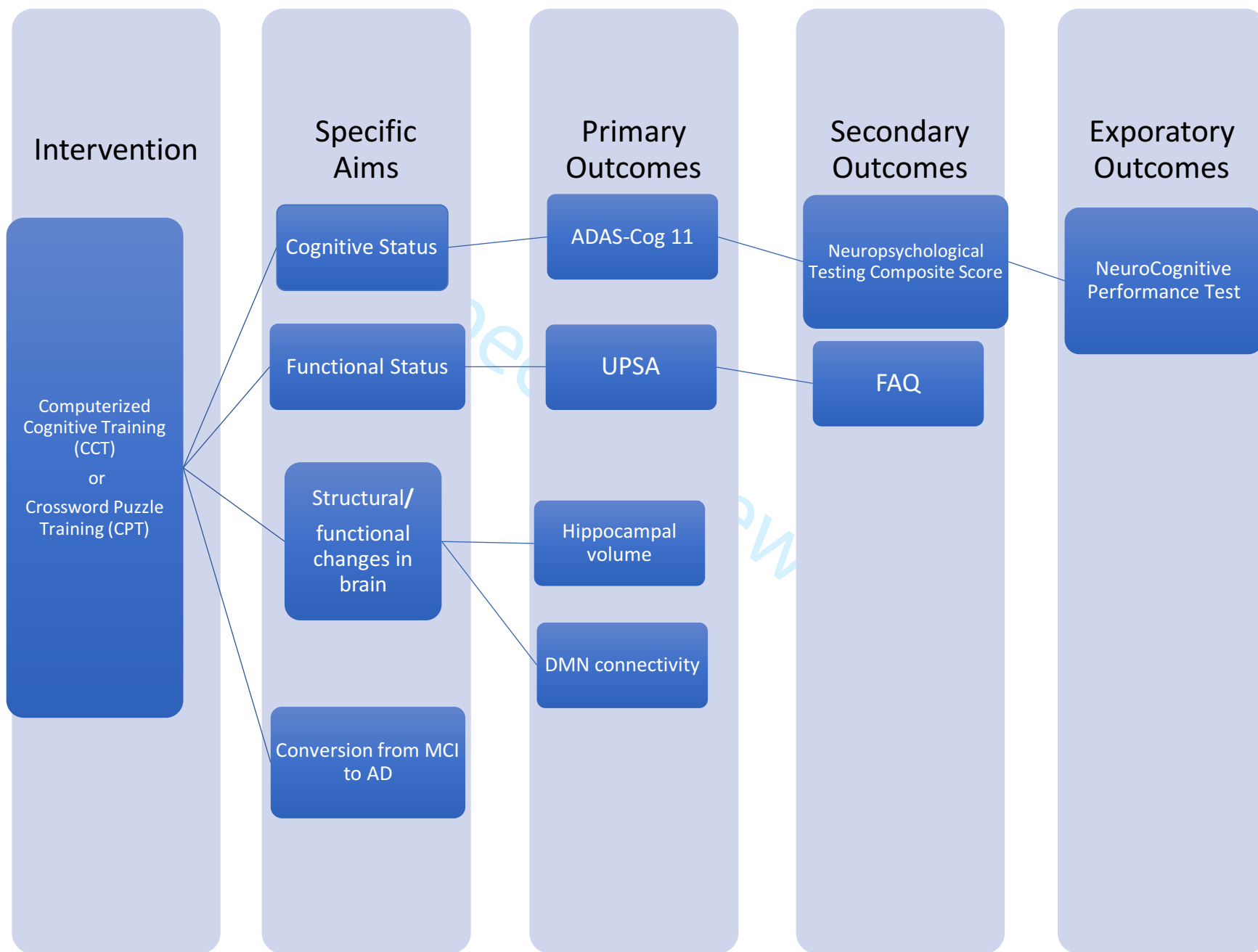
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# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	7; 20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1;20

1	Roles and	#5b	Name and contact information for the trial sponsor	1
2	responsibilities:			
3	sponsor contact			
4	information			
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7				
8	Roles and	#5c	Role of study sponsor and funders, if any, in study	7;20
9	responsibilities:		design; collection, management, analysis, and	
10	sponsor and funder		interpretation of data; writing of the report; and the	
11			decision to submit the report for publication, including	
12			whether they will have ultimate authority over any of	
13			these activities	
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18	Roles and	#5d	Composition, roles, and responsibilities of the	18-19
19	responsibilities:		coordinating centre, steering committee, endpoint	
20	committees		adjudication committee, data management team, and	
21			other individuals or groups overseeing the trial, if	
22			applicable (see Item 21a for data monitoring committee)	
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27	Background and	#6a	Description of research question and justification for	4-6
28	rationale		undertaking the trial, including summary of relevant	
29			studies (published and unpublished) examining benefits	
30			and harms for each intervention	
31				
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34	Background and	#6b	Explanation for choice of comparators	4-6
35	rationale: choice of			
36	comparators			
37				
38				
39	Objectives	#7	Specific objectives or hypotheses	12-13,
40				16-17
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43	Trial design	#8	Description of trial design including type of trial (eg,	6-16
44			parallel group, crossover, factorial, single group),	
45			allocation ratio, and framework (eg, superiority,	
46			equivalence, non-inferiority, exploratory)	
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50	Study setting	#9	Description of study settings (eg, community clinic,	6-7
51			academic hospital) and list of countries where data will	
52			be collected. Reference to where list of study sites can	
53			be obtained	
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1	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
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8	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-14
9	description			
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13	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	15
14	modifications			
15				
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20	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11-12
21	adherence			
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26	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16
27	concomitant care			
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30	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13, 16-17
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42	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13-15, 23
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49	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16-18
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56	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7, 16
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1	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	9
2	generation		computer-generated random numbers), and list of any	
3			factors for stratification. To reduce predictability of a	
4			random sequence, details of any planned restriction	
5			(eg, blocking) should be provided in a separate	
6			document that is unavailable to those who enrol	
7			participants or assign interventions	
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13	Allocation	#16b	Mechanism of implementing the allocation sequence	9-12
14	concealment		(eg, central telephone; sequentially numbered, opaque,	
15	mechanism		sealed envelopes), describing any steps to conceal the	
16			sequence until interventions are assigned	
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20	Allocation:	#16c	Who will generate the allocation sequence, who will	9-12
21	implementation		enrol participants, and who will assign participants to	
22			interventions	
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25	Blinding (masking)	#17a	Who will be blinded after assignment to interventions	9, 12
26			(eg, trial participants, care providers, outcome	
27			assessors, data analysts), and how	
28				
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31	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	10, 12
32	emergency		permissible, and procedure for revealing a participant's	
33	unblinding		allocated intervention during the trial	
34				
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36	Data collection plan	#18a	Plans for assessment and collection of outcome,	13-17
37			baseline, and other trial data, including any related	
38			processes to promote data quality (eg, duplicate	
39			measurements, training of assessors) and a description	
40			of study instruments (eg, questionnaires, laboratory	
41			tests) along with their reliability and validity, if known.	
42			Reference to where data collection forms can be found,	
43			if not in the protocol	
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50	Data collection plan:	#18b	Plans to promote participant retention and complete	11, 13-
51	retention		follow-up, including list of any outcome data to be	15
52			collected for participants who discontinue or deviate	
53			from intervention protocols	
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57	Data management	#19	Plans for data entry, coding, security, and storage,	15
58			including any related processes to promote data quality	
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(eg, double data entry; range checks for data values).

Reference to where details of data management procedures can be found, if not in the protocol

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6	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-17
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13	Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17
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17	Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
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24	Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15, 19
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36	Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	19
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43	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14-15; 19
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50	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
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55	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18
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1	Protocol	#25	Plans for communicating important protocol	18-19
2	amendments		modifications (eg, changes to eligibility criteria,	
3			outcomes, analyses) to relevant parties (eg,	
4			investigators, REC / IRBs, trial participants, trial	
5			registries, journals, regulators)	
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9	Consent or assent	#26a	Who will obtain informed consent or assent from	7, 9
10			potential trial participants or authorised surrogates, and	
11			how (see Item 32)	
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15	Consent or assent:	#26b	Additional consent provisions for collection and use of	N/A
16	ancillary studies		participant data and biological specimens in ancillary	
17			studies, if applicable	
18				
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20	Confidentiality	#27	How personal information about potential and enrolled	18
21			participants will be collected, shared, and maintained in	
22			order to protect confidentiality before, during, and after	
23			the trial	
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27	Declaration of	#28	Financial and other competing interests for principal	20
28	interests		investigators for the overall trial and each study site	
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31	Data access	#29	Statement of who will have access to the final trial	N/A
32			dataset, and disclosure of contractual agreements that	
33			limit such access for investigators	
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37	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and	N/A
38	trial care		for compensation to those who suffer harm from trial	
39			participation	
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42	Dissemination	#31a	Plans for investigators and sponsor to communicate trial	19
43	policy: trial results		results to participants, healthcare professionals, the	
44			public, and other relevant groups (eg, via publication,	
45			reporting in results databases, or other data sharing	
46			arrangements), including any publication restrictions	
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51	Dissemination	#31b	Authorship eligibility guidelines and any intended use of	19-20
52	policy: authorship		professional writers	
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55	Dissemination	#31c	Plans, if any, for granting public access to the full	N/A
56	policy: reproducible		protocol, participant-level dataset, and statistical code	
57	research			
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1	Informed consent	#32	Model consent form and other related documentation	N/A
2	materials		given to participants and authorised surrogates	
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5	Biological	#33	Plans for collection, laboratory evaluation, and storage	16
6	specimens		of biological specimens for genetic or molecular	
7			analysis in the current trial and for future use in ancillary	
8			studies, if applicable	
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## Author notes

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