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The COgnitive-Pulmonary Disease (COgnitive-PD) study: protocol of a longitudinal observational comparative study on neuropsychological functioning of COPD patients

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Abstract

Introduction: Intact cognitive functioning is necessary for patients with chronic obstructive pulmonary disease (COPD) to understand the value of healthy lifestyle guidelines, to make informed decisions, and subsequently act upon it. Nevertheless, brain abnormalities and cognitive impairment have been found in patients with COPD. To date, it remains unknown which cognitive domains are affected and its possible consequences. Therefore, objectives of the study described are to determine neuropsychological functioning in patients with COPD, and its influence on health status, daily functioning, and pulmonary rehabilitation outcome. Further, structural and functional brain abnormalities and the relationship with cognitive and daily functioning will be explored.

Methods and analysis: A longitudinal observational comparative study will be performed in 183 COPD patients referred for pulmonary rehabilitation and in 90 healthy control subjects. Demographic and clinical characteristics, activities of daily living and knowledge about COPD will be assessed. Baseline cognitive functioning will be compared between patients and controls using a detailed neuropsychological testing battery. A magnetic resonance imaging (MRI) sub study will be performed to compare brain abnormalities between 35 COPD patients with and 35 COPD patients without cognitive impairment. Patients will be recruited between November 2013 and November 2015.

Ethics and dissemination: The study has been approved by the Medical Ethics Committee of the University Hospital Maastricht and Maastricht University (NL45127.068.13/METC 13-3-035) and is registered in the Dutch trial register. All participants will provide written informed consent and can withdraw from the study at any point in time. Assessment and home visit data material will be managed anonymously. The results obtained can be used to optimize patient-oriented treatment for cognitively impaired COPD patients. The findings will be disseminated in international peer-reviewed journals and through research conferences.

Article summary

Article focus

- The present article describes the study protocol of a study aimed to examine neuropsychological functioning of patients with chronic obstructive pulmonary disease (COPD).
- It is hypothesised that patients with COPD have worse neuropsychological functioning compared to healthy controls.

Key messages

- The study will potentially show that patients with COPD referred for pulmonary rehabilitation have cognitive impairment in specific cognitive domains, that cognitive impairment will affect outcomes of pulmonary rehabilitation, and that functional and/or structural brain abnormalities are related to cognitive and daily functioning in these patients.
- Knowledge on cognitive functioning in patients with COPD is relevant for optimizing patient-oriented treatment for COPD patients.

Strengths and limitations of this study

- The study uses a comprehensive neuropsychological testing battery and novel imaging techniques to investigate cognitive functioning in specific cognitive domains and functional and structural brain abnormalities.
- Recruitment in a pulmonary rehabilitation center allows exploration of the effects of cognitive impairment on pulmonary rehabilitation outcomes and daily functioning in COPD patients. However, this could potentially limit generalizability of the results due to recruitment of patients who experience limitations in daily life activities.

Background

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease of the lungs, that is usually progressive.[1] It is a major course of morbidity and mortality worldwide.[2] Patients with COPD often suffer from extra-pulmonary features, such as cardiovascular disease, exercise intolerance, osteoporosis, and psychological symptoms.[1 3-5]. Patients with COPD may suffer from cognitive impairment. The incidence of cognitive impairment in patients with COPD varies in different studies from 12-88%,[6]. It may lead to increased dyspnea and fatigue,[7] incorrect use of inhaler devices and low compliance with medical treatment.[8] This might increase the exacerbation risk and could result in worse health outcomes.[9] Indeed, cognitive impairment has been found to predict mortality in hypoxemic patients with COPD.[10]

A recent review article indicates a specific pattern of cognitive impairment in patients with COPD.[11] This suggests that COPD is associated with specific abnormalities in brain structure. However, cognitive functioning has mostly been studied with broad-scale measurements, which do not separate specific cognitive functions, such as psychomotor speed, memory, cognitive flexibility, and planning.[12] Therefore, no clear statement can be made about the incidence and clinical implications of cognitive impairment in specific cognitive domains in patients with COPD. Insight in cognitive functioning is of great importance in order to optimize self-management skills of patients with COPD. Indeed, cognitive deficits may lead to difficulties in managing their disease and negatively affect their treatment and in particular the efficacy of a pulmonary rehabilitation program.[13] Therefore, the aim of the study described here is to compare cognitive functioning in patients with COPD referred for pulmonary rehabilitation and subjects without COPD. More specific, objectives of the present study are to:

(1) examine whether and to what extent cognitive functioning is impaired in patients with COPD referred for pulmonary rehabilitation, compared to a control group matched on smoking status, age and educational level without COPD in the following domains: psychomotor speed, memory, cognitive flexibility, and planning;
(2) investigate clinical and demographic characteristics of patients with COPD with cognitive impairment;
(3) explore whether and to what extent cognitive functioning of patients with COPD referred for pulmonary rehabilitation is related to problems in daily functioning;
(4) examine whether and to what extent cognitive functioning affects outcomes of pulmonary rehabilitation (general psychological functioning, knowledge about COPD, need for information, daily functioning, and functional exercise capacity);
(5) determine the presence of functional and structural brain abnormalities in patients with COPD with and without cognitive dysfunction.

We hypothesize that patients with COPD have worse cognitive functioning on all of the above mentioned domains compared to healthy controls. Further, COPD patients with cognitive impairments will potentially have worse clinical characteristics, experience more often limitations in daily functioning and have worse outcomes of pulmonary rehabilitation compared to COPD patients without cognitive impairment. At last, COPD patients

with brain abnormalities are suspected to have more often cognitive impairments and to experience more often limitations in daily functioning.

Methods and analysis

Study design

A longitudinal observational comparative study will be performed. Patients will be recruited between November 2013 and November 2015. During the 3-day assessment at CIRO+, centre of expertise for chronic organ failure[14], patients will be invited to participate in the study. The 3-day assessment includes as part of the clinical routine the evaluation of physical functioning, psychosocial functioning, co-existing morbidities, exercise capacity, daily functioning and health status, as published before.[5 15] Before start of the pulmonary rehabilitation program, the patient will be visited at home for neuropsychological examination. After completion of the pulmonary rehabilitation program, all patients will undergo an outcome assessment. Baseline test will be repeated and the results of initial and outcome assessments will be available for the study in the electronic patient record.

As part of a magnetic resonance imaging (MRI) sub study, a subgroup of the COPD patients will undergo a MRI scan of the brain in order to determine the presence of brain abnormalities in COPD patients with and without cognitive impairment. The MRI-scan will be performed after the 3-day assessment and before the start of the pulmonary rehabilitation program (see figure 1).

Study population

In total, the study will include 183 patients with clinically stable COPD, based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) document,[1] referred for pulmonary rehabilitation. Subjects with clinically unstable COPD in the past 4 weeks, subjects with a diagnosis of dementia in their medical history, and/or subjects who do not master the Dutch language sufficiently will not be eligible to participate. To develop a representative control group, 90 partners, brothers or sisters of patients with COPD participating in this study will be invited to participate in this study. Controls will be matched with a COPD patient on smoking status (non-smoker, ex-smoker or smoker), age (SD=10 years) and education (SD= 1 level according to the scoring system of the Central Bureau of Statistics (CBS) Dutch educational system.[16] Control subjects with a diagnosis of COPD, asthma, or dementia in their medical history are ineligible to participate, as well as subjects who have Dutch language difficulties.

A subgroup of 35 patients with COPD and cognitive impairment and 35 without cognitive impairment will be included in the MRI sub-study. Subjects are excluded when they suffer from claustrophobia or when they have

a cardiac pacemaker, cochlear implant, neuro-stimulator, metal fragments in the eyes, and/or other electronic or metal implants.

Measures

Table 1 gives an overview of the variables assessed and instruments used.

Primary outcome

Our primary outcome, cognitive functioning, consists of four compound performance indices, namely psychomotor speed, memory, cognitive flexibility and planning. These will be measured with a detailed neuropsychological testing battery consisting of the following subtests:

(a) A validated Dutch translation of the Cognitive Failure Questionnaire (CFQ)[17] which is a 25-item self-report inventory and comprises four main subscales: absent-mindedness, social interactions, names and words, and orientation.[18] Participants are asked to indicate on a 5-point scale how often they experience subjective cognitive failures. The scale ranges from 'never (0)', 'very rarely (1)', 'occasionally (2)', 'quite often (3)', to 'very often (4)'. Total scores range between 0-100, with a higher scores indicating more subjectively experienced cognitive failures.

(b) A shortened form of the Groninger Intelligence Test (GIT)[19] will be used to determine general intelligence. Six subtasks will be administered: (1) Vocabulary: measures verbal comprehension. In this subtest 20 words of increasing difficulty are presented of which the participant has to choose the synonym out of five alternatives. The total score ranges between 0-20, with higher scores reflecting higher level of verbal intelligence; (2) Mental rotation: measures visualization. This subtest requires participants to decide which of several smaller geometric shapes from a larger set are needed to fill a larger geometric figure. Total scores ranges between 0-20, with higher scores reflecting higher level of visuo-spatial performance; (3) Figure Discovery: measures perceptual intelligence. In this subtest the subject is shown 20 cards with silhouettes of incomplete pictures of familiar objects or animals and then has to estimate what the picture depicts. The total score ranges between 0-20, with higher scores reflecting higher level of perceptual intelligence; (4) Doing sums: measures numeracy. This subtest requires participants to complete as many adding sums as possible within a time period of 1 minute. The total score ranges between 0-32, with higher scores reflecting higher level of numeracy; (5) Analogies: measures reasoning. In this subtest the subject has to choose 1 from 5 possibilities that correctly completes a 3 x 2 matrix of logical semantic relations (e.g., black-white, high-low, hot-?). The total score ranges between 0-20, with higher scores reflecting higher level of reasoning; (6) Fluency: measures word fluency. The Animal Naming Task and the Profession Naming Task are used to assess semantic verbal fluency and require patients to generate the names of as many animals respectively professions as possible within 60 seconds. Scores are determined by summing correct responses and reflect strategy-driven retrieval of information from semantic memory.

(c) The Concept Shifting Test (CST)[20] which is a simple pen-and-paper test which measures concept shifting and executive functioning. This test consists of three subtasks. On each test sheet, 16 small

circles are grouped in a larger circle. The small circles contain numbers, letters, or both, appearing in a fixed random order. Participants are requested to cross out the items in the right order. In the final part of the test, they have to alternate between numbers (1–8) and letters (A–H). The time needed to complete each subtask and errors will be recorded. Finally, participants are presented with a condition to control for basic motor speed in which empty circles have to be marked as fast as possible in a clockwise manner. The difference between the score for the last part, corrected for basic motor speed, and the mean score for the first and second parts also corrected for basic motor speed, represent the time needed for cognitive shifting. Cognitive shifting (or mental set shifting) is considered to be part of executive functioning.[20]

(d) The Stroop Colour-Word Test (SCW)[21 22] will be used to assess cognitive flexibility and is composed of three trials using word, color, and interference cards. The first card shows names of colors, which have to be read out loud, printed in black. The second card shows patches of colors, which have to be named. The last card shows names of colors printed in incongruously colored ink and participants are instructed to name the color of the ink in the printed words. Errors, self-corrected errors, and time of completion for all trials will be recorded. The time needed for the last card will be subtracted from the mean score for the first and second cards to obtain an interference score. This interference score can be regarded as a measure of inhibition of a habitual response (reading) which is part of the domain of executive functioning.

(e) The Letter Digit Substitution Test (LDST)[23] will be used as a measure of information processing speed. A code is presented at the top of the test form, with 10 digit/letter combinations. The participants fill in digits in blank squares indexed with a letter using the code key. The key and the stimuli are the same for the oral and written versions of the LDST. The written LDST version will be administered first, immediately followed by the oral version. The number of correct substitutions made in 60 seconds is the dependent variable for both test versions.

(f) The 15-word learning task (WLT-15)[24] visual version, will be used in order to measure memory and verbal learning. In this test, 15 words are visually presented, one after the other, at 2-s intervals. The participants are then asked to recall as many words as possible, in a random order. This procedure will be repeated five times. When the fifth trial has completed, a fixed battery of other cognitive tests will be administered for about 20 minutes. After the delay, unexpectedly for the participant, the instruction will be given to recall the words learned (delayed recall). This will be followed immediately by a recognition test, involving yes/no recognition of the fifteen words intermixed with fifteen nontarget words. Dependent variables are the total number of recalled words in the first three trials, the number of words recalled after 20 minutes and the number of words recognized in the recognition trial.

(g) The key-search of the Behavioural Assessment of the Dysexecutive Syndrome will be used as a measure of executive functioning.[25] It is claimed that this test assesses ability to plan a strategy to solve a problem (finding a key lost in a field). The score is based on a number of criteria, including

whether the rater believes the strategy to be systematic, efficient and likely to be effective. A penalty is imposed for lack of speed.

(h) The zoo-map test of the Behavioural Assessment of the Dysexecutive Syndrome as a measure of executive functions.[25] This is a test to assess ability independently to formulate and implement a plan (high demand condition) and to follow a pre-formulated plan (low demand condition). It involves plotting or following a route through a map that does not contravene a set of rules. The score is based on the successful implementation of the plan. Penalties are imposed for rule breaks and lack of speed.

(i) Global cognitive functioning was assessed with the Mini-Mental State Examination (MMSE)[26] as a brief screening for global cognitive functioning. This test consists of questions on orientation to time and place, registration, attention and calculation, recall, language, and visual construction to measure global cognitive functioning. The MMSE consists of 20 questions and the maximum score to achieve is 30 points, with a higher score indicating a better cognitive performance. A score of 26-30 indicates 'normal cognitive functioning', a score of 24 or 25 'borderline normal cognitive functioning', a score below 24 'cognitive impairment'[27] and a score below 18 'severe cognitive impairment'[28].

(j) Digit span from the Wechsler Adult Intelligence Scale III (WAIS-III)[29] as a measure of short-term memory. This test consists of two parts, namely orally presented digits forward and digits backwards. Subjects are required to repeat 3 - 9 digits forward and 2 - 9 digits backwards. There are two trials at each series length, and the test continues until both trials of a series length are failed. One point is awarded for each correct trial.

Secondary outcomes

Age, educational level and marital status will be obtained from the patient records. Psychological factors may influence cognitive functioning. Therefore symptoms of anxiety and depression, personality, psychopathology, coping style and disease-specific health status will be measured using the questionnaires mentioned in table 1. Problems in daily functioning will be measured by the Canadian Occupational Performance Measure's semi-structured interview (COPM)[30]. The COPM is an outcome measure designed for use by occupational therapists to assess client outcomes in the areas of self-care, productivity and leisure.[31] The CIROPD, a knowledge questionnaire developed by CIRO+, Horn will assess what persons know about COPD. The CIROPD is available from authors upon request.

Conventional MRI scans will be analysed on brain atrophy, white matter lesions, hippocampal volume and vascular abnormalities by skilled laboratory technicians. In addition, resting state functional MRI (rs-fMRI) and diffusion tensor imaging (DTI) will be used. In diffusion weighted imaging (DWI) the MR signal is made sensitive to tissue water diffusion in a certain direction. In DTI, for each voxel the diffusion weighted signal is evaluated in several directions to which a diffusion tensor is fitted. Because in white matter the voxel diffusion coefficient is maximal in the direction parallel to the fiber orientation within that voxel, DTI is a technique to study white matter architecture.[32] fMRI specifically visualizes neuronal activity related changes in cerebral perfusion and thus provides unique insights into the localization of cognitive functions. In rs-fMRI no cognitive challenge is

presented and the spontaneous fluctuation of neuronal activity is assessed. Brain areas that show synchronised activity over time are functionally connected.[33] In conventional MRI the signal intensity of a brain region reflects the local composition of the brain tissue. In connectivity studies, the signal intensity of a brain region will also provide information of the structural connections (DTI) and functional connections (rs-fMRI).

Planned statistical analyses

To answer objective 1, cross-sectional analyses will be used to evaluate differences in cognitive functioning in specific domains between 90 COPD patients and their matched controls. T-test will be used for parametric distributed continuous data, Mann-Whitney U test for non-parametric distributed ordinal data, and $\chi 2$ test for categorical variables. Multivariate analyzes will be used to correct for possible confounders.

To limit the number of dependent variables and to improve the robustness of the underlying cognitive construct, the raw test scores will be clustered in four compound performance indices, namely psychomotor speed, memory, cognitive flexibility and planning. For all participants the raw scores will be transformed into Z-scores (Z={x-mean}/SD).[34 35] By transforming raw scores to Z-scores, performances can be compared and individual test performances can be classified. This enables us to distinguish between impaired and non-impaired performances on the neuropsychological testing battery. Z-scores from tests that were included in each compound performance index will be averaged. The factor psychomotor speed, which refers to the speed at which different cognitive operations can be executed, will be created from performance indices on the Stroop Colour-Word Test (initial condition), Concept Shifting test (the time required for the initial condition) and the Letter Digit Substitution Test (raw scores). The memory score will be derived from the total score, the maximum score and delayed recall score of the 15-WLT and the maximum score on the Digit span. The cognitive flexibility score will include the time required for the third condition of the CST (alternating letter/digit cancellation) and the time required for subtask three of the SCWI. Finally, planning will consist of total scores on the key research and the total scores on the first condition of the Zoo map test. In addition, the total score of the MMSE will be used as a general cognitive measure. The sum of the six standardized subscale scores of the GIT will be multiplied by 9/6, yielding an estimate of the complete test score. This estimate will be converted into an IQ score. The sum score of the CFQ will be used as a measure of subjective cognitive functioning.

To answer objective 2, two COPD groups will be created: 'worst scoring COPD patients' differ - 1SD on the overall compound scores of the neuropsychological testing battery compared to the overall compound scores of the MAAS study and best scoring COPD patients differ +1 SD on the overall compound scores of the neuropsychological testing battery compared to the overall compound scores of the MAAS study.[36] Cross-sectional analyses will be used to determine whether there are significant differences regarding clinical and demographic characteristics between these two groups.

To answer objectives 2, 3 and 4, correlation analysis/multivariate regression analysis will be used. Potential predictors are defined as variables with a marginally significant association ($p<0.10$) with the outcome variable. Only these variables will be included in the subsequent regression analyses to determine the most important predictors. In general, effects with a two-tailed <0.05 are considered statistically significant.

To answer objective 5, cross-sectional analyses will be used to evaluate differences in brain abnormalities between COPD patients with and without cognitive impairment. Correlation analysis/multivariate regression analysis will be used to assess the relationship between brain abnormalities and cognitive and daily functioning. Significant correlations will be included in the subsequent regression analyses.

Participants who successfully complete initial assessment and the home visit will be assessed for the first three objectives. Patients who do not complete the outcome assessment will be excluded for the fourth objective. Missing data will be processed without imputation. Post-hoc tests with Bonferroni correction will be used in order to increase the validity of the research and to correct p-values in large quantities of statistical tests. Furthermore, the data will be adjusted for gender and pack years.

Sample size and power calculation

A sample size calculation with a power of 95%, effect size=0.25, and $\alpha=0.05$ showed that 175 participants are needed to answer our first objective. Therefore, 90 patients and 90 matched controls will be included. Our secondary objectives are based on a 4-point difference on the St. George's Respiratory Questionnaire. Because this concerns a clinically relevant difference, we expect greater differences on our secondary objectives, compared to our main aim. Therefore we opted for a power of 80%. With regard to an expected drop-out rate of 10%, the sample size includes 183 patients and 90 controls.

Monitoring

The study will be monitored once a year by independent healthcare professionals from CIRO+, according to the guidelines of the Dutch Federation of University Medical Centres (NFU) and will be conducted in accordance with the Medical Research Involving Human Subjects Act (WMO).

Ethics and dissemination

Ethical considerations

The study has been approved by the Medical Ethics Committee of the University Hospital Maastricht and Maastricht University (NL45127.068.13/METC 13-3-035) and is registered in the Dutch trial register. The study is based on informed written consent, and participants can withdraw from the study at any point in time. The study is non-invasive and imposes no significant risks. Data material will be managed confidentially and anonymously.

Dissemination

Results will be disseminated through regional, national and international research conferences and in articles published in international peer-reviewed journals.

Discussion

The Cognitive-PD study has several strengths and methodological considerations which are discussed below.

Strengths

The approach of our project differs considerably from other studies on neuropsychological factors in COPD by its predominant focus on cognitive functioning in specific domains. So far, in previous studies, cognitive functioning was often assessed using a single scale to measure global cognitive functioning (e.g. the Mini-Mental State Examination; MMSE).[9 37] The COgnitive-PD study uses a comprehensive neuropsychological testing battery and novel imaging techniques. Hereby, cognitive functioning in specific domains in patients with COPD can be adequately pictured in COPD patients. Next to the local composition of the brain tissue, rs-fMRI and DTI will give information of the structural connections (DTI) and functional connections (rs-fMRI). Furthermore, recruitment of participants in a pulmonary rehabilitation center allows us to further explore the effects of domain-specific cognitive skills on pulmonary rehabilitation outcomes and daily functioning in COPD patients. Insight in the incidence and clinical implications of cognitive impairment will help to adjust disease-management programs and pulmonary rehabilitation to patient's needs and capacity.

Methodological considerations

Confounding factors may influence the comparison between groups. However, we will use matching on smoking status, age and educational level as a technique to create similar groups of participants. Further, recruitment in a rehabilitation centre will provide in particular COPD patients experiencing moderate to very severe limitations in daily life activities,[31 38] which may decrease the generalizability of the results to the general population of patients with COPD. Finally, due to the cross-sectional assessment of cognitive functioning, we are not able to set conclusions about causal relationships, for example between comorbidities and cognitive functioning.

Conclusions

In conclusion, the Cognitive-PD study findings will give more insight into neuropsychological functioning in patients with COPD and shed light on the impact of cognitive impairment on pulmonary rehabilitation. This could help to adjust disease management and pulmonary rehabilitation programs to the needs and capacity of cognitively impaired patients with COPD.

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Contributors

FAHMC, DJAJ and MAS designed and established the study. All authors contributed to the writing of this manuscript, read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Ethical approval

The Medical Ethics Committee of the University Hospital Maastricht and Maastricht University (NL45127.068.13/METC 13-3-035).

References

1. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013;187(4):347-65.
2. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006;367(9524):1747-57.
3. Graat-Verboom L, Wouters EF, Smeenk FW, van den Borne BE, Lunde R, Spruit MA. Current status of research on osteoporosis in COPD: a systematic review. *Eur Respir J* 2009;34(1):209-18.
4. Spruit MA, Pennings HJ, Janssen PP, Does JD, Scroyen S, Akkermans MA, et al. Extra-pulmonary features in COPD patients entering rehabilitation after stratification for MRC dyspnea grade. *Respir Med* 2007;101(12):2454-63.
5. Vanfleteren LE, Spruit MA, Groenen M, Gaffron S, van Empel VP, Bruijnzeel PL, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013;187(7):728-35.
6. Hynninen KM, Breitve MH, Wiborg AB, Pallesen S, Nordhus IH. Psychological characteristics of patients with chronic obstructive pulmonary disease: a review. *Journal of psychosomatic research* 2005;59(6):429-43.
7. Meek PM, Lareau SC, Anderson D. Memory for symptoms in COPD patients: how accurate are their reports? *Eur Respir J* 2001;18(3):474-81.
8. Allen SC, Jain M, Ragab S, Malik N. Acquisition and short-term retention of inhaler techniques require intact executive function in elderly subjects. *Age Ageing* 2003;32(3):299-302.
9. Dodd JW, Charlton RA, van den Broek MD, Jones PW. Cognitive Dysfunction in Patients Hospitalized with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (COPD). *Chest* 2013.
10. Antonelli-Incalzi R, Corsonello A, Pedone C, Trojano L, Acanfora D, Spada A, et al. Drawing impairment predicts mortality in severe COPD. *Chest* 2006;130(6):1687-94.
11. Dodd JW, Getov SV, Jones PW. Cognitive function in COPD. *Eur Respir J* 2010;35(4):913-22.
12. Meek PM. Cognitive Function. In: Nici L, ZuWallack R, editors. *Chronic Obstructive Pulmonary Disease: Comorbidities and Systemic Consequences*. New York: Humana Press, 2012:119-36.
13. Dijkstra JB, Strik JJ, Lousberg R, Prickaerts J, Riedel WJ, Jolles J, et al. Atypical cognitive profile in patients with depression after myocardial infarction. *J Affect Disord* 2002;70(2):181-90.
14. Spruit MA, Vanderhoven-Augustin I, Janssen PP, Wouters EF. Integration of pulmonary rehabilitation in COPD. *Lancet* 2008;371(9606):12-3.
15. Sillen MJ, Franssen FM, Delbressine JM, Uszko-Lencer NH, Vanfleteren LE, Rutten EP, et al. Heterogeneity in clinical characteristics and co-morbidities in dyspneic individuals with COPD GOLD D: findings of the DICES trial. *Respir Med* 2013;107(8):1186-94.
16. CBS. *Standaard Beroepenclassificatie 1992 – editie 2001*. Den Haag: SDU, 2001.
17. Merckelbach H, Muris P, Nijman H, de Jong PJ. Self-reported cognitive failures and neurotic symptomatoloy. *Pers Indiv Differ* 1996;20(6):715-24.
18. Wallace JC, Kass SJ, Stanny CJ. The cognitive failures questionnaire revisited: dimensions and correlates. *J Gen Psychol* 2002;129(3):238-56.
19. Luteijn F, Barelds, D.P.F. *GIT-2: Groninger Intelligentie Test 2. Handleiding.* Amsterdam: Pearson Assessment and Information B.V.
20. Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. The Concept Shifting Test: adult normative data. *Psychol Assess* 2006;18(4):424-32.
21. Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. The Stroop color-word test: influence of age, sex, and education; and normative data for a large sample across the adult age range. *Assessment* 2006;13(1):62-79.
22. Stroop J. Studies of interference in serial verbal reactions. *Journal of Experimental Psychology* 1935;18:20.
23. van der Elst W, van Boxtel MP, van Breukelen GJ, Jolles J. The Letter Digit Substitution Test: normative data for 1,858 healthy participants aged 24-81 from the Maastricht Aging Study (MAAS): influence of age, education, and sex. *J Clin Exp Neuropsychol* 2006;28(6):998-1009.
24. Van der Elst W, van Boxtel MP, van Breukelen GJ, Jolles J. Rey's verbal learning test: normative data for 1855 healthy participants aged 24-81 years and the influence of age, sex, education, and mode of presentation. *J Int Neuropsychol Soc* 2005;11(3):290-302.
25. Wilson BA, Aldermann, N., Burgess, B.W., et al. . *Behavioural assessment of the dysexecutive syndrome.* Bury St Edmunds: Thames Valley Test Co, 1998.

26. Cockrell JR, Folstein MF. Mini-Mental State Examination (MMSE). *Psychopharmacol Bull* 1988;24(4):689-92.
27. Coyle JT. Use it or lose it--do effortful mental activities protect against dementia? *N Engl J Med* 2003;348(25):2489-90.
28. Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA* 2002;288(18):2271-81.
29. Wechsler D. *Wechsler Adult Intelligence Scale—Revised*. San Antonio, TX: The Psychological Corporation, 1981.
30. Law M, Baptiste S, McColl M, Opzoomer A, Polatajko H, Pollock N. The Canadian occupational performance measure: an outcome measure for occupational therapy. *Can J Occup Ther* 1990;57(2):82-7.
31. Annegarn J, Meijer K, Passos VL, Stute K, Wiechert J, Savelberg HH, et al. Problematic activities of daily life are weakly associated with clinical characteristics in COPD. *J Am Med Dir Assoc* 2012;13(3):284-90.
32. Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. In vivo fiber tractography using DT-MRI data. *Magn Reson Med* 2000;44(4):625-32.
33. Rogers BP, Morgan VL, Newton AT, Gore JC. Assessing functional connectivity in the human brain by fMRI. *Magn Reson Imaging* 2007;25(10):1347-57.
34. van Boxtel MP, Buntinx F, Houx PJ, Metsemakers JF, Knottnerus A, Jolles J. The relation between morbidity and cognitive performance in a normal aging population. *J Gerontol A Biol Sci Med Sci* 1998;53(2):M147-54.
35. de Groot JC, de Leeuw FE, Oudkerk M, van Gijn J, Hofman A, Jolles J, et al. Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. *Ann Neurol* 2000;47(2):145-51.
36. Jolles J, van Boxtel MP, Ponds RW, Metsemakers JF, Houx PJ. [The Maastricht aging study (MAAS). The longitudinal perspective of cognitive aging]. *Tijdschr Gerontol Geriatr* 1998;29(3):120-9.
37. Barberger-Gateau P, Commenges D, Gagnon M, Letenneur L, Sauvel C, Dartigues JF. Instrumental activities of daily living as a screening tool for cognitive impairment and dementia in elderly community dwellers. *J Am Geriatr Soc* 1992;40(11):1129-34.
38. Vaes AW, Wouters EF, Franssen FM, Uszko-Lencer NH, Stakenborg KH, Westra M, et al. Task-related oxygen uptake during domestic activities of daily life in patients with COPD and healthy elderly subjects. *Chest* 2011;140(4):970-9.
39. Zigmond AS SR. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:10.
40. Beck AT WC, Mendelson M, Mock J, Erbaugh, J. An inventory for measuring depression. . *Archives of General Psychiatry* 1961;4:11.
41. Luteijn F SJ, Van Dijk H. . *Eerste herziene NPV handleiding.* Lisse: Swets & Zeitlinger, 1985.
42. Derogatis LR LR, Covi L. SCL-90: an outpatient psychiatric rating scalepreliminary report. *Psychopharm Bull* 1973;9:16.
43. Schreurs PJG, Van de Willige G, Brosschot JF, Tellegen B. *De Utrechtse Coping Lijst: UCL-handleiding*. Lisse: Swets & Zeitlinger, 1987.
44. Jones PW QF, Baveystock CM, Littlejohns P. A selfcomplete measure of health status for chronic airflow limitation. *Am Rev Respir Dis* 1992(145):7.
45. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009;34(3):648-54.
46. Hyland ME, Jones RC, Hanney KE. The Lung Information Needs Questionnaire: Development, preliminary validation and findings. *Respir Med* 2006;100(10):1807-16.
47. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-83.
48. Hernandes NA, Wouters EF, Meijer K, Annegarn J, Pitta F, Spruit MA. Reproducibility of 6-minute walking test in patients with COPD. *Eur Respir J* 2010.

Tables

Table 1. **Primary and secondary outcomes in de COgnitive-PD study**

	Instrument	T0	T1	T1A	T1B	T2
Primary outcome						
COGNITIVE FUNCTIONING	Cognitive Failure Questionnaire[17]			X		
	'Groninger Intelligentie Test' (vocabulary, mental rotation, figure discovery, doing sums, analogies and fluency)[19]			X		
	Concept Shifting Test[20]			X		
	Stroop Color-Word Interference test[21 22]			X		
	Letter Digit Substitution Test[23]			X		
	15-word learning task[24]			X		
	Behavioural Assessment of the Dysexecutive Syndrome (key-search and zoo-map test)[25]			X		
	Mini-Mental State Examination[26]			X		
	Wechsler Adult Intelligence Scale III (digit span)[29]			X		
Secondary outcomes						
DEMOGRAPHIC CHARACTERISTICS						
Age	N.A.	X				
Educational level	CBS Dutch educational system[16]	X				
Marital status				X		
CLINICAL CHARACTERISTICS						
General psychological functioning						
Anxiety and depression symptoms	Hospital Anxiety and Depression scale[39] Beck Depression Inventory[40]	X				X
Personality	Dutch Personality Questionnaire[41]	X		X		
Psychopathology	Symptom Checklist-90[42]			X		
Coping style	Utrecht Coping List[43]	X				
Disease-specific health status	St George Respiratory Questionnaire[44]; COPD assessment test[45]	P				P
Other clinical characteristics						
Information needs	Lung Information Needs Questionnaire[46]			P		P
Arterial blood gases including PaO_2, $PaCO_2$ and SaO_2	Arterial blood gas	P				P
Medical history	Charlson comorbidity index[47]			X		
Resting transcutaneous oxygen saturation, lung function (FEV_1 and FVC), and DLCO		X				X
Use of inhaled and systemic corticosteroids, diagnosis of OSAS, oxygen therapy		X				
Smoking behaviour		X				X
Height, weight and BMI		X				X

Functional exercise capacity	6-minute walk test[48]	X				X
Fatigue	Borg scale[48]	X				X
PROBLEM AREAS IN DAILY FUNCTIONING	Canadian Occupational Performance Measure[30]	P				P
KNOWLEDGE ABOUT THE LUNG DISEASE	CIROPD			P		P
BRAIN ABNORMALITIES						
Brain atrophy	Traditional MRI				P	
White matter lesions	Traditional MRI				P	
Hippocampal volume	Traditional MRI				P	
Vascular abnormalities	Traditional MRI				P	
Structural connectivity	Diffusion tensor imaging				P	
Functional connectivity	Resting state functional MRI				P	

COgnitive-PD, COgnitive- Pulmonary Disease; P, patient group only; T0, 3-day assessment; T1, before pulmonary rehabilitation; T1A, home visit; T1B, MRI scan of the brains; T2, 2-day outcome assessment; X, instrument used in both patients and controls (however, in patients assessments take place in one day at a single visit to the pulmonary rehabilitation centre); N.A., not applicable; CBS, Central Bureau of Statistics; COPD, Chronic Obstructive Pulmonary Disease; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; SaO_2, oxygen saturation; FEV_1, Forced expiratory volume in 1 second; FVC, Forced vital capacity; DLCO, diffusing capacity; OSAS, Obstructive Sleep Apnea Syndrome; and MRI, magnetic resonance imaging.

Figures

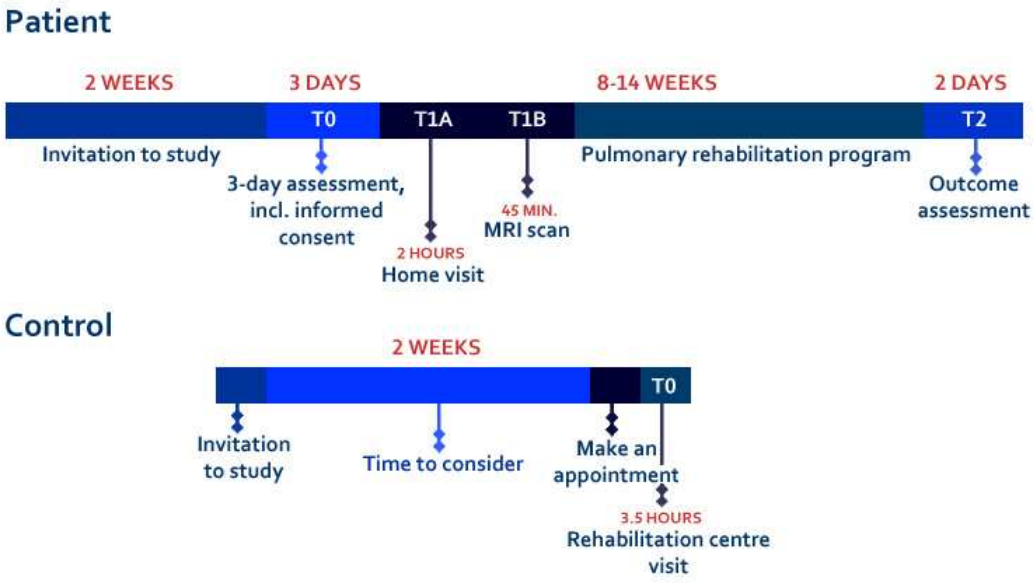

Figure 1. **Study design**

Appendices

Informed consent patient

Informed consent control

Informed consent

(PATIENT)

In order to participate in the study: **"Neuropsychological functioning of COPD patients and the influence on health status, daily functioning and the outcome of pulmonary rehabilitation".** (NL45127.068.13, version 2, September 5, 2013)

√ I have read the invitation letter for controls, including a detailed description of the goals and intentions of the study (version 2, September 5, 2013). I was allowed to ask additional questions. My questions were sufficiently answered. I had plenty of time to decide whether I want to participate in the study.

√ I know that participation is voluntary. I'm aware of the fact that I can withdraw from the study at any point in time. I do not have to declare a reason.

√ I know some people can see my test results. These people are listed in the general brochure 'Medisch-wetenschappelijk onderzoek'.

√ I give permission to use my test results for purposes listed in the invitation letter.

√ I authorize the investigator to contact me and refer me to a specialist for further diagnosis and follow-up when abnormal findings are found on the neuropsychological examination or the possible MRI scan of the brain, or if there is a suspicion of a depression based on the questionnaires.

√ I give permission to store my test results for a maximum of 15 years upon completion of this research.

- I **do / do not*** give permission to approach me an MRI scan of the brain.
- I **do / do not*** give permission to approach me for future research.

I agree on participating to this study.

Name:

Signature: Date : __ / __ / __

(To be completed by the researcher)

I hereby declare that I have fully informed the participant about the study.

If any relevant adverse consequences for participation should appear during the study, I will inform the participant in time.

Name researcher:

Signature: Date: __ / __ / __

Informed consent

(CONTROL)

In order to participate in the study: **"Neuropsychological functioning of COPD patients and the influence on health status, daily functioning and the outcome of pulmonary rehabilitation".** (NL45127.068.13, version 2, September 5, 2013)

√ I have read the invitation letter for controls, including a detailed description of the goals and intentions of the study (version 2, September 5, 2013). I was allowed to ask additional questions. My questions were sufficiently answered. I had plenty of time to decide whether I want to participate in the study.

√ I know that participation is voluntary. I'm aware of the fact that I can withdraw from the study at any point in time. I do not have to declare a reason.

√ I know some people can see my test results. These people are listed in the general brochure 'Medisch-wetenschappelijk onderzoek'.

√ I give permission to use my test results for purposes listed in the invitation letter.

√ I authorize the investigator to contact me and refer me to a specialist for further diagnosis and follow-up when abnormal findings are found on the neuropsychological examination or if there is a suspicion of a depression based on the questionnaires.

√ I give permission to store my test results for a maximum of 15 years upon completion of this research.

- I **do / do not*** give permission to approach me for future research.

I agree on participating to this study.

Name:

Signature: Date : __ / __ / __

(To be completed by the researcher)

I hereby declare that I have fully informed the participant about the study.

If any relevant adverse consequences for participation should appear during the study, I will inform the participant in time.

Name researcher:

Signature: Date: __ / __ / __

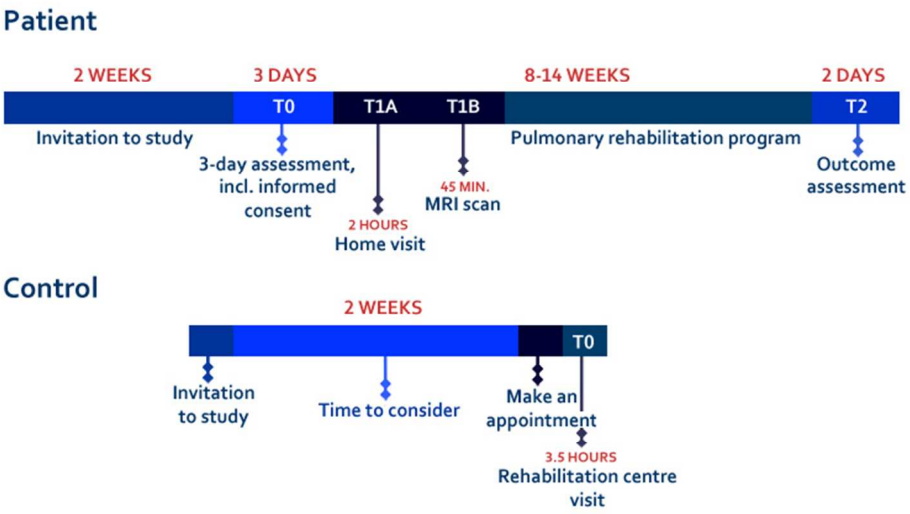

Figure 1. Study design

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
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	1, 10
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_____
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 12
	5b	Name and contact information for the trial sponsor	125
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n.a.

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	_____
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
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)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-9, 15-16
	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)	_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____
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	6-9, 15-16
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)	5, 15-16

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	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n.a.
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n.a.
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n.a.
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n.a.
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n.a.
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-9, 15-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (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	10
Statistical methods	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	9-10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
	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)	10
Methods: Monitoring			
Data monitoring	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	10
	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	_____
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	_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
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)	_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____
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	_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____
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	_____
Dissemination policy	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	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

The COgnitive-Pulmonary Disease (COgnitive-PD) study: protocol of a longitudinal observational comparative study on neuropsychological functioning of COPD patients

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The COgnitive-Pulmonary Disease (COgnitive-PD) study: protocol of a longitudinal observational comparative study on neuropsychological functioning of COPD patients

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Number of figures: 1

Abstract

Introduction: Intact cognitive functioning is necessary for patients with chronic obstructive pulmonary disease (COPD) to understand the value of healthy lifestyle guidelines, to make informed decisions, and subsequently act upon it. Nevertheless, brain abnormalities and cognitive impairment have been found in patients with COPD. To date, it remains unknown which cognitive domains are affected and its possible consequences. Therefore, objectives of the study described are to determine neuropsychological functioning in patients with COPD, and its influence on health status, daily functioning, and pulmonary rehabilitation outcome. Further, structural and functional brain abnormalities and the relationship with cognitive and daily functioning will be explored.

Methods and analysis: A longitudinal observational comparative study will be performed in 183 COPD patients referred for pulmonary rehabilitation and in 90 healthy control subjects. Demographic and clinical characteristics, activities of daily living and knowledge about COPD will be assessed. Baseline cognitive functioning will be compared between patients and controls using a detailed neuropsychological testing battery. A magnetic resonance imaging (MRI) sub study will be performed to compare brain abnormalities between 35 COPD patients with and 35 COPD patients without cognitive impairment. Patients will be recruited between November 2013 and November 2015.

Ethics and dissemination: The study has been approved by the Medical Ethics Committee of the University Hospital Maastricht and Maastricht University (NL45127.068.13/METC 13-3-035) and is registered in the Dutch trial register. All participants will provide written informed consent and can withdraw from the study at any point in time. Assessment and home visit data material will be managed anonymously. The results obtained can be used to optimize patient-oriented treatment for cognitively impaired COPD patients. The findings will be disseminated in international peer-reviewed journals and through research conferences.

Article summary

Article focus

- The present article describes the study protocol of a study aimed to examine neuropsychological functioning of patients with chronic obstructive pulmonary disease (COPD).
- It is hypothesised that patients with COPD have worse neuropsychological functioning compared to healthy controls.

Key messages

- The study will potentially show that patients with COPD referred for pulmonary rehabilitation have cognitive impairment in specific cognitive domains, that cognitive impairment will affect outcomes of pulmonary rehabilitation, and that functional and/or structural brain abnormalities are related to cognitive and daily functioning in these patients.
- Knowledge on cognitive functioning in patients with COPD is relevant for optimizing patient-oriented treatment for COPD patients.

Strengths and limitations of this study

- The study uses a comprehensive neuropsychological testing battery and novel imaging techniques to investigate cognitive functioning in specific cognitive domains and functional and structural brain abnormalities.
- Recruitment in a pulmonary rehabilitation center allows exploration of the effects of cognitive impairment on pulmonary rehabilitation outcomes and daily functioning in COPD patients. However, this could potentially limit generalizability of the results due to recruitment of patients who experience limitations in daily life activities.

Background

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease of the lungs, that is usually progressive.[1] It is a major course of morbidity and mortality worldwide.[2] Patients with COPD often suffer from extra-pulmonary features, such as cardiovascular disease, exercise intolerance, osteoporosis, and psychological symptoms.[1, 3-5]. Patients with COPD may suffer from cognitive impairment.[6] The incidence of cognitive impairment in patients with COPD varies in different studies from 12-88%,[7]. It may lead to increased dyspnea and fatigue,[8] incorrect use of inhaler devices and low compliance with medical treatment.[9] This might increase the exacerbation risk and could result in worse health outcomes.[10] Indeed, cognitive impairment has been found to predict mortality in hypoxemic patients with COPD.[11]

A recent review article indicates a specific pattern of cognitive impairment in patients with COPD.[12] This suggests that COPD is associated with specific abnormalities in brain structure. However, cognitive functioning has mostly been studied with broad-scale measurements, which do not separate specific cognitive functions, such as psychomotor speed, memory, cognitive flexibility, and planning.[13] Therefore, no clear statement can be made about the incidence and clinical implications of cognitive impairment in specific cognitive domains in patients with COPD. Insight in cognitive functioning is of great importance in order to optimize self-management skills of patients with COPD. Indeed, cognitive deficits may lead to difficulties in managing their disease and negatively affect their treatment and in particular the efficacy of a pulmonary rehabilitation program.[14] Therefore, the aim of the study described here is to compare cognitive functioning in patients with COPD referred for pulmonary rehabilitation and subjects without COPD. More specific, objectives of the present study are to:

(1) examine whether and to what extent cognitive functioning is impaired in patients with COPD referred for pulmonary rehabilitation, compared to a control group matched on smoking status, age and educational level without COPD in the following domains: psychomotor speed, memory, cognitive flexibility, and planning;
(2) investigate clinical and demographic characteristics of patients with COPD with cognitive impairment;
(3) explore whether and to what extent cognitive functioning of patients with COPD referred for pulmonary rehabilitation is related to problems in daily functioning;
(4) examine whether and to what extent cognitive functioning affects outcomes of pulmonary rehabilitation (general psychological functioning, knowledge about COPD, need for information, daily functioning, and functional exercise capacity);
(5) determine the presence of functional and structural brain abnormalities in patients with COPD with and without cognitive dysfunction.

We hypothesize that COPD patients with more severe airflow limitation have worse cognitive functioning on all of the above mentioned domains, compared to patients with less severe disease. Moreover, patients with COPD have worse cognitive functioning compared to healthy controls. Further, COPD patients with cognitive impairments will potentially have worse clinical characteristics, experience more often limitations in daily

functioning and have worse outcomes of pulmonary rehabilitation compared to COPD patients without cognitive impairment. At last, COPD patients with brain abnormalities are suspected to have more often cognitive impairments and to experience more often limitations in daily functioning.

Methods and analysis

Study design

A longitudinal observational comparative study will be performed. Patients who enter pulmonary rehabilitation at CIRO+ will be recruited between November 2013 and November 2015. They are referred to CIRO+ for interdisciplinary assessment when they are symptomatic or complain of having decreased daily life-activity at outpatient consultation with their chest physician, even if receiving optimum drug treatment. During the 3-day assessment at CIRO+, centre of expertise for chronic organ failure[15], patients will be invited to participate in the study. The 3-day assessment includes as part of the clinical routine the evaluation of physical functioning, psychosocial functioning, co-existing morbidities, exercise capacity, daily functioning and health status, as published before.[5, 16] Before start of the pulmonary rehabilitation program, the patient will be visited at home for neuropsychological examination. After completion of the pulmonary rehabilitation program, all patients will undergo an outcome assessment. Baseline test will be repeated and the results of initial and outcome assessments will be available for the study in the electronic patient record.

As part of a magnetic resonance imaging (MRI) sub study, a subgroup of the COPD patients will undergo a MRI scan of the brain in order to determine the presence of brain abnormalities in COPD patients with and without cognitive impairment. The MRI-scan will be performed after the 3-day assessment and before the start of the pulmonary rehabilitation program (see figure 1).

Study population

In total, the study will include 183 patients with clinically stable COPD, based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) document,[1] referred for pulmonary rehabilitation. Subjects with clinically unstable COPD in the past 4 weeks, subjects with a diagnosis of dementia in their medical history, and/or subjects who do not master the Dutch language sufficiently will not be eligible to participate. To develop a representative control group, 90 controls will be included. Controls will be matched with a COPD patient on smoking status (non-smoker, ex-smoker or smoker), age (SD=10 years) and education (SD= 1 level according to the scoring system of the Central Bureau of Statistics (CBS) Dutch educational system.[17] Control subjects with a diagnosis of COPD, asthma, or dementia in their medical history are ineligible to participate, as well as subjects who have Dutch language difficulties.

A subgroup of 35 patients with COPD and cognitive impairment and 35 without cognitive impairment will be included in the MRI sub-study. Subjects are excluded when they suffer from claustrophobia or when they have a cardiac pacemaker, cochlear implant, neuro-stimulator, metal fragments in the eyes, and/or other electronic or metal implants.

Measures

Table 1 gives an overview of the variables assessed and instruments used.

Primary outcome

Our primary outcome, cognitive functioning, consists of four compound performance indices, namely psychomotor speed, memory, cognitive flexibility and planning. These will be measured with a detailed neuropsychological testing battery consisting of the following subtests:

(a) A validated Dutch translation of the Cognitive Failure Questionnaire (CFQ)[18] which is a 25-item self-report inventory and comprises four main subscales: absent-mindedness, social interactions, names and words, and orientation.[19] Participants are asked to indicate on a 5-point scale how often they experience subjective cognitive failures. The scale ranges from 'never (0)', 'very rarely (1)', 'occasionally (2)', 'quite often (3)', to 'very often (4)'. Total scores range between 0-100, with a higher scores indicating more subjectively experienced cognitive failures.

(b) A shortened form of the Groninger Intelligence Test (GIT)[20] will be used to determine general intelligence. Six subtasks will be administered: (1) Vocabulary: measures verbal comprehension. In this subtest 20 words of increasing difficulty are presented of which the participant has to choose the synonym out of five alternatives. The total score ranges between 0-20, with higher scores reflecting higher level of verbal intelligence; (2) Mental rotation: measures visualization. This subtest requires participants to decide which of several smaller geometric shapes from a larger set are needed to fill a larger geometric figure. Total scores ranges between 0-20, with higher scores reflecting higher level of visuo-spatial performance; (3) Figure Discovery: measures perceptual intelligence. In this subtest the subject is shown 20 cards with silhouettes of incomplete pictures of familiar objects or animals and then has to estimate what the picture depicts. The total score ranges between 0-20, with higher scores reflecting higher level of perceptual intelligence; (4) Doing sums: measures numeracy. This subtest requires participants to complete as many adding sums as possible within a time period of 1 minute. The total score ranges between 0-32, with higher scores reflecting higher level of numeracy; (5) Analogies: measures reasoning. In this subtest the subject has to choose 1 from 5 possibilities that correctly completes a 3 x 2 matrix of logical semantic relations (e.g., black-white, high-low, hot-?). The total score ranges between 0-20, with higher scores reflecting higher level of reasoning; (6) Fluency: measures word fluency. The Animal Naming Task and the Profession Naming Task are used to assess semantic verbal fluency and require patients to generate the names of as many animals respectively professions as possible within 60 seconds. Scores are determined by summing correct responses and reflect strategy-driven retrieval of information from semantic memory.

(c) The Concept Shifting Test (CST)[21] which is a simple pen-and-paper test which measures concept shifting and executive functioning. This test consists of three subtasks. On each test sheet, 16 small circles are grouped in a larger circle. The small circles contain numbers, letters, or both, appearing in a fixed random order. Participants are requested to cross out the items in the right order. In the final part of the test, they have to alternate between numbers (1–8) and letters (A–H). The time needed to complete each subtask and errors will be recorded. Finally, participants are presented with a condition to control for basic motor speed in which empty circles have to be marked as fast as possible in a clockwise manner. The difference between the score for the last part, corrected for basic motor speed, and the mean score for the first and second parts also corrected for basic motor speed, represent the time needed for cognitive shifting. Cognitive shifting (or mental set shifting) is considered to be part of executive functioning.[21]

(d) The Stroop Colour-Word Test (SCW)[22, 23] will be used to assess cognitive flexibility and is composed of three trials using word, color, and interference cards. The first card shows names of colors, which have to be read out loud, printed in black. The second card shows patches of colors, which have to be named. The last card shows names of colors printed in incongruously colored ink and participants are instructed to name the color of the ink in the printed words. Errors, self-corrected errors, and time of completion for all trials will be recorded. The time needed for the last card will be subtracted from the mean score for the first and second cards to obtain an interference score. This interference score can be regarded as a measure of inhibition of a habitual response (reading) which is part of the domain of executive functioning.

(e) The Letter Digit Substitution Test (LDST)[24] will be used as a measure of information processing speed. A code is presented at the top of the test form, with 10 digit/letter combinations. The participants fill in digits in blank squares indexed with a letter using the code key. The key and the stimuli are the same for the oral and written versions of the LDST. The written LDST version will be administered first, immediately followed by the oral version. The number of correct substitutions made in 60 seconds is the dependent variable for both test versions.

(f) The 15-word learning task (WLT-15)[25] visual version, will be used in order to measure memory and verbal learning. In this test, 15 words are visually presented, one after the other, at 2-s intervals. The participants are then asked to recall as many words as possible, in a random order. This procedure will be repeated five times. When the fifth trial has completed, a fixed battery of other cognitive tests will be administered for about 20 minutes. After the delay, unexpectedly for the participant, the instruction will be given to recall the words learned (delayed recall). This will be followed immediately by a recognition test, involving yes/no recognition of the fifteen words intermixed with fifteen nontarget words. Dependent variables are the total number of recalled words in the first three trials, the number of words recalled after 20 minutes and the number of words recognized in the recognition trial.

(g) The key-search of the Behavioural Assessment of the Dysexecutive Syndrome will be used as a measure of executive functioning.[26] It is claimed that this test assesses ability to plan a strategy to

solve a problem (finding a key lost in a field). The score is based on a number of criteria, including whether the rater believes the strategy to be systematic, efficient and likely to be effective. A penalty is imposed for lack of speed.

(h) The zoo-map test of the Behavioural Assessment of the Dysexecutive Syndrome as a measure of executive functions.[26] This is a test to assess ability independently to formulate and implement a plan (high demand condition) and to follow a pre-formulated plan (low demand condition). It involves plotting or following a route through a map that does not contravene a set of rules. The score is based on the successful implementation of the plan. Penalties are imposed for rule breaks and lack of speed.

(i) Global cognitive functioning was assessed with the Mini-Mental State Examination (MMSE)[27] as a brief screening for global cognitive functioning. This test consists of questions on orientation to time and place, registration, attention and calculation, recall, language, and visual construction to measure global cognitive functioning. The MMSE consists of 20 questions and the maximum score to achieve is 30 points, with a higher score indicating a better cognitive performance. A score of 26-30 indicates 'normal cognitive functioning', a score of 24 or 25 'borderline normal cognitive functioning', a score below 24 'cognitive impairment'[28] and a score below 18 'severe cognitive impairment'[29].

(j) Digit span from the Wechsler Adult Intelligence Scale III (WAIS-III)[30] as a measure of short-term memory. This test consists of two parts, namely orally presented digits forward and digits backwards. Subjects are required to repeat 3 - 9 digits forward and 2 - 9 digits backwards. There are two trials at each series length, and the test continues until both trials of a series length are failed. One point is awarded for each correct trial.

Secondary outcomes

Age, educational level and marital status will be obtained from the patient records. Psychological factors may influence cognitive functioning. Therefore symptoms of anxiety and depression, personality, psychopathology, coping style and disease-specific health status will be measured using the questionnaires mentioned in table 1. Problems in daily functioning will be measured by the Canadian Occupational Performance Measure's semi-structured interview (COPM)[31]. The COPM is an outcome measure designed for use by occupational therapists to assess client outcomes in the areas of self-care, productivity and leisure.[32] The CIROPD, a knowledge questionnaire developed by CIRO+, Horn will assess what persons know about COPD. The CIROPD is available from authors upon request.

Conventional MRI scans will be analysed on brain atrophy, white matter lesions, hippocampal volume and vascular abnormalities by skilled laboratory technicians. In addition, resting state functional MRI (rs-fMRI) and diffusion tensor imaging (DTI) will be used. In diffusion weighted imaging (DWI) the MR signal is made sensitive to tissue water diffusion in a certain direction. In DTI, for each voxel the diffusion weighted signal is evaluated in several directions to which a diffusion tensor is fitted. Because in white matter the voxel diffusion coefficient is maximal in the direction parallel to the fiber orientation within that voxel, DTI is a technique to study white matter architecture.[33] fMRI specifically visualizes neuronal activity related changes in cerebral perfusion and

thus provides unique insights into the localization of cognitive functions. In rs-fMRI no cognitive challenge is presented and the spontaneous fluctuation of neuronal activity is assessed. Brain areas that show synchronised activity over time are functionally connected.[34] In conventional MRI the signal intensity of a brain region reflects the local composition of the brain tissue. In connectivity studies, the signal intensity of a brain region will also provide information of the structural connections (DTI) and functional connections (rs-fMRI).

Planned statistical analyses

To answer objective 1, cross-sectional analyses will be used to evaluate differences in cognitive functioning in specific domains between 90 COPD patients (stratified into GOLD stages for severity of COPD) and their matched controls. T-test will be used for parametric distributed continuous data, Mann-Whitney U test for non-parametric distributed ordinal data, and $\chi 2$ test for categorical variables. Multivariate analyzes will be used to correct for possible confounders, including comorbidities.

To limit the number of dependent variables and to improve the robustness of the underlying cognitive construct, the raw test scores will be clustered in four compound performance indices, namely psychomotor speed, memory, cognitive flexibility and planning. For all participants the raw scores will be transformed into Z-scores (Z={x-mean}/SD).[35, 36] By transforming raw scores to Z-scores, performances can be compared and individual test performances can be classified. This enables us to distinguish between impaired and non-impaired performances on the neuropsychological testing battery. Z-scores from tests that were included in each compound performance index will be averaged. The factor psychomotor speed, which refers to the speed at which different cognitive operations can be executed, will be created from performance indices on the Stroop Colour-Word Test (initial condition), Concept Shifting test (the time required for the initial condition) and the Letter Digit Substitution Test (raw scores). The memory score will be derived from the total score, the maximum score and delayed recall score of the 15-WLT and the maximum score on the Digit span. The cognitive flexibility score will include the time required for the third condition of the CST (alternating letter/digit cancellation) and the time required for subtask three of the SCWI. Finally, planning will consist of total scores on the key research and the total scores on the first condition of the Zoo map test. In addition, the total score of the MMSE will be used as a general cognitive measure. The sum of the six standardized subscale scores of the GIT will be multiplied by 9/6, yielding an estimate of the complete test score. This estimate will be converted into an IQ score. The sum score of the CFQ will be used as a measure of subjective cognitive functioning.

To answer objective 2, two COPD groups will be created: 'worst scoring COPD patients' differ - 1SD on the overall compound scores of the neuropsychological testing battery compared to the overall compound scores of the MAAS study and best scoring COPD patients differ +1 SD on the overall compound scores of the neuropsychological testing battery compared to the overall compound scores of the MAAS study.[37] Cross-sectional analyses will be used to determine whether there are significant differences regarding clinical (such as results of blood gases, lung function etc.) and demographic characteristics between these two groups.

To answer objectives 2, 3 and 4, correlation analysis/multivariate regression analysis will be used. Potential predictors are defined as variables with a marginally significant association ($p<0.10$) with the outcome variable. Only these variables will be included in the subsequent regression analyses to determine the most important predictors. In general, effects with a two-tailed <0.05 are considered statistically significant.

To answer objective 5, cross-sectional analyses will be used to evaluate differences in brain abnormalities between COPD patients with and without cognitive impairment. Correlation analysis/multivariate regression analysis will be used to assess the relationship between brain abnormalities and cognitive and daily functioning. Significant correlations will be included in the subsequent regression analyses.

Participants who successfully complete initial assessment and the home visit will be assessed for the first three objectives. Patients who do not complete the outcome assessment will be excluded for the fourth objective. Missing data will be processed without imputation. Post-hoc tests with Bonferroni correction will be used in order to increase the validity of the research and to correct p-values in large quantities of statistical tests. Furthermore, the data will be adjusted for gender and pack years.

Sample size and power calculation

A sample size calculation with a power of 95%, effect size=0.25, and $\alpha=0.05$ showed that 175 participants are needed to answer our first objective. Therefore, 90 patients and 90 matched controls will be included. Our secondary objectives are based on a 4-point difference on the St. George's Respiratory Questionnaire. Because this concerns a clinically relevant difference, we expect greater differences on our secondary objectives, compared to our main aim. Therefore we opted for a power of 80%. With regard to an expected drop-out rate of 10%, the sample size includes 183 patients and 90 controls.

Monitoring

The study will be monitored once a year by independent healthcare professionals from CIRO+, according to the guidelines of the Dutch Federation of University Medical Centres (NFU) and will be conducted in accordance with the Medical Research Involving Human Subjects Act (WMO).

Ethics and dissemination

Ethical considerations

The study has been approved by the Medical Ethics Committee of the University Hospital Maastricht and Maastricht University (NL45127.068.13/METC 13-3-035) and is registered in the Dutch trial register. The study is based on informed written consent, and participants can withdraw from the study at any point in time. The study is non-invasive and imposes no significant risks. Data material will be managed confidentially and anonymously.

Dissemination

Results will be disseminated through regional, national and international research conferences and in articles published in international peer-reviewed journals.

Discussion

The Cognitive-PD study has several strengths and methodological considerations which are discussed below.

Strengths

The approach of our project differs considerably from other studies on neuropsychological factors in COPD by its predominant focus on cognitive functioning in specific domains. So far, in previous studies, cognitive functioning was often assessed using a single scale to measure global cognitive functioning (e.g. the Mini-Mental State Examination; MMSE).[10, 38] The COgnitive-PD study uses a comprehensive neuropsychological testing battery and novel imaging techniques. Hereby, cognitive functioning in specific domains in patients with COPD can be adequately pictured in COPD patients. Next to the local composition of the brain tissue, rs-fMRI and DTI will give information of the structural connections (DTI) and functional connections (rs-fMRI). Furthermore, recruitment of participants in a pulmonary rehabilitation center allows us to further explore the effects of domain-specific cognitive skills on pulmonary rehabilitation outcomes and daily functioning in COPD patients. Insight in the incidence and clinical implications of cognitive impairment will help to adjust disease-management programs and pulmonary rehabilitation to patient's needs and capacity.

Methodological considerations

Confounding factors may influence the comparison between groups. However, we will use matching on smoking status, age and educational level as a technique to create similar groups of participants. The data will also be adjusted for confounding factors such as bronchodilator drugs, IQ level, and gender. Audio and visual functions must be intact in COPD patients and controls to obtain reliable measurements. However, whether the participant has impairment in hearing and vision will be assessed during the home visit. Further, recruitment in a rehabilitation centre will provide in particular COPD patients experiencing moderate to very severe limitations in daily life activities,[32, 39] which may decrease the generalizability of the results to the general population of patients with COPD. Finally, due to the cross-sectional assessment of cognitive functioning, we are not able to set conclusions about causal relationships, for example between comorbidities and cognitive functioning.

Conclusions

In conclusion, the Cognitive-PD study findings will give more insight into neuropsychological functioning in patients with COPD and shed light on the impact of cognitive impairment on pulmonary rehabilitation. This could help to adjust disease management and pulmonary rehabilitation programs to the needs and capacity of cognitively impaired patients with COPD.

Contributors

FAHMC, DJAJ and MAS designed and established the study. All authors contributed to the writing of this manuscript, read and approved the final manuscript.

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Competing interests

None declared.

Ethical approval

The Medical Ethics Committee of the University Hospital Maastricht and Maastricht University (NL45127.068.13/METC 13-3-035).

References

1. Vestbo, J., et al., *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary.* Am J Respir Crit Care Med, 2013. **187**(4): p. 347-65.
2. Lopez, A.D., et al., *Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data.* Lancet, 2006. **367**(9524): p. 1747-57.
3. Graat-Verboom, L., et al., *Current status of research on osteoporosis in COPD: a systematic review.* Eur Respir J, 2009. **34**(1): p. 209-18.
4. Spruit, M.A., et al., *Extra-pulmonary features in COPD patients entering rehabilitation after stratification for MRC dyspnea grade.* Respir Med, 2007. **101**(12): p. 2454-63.
5. Vanfleteren, L.E., et al., *Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2013. **187**(7): p. 728-35.
6. Schou, L., et al., *Cognitive dysfunction in patients with chronic obstructive pulmonary disease--a systematic review.* Respir Med, 2012. **106**(8): p. 1071-81.
7. Hynninen, K.M., et al., *Psychological characteristics of patients with chronic obstructive pulmonary disease: a review.* Journal of psychosomatic research, 2005. **59**(6): p. 429-43.
8. Meek, P.M., S.C. Lareau, and D. Anderson, *Memory for symptoms in COPD patients: how accurate are their reports?* Eur Respir J, 2001. **18**(3): p. 474-81.
9. Allen, S.C., et al., *Acquisition and short-term retention of inhaler techniques require intact executive function in elderly subjects.* Age Ageing, 2003. **32**(3): p. 299-302.
10. Dodd, J.W., et al., *Cognitive Dysfunction in Patients Hospitalized with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (COPD).* Chest, 2013.
11. Antonelli-Incalzi, R., et al., *Drawing impairment predicts mortality in severe COPD.* Chest, 2006. **130**(6): p. 1687-94.
12. Dodd, J.W., S.V. Getov, and P.W. Jones, *Cognitive function in COPD.* The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology, 2010. **35**(4): p. 913-22.
13. Meek, P.M., *Cognitive Function*, in *Chronic Obstructive Pulmonary Disease: Comorbidities and Systemic Consequences*, L. Nici and R. ZuWallack, Editors. 2012, Humana Press: New York. p. 119-136.
14. Dijkstra, J.B., et al., *Atypical cognitive profile in patients with depression after myocardial infarction.* Journal of affective disorders, 2002. **70**(2): p. 181-90.
15. Spruit, M.A., et al., *Integration of pulmonary rehabilitation in COPD.* Lancet, 2008. **371**(9606): p. 12-3.
16. Sillen, M.J., et al., *Heterogeneity in clinical characteristics and co-morbidities in dyspneic individuals with COPD GOLD D: findings of the DICES trial.* Respir Med, 2013. **107**(8): p. 1186-94.
17. CBS, *Standaard Beroepenclassificatie 1992 – editie 2001*. 2001, Den Haag: SDU.
18. Merckelbach, H., et al., *Self-reported cognitive failures and neurotic symptomatoloy.* Pers Indiv Differ, 1996. **20**(6): p. 715-724.
19. Wallace, J.C., S.J. Kass, and C.J. Stanny, *The cognitive failures questionnaire revisited: dimensions and correlates.* J Gen Psychol, 2002. **129**(3): p. 238-56.
20. Luteijn, F., Barelds, D.P.F., *GIT-2: Groninger Intelligentie Test 2. Handleiding.*, Amsterdam: Pearson Assessment and Information B.V.
21. Van der Elst, W., et al., *The Concept Shifting Test: adult normative data.* Psychol Assess, 2006. **18**(4): p. 424-32.
22. Van der Elst, W., et al., *The Stroop color-word test: influence of age, sex, and education; and normative data for a large sample across the adult age range.* Assessment, 2006. **13**(1): p. 62-79.
23. Stroop, J., *Studies of interference in serial verbal reactions.* Journal of Experimental Psychology, 1935. **18**: p. 20.
24. van der Elst, W., et al., *The Letter Digit Substitution Test: normative data for 1,858 healthy participants aged 24-81 from the Maastricht Aging Study (MAAS): influence of age, education, and sex.* J Clin Exp Neuropsychol, 2006. **28**(6): p. 998-1009.
25. Van der Elst, W., et al., *Rey's verbal learning test: normative data for 1855 healthy participants aged 24-81 years and the influence of age, sex, education, and mode of presentation.* J Int Neuropsychol Soc, 2005. **11**(3): p. 290-302.
26. Wilson, B.A., Aldermann, N., Burgess, B.W., et al. , *Behavioural assessment of the dysexecutive syndrome.* 1998, Bury St Edmunds: Thames Valley Test Co.
27. Cockrell, J.R. and M.F. Folstein, *Mini-Mental State Examination (MMSE).* Psychopharmacol Bull, 1988. **24**(4): p. 689-92.

28. Coyle, J.T., *Use it or lose it--do effortful mental activities protect against dementia?* N Engl J Med, 2003. **348**(25): p. 2489-90.
29. Ball, K., et al., *Effects of cognitive training interventions with older adults: a randomized controlled trial.* JAMA, 2002. **288**(18): p. 2271-81.
30. Wechsler, D., *Wechsler Adult Intelligence Scale—Revised*. 1981, San Antonio, TX: The Psychological Corporation.
31. Law, M., et al., *The Canadian occupational performance measure: an outcome measure for occupational therapy.* Can J Occup Ther, 1990. **57**(2): p. 82-7.
32. Annegarn, J., et al., *Problematic activities of daily life are weakly associated with clinical characteristics in COPD.* J Am Med Dir Assoc, 2012. **13**(3): p. 284-90.
33. Basser, P.J., et al., *In vivo fiber tractography using DT-MRI data.* Magn Reson Med, 2000. **44**(4): p. 625-32.
34. Rogers, B.P., et al., *Assessing functional connectivity in the human brain by fMRI.* Magn Reson Imaging, 2007. **25**(10): p. 1347-57.
35. van Boxtel, M.P., et al., *The relation between morbidity and cognitive performance in a normal aging population.* J Gerontol A Biol Sci Med Sci, 1998. **53**(2): p. M147-54.
36. de Groot, J.C., et al., *Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study.* Ann Neurol, 2000. **47**(2): p. 145-51.
37. Jolles, J., et al., *[The Maastricht aging study (MAAS). The longitudinal perspective of cognitive aging].* Tijdschr Gerontol Geriatr, 1998. **29**(3): p. 120-9.
38. Barberger-Gateau, P., et al., *Instrumental activities of daily living as a screening tool for cognitive impairment and dementia in elderly community dwellers.* Journal of the American Geriatrics Society, 1992. **40**(11): p. 1129-34.
39. Vaes, A.W., et al., *Task-related oxygen uptake during domestic activities of daily life in patients with COPD and healthy elderly subjects.* Chest, 2011. **140**(4): p. 970-9.
40. Zigmond AS, S.R., *The hospital anxiety and depression scale.* Acta Psychiatr Scand, 1983. **67**: p. 10.
41. Beck AT, W.C., Mendelson M, Mock J, Erbaugh, J, *An inventory for measuring depression.* . Archives of General Psychiatry, 1961. **4**: p. 11.
42. Luteijn F, S.J., Van Dijk H. , *Eerste herziene NPV handleiding.* 1985, Lisse: Swets & Zeitlinger.
43. Derogatis LR, L.R., Covi L, *SCL-90: an outpatient psychiatric rating scalepreliminary report.* Psychopharm Bull, 1973. **9**: p. 16.
44. Schreurs, P.J.G., et al., *De Utrechtse Coping Lijst: UCL-handleiding*. 1987, Lisse: Swets & Zeitlinger.
45. Jones PW, Q.F., Baveystock CM, Littlejohns P., *A selfcomplete measure of health status for chronic airflow limitation.* Am Rev Respir Dis, 1992(145): p. 7.
46. Jones, P.W., et al., *Development and first validation of the COPD Assessment Test.* Eur Respir J, 2009. **34**(3): p. 648-54.
47. Hyland, M.E., R.C. Jones, and K.E. Hanney, *The Lung Information Needs Questionnaire: Development, preliminary validation and findings.* Respir Med, 2006. **100**(10): p. 1807-16.
48. Charlson, M.E., et al., *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* J Chronic Dis, 1987. **40**(5): p. 373-83.
49. Hernandes, N.A., et al., *Reproducibility of 6-minute walking test in patients with COPD.* Eur Respir J, 2010.

Tables

Table 1. **Primary and secondary outcomes in de COgnitive-PD study**

	Instrument	T0	T1	T1A	T1B	T2
Primary outcome						
COGNITIVE FUNCTIONING	Cognitive Failure Questionnaire[18]			X		
	'Groninger Intelligentie Test' (vocabulary, mental rotation, figure discovery, doing sums, analogies and fluency)[20]			X		
	Concept Shifting Test[21]			X		
	Stroop Color-Word Interference test[22, 23]			X		
	Letter Digit Substitution Test[24]			X		
	15-word learning task[25]			X		
	Behavioural Assessment of the Dysexecutive Syndrome (key-search and zoo-map test)[26]			X		
	Mini-Mental State Examination[27]			X		
	Wechsler Adult Intelligence Scale III (digit span)[30]			X		
Secondary outcomes						
DEMOGRAPHIC CHARACTERISTICS						
Age	N.A.	X				
Educational level	CBS Dutch educational system[17]	X				
Marital status				X		
CLINICAL CHARACTERISTICS						
General psychological functioning						
Anxiety and depression symptoms	Hospital Anxiety and Depression scale[40] Beck Depression Inventory[41]	X				X
Personality	Dutch Personality Questionnaire[42]	X		X		
Psychopathology	Symptom Checklist-90[43]			X		
Coping style	Utrecht Coping List[44]	X				
Disease-specific health status	St George Respiratory Questionnaire[45]; COPD assessment test[46]	P				P
Other clinical characteristics						
Information needs	Lung Information Needs Questionnaire[47]			P		P
Arterial blood gases including PaO_2, $PaCO_2$ and SaO_2	Arterial blood gas	P				P
Medical history	Charlson comorbidity index[48]			X		
Resting transcutaneous oxygen saturation, lung function (FEV_1 and FVC), and DLCO		X				X
Use of inhaled and systemic corticosteroids, diagnosis of OSAS, oxygen therapy		X				
Smoking behaviour		X				X

Height, weight and BMI		X				X
Functional exercise capacity	6-minute walk test[49]	X				X
Fatigue	Borg scale[49]	X				X
Dyspnea	Borg scale[49]	X				X
PROBLEM AREAS IN DAILY FUNCTIONING	Canadian Occupational Performance Measure[31]	P				P
KNOWLEDGE ABOUT THE LUNG DISEASE	CIROPD			P		P
BRAIN ABNORMALITIES						
Brain atrophy	Traditional MRI				P	
White matter lesions	Traditional MRI				P	
Hippocampal volume	Traditional MRI				P	
Vascular abnormalities	Traditional MRI				P	
Structural connectivity	Diffusion tensor imaging				P	
Functional connectivity	Resting state functional MRI				P	

COgnitive-PD, COgnitive- Pulmonary Disease; P, patient group only; T0, 3-day assessment; T1, before pulmonary rehabilitation; T1A, home visit; T1B, MRI scan of the brains; T2, 2-day outcome assessment; X, instrument used in both patients and controls (however, in patients assessments take place in one day at a single visit to the pulmonary rehabilitation centre); N.A., not applicable; CBS, Central Bureau of Statistics; COPD, Chronic Obstructive Pulmonary Disease; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; SaO_2, oxygen saturation; FEV_1, Forced expiratory volume in 1 second; FVC, Forced vital capacity; DLCO, diffusing capacity; OSAS, Obstructive Sleep Apnea Syndrome; and MRI, magnetic resonance imaging.

Figure 1. **Study design**

Appendices

Informed consent patient

Informed consent control

The COgnitive-Pulmonary Disease (COgnitive-PD) study: protocol of a longitudinal observational comparative study on neuropsychological functioning of COPD patients

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Abstract

Introduction: Intact cognitive functioning is necessary for patients with chronic obstructive pulmonary disease (COPD) to understand the value of healthy lifestyle guidelines, to make informed decisions, and subsequently act upon it. Nevertheless, brain abnormalities and cognitive impairment have been found in patients with COPD. To date, it remains unknown which cognitive domains are affected and its possible consequences. Therefore, objectives of the study described are to determine neuropsychological functioning in patients with COPD, and its influence on health status, daily functioning, and pulmonary rehabilitation outcome. Further, structural and functional brain abnormalities and the relationship with cognitive and daily functioning will be explored.

Methods and analysis: A longitudinal observational comparative study will be performed in 183 COPD patients referred for pulmonary rehabilitation and in 90 healthy control subjects. Demographic and clinical characteristics, activities of daily living and knowledge about COPD will be assessed. Baseline cognitive functioning will be compared between patients and controls using a detailed neuropsychological testing battery. A magnetic resonance imaging (MRI) sub study will be performed to compare brain abnormalities between 35 COPD patients with and 35 COPD patients without cognitive impairment. Patients will be recruited between November 2013 and November 2015.

Ethics and dissemination: The study has been approved by the Medical Ethics Committee of the University Hospital Maastricht and Maastricht University (NL45127.068.13/METC 13-3-035) and is registered in the Dutch trial register. All participants will provide written informed consent and can withdraw from the study at any point in time. Assessment and home visit data material will be managed anonymously. The results obtained can be used to optimize patient-oriented treatment for cognitively impaired COPD patients. The findings will be disseminated in international peer-reviewed journals and through research conferences.

Article summary

Article focus

- The present article describes the study protocol of a study aimed to examine neuropsychological functioning of patients with chronic obstructive pulmonary disease (COPD).
- It is hypothesised that patients with COPD have worse neuropsychological functioning compared to healthy controls.

Key messages

- The study will potentially show that patients with COPD referred for pulmonary rehabilitation have cognitive impairment in specific cognitive domains, that cognitive impairment will affect outcomes of pulmonary rehabilitation, and that functional and/or structural brain abnormalities are related to cognitive and daily functioning in these patients.
- Knowledge on cognitive functioning in patients with COPD is relevant for optimizing patient-oriented treatment for COPD patients.

Strengths and limitations of this study

- The study uses a comprehensive neuropsychological testing battery and novel imaging techniques to investigate cognitive functioning in specific cognitive domains and functional and structural brain abnormalities.
- Recruitment in a pulmonary rehabilitation center allows exploration of the effects of cognitive impairment on pulmonary rehabilitation outcomes and daily functioning in COPD patients. However, this could potentially limit generalizability of the results due to recruitment of patients who experience limitations in daily life activities.

Background

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease of the lungs, that is usually progressive.[1] It is a major course of morbidity and mortality worldwide.[2] Patients with COPD often suffer from extra-pulmonary features, such as cardiovascular disease, exercise intolerance, osteoporosis, and psychological symptoms.[1, 3-5]. Patients with COPD may suffer from cognitive impairment.[6] The incidence of cognitive impairment in patients with COPD varies in different studies from 12-88%,[7]. It may lead to increased dyspnea and fatigue,[8] incorrect use of inhaler devices and low compliance with medical treatment.[9] This might increase the exacerbation risk and could result in worse health outcomes.[10] Indeed, cognitive impairment has been found to predict mortality in hypoxemic patients with COPD.[11]

A recent review article indicates a specific pattern of cognitive impairment in patients with COPD.[12] This suggests that COPD is associated with specific abnormalities in brain structure. However, cognitive functioning has mostly been studied with broad-scale measurements, which do not separate specific cognitive functions, such as psychomotor speed, memory, cognitive flexibility, and planning.[13] Therefore, no clear statement can be made about the incidence and clinical implications of cognitive impairment in specific cognitive domains in patients with COPD. Insight in cognitive functioning is of great importance in order to optimize self-management skills of patients with COPD. Indeed, cognitive deficits may lead to difficulties in managing their disease and negatively affect their treatment and in particular the efficacy of a pulmonary rehabilitation program.[14] Therefore, the aim of the study described here is to compare cognitive functioning in patients with COPD referred for pulmonary rehabilitation and subjects without COPD. More specific, objectives of the present study are to:

(1) examine whether and to what extent cognitive functioning is impaired in patients with COPD referred for pulmonary rehabilitation, compared to a control group matched on smoking status, age and educational level without COPD in the following domains: psychomotor speed, memory, cognitive flexibility, and planning;

(2) investigate clinical and demographic characteristics of patients with COPD with cognitive impairment;

(3) explore whether and to what extent cognitive functioning of patients with COPD referred for pulmonary rehabilitation is related to problems in daily functioning;

(4) examine whether and to what extent cognitive functioning affects outcomes of pulmonary rehabilitation (general psychological functioning, knowledge about COPD, need for information, daily functioning, and functional exercise capacity);

(5) determine the presence of functional and structural brain abnormalities in patients with COPD with and without cognitive dysfunction.

We hypothesize that COPD patients with more severe airflow limitation have worse cognitive functioning on all of the above mentioned domains, compared to patients with less severe disease. ~~We hypothesize that~~ Moreover, patients with COPD have worse ~~cognitiv~~cognitive functioning ~~on all of the above mentioned domains~~ compared to healthy controls~~, which will increase with the severity of COPD~~. Further, COPD patients

with cognitive impairments will potentially have worse clinical characteristics, experience more often limitations in daily functioning and have worse outcomes of pulmonary rehabilitation compared to COPD patients without cognitive impairment. At last, COPD patients with brain abnormalities are suspected to have more often cognitive impairments and to experience more often limitations in daily functioning.

Methods and analysis

Study design

A longitudinal observational comparative study will be performed. Patients who enter pulmonary rehabilitation at CIRO+ will be recruited between November 2013 and November 2015. They are referred to CIRO+ for interdisciplinary assessment when they are symptomatic or complain of having decreased daily life-activity at outpatient consultation with their chest physician, even if receiving optimum drug treatment. During the 3-day assessment at CIRO+, centre of expertise for chronic organ failure[15], patients will be invited to participate in the study. The 3-day assessment includes as part of the clinical routine the evaluation of physical functioning, psychosocial functioning, co-existing morbidities, exercise capacity, daily functioning and health status, as published before.[5, 16] Before start of the pulmonary rehabilitation program, the patient will be visited at home for neuropsychological examination. After completion of the pulmonary rehabilitation program, all patients will undergo an outcome assessment. Baseline test will be repeated and the results of initial and outcome assessments will be available for the study in the electronic patient record.

As part of a magnetic resonance imaging (MRI) sub study, a subgroup of the COPD patients will undergo a MRI scan of the brain in order to determine the presence of brain abnormalities in COPD patients with and without cognitive impairment. The MRI-scan will be performed after the 3-day assessment and before the start of the pulmonary rehabilitation program (see figure 1).

Study population

In total, the study will include 183 patients with clinically stable COPD, based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) document,[1] referred for pulmonary rehabilitation. Subjects with clinically unstable COPD in the past 4 weeks, subjects with a diagnosis of dementia in their medical history, and/or subjects who do not master the Dutch language sufficiently will not be eligible to participate. To develop a representative control group, 90 ~~partners, brothers or sisters of patients with COPD participating in this study will be invited to participate in this study~~controls will be included. Controls will be matched with a COPD patient on smoking status (non-smoker, ex-smoker or smoker), age (SD=10 years) and education (SD= 1 level according to the scoring system of the Central Bureau of Statistics (CBS) Dutch educational system.[17] Control subjects with a diagnosis of COPD, asthma, or dementia in their medical history are ineligible to participate, as well as subjects who have Dutch language difficulties.

A subgroup of 35 patients with COPD and cognitive impairment and 35 without cognitive impairment will be included in the MRI sub-study. Subjects are excluded when they suffer from claustrophobia or when they have a cardiac pacemaker, cochlear implant, neuro-stimulator, metal fragments in the eyes, and/or other electronic or metal implants.

Measures

Table 1 gives an overview of the variables assessed and instruments used.

Primary outcome

Our primary outcome, cognitive functioning, consists of four compound performance indices, namely psychomotor speed, memory, cognitive flexibility and planning. These will be measured with a detailed neuropsychological testing battery consisting of the following subtests:

(a) A validated Dutch translation of the Cognitive Failure Questionnaire (CFQ)[18] which is a 25-item self-report inventory and comprises four main subscales: absent-mindedness, social interactions, names and words, and orientation.[19] Participants are asked to indicate on a 5-point scale how often they experience subjective cognitive failures. The scale ranges from 'never (0)', 'very rarely (1)', 'occasionally (2)', 'quite often (3)', to 'very often (4)'. Total scores range between 0-100, with a higher scores indicating more subjectively experienced cognitive failures.

(b) A shortened form of the Groninger Intelligence Test (GIT)[20] will be used to determine general intelligence. Six subtasks will be administered: (1) Vocabulary: measures verbal comprehension. In this subtest 20 words of increasing difficulty are presented of which the participant has to choose the synonym out of five alternatives. The total score ranges between 0-20, with higher scores reflecting higher level of verbal intelligence; (2) Mental rotation: measures visualization. This subtest requires participants to decide which of several smaller geometric shapes from a larger set are needed to fill a larger geometric figure. Total scores ranges between 0-20, with higher scores reflecting higher level of visuo-spatial performance; (3) Figure Discovery: measures perceptual intelligence. In this subtest the subject is shown 20 cards with silhouettes of incomplete pictures of familiar objects or animals and then has to estimate what the picture depicts. The total score ranges between 0-20, with higher scores reflecting higher level of perceptual intelligence; (4) Doing sums: measures numeracy. This subtest requires participants to complete as many adding sums as possible within a time period of 1 minute. The total score ranges between 0-32, with higher scores reflecting higher level of numeracy; (5) Analogies: measures reasoning. In this subtest the subject has to choose 1 from 5 possibilities that correctly completes a 3 x 2 matrix of logical semantic relations (e.g., black-white, high-low, hot-?). The total score ranges between 0-20, with higher scores reflecting higher level of reasoning; (6) Fluency: measures word fluency. The Animal Naming Task and the Profession Naming Task are used to assess semantic verbal fluency and require patients to generate the names of as many animals respectively

professions as possible within 60 seconds. Scores are determined by summing correct responses and reflect strategy-driven retrieval of information from semantic memory.

(c) The Concept Shifting Test (CST)[21] which is a simple pen-and-paper test which measures concept shifting and executive functioning. This test consists of three subtasks. On each test sheet, 16 small circles are grouped in a larger circle. The small circles contain numbers, letters, or both, appearing in a fixed random order. Participants are requested to cross out the items in the right order. In the final part of the test, they have to alternate between numbers (1–8) and letters (A–H). The time needed to complete each subtask and errors will be recorded. Finally, participants are presented with a condition to control for basic motor speed in which empty circles have to be marked as fast as possible in a clockwise manner. The difference between the score for the last part, corrected for basic motor speed, and the mean score for the first and second parts also corrected for basic motor speed, represent the time needed for cognitive shifting. Cognitive shifting (or mental set shifting) is considered to be part of executive functioning.[21]

(d) The Stroop Colour-Word Test (SCW)[22, 23] will be used to assess cognitive flexibility and is composed of three trials using word, color, and interference cards. The first card shows names of colors, which have to be read out loud, printed in black. The second card shows patches of colors, which have to be named. The last card shows names of colors printed in incongruously colored ink and participants are instructed to name the color of the ink in the printed words. Errors, self-corrected errors, and time of completion for all trials will be recorded. The time needed for the last card will be subtracted from the mean score for the first and second cards to obtain an interference score. This interference score can be regarded as a measure of inhibition of a habitual response (reading) which is part of the domain of executive functioning.

(e) The Letter Digit Substitution Test (LDST)[24] will be used as a measure of information processing speed. A code is presented at the top of the test form, with 10 digit/letter combinations. The participants fill in digits in blank squares indexed with a letter using the code key. The key and the stimuli are the same for the oral and written versions of the LDST. The written LDST version will be administered first, immediately followed by the oral version. The number of correct substitutions made in 60 seconds is the dependent variable for both test versions.

(f) The 15-word learning task (WLT-15)[25] visual version, will be used in order to measure memory and verbal learning. In this test, 15 words are visually presented, one after the other, at 2-s intervals. The participants are then asked to recall as many words as possible, in a random order. This procedure will be repeated five times. When the fifth trial has completed, a fixed battery of other cognitive tests will be administered for about 20 minutes. After the delay, unexpectedly for the participant, the instruction will be given to recall the words learned (delayed recall). This will be followed immediately by a recognition test, involving yes/no recognition of the fifteen words intermixed with fifteen nontarget words. Dependent variables are the total number of recalled words in the first three trials, the number of words recalled after 20 minutes and the number of words recognized in the recognition trial.

(g) The key-search of the Behavioural Assessment of the Dysexecutive Syndrome will be used as a measure of executive functioning.[26] It is claimed that this test assesses ability to plan a strategy to solve a problem (finding a key lost in a field). The score is based on a number of criteria, including whether the rater believes the strategy to be systematic, efficient and likely to be effective. A penalty is imposed for lack of speed.

(h) The zoo-map test of the Behavioural Assessment of the Dysexecutive Syndrome as a measure of executive functions.[26] This is a test to assess ability independently to formulate and implement a plan (high demand condition) and to follow a pre-formulated plan (low demand condition). It involves plotting or following a route through a map that does not contravene a set of rules. The score is based on the successful implementation of the plan. Penalties are imposed for rule breaks and lack of speed.

(i) Global cognitive functioning was assessed with the Mini-Mental State Examination (MMSE)[27] as a brief screening for global cognitive functioning. This test consists of questions on orientation to time and place, registration, attention and calculation, recall, language, and visual construction to measure global cognitive functioning. The MMSE consists of 20 questions and the maximum score to achieve is 30 points, with a higher score indicating a better cognitive performance. A score of 26-30 indicates 'normal cognitive functioning', a score of 24 or 25 'borderline normal cognitive functioning', a score below 24 'cognitive impairment'[28] and a score below 18 'severe cognitive impairment'[29].

(j) Digit span from the Wechsler Adult Intelligence Scale III (WAIS-III)[30] as a measure of short-term memory. This test consists of two parts, namely orally presented digits forward and digits backwards. Subjects are required to repeat 3 - 9 digits forward and 2 - 9 digits backwards. There are two trials at each series length, and the test continues until both trials of a series length are failed. One point is awarded for each correct trial.

Secondary outcomes

Age, educational level and marital status will be obtained from the patient records. Psychological factors may influence cognitive functioning. Therefore symptoms of anxiety and depression, personality, psychopathology, coping style and disease-specific health status will be measured using the questionnaires mentioned in table 1. Problems in daily functioning will be measured by the Canadian Occupational Performance Measure's semi-structured interview (COPM)[31]. The COPM is an outcome measure designed for use by occupational therapists to assess client outcomes in the areas of self-care, productivity and leisure.[32] The CIROPD, a knowledge questionnaire developed by CIRO+, Horn will assess what persons know about COPD. The CIROPD is available from authors upon request.

Conventional MRI scans will be analysed on brain atrophy, white matter lesions, hippocampal volume and vascular abnormalities by skilled laboratory technicians. In addition, resting state functional MRI (rs-fMRI) and diffusion tensor imaging (DTI) will be used. In diffusion weighted imaging (DWI) the MR signal is made sensitive to tissue water diffusion in a certain direction. In DTI, for each voxel the diffusion weighted signal is evaluated in several directions to which a diffusion tensor is fitted. Because in white matter the voxel diffusion coefficient

is maximal in the direction parallel to the fiber orientation within that voxel, DTI is a technique to study white matter architecture.[33] fMRI specifically visualizes neuronal activity related changes in cerebral perfusion and thus provides unique insights into the localization of cognitive functions. In rs-fMRI no cognitive challenge is presented and the spontaneous fluctuation of neuronal activity is assessed. Brain areas that show synchronised activity over time are functionally connected.[34] In conventional MRI the signal intensity of a brain region reflects the local composition of the brain tissue. In connectivity studies, the signal intensity of a brain region will also provide information of the structural connections (DTI) and functional connections (rs-fMRI).

Planned statistical analyses

To answer objective 1, cross-sectional analyses will be used to evaluate differences in cognitive functioning in specific domains between 90 COPD patients (stratified into GOLD stages for severity of COPD) and their matched controls. T-test will be used for parametric distributed continuous data, Mann-Whitney U test for non-parametric distributed ordinal data, and $\chi 2$ test for categorical variables. Multivariate analyzes will be used to correct for possible confounders, including comorbidities.

To limit the number of dependent variables and to improve the robustness of the underlying cognitive construct, the raw test scores will be clustered in four compound performance indices, namely psychomotor speed, memory, cognitive flexibility and planning. For all participants the raw scores will be transformed into Z-scores (Z={x-mean}/SD).[35, 36] By transforming raw scores to Z-scores, performances can be compared and individual test performances can be classified. This enables us to distinguish between impaired and non-impaired performances on the neuropsychological testing battery. Z-scores from tests that were included in each compound performance index will be averaged. The factor psychomotor speed, which refers to the speed at which different cognitive operations can be executed, will be created from performance indices on the Stroop Colour-Word Test (initial condition), Concept Shifting test (the time required for the initial condition) and the Letter Digit Substitution Test (raw scores). The memory score will be derived from the total score, the maximum score and delayed recall score of the 15-WLT and the maximum score on the Digit span. The cognitive flexibility score will include the time required for the third condition of the CST (alternating letter/digit cancellation) and the time required for subtask three of the SCWI. Finally, planning will consist of total scores on the key research and the total scores on the first condition of the Zoo map test. In addition, the total score of the MMSE will be used as a general cognitive measure. The sum of the six standardized subscale scores of the GIT will be multiplied by 9/6, yielding an estimate of the complete test score. This estimate will be converted into an IQ score. The sum score of the CFQ will be used as a measure of subjective cognitive functioning.

To answer objective 2, two COPD groups will be created: 'worst scoring COPD patients' differ - 1SD on the overall compound scores of the neuropsychological testing battery compared to the overall compound scores of the MAAS study and best scoring COPD patients differ +1 SD on the overall compound scores of the neuropsychological testing battery compared to the overall compound scores of the MAAS study.[37] Cross-

sectional analyses will be used to determine whether there are significant differences regarding clinical (such as results of blood gases, lung function etc.) and demographic characteristics between these two groups.

To answer objectives 2, 3 and 4, correlation analysis/multivariate regression analysis will be used. Potential predictors are defined as variables with a marginally significant association ($p<0.10$) with the outcome variable. Only these variables will be included in the subsequent regression analyses to determine the most important predictors. In general, effects with a two-tailed <0.05 are considered statistically significant.

To answer objective 5, cross-sectional analyses will be used to evaluate differences in brain abnormalities between COPD patients with and without cognitive impairment. Correlation analysis/multivariate regression analysis will be used to assess the relationship between brain abnormalities and cognitive and daily functioning. Significant correlations will be included in the subsequent regression analyses.

Participants who successfully complete initial assessment and the home visit will be assessed for the first three objectives. Patients who do not complete the outcome assessment will be excluded for the fourth objective. Missing data will be processed without imputation. Post-hoc tests with Bonferroni correction will be used in order to increase the validity of the research and to correct p-values in large quantities of statistical tests. Furthermore, the data will be adjusted for gender and pack years.

Sample size and power calculation

A sample size calculation with a power of 95%, effect size=0.25, and $\alpha=0.05$ showed that 175 participants are needed to answer our first objective. Therefore, 90 patients and 90 matched controls will be included. Our secondary objectives are based on a 4-point difference on the St. George's Respiratory Questionnaire. Because this concerns a clinically relevant difference, we expect greater differences on our secondary objectives, compared to our main aim. Therefore we opted for a power of 80%. With regard to an expected drop-out rate of 10%, the sample size includes 183 patients and 90 controls.

Monitoring

The study will be monitored once a year by independent healthcare professionals from CIRO+, according to the guidelines of the Dutch Federation of University Medical Centres (NFU) and will be conducted in accordance with the Medical Research Involving Human Subjects Act (WMO).

Ethics and dissemination

Ethical considerations

The study has been approved by the Medical Ethics Committee of the University Hospital Maastricht and Maastricht University (NL45127.068.13/METC 13-3-035) and is registered in the Dutch trial register. The study is based on informed written consent, and participants can withdraw from the study at any point in time. The

study is non-invasive and imposes no significant risks. Data material will be managed confidentially and anonymously.

Dissemination

Results will be disseminated through regional, national and international research conferences and in articles published in international peer-reviewed journals.

Discussion

The Cognitive-PD study has several strengths and methodological considerations which are discussed below.

Strengths

The approach of our project differs considerably from other studies on neuropsychological factors in COPD by its predominant focus on cognitive functioning in specific domains. So far, in previous studies, cognitive functioning was often assessed using a single scale to measure global cognitive functioning (e.g. the Mini-Mental State Examination; MMSE).[10, 38] The COgnitive-PD study uses a comprehensive neuropsychological testing battery and novel imaging techniques. Hereby, cognitive functioning in specific domains in patients with COPD can be adequately pictured in COPD patients. Next to the local composition of the brain tissue, rs-fMRI and DTI will give information of the structural connections (DTI) and functional connections (rs-fMRI). Furthermore, recruitment of participants in a pulmonary rehabilitation center allows us to further explore the effects of domain-specific cognitive skills on pulmonary rehabilitation outcomes and daily functioning in COPD patients. Insight in the incidence and clinical implications of cognitive impairment will help to adjust disease-management programs and pulmonary rehabilitation to patient's needs and capacity.

Methodological considerations

Confounding factors may influence the comparison between groups. However, we will use matching on smoking status, age and educational level as a technique to create similar groups of participants. The data will also be adjusted for confounding factors such as bronchodilator drugs, IQ level, and gender. ~~Also, a~~Audio and visual functions must be intact in COPD patients and controls to obtain reliable measurements. However, whether the participant has impairment in hearing and vision will be ~~asked~~assessed during the home visit. Further, recruitment in a rehabilitation centre will provide in particular COPD patients experiencing moderate to very severe limitations in daily life activities,[32, 39] which may decrease the generalizability of the results to the general population of patients with COPD. Finally, due to the cross-sectional assessment of cognitive functioning, we are not able to set conclusions about causal relationships, for example between comorbidities and cognitive functioning.

Conclusions

In conclusion, the Cognitive-PD study findings will give more insight into neuropsychological functioning in patients with COPD and shed light on the impact of cognitive impairment on pulmonary rehabilitation. This could help to adjust disease management and pulmonary rehabilitation programs to the needs and capacity of cognitively impaired patients with COPD.

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Contributors

FAHMC, DJAJ and MAS designed and established the study. All authors contributed to the writing of this manuscript, read and approved the final manuscript.

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Competing interests

None declared.

~~The authors declare that they have no competing interests.~~

Ethical approval

The Medical Ethics Committee of the University Hospital Maastricht and Maastricht University (NL45127.068.13/METC 13-3-035).

References

1. Vestbo, J., et al., *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary.* Am J Respir Crit Care Med, 2013. **187**(4): p. 347-65.
2. Lopez, A.D., et al., *Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data.* Lancet, 2006. **367**(9524): p. 1747-57.
3. Graat-Verboom, L., et al., *Current status of research on osteoporosis in COPD: a systematic review.* Eur Respir J, 2009. **34**(1): p. 209-18.
4. Spruit, M.A., et al., *Extra-pulmonary features in COPD patients entering rehabilitation after stratification for MRC dyspnea grade.* Respir Med, 2007. **101**(12): p. 2454-63.
5. Vanfleteren, L.E., et al., *Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2013. **187**(7): p. 728-35.
6. Schou, L., et al., *Cognitive dysfunction in patients with chronic obstructive pulmonary disease--a systematic review.* Respir Med, 2012. **106**(8): p. 1071-81.
7. Hynninen, K.M., et al., *Psychological characteristics of patients with chronic obstructive pulmonary disease: a review.* Journal of psychosomatic research, 2005. **59**(6): p. 429-43.
8. Meek, P.M., S.C. Lareau, and D. Anderson, *Memory for symptoms in COPD patients: how accurate are their reports?* Eur Respir J, 2001. **18**(3): p. 474-81.
9. Allen, S.C., et al., *Acquisition and short-term retention of inhaler techniques require intact executive function in elderly subjects.* Age Ageing, 2003. **32**(3): p. 299-302.
10. Dodd, J.W., et al., *Cognitive Dysfunction in Patients Hospitalized with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (COPD).* Chest, 2013.
11. Antonelli-Incalzi, R., et al., *Drawing impairment predicts mortality in severe COPD.* Chest, 2006. **130**(6): p. 1687-94.
12. Dodd, J.W., S.V. Getov, and P.W. Jones, *Cognitive function in COPD.* The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology, 2010. **35**(4): p. 913-22.
13. Meek, P.M., *Cognitive Function*, in *Chronic Obstructive Pulmonary Disease: Comorbidities and Systemic Consequences*, L. Nici and R. ZuWallack, Editors. 2012, Humana Press: New York. p. 119-136.
14. Dijkstra, J.B., et al., *Atypical cognitive profile in patients with depression after myocardial infarction.* Journal of affective disorders, 2002. **70**(2): p. 181-90.
15. Spruit, M.A., et al., *Integration of pulmonary rehabilitation in COPD.* Lancet, 2008. **371**(9606): p. 12-3.
16. Sillen, M.J., et al., *Heterogeneity in clinical characteristics and co-morbidities in dyspneic individuals with COPD GOLD D: findings of the DICES trial.* Respir Med, 2013. **107**(8): p. 1186-94.
17. CBS, *Standaard Beroepenclassificatie 1992 – editie 2001*. 2001, Den Haag: SDU.
18. Merckelbach, H., et al., *Self-reported cognitive failures and neurotic symptomatoloy.* Pers Indiv Differ, 1996. **20**(6): p. 715-724.
19. Wallace, J.C., S.J. Kass, and C.J. Stanny, *The cognitive failures questionnaire revisited: dimensions and correlates.* J Gen Psychol, 2002. **129**(3): p. 238-56.
20. Luteijn, F., Barelds, D.P.F., *GIT-2: Groninger Intelligentie Test 2. Handleiding.*, Amsterdam: Pearson Assessment and Information B.V.
21. Van der Elst, W., et al., *The Concept Shifting Test: adult normative data.* Psychol Assess, 2006. **18**(4): p. 424-32.
22. Van der Elst, W., et al., *The Stroop color-word test: influence of age, sex, and education; and normative data for a large sample across the adult age range.* Assessment, 2006. **13**(1): p. 62-79.
23. Stroop, J., *Studies of interference in serial verbal reactions.* Journal of Experimental Psychology, 1935. **18**: p. 20.
24. van der Elst, W., et al., *The Letter Digit Substitution Test: normative data for 1,858 healthy participants aged 24-81 from the Maastricht Aging Study (MAAS): influence of age, education, and sex.* J Clin Exp Neuropsychol, 2006. **28**(6): p. 998-1009.
25. Van der Elst, W., et al., *Rey's verbal learning test: normative data for 1855 healthy participants aged 24-81 years and the influence of age, sex, education, and mode of presentation.* J Int Neuropsychol Soc, 2005. **11**(3): p. 290-302.
26. Wilson, B.A., Aldermann, N., Burgess, B.W., et al. , *Behavioural assessment of the dysexecutive syndrome.* 1998, Bury St Edmunds: Thames Valley Test Co.
27. Cockrell, J.R. and M.F. Folstein, *Mini-Mental State Examination (MMSE).* Psychopharmacol Bull, 1988. **24**(4): p. 689-92.

28. Coyle, J.T., *Use it or lose it--do effortful mental activities protect against dementia?* N Engl J Med, 2003. **348**(25): p. 2489-90.
29. Ball, K., et al., *Effects of cognitive training interventions with older adults: a randomized controlled trial.* JAMA, 2002. **288**(18): p. 2271-81.
30. Wechsler, D., *Wechsler Adult Intelligence Scale—Revised*. 1981, San Antonio, TX: The Psychological Corporation.
31. Law, M., et al., *The Canadian occupational performance measure: an outcome measure for occupational therapy.* Can J Occup Ther, 1990. **57**(2): p. 82-7.
32. Annegarn, J., et al., *Problematic activities of daily life are weakly associated with clinical characteristics in COPD.* J Am Med Dir Assoc, 2012. **13**(3): p. 284-90.
33. Basser, P.J., et al., *In vivo fiber tractography using DT-MRI data.* Magn Reson Med, 2000. **44**(4): p. 625-32.
34. Rogers, B.P., et al., *Assessing functional connectivity in the human brain by fMRI.* Magn Reson Imaging, 2007. **25**(10): p. 1347-57.
35. van Boxtel, M.P., et al., *The relation between morbidity and cognitive performance in a normal aging population.* J Gerontol A Biol Sci Med Sci, 1998. **53**(2): p. M147-54.
36. de Groot, J.C., et al., *Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study.* Ann Neurol, 2000. **47**(2): p. 145-51.
37. Jolles, J., et al., *[The Maastricht aging study (MAAS). The longitudinal perspective of cognitive aging].* Tijdschr Gerontol Geriatr, 1998. **29**(3): p. 120-9.
38. Barberger-Gateau, P., et al., *Instrumental activities of daily living as a screening tool for cognitive impairment and dementia in elderly community dwellers.* Journal of the American Geriatrics Society, 1992. **40**(11): p. 1129-34.
39. Vaes, A.W., et al., *Task-related oxygen uptake during domestic activities of daily life in patients with COPD and healthy elderly subjects.* Chest, 2011. **140**(4): p. 970-9.
40. Zigmond AS, S.R., *The hospital anxiety and depression scale.* Acta Psychiatr Scand, 1983. **67**: p. 10.
41. Beck AT, W.C., Mendelson M, Mock J, Erbaugh, J, *An inventory for measuring depression.* . Archives of General Psychiatry, 1961. **4**: p. 11.
42. Luteijn F, S.J., Van Dijk H. , *Eerste herziene NPV handleiding.* 1985, Lisse: Swets & Zeitlinger.
43. Derogatis LR, L.R., Covi L, *SCL-90: an outpatient psychiatric rating scalepreliminary report.* Psychopharm Bull, 1973. **9**: p. 16.
44. Schreurs, P.J.G., et al., *De Utrechtse Coping Lijst: UCL-handleiding*. 1987, Lisse: Swets & Zeitlinger.
45. Jones PW, Q.F., Baveystock CM, Littlejohns P., *A selfcomplete measure of health status for chronic airflow limitation.* Am Rev Respir Dis, 1992(145): p. 7.
46. Jones, P.W., et al., *Development and first validation of the COPD Assessment Test.* Eur Respir J, 2009. **34**(3): p. 648-54.
47. Hyland, M.E., R.C. Jones, and K.E. Hanney, *The Lung Information Needs Questionnaire: Development, preliminary validation and findings.* Respir Med, 2006. **100**(10): p. 1807-16.
48. Charlson, M.E., et al., *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* J Chronic Dis, 1987. **40**(5): p. 373-83.
49. Hernandes, N.A., et al., *Reproducibility of 6-minute walking test in patients with COPD.* Eur Respir J, 2010.

Tables

Table 1. **Primary and secondary outcomes in de COgnitive-PD study**

	Instrument	T0	T1	T1A	T1B	T2
Primary outcome						
COGNITIVE FUNCTIONING	Cognitive Failure Questionnaire[18]			X		
	'Groninger Intelligentie Test' (vocabulary, mental rotation, figure discovery, doing sums, analogies and fluency)[20]			X		
	Concept Shifting Test[21]			X		
	Stroop Color-Word Interference test[22, 23]			X		
	Letter Digit Substitution Test[24]			X		
	15-word learning task[25]			X		
	Behavioural Assessment of the Dysexecutive Syndrome (key-search and zoo-map test)[26]			X		
	Mini-Mental State Examination[27]			X		
	Wechsler Adult Intelligence Scale III (digit span)[30]			X		
Secondary outcomes						
DEMOGRAPHIC CHARACTERISTICS						
Age	N.A.	X				
Educational level	CBS Dutch educational system[17]	X				
Marital status				X		
CLINICAL CHARACTERISTICS						
General psychological functioning						
Anxiety and depression symptoms	Hospital Anxiety and Depression scale[40] Beck Depression Inventory[41]	X				X
Personality	Dutch Personality Questionnaire[42]	X		X		
Psychopathology	Symptom Checklist-90[43]			X		
Coping style	Utrecht Coping List[44]	X				
Disease-specific health status	St George Respiratory Questionnaire[45]; COPD assessment test[46]	P				P
Other clinical characteristics						
Information needs	Lung Information Needs Questionnaire[47]			P		P
Arterial blood gases including PaO_2, $PaCO_2$ and SaO_2	Arterial blood gas	P				P
Medical history	Charlson comorbidity index[48]			X		
Resting transcutaneous oxygen saturation, lung function (FEV_1 and FVC), and DLCO		X				X
Use of inhaled and systemic corticosteroids, diagnosis of OSAS, oxygen therapy		X				
Smoking behaviour		X				X

Height, weight and BMI		X				X
Functional exercise capacity	6-minute walk test[49]	X				X
Fatigue	Borg scale[49]	X				X
Dyspnea	Borg scale[49]	X				X
PROBLEM AREAS IN DAILY FUNCTIONING	Canadian Occupational Performance Measure[31]	P				P
KNOWLEDGE ABOUT THE LUNG DISEASE	CIROPD			P		P
BRAIN ABNORMALITIES						
Brain atrophy	Traditional MRI				P	
White matter lesions	Traditional MRI				P	
Hippocampal volume	Traditional MRI				P	
Vascular abnormalities	Traditional MRI				P	
Structural connectivity	Diffusion tensor imaging				P	
Functional connectivity	Resting state functional MRI				P	

COgnitive-PD, COgnitive- Pulmonary Disease; P, patient group only; T0, 3-day assessment; T1, before pulmonary rehabilitation; T1A, home visit; T1B, MRI scan of the brains; T2, 2-day outcome assessment; X, instrument used in both patients and controls (however, in patients assessments take place in one day at a single visit to the pulmonary rehabilitation centre); N.A., not applicable; CBS, Central Bureau of Statistics; COPD, Chronic Obstructive Pulmonary Disease; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; SaO_2, oxygen saturation; FEV_1, Forced expiratory volume in 1 second; FVC, Forced vital capacity; DLCO, diffusing capacity; OSAS, Obstructive Sleep Apnea Syndrome; and MRI, magnetic resonance imaging.

Figures

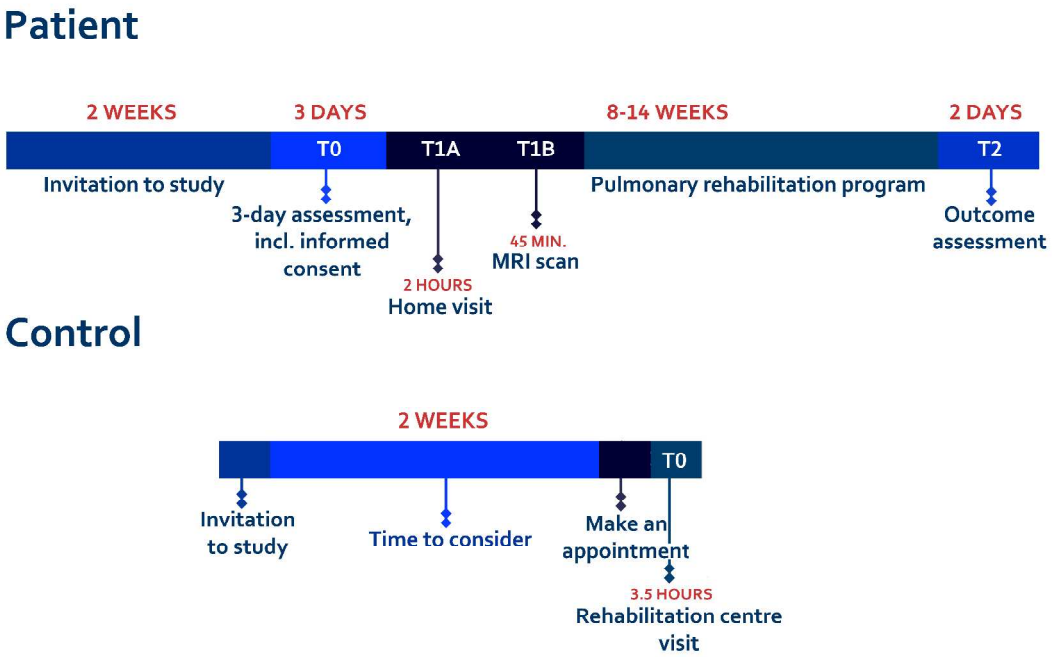


Figure 1. **Study design**

Appendices

Informed consent patient

Informed consent control

Informed consent

(PATIENT)

In order to participate in the study: **"Neuropsychological functioning of COPD patients and the influence on health status, daily functioning and the outcome of pulmonary rehabilitation".** (NL45127.068.13, version 2, September 5, 2013)

√ I have read the invitation letter for controls, including a detailed description of the goals and intentions of the study (version 2, September 5, 2013). I was allowed to ask additional questions. My questions were sufficiently answered. I had plenty of time to decide whether I want to participate in the study.

√ I know that participation is voluntary. I'm aware of the fact that I can withdraw from the study at any point in time. I do not have to declare a reason.

√ I know some people can see my test results. These people are listed in the general brochure 'Medisch-wetenschappelijk onderzoek'.

√ I give permission to use my test results for purposes listed in the invitation letter.

√ I authorize the investigator to contact me and refer me to a specialist for further diagnosis and follow-up when abnormal findings are found on the neuropsychological examination or the possible MRI scan of the brain, or if there is a suspicion of a depression based on the questionnaires.

√ I give permission to store my test results for a maximum of 15 years upon completion of this research.

- I **do / do not*** give permission to approach me an MRI scan of the brain.
- I **do / do not*** give permission to approach me for future research.

I agree on participating to this study.

Name:

Signature: Date : __ / __ / __

(To be completed by the researcher)

I hereby declare that I have fully informed the participant about the study.

If any relevant adverse consequences for participation should appear during the study, I will inform the participant in time.

Name researcher:

Signature: Date: __ / __ / __

Informed consent

(CONTROL)

In order to participate in the study: **"Neuropsychological functioning of COPD patients and the influence on health status, daily functioning and the outcome of pulmonary rehabilitation".** (NL45127.068.13, version 2, September 5, 2013)

√ I have read the invitation letter for controls, including a detailed description of the goals and intentions of the study (version 2, September 5, 2013). I was allowed to ask additional questions. My questions were sufficiently answered. I had plenty of time to decide whether I want to participate in the study.

√ I know that participation is voluntary. I'm aware of the fact that I can withdraw from the study at any point in time. I do not have to declare a reason.

√ I know some people can see my test results. These people are listed in the general brochure 'Medisch-wetenschappelijk onderzoek'.

√ I give permission to use my test results for purposes listed in the invitation letter.

√ I authorize the investigator to contact me and refer me to a specialist for further diagnosis and follow-up when abnormal findings are found on the neuropsychological examination or if there is a suspicion of a depression based on the questionnaires.

√ I give permission to store my test results for a maximum of 15 years upon completion of this research.

- I **do / do not*** give permission to approach me for future research.

I agree on participating to this study.

Name:

Signature: Date : __ / __ / __

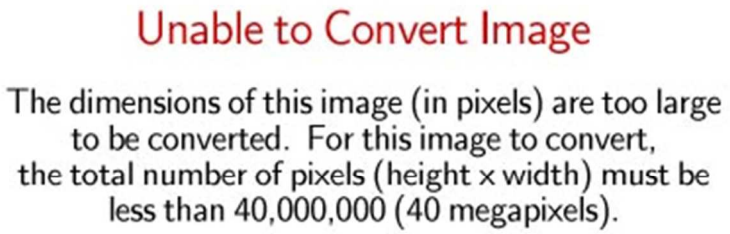
(To be completed by the researcher)

I hereby declare that I have fully informed the participant about the study.

If any relevant adverse consequences for participation should appear during the study, I will inform the participant in time.

Name researcher:

Signature: Date: __ / __ / __



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
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	1, 10
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_____
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 12
	5b	Name and contact information for the trial sponsor	125
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n.a.

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	_____
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
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)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-9, 15-16
	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)	_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____
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	6-9, 15-16
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)	5, 15-16

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	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n.a.
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n.a.
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n.a.
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n.a.
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n.a.
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-9, 15-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (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	10
Statistical methods	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	9-10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
	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)	10
Methods: Monitoring			
Data monitoring	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	10
	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	_____
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	_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
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)	_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____
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	_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____
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	_____
Dissemination policy	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	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.