# A randomised placebo-controlled study into the feasibility and efficacy of working memory training in chronic obstructive pulmonary disease: the study protocol

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# Abstract

Background General cognitive impairment is highly prevalent in patients with chronic obstructive pulmonary disease (COPD). Domain-specific cognitive impairments include deficits in working memory (WM), cognitive flexibility, verbal memory, planning and psychomotor speed. These impairments may be associated with poor health behaviours, such as a sedentary lifestyle and low-quality diet. Cognitive training may reverse these effects. Recent evidence suggests that WM training is linked to self-control and, indirectly, to improved lifestyle behaviour including increased physical activity. We aim to investigate the efficacy of WM training (WMT) in patients with COPD on cognitive performance, cognitive stress susceptibility and perception, self-control, and adherence to personalised physical activity and dietary behaviour goals. Methods A double blind, placebo-controlled randomised trial will be conducted in 60 patients with COPD. The trial will consist of two phases; 12 weeks of active WM training or sham training followed by 12 weeks of maintenance. Prior to the WMT, before the first phase, participants in both the sham (n=30) and training group (n=30) will set dietary and physical activity goals based on their dietary intake and physical activity profile using validated tools. Cognitive performance will be examined using the Cambridge Neuropsychological Test Automated Battery. The primary outcome of this study will be change in cognitive performance. Secondary outcomes will be self-control (impulsivity), compliance, stress susceptibility and perception, change in dietary intake and daily physical activity level and pattern. Discussion This trial will attempt to determine if cognitive performance can be improved in patients with COPD by WMT. Moreover, WM plays a key role in self-regulation of behaviour, i.e. resisting hedonic impulses in exchange for more deliberate evaluations and the achievement of long-term goals. Therefore, we expect that WMT will also have a positive impact on health behaviours. Registration Clinicaltrials.gov registration: NCT03073954, https://clinicaltrials.gov/ct2/show/NCT03073954?term=NCT03073954&rank=1


# Background

Chronic obstructive pulmonary disease (COPD) is a serious respiratory condition which affected more that 251 million individuals in 2016 (1), and from 2016 to 2040 is estimated to become the fourth leading cause of life years lost (2). Chronic obstructive pulmonary disease is characterised by persistent respiratory symptoms and airflow limitation (3), which is often associated with substantial morbidity and mortality (4). In addition, COPD patients often suffer from musculoskeletal impairments (5), cardiovascular comorbidity (6, 7) as well as anxiety (8) and depression (9). Moreover, COPD patients are at increased risk for cognitive impairment with adverse clinical consequences (10).

### Cognitive impairment in COPD

A recent meta-analysis found a prevalence of CI of 32% among patients with COPD (11). Multiple factors contribute to CI in COPD, including smoking (12), dietary insufficiencies (13), an inactive lifestyle (14, 15) and hypoxia in advanced disease (16).

## Why are cognitive impairments relevant in COPD?

Impairments in working memory (WM) or other cognitive areas can have a significant impact on patients. Cognitive impairments in general can reduce quality of life, physical activity, social interaction (11) and medication adherence in affected patients (17). Moreover, it can lead to short-term memory problems, loss of initiative, difficulties with concentration and fatigue (18). As a result of these consequences, daily activities such as house work may become more difficult (18), and the risk of all-cause hospitalisation increases (19). These issues can be further complicated in COPD due to the presence of anxiety and stress. This is particularly relevant to individuals with COPD, as compared to their peers, they experience stronger detrimental mental and quality of life effects when faced with life event related stress (20). Animal model research suggests that these effects can be further compounded as repeated stress has been shown to cause cognitive impairment (21) and can induce depressive and anxiety like behaviours, in addition to memory deficits (22). Taken together, this suggests that any existing cognitive impairment may be worsened by inherent stress exposure. Therefore, ways to help temper disease and stress related cognitive impairment are of considerable interest.

## Why consider cognitive training in the overall management of COPD?

Cognitive training is an area of translational neuroscience which is gaining interest (23). The most recent meta-analysis on working memory training (WMT) suggests WMT is effective in various populations, but that these effects as well as transfer effects tend to be small (24). However, these results are primarily from relatively healthy populations, with normal levels of cognitive functioning, and perhaps leave little room for improvement. Individuals with COPD more frequently experience cognitive impairment (10); approximately 56.7% of patients with COPD are affected by cognitive impairment, compared to 13.3% of aged matched peers (10), which can also worsen over time (25, 26). When cognitive function is affected, typically attention, memory, executive functions and WM are affected (27, 28). This is similar to the pattern which has been observed in patients with traumatic brain injury (TBI). In patients with TBI, attention, memory and executive functions are most commonly affected (29). Interestingly, the mild results observed in various populations become more striking if results are focused on patients with a TBI. Specifically, WMT resulted in a moderate and long lasting improvement in untrained WM tasks, small improvements in evaluations of everyday life functioning, cognitive control and reasoning (30). Moreover, WMT has been observed to increase prefrontal cortex neural activity and increase the strength of the connectivity between the prefrontal cortex and other brain areas (31).

## Working memory and health behaviours

Recent research has demonstrated the importance of self-control in the regulation of health behaviours, including physical activity (32). Low levels of self-control are associated with reduced compliance to physical activity (33, 34) and healthy diets (34), obesity, substance abuse, and procrastination (35). On the other hand, individuals with high self-control are better able to control their thoughts, regulate their emotions and inhibit their impulses (36).

Self-control is a part of the executive functions, which are a family of top-down mental processes which allow one to concentrate and pay attention to non-instinctual tasks (37). There are three primary executive functions: inhibition [inhibitory control, self-control (behavioural inhibition) and interference control (selective attention and cognitive inhibition)], WM, and cognitive flexibility (37, 38). Working memory, the ability to select and hold goal-relevant information for a short time, enables us to engage in complex goal-orientated behaviour by managing sensory inputs (23) and plays a key role in cognitive control (39). Individual differences in WM capacity are related to the ability to inhibit automatic responses, in favour of more opportune controlled-processing responses (40).

Employing these executive functions costs energy. Simply said it is easier to give in to temptation and to continue to engage in "automatic" reactions than to carefully think about what to do next (37). The dual process theories of behaviour suggest that the balance between controlled (executive system) and impulsive (impulsive system) behaviour are due to the interaction between these systems (40). In addition, based on this theory strengthening the executive system could improve goal orientated behaviour by improving control over automatic impulses (40, 41).

## The COGtrain Trial

Lack of physical activity, albeit often not classified as detrimental as illicit drug or alcohol use, can cause considerable damage. Specifically, physical inactivity is a predictor of worse COPD outcomes including progression of exercise intolerance (47) and increased risk of mortality, and is unfortunately frequently observed in patients with COPD (48). Reducing sedentary behaviour is therefore an important COPD management goal and an integrative part of pulmonary rehabilitation (PR). However, behavioural translation of improved physical capacity after PR to a more active lifestyle is inconsistent (49-51). These inconsistencies likely have different drivers but one may be related to low levels of self-control.

Working memory training may enhance self-control by improving attentional control, the efficiency with which attention is regulated towards relevant and away from irrelevant material (52), and thus aid in maintaining goal relevant information and resisting distraction (53). These changes could then potentially improve health-related behaviours and in turn could lead to improvements in quality of life. However, it remains to be determined if WMT is effective in patients with COPD, and if it will impact further reaching areas such as behaviour, and if patients will accept online training modules. Therefore the primary objective of the present clinical trial is to investigate the feasibility and efficacy of WMT in conjunction with goal setting in patients with COPD on cognitive performance (executive function, episodic memory, visual memory, information processing, and sustained attention). Furthermore, we aim to assess the impact of WMT on self-control (impulsivity), stress susceptibility, perception and compliance to pre-defined individual daily physical activity level and pattern, and dietary advice goals as well as stress.

*Hypotheses*

- Working memory training enhances cognitive performance in patients with COPD.

- Working memory training facilitates the transfer of healthy lifestyle goals to a healthier lifestyle in patients with COPD.
- Improved cognitive performance reduces stress susceptibility in patients with COPD.

# Methods

### Patient population

This study will include a population of patients with COPD from the region of South Limburg, the Netherlands. Patients are eligible if they have a diagnosis of COPD based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (3) and if they are not affected by any of the exclusion criteria (Table 1). Once participants have agreed to participate in the study they will be randomly allocated into the treatment or control arm. All measurements will be performed at Maastricht University Medical Center.

*Table 1: Exclusion Criteria*

| Exclusion criteria |
|---|
| Disease and/or disability limiting ability to undergo neuropsychological testing and/or WMT (e.g. blindness, stroke, or lack of hand control) |
| Neurological disorders (e.g. Alzheimer's Disease, Parkinson's, Huntington's disease) |
| Insufficient mastery of the Dutch language |
| Participation in an inpatient PR programme during study period |
| Participation in another intervention study during study period |

Patients will be recruited using local advertising in newspapers, magazines, and local physiotherapy practices. In addition, patients who have participated in previous studies and have indicated that they may be contacted for future studies, as well as COPD patients visiting the outpatient clinics will be approached.

### Intervention

A double blind, placebo-controlled randomised trial will be conducted on 60 patients with COPD. The trial consists of two phases; 12 weeks of intensive training (n=30) or sham training (n=30) (T0-T12) followed by 12 weeks of active follow-up (T12-T24) (figure 1). Of the 30 sessions, patients may miss five sessions. After they have missed three sessions the investigators will be notified and contact the participants. If patients miss more than five training sessions they will be withdrawn from the study. Patients will be evaluated at a screening appointment, baseline, T12 and T24.

This study followed the Spirit Guidelines (54), refer to supplementary materials and Supplementary table 1. All assessments will be performed by MvB, LS and SM.

## Working memory training

The WMT consists of three different tasks: a visuospatial task, a backward digit span task, and a letter span task. In the visuospatial task, participants will be shown a four-by-four grid of squares, some of which flash in blue one after the other. Participants will be required to recall which squares flashed in blue and in which order, by clicking the squares. In the backward digit span task, numbers will be presented on a computer screen, and the participants will be required to reproduce the sequence in the reverse order. Lastly, in the letter span task, letters will be presented one by one in the centre of the screen, and simultaneously with every letter, an accompanying arm will light up (see Figure 2). After all letters have been presented along with their corresponding arms, one arm will light up in red, and participants are required to indicate the letter belonging to that arm on the keyboard of the computer. Participants in the control (sham) group will receive the same tasks as those in the training group but in contrast to the intervention group the tasks will not increase in difficulty by increasing the number of digits, or complexity of the pattern to be recalled (45).

In the first phase of the study, participants will receive 30 training sessions over a 12-week period, and have to complete at least 25 sessions. Participants will receive a link to every session through e-mail, and have 48 hours to complete a session after receiving the e-mail. In phase two (T12-T24) we will investigate the longer-term effects of the intervention. There is evidence to support the maintenance of the training effect after the cessation of the intervention (55-58). However, providing booster sessions could greatly enhance the long-term effects of the training. Ball et al. (59) demonstrated that one booster session compensated for nearly five months of cognitive decline, and the positive results of the training intervention were apparent for years after it ended. Given the potential benefits of booster sessions we will therefore offer the participants one booster session per week for three months in the maintenance phase (phase two) after completion of the training.

## Goal setting

Behaviour with respect to physical activity and dietary intake will be measured at T0 and at the end of phase 1 (T12) and 2 (T24) in both the intervention and the control group. Physical activity data will be collected by an ActivPAL$^{TM}$ accelerometer. This device provides a well-established measurement of both physical activity and sedentary time. Subjects wear the accelerometer fastened to their leg with Tegaderm$^{TM}$ adhesive tape for 7 consecutive days. The ActivPAL$^{TM}$ calculates body posture as sitting/lying, standing, and stepping and energy expenditure (METs) using static and dynamic acceleration information (60). Energy expenditure can then be classified from the ActivPAL$^{TM}$ into sedentary (G1.5 METs), light (1.5–2.99 METs), and MVPA (>3 METs) intensity (60).

Dietary intake will be monitored using a 24-hour recall questionnaire in the form of an interview. Participants will be asked if the past 24 hours were reflective of typical dietary intake. If dietary intake

varied significantly from normal, participants will be asked to recall their intake on the previous day.

After having analysed the accelerometry data and the dietary questionnaire, participants will be informed about the results by a trained research assistant. Dietary and/or physical activity goals will then be set by the patients together with the research assistant. Representative scores will be calculated based on the Alternative Healthy Eating Index (AHEI) (61) to aid participants in understanding how they can improve their diets. Information will be presented as a score and in graphical form for individual categories such as fruit, vegetable, red meat, excessive alcohol consumption, among others, for easy interpretation and guided goal setting discussions. Physical activity will be presented as daily step counts, and percent time spent in sitting, standing and moving activities in the form of graphs. The graphs will also clearly show the time of day which type of activity was performed. Goals can include dietary changes such as reducing alcohol, red meat, increasing whole grains, fruit and or vegetable consumption; physical activity will be in the form of steps per day.

### Study parameters and endpoints

The study parameters are listed in Table 2. Study participants will visit twice, separated by a week, before the study (T0) to determine baseline performance. Additionally, they will be tested at the end of phase one after 12 weeks (T12) and at the end of phase two after 24 weeks (T24). All measurements will be taken by the trained investigators.

### Primary outcome: measures of cognitive function

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a widely used cognitive function assessment tool which has been used in a large range of clinical and non-clinical studies. Using the CANTAB system, we will test WM, cognitive flexibility, and planning with the motor screening task, paired associated learning task, reaction time task, delated matching to sample task and a spatial WM task. Furthermore, we will administer the Stop-Signal Task (SST) as a measure of impulsivity.

As an additional measure of cognitive function, we administer the Addenbrooke's Cognition Examination Revised (ACE-R); a brief test battery which assesses five domains, namely: orientation and attention, memory, verbal fluency, language and visuospatial ability. The ACE-R is a comprehensive screening tool, and has good psychometric properties: both sensitivity and specificity are around 0.9 (62-64).

### Secondary measurement outcomes

Additional outcome measures will include a measure of perceived stress (Cohen's Perceived Stress Scale (PSS)) (65), chronic stress (hair cortisol) (66), acute stress (salivary cortisol awakening response (CAR)) (67), stress response (socially evaluated cold pressor test (SECPT)) (68), functional exercise capacity (6 minute walk test) (69), physical performance (short performance test battery (SPBB)) (70), disease-specific health status (COPD assessment test, (CAT)) (71), motivation for exercise and dietary intake (Behavioral Regulation in Exercise Questionnaire-2 (BREQ-2)) (72), the Regulation of Eating Behavior

Scale REBS (73), depression (Beck depression inventory (BDI-II)) (74), anxiety (generalised anxiety disorder-7 (GAD-7)) (75) and dietary intake (Food frequency questionnaire (FFQ)).

*Table 2 – Measurement timing of study parameters*

| *Primary outcomes* | *Instrument* | *T0* | *T1* | *T12* | *T24* |
|---|---|---|---|---|---|
| **Cognitive performance** | | | | | |
| | Cambridge Neuropsychological Test Automated Battery | X* | X | X | X |
| | The Addenbrooke's Cognitive Examination Revised | | X | | |
| *Secondary outcomes* | | | | | |
| **Cognitive stress susceptibility and perception** | | | | | |
| *Chronic stress* | The Perceived Stress Scale | | | X | X | X |
| | Hair cortisol | | | X | X | |
| | Salivary cortisol awakening response | | | X | X | |
| *Acute stress* | Socially Evaluated Cold pressor test | | | X | X | X |
| **Physical activity** | | | | | |
| | Accelerometer: step count, gait variability | | | X | X | X |
| | 6-minute walking test | X | | X | X | X |
| **Balance** | | | | | |
| | Short Performance Battery | | | X | X | X |
| **Quality of life** | | | | | |
| | COPD assessment test | | | X | X | X |
| **Motivational questionnaires** | | | | | |
| | Behavioural Regulation in Exercise Questionnaire-2 | X | | | | X |
| | Regulation of Eating Behaviour Scale | X | | | | X |
| **Psychological wellbeing** | | | | | |
| | Beck Depression Inventory- second edition | | | X | X | X |
| | Generalised Anxiety Disorder-7 | | | X | X | X |
| **Dietary intake** | | | | | |
| | Food Frequency Questionnaire | X | | | X | X |

*Other characteristics*

| | | | | |
|---|---|---|---|---|
| **Socioeconomic variables** | | | | |
| Age, gender, education level | X[$] | X[$] | | |
| **Anthropometry** | | | | |
| Height | X[$] | X[$] | | |
| Bioelectrical impedance | X[$] | X[$] | X | X |
| Waist circumference | X[$] | X[$] | | |
| Weight | X[$] | X[$] | X | X |
| **Other clinical characteristics** | | | | |
| Smoking status, , exacerbations, COPD Gold classification, spirometry | X | | | |
| **Medication** | | | | |
| Questionnaire | | X | X | X |
| **Manipulation Check** | | | | |
| Manipulation check | | | X | X |
| **Compliance and accessibility** | | | | |
| Training compliance | | | X | X |

* Required to compensate for any possible learning effects.

[$] Measurements may be taken at screening or T1.

### Manipulation check

This will be done in the form of a very short structured interview in which the participant will be asked to recall and name the specific dietary and physical activity goals they made at the beginning of the intervention. This test will be administered in a way similar to that of Hatchell and colleagues (76), where participants are asked to recall key health messages from their personalised healthy lifestyle advice sessions. Patient responses will be recorded in writing. The recalled points will be compared to the personalised advice given to the participant. Responses will then be scored as follows: 0 points – field blank or no recall of the message content; 1 point – key points not directly related to the message themes; 2 points – key points directly related to the message themes (76). Patients who recall more information will be given higher scores.

### Compliance and accessibility

Training compliance will serve as a measure of compliance and accessibility of the WMT. During the trial, patient participation in the online sessions will be recorded. Here we can examine participant engagement to the training (total time spent), number of completed sessions, answer patterns as well as monitor attrition rate.

# Statistical Analysis

Data analyses will be conducted according to the intention-to-treat principle using the statistical package IBM SPSS Statistics for Windows, version 25.0 (SPSS, Inc., Chicago, IL). All subjects who complete the study will be included in the analysis of the primary outcome. Missing data will be considered as missing at random and will not be imputed. Two-sided *p*-values less than 0.05 will be claimed as statistically significant. No interim analysis will be performed.

Demographic and clinical background information including socioeconomic status, age, gender, education level, smoking status, alcohol intake, medication use, oxygen therapy, exacerbations, comorbidities, COPD Gold classification, and spirometry will be collected at baseline.

To determine the effects of WMT on our primary and secondary parameters, assuming the data meets the requirements, a two-way Repeated Measures Analysis of Variance with time (baseline compared to Post-intervention and 3-month secondary follow-up) and group (intervention compared to placebo) as independent variables will be used to compare mean changes. If the data are not normally distributed, the data will be log-transformed in order to normalize the distribution. Effect sizes will be reported as Cohen's d, computed as the difference in performance at baseline and post-intervention or 6-month follow-up between the two groups. Effect sizes of 0.8 are considered large and effect sizes between 0.5 and 0.8 are moderate. If participants withdraw from the study (either because they miss more than five sessions or because they terminate their participation themselves), their data will be used up to the point of their withdrawal, although techniques such as multiple imputation will not be used to deal with missing data.

### Sample size and power

The sample size calculation was calculated with G*Power 3.1.9.4 and sample sizes used in the most comparable studies from literature. In a recent Canadian study examining the effects of cognitive training on cognitive decline, the authors reported an effect size of the training of $f = 0.475$ (77). When taking into account a two-tailed paired-samples *t*-test, an α of 0.05 and a power of 95% these parameters result in a required sample size of 60 individuals, or 30 per group.

### Randomisation

The randomisation will be performed by an independent researcher via www.randomization.com, before the participants start the training. A randomisation block will be used with 70 subjects randomised in 7 blocks (10 per block, 5x control and 5x active training) (allowing for drop out). After 40 subjects have been randomised, the same independent researcher will verify if the distribution between the groups on the basis of age and gender is similar. All researchers involved will remain blinded until the completion of the study and analysis.

### Data management and monitoring

Participant data is stored on a secured network server accessible only to the researchers. All paper documents are stored in a secured cabinet located at Maastricht University Medical Center. Data is entered into the database by the researchers or research assistants, which is then periodically examined by the data monitor. After completion of the study the database will be cleaned and compared to original documentation in the case of obscure values.

Data monitoring is performed by the independent Clinical Trials Centre Maastricht (CTCM) committee at trial commencement, trial closing and at least twice during the course of the study.

# Discussion

We hypothesise that it is possible to improve WM in patients with COPD. Moreover, because WM plays a key role in this self-regulation of behaviour, i.e. resisting hedonic impulses in exchange for more deliberate evaluations and the achievement of long-term goals, we expect that WMT will also have a positive influence on diet and physical activity.

### Anticipated clinical implications

If the results of this study are positive it would indicate that WMT should be adopted in COPD management given the prevalence of (mild) cognitive impairment in COPD patients. Adding WMT would be a simple addition to any programme as patients can complete the training without supervision either in a home or in a rehabilitation setting given. Future updates will likely allow this type of training to be performed on tablets or smart mobile phones and offline. Positive results in this study also imply a greater need to create awareness among patients with COPD and their caregivers and physicians to remain cognitively active, for instance through reading newspapers or playing cognitively challenging games such as chess or sudoku.

### Trial status

The trial started on 19 October 2017. At the time of submission, the recruitment was finished. The final sample size is 68 participants, 52 of which are currently foreseen to complete the entire intervention. Data collection will be completed in February 2020. This study follows the SPIRIT guidelines (see Additional file 2 for the checklist).

# Abbreviations

| | |
|---|---|
| AHEI | Alternative Healthy Eating Index |
| ACE-R | Addenbrooke's Cognition Examination Revised (ACE-R) |
| BDI-II | Beck depression inventory |
| BREQ-2 | Behavioural Regulation in Exercise Questionnaire-2 |

| | |
|---|---|
| CANTAB | Cambridge Neuropsychological Test Automated Battery |
| CAR | Cortisol awakening response |
| CAT | COPD assessment test |
| COPD | Chronic obstructive pulmonary disease |
| CTCM | Clinical Trials Centre Maastricht |
| FFQ | Food frequency questionnaire |
| GAD-7 | Generalized anxiety disorder – 7 |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| METC | Ethics Committee of Maastricht University |
| METS | Metabolic equivalents |
| MUMC+ | Maastricht University Medical Centre+ |
| MVPA | Moderate to vigorous activity bouts |
| N | Number |
| PR | Pulmonary rehabilitation |
| PSS | Cohen's Perceived Stress Scale |
| REBS | Regulation of Eating Behavior Scale |
| SECPT | Socially evaluated cold pressor test |
| SPBB | Short performance test battery |
| SST | Stop signal task |
| TBI | Traumatic brain injury |
| T0-T24 | Time 0, Time 1 week, Time 12 weeks, Time 24 weeks |
| WM | working memory |
| WMT | working memory training |

# Declarations

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## Availability of data and materials

Not applicable.

## Related articles

This manuscript or any publication regarding this study has neither been submitted nor published in any other journal.

## Author's Contributions

SM did the literature search and did the statistical power calculation in consultation with AS. SM wrote the first draft of the article. KH, MvB, FF, DJ, HG and AS gave valuable input in drafting the manuscript. In collaboration with MvB and LS, SM wrote the medical ethical protocol for the study, which was also carefully reviewed by KH, FF, DJ, HG and AS. All authors critically revised the manuscript for intellectual content, finally approved of the version to be published, and agree to be held accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Ethical considerations

The study was registered at ClinicalTrials.gov (NCT03073954) and was approved by the local Ethics Committee of Maastricht University (METC) in June 2017 (**NL59883.068.17/ METC173010).** Any required amendments to the study will be submitted for approval by the local accredited METC, and implemented after favourable opinion by the METC. No measurements will be carried out before written and informed consent has been obtained by the investigators. Participants can withdraw from the study at any point. The total burden of participation consists of approximately 30 online cognitive training sessions of 20 to 30 minutes each, in the form of a game on a mobile device or computer, as well as outcome assessment at baseline and after 12 weeks. In addition, participants will be asked to complete maintenance online cognitive training sessions, once per week during the 3-month follow-up period.

## Dissemination

The findings of the study will be disseminated through peer-reviewed journals, national and international conference presentations and to the COPD patients through a newsletter and/ or presentation.

### Patient and Public Involvement statement

This study was designed to meet an unmet need, to improve adherence to patient rehabilitation programmes and thus patient outcomes. Patients were not involved in the direct design of the study but patient burden was considered carefully by the researchers. Furthermore, patients are not involved in recruitment and conduct of the study beyond their own participation and personal responses to study advertisements. Study results will be communicated with participants as discussed in the dissemination section.

### Consent for publication

Not applicable.

### Competing interest's statement

Authors declare no conflicting interests.

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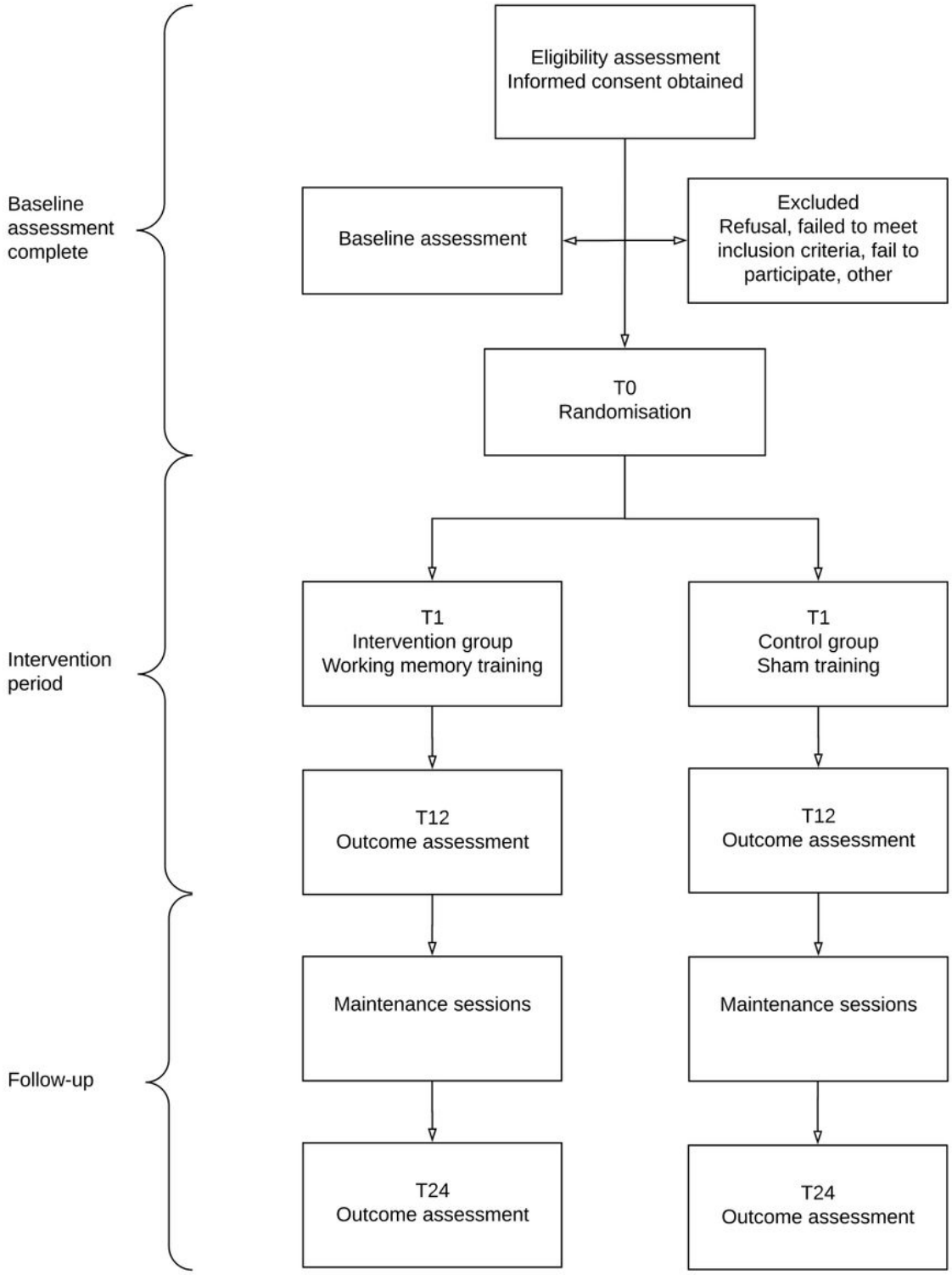
# Figures




## Figure 1

The trial consists of two phases; 12 weeks of intensive training (n=30) or sham training (n=30) (T0-T12) followed by 12 weeks of active follow-up (T12-T24)

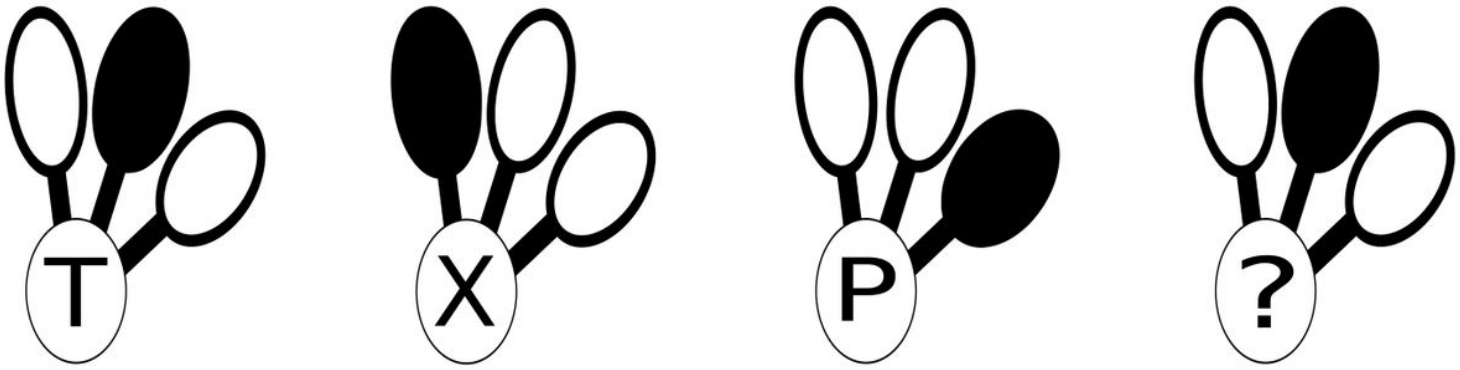
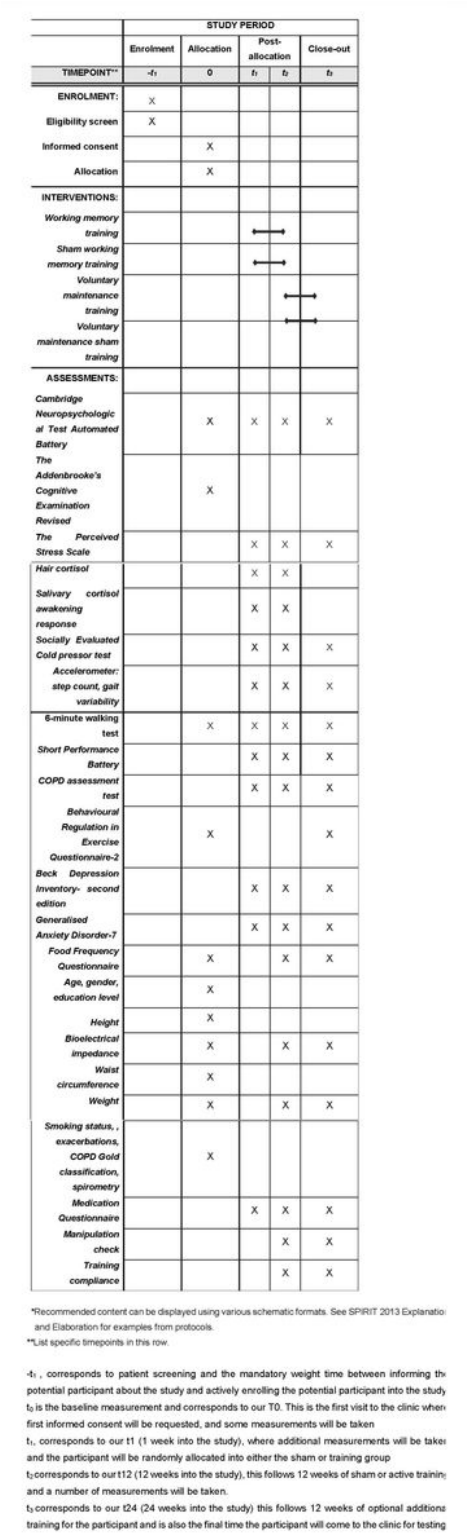



**Figure 2**

In the letter span task, letters will be presented one by one in the centre of the screen, and simultaneously with every letter, an accompanying arm will light up



| | STUDY PERIOD | | | | |
|---|---|---|---|---|---|
| | Enrolment | Allocation | Post-allocation | | Close-out |
| TIMEPOINT** | $-t_1$ | 0 | $t_1$ | $t_2$ | $t_3$ |
| ENROLMENT: | X | | | | |
| Eligibility screen | X | | | | |
| Informed consent | | X | | | |
| Allocation | | X | | | |
| INTERVENTIONS: | | | | | |
| *Working memory training* | | | ← | → | |
| *Sham working memory training* | | | ← | → | |
| *Voluntary maintenance training* | | | | ← | → |
| *Voluntary maintenance sham training* | | | | ← | → |
| ASSESSMENTS: | | | | | |
| *Cambridge Neuropsychological Test Automated Battery* | | X | X | X | X |
| *The Addenbrooke's Cognitive Examination Revised* | | X | | | |
| *The Perceived Stress Scale* | | | X | X | X |
| *Hair cortisol* | | | X | X | |
| *Salivary cortisol awakening response* | | | X | X | |
| *Socially Evaluated Cold pressor test* | | | X | X | X |
| *Accelerometer: step count, gait variability* | | | X | X | X |
| 6-minute walking test | | X | X | X | X |
| *Short Performance Battery* | | | X | X | X |
| *COPD assessment test* | | | X | X | X |
| *Behavioural Regulation in Exercise Questionnaire-2* | | X | | | X |
| *Beck Depression Inventory- second edition* | | | X | X | X |
| *Generalised Anxiety Disorder-7* | | | X | X | X |
| *Food Frequency Questionnaire* | | X | | X | X |
| *Age, gender, education level* | | X | | | |
| *Height* | | X | | | |
| *Bioelectrical impedance* | | X | | X | X |
| *Waist circumference* | | X | | | |
| *Weight* | | X | | X | X |
| *Smoking status, , exacerbations, COPD Gold classification, spirometry* | | X | | | |
| *Medication Questionnaire* | | | X | X | X |
| *Manipulation check* | | | | X | X |
| *Training compliance* | | | | X | X |

*Recommended content can be displayed using various schematic formats. See SPIRIT 2013 Explanatio
and Elaboration for examples from protocols.
**List specific timepoints in this row.

$-t_1$ , corresponds to patient screening and the mandatory weight time between informing th
potential participant about the study and actively enrolling the potential participant into the study
$t_0$ is the baseline measurement and corresponds to our T0. This is the first visit to the clinic wher
first informed consent will be requested, and some measurements will be taken
$t_1$, corresponds to our t1 (1 week into the study), where additional measurements will be take
and the participant will be randomly allocated into either the sham or training group
$t_2$ corresponds to our t12 (12 weeks into the study), this follows 12 weeks of sham or active trainin
and a number of measurements will be taken.
$t_3$ corresponds to our t24 (24 weeks into the study) this follows 12 weeks of optional additiona
training for the participant and is also the final time the participant will come to the clinic for testing

## Figure 3

SPIRIT figure. *Recommended content can be displayed using various schematic formats. See SPIRIT 2013 Explanation and Elaboration for examples from protocols. **List specific timepoints in this row. -t1 , corresponds to patient screening and the mandatory weight time between informing the potential participant about the study and actively enrolling the potential participant into the study t0 is the baseline measurement and corresponds to our T0. This is the first visit to the clinic where first informed consent

will be requested, and some measurements will be taken t1, corresponds to our t1 (1 week into the study), where additional measurements will be taken and the participant will be randomly allocated into either the sham or training group t2 corresponds to our t12 (12 weeks into the study), this follows 12 weeks of sham or active training and a number of measurements will be taken. t3 corresponds to our t24 (24 weeks into the study) this follows 12 weeks of optional additional training for the participant and is also the final time the participant will come to the clinic for testing.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable.pdf
- SPIRITChecklistcogtrain.doc