Introduction of a Dyspnea Service in the Netherlands

Research protocol

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PROTOCOL TITLE 'Introduction of a Dyspnea Service in the Netherlands >'

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TABLE OF CONTENTS

List of abbreviations **4**
Summary **5**
1 Introduction and rationale **6**
2 Objectives **8**
3 Study Design **9**
4 Study population **12**
5 Treatment of subjects **14**
6 Methods **15**
7 Statistics **16**
8 Ethical considerations **17**
9 Safety reporting **18**
10 Administrative aspects **19**
11 References **20**

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
ADD	**Ademen Denken Doen (Dutch translation of Breathing Thinking Functioning)**
AE	**Adverse Event**
BTF	**Breathing Thinking Functioning**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
COPD	**Chronic obstructive pulmonary disease**
CRF	**Case Report Form**
CRQ	**Chronic respiratory (disease) questionnaire**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
MRC	**Medical Research Counsil (MRC dyspnea score)**
NRS	**Numeric Rating Scale**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: In severe COPD, breathlessness is a distressing symptom which has a huge impact on quality of life. Management of breathlessness is complex and should comprise both pharmacological and non-pharmacological interventions, tailored to the individual needs of the patient and provided by a multidisciplinary team. Such 'breathlessness services' have been developed in recent years, mainly in the United Kingdom. In the Netherlands, these services do not yet exist in primary or secondary care.

Objectives:

To assess feasibility of a Dutch breathlessness service, and to evaluate patient satisfaction.

Study design: Single-centre, non-blinded mixed-methods, cohort feasibility study.

Study population: Patients with COPD (diagnosed by a pulmonologist, postbronchodilatator FEV1/FVC below the lower limit of normal) and refractory dyspnea (troubled by breathlessness in spite of optimization of COPD treatment) who are able to visit the outpatient clinic.

Intervention:

The intervention will be delivered by a multidisciplinary team, formed by a pulmonologist, a physiotherapist with expertise in COPD, and 3 respiratory nurses. For every patient, an individual management plan will be developed, based on the Breathing Thinking Functioning-model (see main document for details). The main intervention is delivered by both the respiratory nurse and the physiotherapist, twice a week for two to six weeks. During these sessions, patients learn strategies to cope with their dyspnea in both a cognitive and functional manner. The pulmonologist will prescribe opioids and/or benzodiazepines if applicable.

Main study parameters/endpoints:

Feasibility: 75% of patients fullfills intervention

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

The only burden for participants will be the hospital visits. However, these visits will be minimised as much as possible by combining them with other hospital visits where possible. If visiting the hospital is too burdensome, home visits will be arranged.

1. INTRODUCTION AND RATIONALE

Chronic Obstructive Pulmonary Disease (COPD) is a progressive disease causing about 7000 deaths in the Netherlands each year, thereby being the fourth leading cause of death (1). Studies have shown a high symptom burden in patients with end-stage COPD, at least similar to patients with incurable lung cancer (2). The main symptom is dyspnea, or breathlessness, which increases as disease progresses. It often results in emergency hospital admissions, which results in a high burden of disease on both patient, relatives and the health care system. Patients with COPD who experience refractory symptoms may be referred to a tertiary rehabilitation centre, where adequate patient education is provided including help with breathlessness, in an inpatient setting. However, patients with advanced respiratory failure are not always eligible for such programmes due to their instability, or they do not wish to be away from home for such a long period of time. Those patients are mostly dependent on their physiotherapist for breathlessness management. However, dyspnea is a complex symptom with cognitive and behavioural aspects. Most physiotherapists are not trained to address breathlessness in its full complexity.
In recent years, Booth and Spathis have developed the breathing-thinking-functioning model (BTF), which conceptualizes the three cognitive and behavioural reactions to dyspnea (3).

Breathing domain: Dyspnea causes dysfunctional breathing patterns with an increased respiratory rate and use of accessory muscles, leading to inefficient (dead space) ventilation. Furthermore, patients with COPD who feel breathless tend to focus on the in-breath instead of on the out-breath.This promotes dynamic hyperinflation which increases the breathlessness and the work of breathing. When addressing the breathing domain, patients learn adequate breathing techniques. Also, they will be given a hand-held fan. Growing evidence suggests that cool airflow from a fan can decrease breathlessness (13).
Thinking domain: misconceptions such as ‘I will suffocate’, but also memories of earlier episodes of dyspnea, lead to anxiety and distress in many patients. This leads to tachypnea which increases dyspnea. When addressing the thinking domain, patients learn that they may feel very breathless but will not suffocate. Also, they will learn how inadequate breathing techniques caused by anxiety influence their complaints.
Functioning domain: Many breathless patients avoid physical activity. This leads to both isolation and deconditioning, which supports the vicious circle of dyspnea. When addressing this domain, patients learn that it is vital to stay as active as possible, and that it may be harmful to always avoid exercise. Also, they learn how to divide their limited energy and to avoid exhaustion.

The intervention that will be investigated in this study is called Ademen Denken Doen (ADD). ADD is a Dutch version of BTF, adjusted to the health care situation in the Netherlands. There are two noteworthy differences between ADD and breathlessness services that have previously been investigated in other countries (mostly the UK and Germany) (6,7,8,9,10):

The first difference concerns participating health care professionals. In existing breathlessness services, palliative care teams have a leading role, including occupational

therapists. The Dutch situation is different since in most hospitals, palliative care is only available as an inpatient service. In the Netherlands, respiratory nurses and physiotherapists play an important role in supporting patients with COPD. Therefore, for this study we will set up an ADD training for respiratory nurses and physiotherapists. In the future, we aim to make the intervention applicable to physiotherapists and respiratory nurses outside our own hospital.

The second difference between existing dyspnea services and ADD concerns the targeted population. ADD is set up primarily for patients with COPD. Existing dyspnea services are not disease-orientated but symptom-orientated, and treat all patients with refractory dyspnea. The main reason for our focus on COPD is that ADD is set up by a pulmonology department instead of a palliative care team. The majority of dyspnoic patients that we see suffer from COPD. As mentioned before, this is a large patient category with a high burden of disease who frequently have unmet needs, which justifies our choice to focus on COPD for this pilot. Furthermore, the etiology of dyspnea is different in COPD from dyspnea in heart failure, cancer or pulmonary fibrosis. COPD leads to dynamic hyperinflation, which is worsened by rapid shallow breathing – a pattern of breathing promoted by anxiety (11). Anxiety is highly prevalent in COPD (12), probably due to its unpredictable course and due to the dyspnea itself. Many patients with COPD report fear of suffocation. Both the dysfunctional breathing pattern and the irrational fears elicited by breathlessness, are key elements of BTF/ADD. We therefore assume that specifically patients with COPD have even more to gain from ADD than patients with other casues of dyspnea. Nevertheless, if this intervention is effective, in the future the service should be made available to other patient groups.

Our goal is to use this feasibility study as a pilot study for a phase III randomised controlled clinical trial, in which effectiveness of ADD will be tested in several Dutch hospitals. In this phase III study, effectiveness will be measured using the CRQ (Chronic Respiratory Disease Questionnaire), domain of mastery. Therefore, we also measure CRQ in this feasibility trial at baseline and after the intervention. If no effect on CRQ is measured in this trial, we need to consider whether the intervention should be adjusted before we set up a phase III trial. However, due to the design of this trial, effectiveness of the intervention cannot be assessed.

2. OBJECTIVES

Primary objective:

to assess feasibility of ADD. Pre-defined criteria for feasibility is: 75 percent of included patients complete the intervention. Based on previous research on dyspnea services, we made the assumption that it is not realistic to expect a higher percentage of completion, since this is an elderly patient population with multimorbidity. Patients who quit the intervention because of a COPD exacerbation are replaced by another participant; however patients may drop out of the intervention for different reasons: because they do not want extra hospital visits, because they do not find the intervention helpful, because of family circumstances or because they have other medical complaints.

Secondary objectives:

1. To describe the components and practical aspects of ADD. These will be described in each patients CRF. Off note, ADD is an intervention that is different for each patient: depending on the most important component for them (breathing/thinking/functioning) and how many sessions they need to learn to control their breathlessness. Therefore we describe the number of sessions in each CRF.
2. To evaluate patiens' experiences with ADD, assessed with semi-structured interviews with patients and carers after 6 weeks.

3. **STUDY DESIGN**

The intervention will be delivered by a multidisciplinary team, formed by a pulmonologist, a physiotherapist with expertise in COPD, and 3 respiratory nurses.
Prior to start of the study, physiotherapist and respiratory nurses receive ADD training by pulmonologist, who has received an BTF training in Cambridge.
Step 1: All pulmonologists, residents and respiratory nurses of the Spaarne Gasthuis recruit patients with COPD with refractory breathlessness who fullfill the inclusion critera (see chapter 4).
Step 2: Patients who are eligible are given an information letter by the recruiting health care professional, or the letter is sent to the patient by a member of the ADD team. After at least 7 days, they receive a call from a member of the ADD team, asking if they have any questions concerning the study and whether they want to participate.
Step 3: Assessment for eligibility by pulmonologist (if not eligible, this is noted in case record form); first appointment within one week.
Step 4: First appointment (approximately 1.5 hrs). Patient comes with key (informal) carer.

- Explanation of ADD by pulmonologist and nurse.
- Patient signs informed consent form
- Aided by nurse, patient fills in the CRQ.
- Informal caregiver gives NRS rating for distress due to patient's breathlessness
- Patient meets physiotherapist
- Current medication is reviewed by pulmonologist. Medication for symptom control is optimised if necessary (e.g., morphine for dyspnea).
- Patient receives ADD booklet with breathing exercises and relaxation exercises and a handheld fan, and explanation why this works (stimulation of the nervus vagus in the face)

Step 5: At the end of the first appointment, the customized intervention program is made together with the patient.

1. All patients will have at least one session with the physiotherapist. The maximum number of sessions is six (once every week).
2. All patients will have weekly contact with the respiratory nurse; at least two times in the hospital (combined with physiotherapist), other contacts may be by telephone. If it is too burdensome for patients to come to the hospital, they will receive a home visit. During these contacts, the nurse will go through the given information again, coach the patient, and assess whether the intervention is helpful for the patient.

Table 1)

	explanation	intervention	Intervention is given by
Breathing	Dysfunctional breathing pattern (too shallow, too quick, not enough time to breath out)	Breathing retraining directions (relaxed tummy breathing, huffing exercises, pursed lip breathing, reduce respiratory rate, focus on the breath out, recovery breathing) Relaxation technique Find comfortable position Breathing round a rectangle Medication (when to take what) Handheld fan with explanation Crisis plan for exacerbation	Physiotherapist pulmonologist (medication) Nurse (crisis plan)
Thinking	Too much focus on breathing Fear of suffocating Traumatic past experiences Distress, anxiety	Explanation: Patients with COPD do not suffocate Episodes of breathlessness will usually stop within 20 minutes Offer anxiety management strategies Offer mindfulness, relaxation (change (shoulder) position Patient specific action plan	Nurse
Functioning	Breathless people avoid activity, which leads to deconditioning	Individualized exercise plan Energy conservation strategies (“pacing” instead of all/nothing pattern) Advise on posture/planning/prioritising Advise on breathing technique during exercise (blow as you go, push things rather than pull them) Advise on nutrition Sleep hygiene assessment whether mobility aids are indicated	Nurse Physiotherapist

Step 6: After the six week study period, patient comes for the final visit together with informal caregiver.

- Aided by nurse, patient fills in the CRQ
- Informal caregiver gives NRS rating for distress due to patient's breathlessness
- Member of ADD team conducts a semi-structured interview with both patient and informal caregiver to explore their experiences with ADD.

Step 7: After the last patient has fulfilled the intervention, the ADD team undergoes a structured interview regarding the intervention.

Main study parameters/endpoints:

Primary endpoint: Feasibility: 75% of included patients fullfills the intervention.

Secondary endpoints:

1. To describe the components and practical aspects of ADD. These will be described in each patients CRF. Off note, ADD is an intervention that is different for each patient: depending on the most important component for them (breathing/thinking/functioning) and how many sessions they need to learn to control their breathlessness. Therefore we describe the number of sessions in each CRF.
2. To evaluate patiens' experiences with ADD, assessed with semi-structured interviews with patients and carers after 6 weeks.

4. STUDY POPULATION

Inclusion criteria

Base population: COPD patients who are treated in the outpatient clinic of the Spaarne Gasthuis.

In order to be eligible to participate in this study, a patient must meet all of the following criteria:

- COPD, diagnosed by a pulmonologist, with postbronchodilatator FEV1/FVC below the lower limit of normal
- refractory dyspnea (troubled by breathlessness in spite of optimization of COPD treatment, MRC dyspnea score at least 2 points). Since dyspnea is a symptom, there are no objective criteria, only questionnaires. As in other studies investigating dyspnea services and pulmonary rehabilitation, we use the MRC score for inclusion, which scores during which activity the patient becomes dyspnoic. A MRC dyspnea score of 2 points indicates dyspnea during hurrying or walking up a slight hill. Off note, this intervention is only offered to patients who complain of dyspnea in their daily life. Many COPD patients have an MRC dyspnea score of 2, but are not troubled by the symptom.
- able to visit the outpatient clinic
- able to read and understand the Dutch language
- mentally competent, as assessed by recruiting health care professional

Exclusion criteria

A potential patient who meets any of the following criteria will be excluded from participation in this study:

- An acute exacerbation of COPD, leading to hospitalisation, in 6 weeks before inclusion.
- An acute exacerbation during the study period, will lead to exclusion with the possibility to re-enter after stabilization. In that case, patients will follow the same study procedures again.
- Active participation in another trial

Sample size calculation

Number of subjects: 20.

Rationale: The primary aim of the present study is to assess feasibility of a new service in the Netherlands. This service is an adjusted variant of an existing service for which there is robust evidence. If ADD is feasible and effective in a pilot study population, we aim to conduct a larger randomised clinical trial regarding effectiveness. In that case, our power

calculation would be comparable to the study by Higginson et al. (9) When using the Chronic Respiratory Disease Questionnaire mastery domain as primary outcome, they calculated that more than 34 patients per group would detect a mean difference of 0·70 (SD 1), a p value of less than 0·05 at power 80%.To allow for a conservative estimated attrition of 40% they planned to recruit at least 110 patients into their study. Since it is a rule of thumb that a pilot study includes at least 10% of subjects for the full study, we would need at least 11 patients for this pilot study. However, we aim to include 20 patients in order to gain as much experience with the intervention as possible, before we decide on conducting an RCT on this subject.

5. TREATMENT OF SUBJECTS

a. Investigational product/treatment

See table 1 in section 3.

b. Use of co-intervention (if applicable)

Study subjects continue using their usual medication.

If medication is adjusted or added by the ADD team, this is noted in the case report form.

6. METHODS

c. Study parameters/endpoints

i. Main feasibility criteria:

75% of included patients complete the intervention.

ii. Secondary study parameters/endpoints

1. Description of components and practical aspects of ADD.
2. semi-structured interviews with patients and carers to evaluate ADD after six weeks.

d. Study procedures

Baseline	Completion of programme
CRQ	CRQ
NRS carer distress	NRS carer distress
	Semi-structured interview with patient and informal caregiver regarding intervention
	Structured interviews with the ADD team regarding the intervention

e. Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences.

i. Specific criteria for withdrawal (if applicable)

Hospitalisation for COPD exacerbation during study period. An acute exacerbation during the study period, will lead to exclusion with the possibility to re-enter after stabilization. In that case, patients will follow the same study procedures again.

f. Replacement of individual subjects after withdrawal

After withdrawal, a new subject will be included in the study.

g. Follow-up of subjects withdrawn from treatment

Withdrawal will be recorded in the case record form. Patients will be approached to re-enter the study after stabilisation in case of COPD exacerbation. In that case, they re-start the programme.

7. STATISTICAL ANALYSIS

Main study parameter/endpoint

Feasibility of ADD: 75% of included patients complete the intervention.

Other endpoints are descriptive.

8. ETHICAL CONSIDERATIONS

h. Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO).

i. Recruitment and consent

Patients will be recruited by all pulmonologists, residents and respiratory nurses working in the Spaarne Gasthuis. The health care professional will inform the patient about the study, and will get their consent to give their information to the research. The researchers will send the patient a letter, in which the study is explained in detail. At least one week later, they will be called by a member of the ADD team who will answer any questions. If the patient is willing to participate, he or she signs the informed consent form at the first visit.

j. Benefits and risks assessment, group relatedness

The burden for participants is deemed acceptable. The patient receives an individual training tailored to his or her needs by experienced health care professionals. During the intervention, the patient has an important say in how further visits are planned. The intervention ends as soon as the patient feels that goals have been reached.
This pilot study is an important step in the development of dyspnea services in the Netherlands. The investigator has shared the study protocol during a meeting with pulmonologists concerning palliative care for COPD (Sectie palliatieve zorg NVALT meeting on the 7th of February 2019). Other pulmonologists are interested to introduce this method in centers for COPD care.

k. Incentives (if applicable)

Participants will receive payment of travel expenses.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

Due to the nature of this study, occurrence of SAEs is not possible.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

9.2.4 Annual safety report

Not applicable.

9.2.5 Follow-up of adverse events

Not applicable.

10 ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

Handling of the personal data in this study will comply with the European General Protection Regulation (in Dutch: AVG). Data will be coded. Data will be kept in an electronic case report form (Reference Manager). This web-based program generates a unique subject identification code, based on number of enrolment into the study, not on patient initials and/or date of birth. The investigators will keep a code list of participants with their identification codes; if necessary this list will reveal which code belongs to which participant. This subject identification code list is safeguarded by the principal investigator. All data will be kept for 15 years.
Reference Manager fullfills all GCP standards for electronic data collection. Investigators who have acces to Research Manager all have a unique password. Research Manager is hosted on a server that fullfills the highest standards of security. Acces to study data will always be given to the health inspection (IGJ) and other legal authorities.

10.2 Amendments

Amendments will only be made to the research protocol after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC.

10.3 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.4 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.
The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.
In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study,

to the accredited METC.

10.5 Public disclosure and publication policy

Research data will be published in a medical journal.

11 REFERENCES

(1) Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012 Dec 15;380(9859):2095-2128.

(2) Gore JM, Brophy CJ, Greenstone MA. How well do we care for patients with end stage chronic obstructive pulmonary disease (COPD)? A comparison of palliative care and quality of life in COPD and lung cancer. Thorax 2000 Dec;55(12):1000-1006.

(3) Spathis A, Booth S, Moffat C, Hurst R, Ryan R, Chin C, et al. The Breathing, Thinking, Functioning clinical model: a proposal to facilitate evidence-based breathlessness management in chronic respiratory disease. NPJ Prim Care Respir Med 2017 Apr 21;27(1):27-017-0024-z.

(4) Gysels M, Higginson IJ. Access to services for patients with chronic obstructive pulmonary disease: the invisibility of breathlessness. J Pain Symptom Manage 2008 Nov;36(5):451-460.

(5) Simon ST, Higginson IJ, Benalia H, Gysels M, Murtagh FE, Spicer J, et al. Episodes of breathlessness: types and patterns - a qualitative study exploring experiences of patients with advanced diseases. Palliat Med 2013 Jun;27(6):524-532.

(6) Bausewein C, Jolley C, Reilly C, Lobo P, Kelly J, Bellas H, et al. Development, effectiveness and cost-effectiveness of a new out-patient Breathlessness Support Service: study protocol of a phase III fast-track randomised controlled trial. BMC Pulm Med 2012 Sep 19;12:58-2466-12-58.

(7) Bausewein C, Schumacher P, Bolzani A. Integrated breathlessness services for people with chronic conditions. Curr Opin Support Palliat Care 2018 Sep;12(3):227-231.

(8) Bausewein C, Schunk M, Schumacher P, Dittmer J, Bolzani A, Booth S. Breathlessness services as a new model of support for patients with respiratory disease. Chron Respir Dis 2018 Feb;15(1):48-59.

(9) Higginson IJ, Bausewein C, Reilly CC, Gao W, Gysels M, Dzingina M, et al. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. Lancet Respir Med 2014 Dec;2(12):979-987.

(10) Brighton LJ, Miller S, Farquhar M, Booth S, Yi D, Gao W, et al. Holistic services for people with advanced disease and chronic breathlessness: a systematic review and meta-analysis. Thorax 2018 Nov 29.

(11) Alius MG, Pane-Farre CA, Von Leupoldt A, Hamm AO. Induction of dyspnea evokes increased anxiety and maladaptive breathing in individuals with high anxiety sensitivity and suffocation fear. Psychophysiology 2013 May;50(5):488-497.

(12) Yohannes AM, Kaplan A, Hanania NA. Anxiety and Depression in Chronic Obstructive Pulmonary Disease: Recognition and Management. Cleve Clin J Med 2018 Feb;85(2 Suppl 1):S11-S18.

(13) Swan F, Booth S. The role of airflow for the relief of chronic refractory breathlessness. Curr Opin Support Palliat Care 2015;9:206-211.